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Allergy and Asthma

The Basics to Best Practices

Springer

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The Basics to Best Practices

With 126 Figures and 182 Tables

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To the memory of my father Mohammad H. Mahmoudi, and to my mother Zohreh, my wife Lily, and my sons Sam and Sina for their continuous support and encouragement.

Preface

It has been a great pleasure to prepare and present this comprehensive resource on allergy and asthma. *Allergy and Asthma: The Basics to Best Practices* is the first comprehensive collection of up-to-date information on allergy and asthma of Springer Nature's Major Reference Works (MRW). In the last five years, a lot has changed in the field of allergy and immunology, one of many reasons that have made the timing of this collection a priority.

The present book consists of 41 chapters and is a collective effort of over 80 known experts in the field. From basic immunology to sublingual immunotherapy, this book covers a wide variety of topics useful to the practice of allergy and immunology. The book also benefits from the expertise of two well-known colleagues, Dennis Ledford, professor of medicine at the University of South Florida, and Tim Craig, professor at Penn State University, as section editors. What makes this and other MRW publications unique is the fact that each peer-reviewed chapter is published electronically prior to the print; this makes the information available to the reader in a timely manner. To show the viability of newly presented information, each chapter is periodically updated to serve as an ongoing resource for new information.

The completion of this book would not have been possible without the support of the editorial team at Springer Nature. I would like to express my gratitude to Caitlin Prim who invited me to head this project and Andrew Spencer, senior editor of MRW projects, Daniela Heller, and NithyaPriya Renganathan. Finally, a special thanks to Richard Lancing, director clinical medicine, who has supported my relationship with Springer and now Springer Nature for my previous five books.

Massoud Mahmoudi, DO., Ph.D.
Editor-in-Chief

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About the Editor-in-Chief

Dr. Massoud Mahmoudi is a practicing internist and allergist in Los Gatos, California. He completed his Ph.D. in Microbiology at the University of North Texas and Wadley Institutes of Molecular Medicine in Texas. Subsequently, he completed three different postdoctoral fellowships at UT Southwestern Medical School at Dallas, Texas, doing research on oncogenes, biology of aging, and tissue plasminogen activator. He then attended A.T. Still University College of Osteopathic Medicine in Kirksville, Missouri, where he completed his DO degree. Subsequently, he attended an internal medicine residency program at Yale University and Rowan University. Then he completed a fellowship in Allergy and Clinical Immunology at the University of California Davis. He is currently President of American Osteopathic College of Allergy and Immunology and faculty member at the University of California San Francisco, Rowan University, and Touro University.

He is the author/editor of 10 books on allergy, immunology, and other medical topics. He was a columnist for local newspaper and the *San Francisco Chronicle*. He has spoken locally and nationally on allergy and immunology and has appeared on local televisions and the Fox News. Dr. Mahmoudi is currently the Editor-in Chief of the peer-reviewed journal *SN Comprehensive Clinical Medicine*, a Springer Nature publication.

Section Editors

Dennis K. Ledford University of South Florida and the James A. Haley V.A. Hospital, Morsani College of Medicine, Tampa, FL, USA

Dennis Ledford is the Ellsworth and Mabel Simmons Professor of Allergy and Immunology at the Morsani College of Medicine, University of South Florida (USF), and the Section Chief of Allergy/Immunology at the James A. Haley VA Hospital, Tampa, Florida. He received his medical degree from the University of Tennessee Health Science Center and completed his internal medicine residency and served as chief medical resident for Dr. Gene Stollerman. A fellowship in rheumatology and immunology followed at New York University and Bellevue Hospital in New York and a fellowship in allergy and immunology at the University of South Florida. Dr. Ledford joined the faculty at the USF Morsani College of Medicine and achieved the rank of professor of medicine in 2000. His clinical responsibilities and student and resident teaching are combined with research interests in molecular identification of pollen, microRNA in nasal disease, and severe, steroid-dependent asthma, and with medical writing and editing. His local and regional activities include past service as President of the Medical Faculty for the USF Morsani COM and President of the Florida Allergy, Asthma and Immunology Society and current service as Head of the Allergy/Immunology Section Florida Hospital Tampa. His national contributions include prior service as an Associate Editor of the *Journal of Allergy and Clinical Immunology*, Chair of the Steering Committee for the Allergy, Asthma and Immunology Education and Research Trust Fund (AAAAI Foundation), President of the American Academy of Allergy, Asthma and Immunology, Co-chair of the ACGME Allergy/Immunology

Residency Review Committee, and Director of the American Board of Allergy and Immunology. He was selected as the outstanding teaching faculty by the medical house staff in 1985 and the Hillsborough County Medical Volunteer of the Year 2001 and has received the Distinguished Clinician Award from the AAAAI in 2014 and the World Allergy Organization in 2015. He was given the Leonard Tow Humanism in Medicine Award in 2015 by the graduating medical school class. In 2017 he was honored with a Foundation Lecture from the AAAAI at the annual meeting in recognition of raising $100,000 for allergy/immunology research. The University of South Florida honored him with the Distinguished Service Award in 2018.

Timothy Craig Pennsylvania State University (PSU), State College, PA, USA

Timothy Craig is Chief of the Allergy/Immunology Section, Director of Allergy and Respiratory Clinical Research, Clinic Director, and Program Director. He graduated valedictorian from NYCOM in 1984. He was in the US Navy for 14 years before leaving for the University of Iowa and finally to PSU.

Dr. Craig has experience in basic research, clinical research, large NHLBI research networks, medical education, postgraduate training, leadership, continuing medical education, and clinical operations.

Dr. Craig has served as a leader in multiple organizations, including Asthma Diagnosis and Treatment Interest Section Chair for the AAAAI. He has served as Chair of the Occupational and Sports Committees for the AAAAI and the ACAAI. Dr. Craig is past President of the Pennsylvania Allergy Association, past Mid-Atlantic Governor for the RSLs, and past board member of the JCAAI and ACAAI. He is on the board of the American Association of Allergy, Asthma and Immunology, HAE Association, and American Lung Association Mid-Atlantic and is Director of PSU Alpha-1-Foundation Clinical Resource Center.

Dr. Craig is a Vietnam Education Foundation Fellow. He has received numerous awards recognizing his excellence in teaching and mentorship, including Distinguished Educator, Dean's Educator Award, Alpha Omega Alpha, Medicine Educator of the Year, and two Medical Student's Teacher of the Year. He is a successful clinical researcher and mentor, has published

over 290 manuscripts and delivered over 450 invited lectures, and serves on numerous editorial boards.

Despite his extensive career, Dr. Craig is most proud of his success as a mentor for premedical students, foreign and American medical students, and postgraduate trainees. His leadership of the Allergy, Asthma and Immunology Fellowship Program has been a success and has graduated multiple well-trained and ethical allergists and immunologists.

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The original version of this book was revised: Dedication and Preface is now added to the Front matter. The correction to this book is available at https://doi.org/10.1007/978-3-030-05147-1

Part I

Introduction

Overview of Immunology and Allergy

1

Stephen C. Jones

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The author wishes to acknowledge Suzanne Jones for reviewing and editing this submission.

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Abstract

Immunological protection of the individual from infection requires the coordinated involvement of numerous tissues, cell types, and secreted factors collectively referred to as the immune system. This is equally true for the immune response to environmental antigens that is the underlying cause of diseases such as allergic asthma and food allergies. This sequence of events is set in motion by a T cell response defined by the cytokines that it produces and their impact on neighboring B cells to produce antibody that uniquely sensitizes the host to the offending allergen. Granule-laden cells of the innate immune system are the ultimate sources of the powerful inflammatory mediators of the allergic response. To fully understand the factors which contribute to the development of allergies and that are discussed in this book, this chapter provides the reader with an introduction to the cellular and chemical mediators of the immune response, beginning with those of the innate immune system. The chapter then works its way to the mediators of the adaptive immune system, along the way covering important topics such as major histocompatibility complex (MHC), antigen processing and presentation, and lymphocyte development. The chapter concludes with an introduction to hypersensitivity mechanisms, focusing on the allergic response.

Keywords

Innate · Adaptive · Hypersensitivity · Effector · Differentiation · CD4 · Allergy

1.1 Introduction

A key component of the maintenance of health and physiological homeostasis is the inherent ability of the host to protect itself from the many potential pathogens with which we share our environment. These measures of protection are diverse and range from keratinized-stratified skin offering a physical barrier to infection to cytotoxic T lymphocytes (CTL) capable of discerning the presence of a foreign cytosolic virus and triggering apoptosis of the infected cell. Collectively, the tissues, cells (known as leukocytes), and secreted factors which provide protection against infection are referred to as the immune system. The mobilization of this system of secreted factors and bone marrow-derived cells, some of which are resident to tissues and others of which circulate through the blood and lymph, takes place in two waves of recruitment and activation. The first wave consists of fairly nonspecific cellular and chemical mediators whose job it is to rapidly eliminate microbes that have entered host tissues. Because this protection is provided by components of the immune system that are always present at maximum capacity to rapidly respond to an infectious threat, this is termed innate or natural immunity. While the benefit of the innate immune response is its rapid mobilization, its limitation is that its mechanisms of protection are fairly nonspecific in that it deals with many different microbes using a fairly restricted set of mechanisms. Additionally, protection by the innate immune system is not enhanced by repeated exposure to a pathogen (i.e., it has no immunological memory). The second wave of the immune response is more finely adapted to deal with the specific pathogen encountered, and as such takes more time to develop. Because this form of immunity adapts to specific infectious agents and is shaped by the host's history of pathogen encounter, it is referred to as adaptive or acquired immunity. It is the adaptive immune response that provides enhanced protection from a pathogen that the host has already encountered, and as such is the functional basis of the practice of vaccination. It is also the adaptive immune system that is responsible for targeting the harmless antigens of the environment known to trigger the allergic response. This chapter begins with an overview of the mediators of the innate and adaptive immune system, followed by an in-depth discussion of their recruitment, activation, and effector function during the antimicrobial response. The chapter also includes a section on the development of the antigen receptors of the adaptive system so that the reader better appreciates the capacity of the immune system to recognize and respond to a

virtually unlimited number of antigens. The chapter concludes with an overview of the ways in which the immune response can cause tissue injury with an emphasis on the allergic response.

1.2 Features of the Innate Immune System

The "ever-present" protection provided by the innate immune system utilizes different anatomical and chemical barriers of the host, including the skin and the epithelial lining of the mucosal surfaces of the airway, gastrointestinal, and reproductive tracts. This barrier is enhanced in the airways by the mucociliary escalator, whereby would-be pathogens are trapped in secreted mucus and forced up by the continuous beating of the cilia which extend from the respiratory epithelium. Low physiological pH, secretion of antimicrobial peptides (defensins and cathelicidins), and the production of opsonizing surfactants are additional chemical measures in the digestive tract and mucous membranes that provide continuous protection from infection. In the event of an epithelial injury providing the opportunity for infection, or the penetration of this first line of defense by a pathogen, additional components of the innate immune system are rapidly mobilized to actively respond to the infectious threat. This includes neutrophils, which are the first cells of the immune system recruited to the site, followed by monocytes-macrophages. Both cell types phagocytose (engulf) and then use proteolytic enzymes and reactive oxygen species to break down pathogens and cellular debris. Natural killer (NK) cells are also rapidly recruited to the site of an infection and are important in response to invading viruses (Brown et al. 2001). Dendritic cells (DCs) in their immature state are resident to the epithelial tissues of the host. These cells also take up pathogens and debris but serve a different ultimate purpose, which is to transport bits of the infectious invader to the draining lymph nodes for recognition by lymphocytes of the adaptive immune system. For this reason, DCs are seen as the bridge between innate and adaptive immunity (Mellman and Steinman 2001). Other cells of the innate immune system, such as mast cells, eosinophils, and basophils, play an important role in the immune response to parasites and helminths but in the absence of such types of pathogens are best known for their roles in acute and chronic allergic responses (Eckman et al. 2010; Galli et al. 2005; Blanchard and Rothenberg 2009). Finally, the innate immune response also includes secreted factors found in blood and tissue fluids. Principal among these are proteins of the complement system, which are produced by the liver and circulate in an inactive form. Activation of the complement system can be triggered in different ways, but ultimately it contributes to the recruitment of neutrophils and destruction of bacterial targets. Additional secreted factors produced early during the immune response include the inflammatory cytokines tumor necrosis factor alpha (TNFα) and interleukin-1 (IL-1), which together have numerous effects on the developing immune response, such as promoting the recruitment and activation of neutrophils and macrophages and the induction of fever.

1.3 Features of the Adaptive Immune System

If the innate immune response does not remove the infectious threat, an adaptive immune response is triggered. The cellular mediators of the adaptive immune response are called lymphocytes. Lymphocytes are found in the bloodstream, lymph, peripheral lymphoid organs (such as the spleen and lymph nodes), mucosal epithelial surfaces, and sites of infection. There are two principal types of lymphocytes: B cells and T cells. Both B and T cells express a diverse repertoire of receptors of the immunoglobulin superfamily that differentiate between normal tissue constituents (i.e., self) and foreign material derived from microbes, referred to as antigen. It is estimated that the cells of the B and T cell compartments have the potential to express as many as 10^{11}–10^{16} different antigen receptors, thereby providing the host with the capacity to recognize and respond to a virtually limitless array of foreign antigen and guaranteeing that no infectious threat will go

unchallenged (Abbas et al. 2012). If there is a downside to this design, it is that maintaining such a diversity of lymphocytes limits the number of cells specific for any one particular microbe. To compensate for this apparent limitation, antigen recognition triggers multiple rounds of clonal expansion of that cell, thereby creating many daughter cells bearing an identical antigen receptor with specificity for the offending microbe. Once the microbe has been cleared and the need for so many cells has passed, a process called "activation-induced cell death" (AICD) will result in the contraction of lymphocyte numbers and the re-establishment of homeostasis. With such an enormous diversity of antigen receptors and aggressive amplification of lymphocyte numbers upon stimulation comes the additional concern of unintended injury to the host. The likelihood of this is dramatically reduced, however, by an elaborate process of "negative selection" that purges the repertoire of developing lymphocytes that express antigen receptors which bind to self-antigen with high affinity, thereby helping to establish tolerance to the components of normal tissue.

Morphologically, B and T cells are indistinguishable but are phenotypically quite unique. To begin with, B and T cells can be distinguished by the expression of certain molecules on their cell surface: B cells uniquely express CD19, CD20, and CD21, whereas T cells express CD2 and CD3. Furthermore, all CD3 T cells can be further subdivided into those which express CD4 and CD8. Before encounter with their foreign antigen, lymphocytes circulate between the blood, peripheral lymphoid organs, and lymph in an inactivated or "naïve" state. Such cells do not exhibit an effector function and instead continuously follow this pattern of recirculation in search of their cognate foreign antigen. Antigen recognition in the peripheral lymphoid organs will interrupt this pattern, and instead of passing from these sites to the lymph and later back to the blood, the lymphocytes will be sequestered as they become activated, undergo clonal expansion, and differentiate into the powerful effector cells of the adaptive immune system (Springer 1994; Zhu et al. 2010). This process takes time, and in an individual who has not been previously exposed to a particular pathogen, a "primary immune response" can take 7–10 days to develop. Thus, it becomes clear why the rapid response of the innate immune system is so important to limiting the early growth of a pathogen while the adaptive immune response develops. The T and B cell response to subsequent exposure to the same pathogen will occur with hastened kinetics (3–5 days), such that the infection may be cleared before the individual feels ill. This enhanced "secondary immune response" is the result of the creation of memory T and B cells during the primary response that respond rapidly and in greater numbers to repeated exposure to the same pathogen (Murphy and Weaver 2017).

Humoral immunity is the term used to describe B cell-mediated immunological protection, which is most effective against extracellular microbes and their toxins. B cells have the capacity to recognize a diverse array of foreign antigenic compounds that may be constituent parts of an invading microbe, including polysaccharides, proteins, lipids, and nucleic acids. Once fully activated, B cells differentiate into plasma cells which produce large amounts of antibody (also called immunoglobulin) that bind with high affinity to the original cognate antigen, thereby neutralizing the pathogen or its toxin or marking it for destruction by the complement system or a phagocyte. Alternatively, T cells are most capable of dealing with intracellular pathogens through mechanisms collectively referred to as cellular immunity. T cell antigen receptors recognize microbial proteins that have been broken down into small peptides and are displayed on the surface of infected cells or professional antigen-presenting cells (APCs). Central to this process of antigen presentation are the major histocompatibility complex (MHC) proteins that serve as the scaffolding used to display foreign peptides to T cells. Once activated, CD4 T cells are most helpful in dealing with intracellular bacteria and fungal pathogens that have the capacity to survive within macrophages after being phagocytosed, whereas CD8 T cells are adept at killing host cells harboring intracellular microbes in their cytoplasm. In addition, CD4 T cells help to orchestrate a fully functional humoral immune

response by providing signals to B cells that induce a process of antibody affinity maturation and functional class switching. A third and functionally distinct subset of T cells is best known for its capacity to suppress the immune response rather than to promote it. These regulatory T cells express the CD4 and CD25 cell surface proteins and have been the focus of intense research over the past 20 years that has clarified some of the ways in which the immune system balances pro- and anti-inflammatory signals (Sakaguchi et al. 2008; Roncarolo et al. 2001).

This chapter will introduce the reader to the principle cellular and chemical mediators of the innate and adaptive waves of the immune response. Because it is the mediators of the adaptive immune system that determine one's likelihood of developing allergies, the focus of this book, more emphasis will be placed on the development, recruitment, and function of these mediators in health and disease.

1.4 The Innate Immune Response

1.4.1 Recruitment and Function of the Cellular Mediators of the Innate Immune Response

The function of the cellular and chemical mediators of the innate immune system is to recognize the presence of tissue injury or microbes that have defeated the epithelial barriers of the body and to quickly control, or even eradicate, the infectious threat. The cellular mediators derive from common myeloid precursor cells in the bone marrow under the influence of growth factors, such as granulocyte colony-stimulating factor (G-CSF) and monocyte colony-stimulating factor (M-CSF), that drives the production of neutrophils and monocytes/macrophages, respectively (Abbas et al. 2012; Wynn et al. 2013).

Activating an innate immune response begins with the tissue macrophages, DCs, and mast cells that are optimally located in the epithelium and other tissues of the body to serve as sentinel cells responsible for sensing the presence of invading microbes and cellular damage (Wynn et al. 2013; Shortman and Liu 2002). Activation of these cells is triggered by the recognition of common structural motifs shared among broad groups of pathogens, referred to as pathogen-associated molecular patterns, or PAMPs. PAMPs are not expressed by host tissues and are often structures that are essential for the survival and infectivity of the microbes (Beutler and Rietschel 2003). Examples are lipopolysaccharide (LPS), a component of the cell wall of gram-negative bacteria, and flagellin, a central component of bacterial flagella. Recognition of these structures is imparted by a collection of germline DNA-encoded receptors referred to as pathogen recognition receptors (PRRs) (Takeuchi and Akira 2010). PRRs are less diverse than lymphocyte antigen receptors and are found widely expressed among different cells of the innate immune system. A major family of PRRs are called Toll-like receptors (TLR), so named because of homology with the Toll gene, first identified by its role during drosophila embryogenesis and later found to be critical for adult fly antimicrobial defense (Beutler and Rietschel 2003; Lemaitre et al. 1996, 1997). TLRs are numbered one through nine, with each recognizing distinct bacterial or viral PAMPs such as LPS, bacterial peptidoglycan, or viral single-stranded or double-stranded RNA (Takeuchi and Akira 2010). TLRs specific for microbial components encountered as part of the cell wall of extracellular bacteria are expressed at the cell surface, while those specific for motifs associated with microbial nucleic acids are found within endosomes, where ingested microbes are digested and their nucleic acids released.

PRR binding to its cognate microbial ligand triggers a cascade of intracellular signaling events resulting in the activation of transcription factors, most notably NF-κB and interferon regulatory factor (IRF). Following activation and translocation into the nucleus, NF-κB will promote the expression of various cytokines and adhesion molecules important for the early recruitment of neutrophils and monocytes to the site of infection, while IRFs drive the production of the antiviral type I interferons (Hiscott et al. 2006; Honda and Taniguchi 2006). Two of the most important cytokines produced as a result of PRR engagement

and NF-κB activation are IL-1 and TNFα (Svanborg et al. 1999). These cytokines play an early role in the recruitment of neutrophils to the site of infection by activating the endothelial cells of local venules. In response, endothelial cells express the adhesion molecules E-selectin and ICAM-1 and VCAM-1 (Alon and Feigelson 2002; Bunting et al. 2002). Carbohydrates expressed by circulating neutrophils bind with relatively low affinity to E-selectin. Stable adhesion to the endothelium requires the local secretion of the chemokine CXCL-8 (IL-8) which triggers a conformational change in the leukocyte integrins LFA-1, MAC-1, and VLA-4, allowing for high-affinity binding to the endothelial ligands, ICAM-1 and VCAM-1 (Yoshie 2000; Luster 2002). Once firmly attached to the endothelium, neutrophils, and later monocytes, will extravasate into the tissue and follow the chemokine gradient to the site of infection. Once in the infected tissue, neutrophils and macrophages engage the pathogen via their PRRs which triggers phagocytosis (uptake) of the microbe into phagosomes. These loaded phagosomes will fuse with lysosomes that contain the reactive oxygen species, nitric oxide, and proteolytic enzymes that destroy the bacteria. In addition to phagocytosis and killing of the pathogen, activated macrophages are significant sources of IL-1 and TNFα, which further enhance the inflammatory reaction and recruitment of inflammatory mediators. IL-6 and IL-12 are also produced by macrophages and are important for triggering the production of acute phase proteins such as C-reactive protein (CRP) by the liver and promoting a cell-mediated adaptive immune response, respectively. IL-12 produced by macrophages is also significant for its activation of NK cells, which in turn enhance macrophage function through their production of the critical cytokine IFNγ (Godshall et al. 2003).

In addition to enhancing the macrophage response, NK cells are important for the innate killing of infected or neoplastic host cells. NK cells are unique in that they derive from the same lymphoid progenitor as T and B cells; however, they do not express a similar repertoire of diverse antigen receptors. Rather, NK cells utilize a complement of killer inhibitory and activating receptors to differentiate between healthy and injured or infected cells, and it is the balance of signals delivered through these receptors that determine the activation of NK cell-mediated killing. One well-described activating receptor, NKG2D, recognizes the MHC class I-like proteins MIC-A and MIC-B that are found on virally infected and tumor cells but not on healthy cells (Bauer et al. 1999; Gonzalez et al. 2006). NKG2D recognition of these molecules delivers signals that activate NK cytolytic killing of infected cell. In contrast, inhibitory receptors recognize the cell surface molecule MHC class I, which is expressed by all healthy nucleated cells and is critical for presentation of cytosolic antigen to CD8 T cells (Borrego et al. 2002; Long 2008). Engagement of inhibitory receptors suppresses NK cell-mediated killing of the MHC class I-bearing cell; however, viruses that replicate in the cytosol and whose antigen is displayed to CD8 T cells via the MHC class I molecule have mechanisms to suppress MHC class I expression. In this situation, inhibition of NK cell activation is lost and signals delivered through the activating receptors will dominate, resulting in NK cell killing of the infected target cell (Vivier et al. 2008).

1.4.2 Complement System

Vasodilation and increased vascular permeability at the site of infection or injury not only will result in the recruitment of cellular mediators such as neutrophils and monocytes but also will draw in components of the complement system which are constitutively found in the blood. The complement system is composed of multiple plasma proteins, many of which are proteolytic enzymes that circulate in an inactive form. Activation of the complement system results in the sequential activation of these enzymes that serve to cleave other complement proteins into “a” and “b” fragments that, as a result, acquire specific functions in the immune response. The culmination of these actions is the creation of a transmembrane channel, called the membrane attack complex (MAC), in bacterial cell walls that disrupts osmotic balance and cause lysis of the microbes.

The cascade of complement protein activation can be initiated by three different pathways. The alternative pathway of activation is initiated as part of the innate immune response and depends upon the low-level spontaneous hydrolysis of the C3 complement protein and formation of C3b. C3b is readily hydrolyzed in the blood and tissue fluid and is only stabilized upon attachment to the surface of a microbe. The microbe-bound C3b then becomes the nucleus for the formation of convertase enzymes that cleave large amounts of C3 and later C5 into biologically active "a" and "b" cleavage products (Gros et al. 2008). The lectin pathway of complement activation is also considered part of the innate immune response; however, it takes longer to become activated because it requires the production of mannose-binding lectin (MBL), an acute phase protein, by the liver. When MBL binds to terminal mannose residues on the surface of microbes, it becomes enzymatically active and cleaves circulating C2 and C4 complement proteins, the products of which contribute to the pathway's C3 and C5 convertase enzymes (Fujita 2002). The classical complement pathway is unique in that it requires the presence of antibody bound to the surface of a microbe to become activated and is therefore considered to be an effector function of the adaptive immune response (McGrath et al. 2006). The bound antibody becomes a target for the C1 complement protein, which is very similar in function to MBL in that once bound to antibody, it becomes enzymatically active to cleave C2 and C4 complement proteins which lead to the pathway's C3 and C5 convertase enzymes. The three complement pathways converge following the formation of the C5 convertases and the creation of large amounts of C5b, which initiates the formation of the (MAC). In addition to microbial lysis by the formation of the MAC, activated complement proteins such as C3a and C5a promote recruitment of neutrophils, while C3b and C4b are highly effective opsinins that enhance microbe phagocytosis (Schraufstatter et al. 2002; Helmy et al. 2006). Complement activation not only plays an important role in immunity to pathogens but also is an important player in tissue damage caused by dysregulated immune responses, such as those seen during autoimmune disease (Hadders et al. 2007).

1.5 The Adaptive Immune Response

1.5.1 Organs and Tissues of the Immune System

While innate immunity is optimal for quickly recognizing the presence of an infectious agent and controlling the infection, it is often insufficient by itself to completely eradicate an infection. In this regard, the importance of the adaptive immune system is illustrated in those individuals with a congenital immunodeficiency that prevents normal T and B cell development and who often succumb to infectious disease within the first year of life unless corrective action is taken, such as a bone marrow transplant.

T and B cells are derived from common lymphoid precursors found in the bone marrow, committing to either lineage under the influence of signals delivered through several cell surface receptors. Signals downstream of these receptors induce lineage-specific transcription factors that promote the creation of either T or B cell antigen receptors. Although both cell types derive from precursors in the bone marrow, they undergo the majority of their differentiation in two different locations: T cells in the thymus and B cells in the bone marrow. The thymus and bone marrow are collectively known as the generative, or primary, lymphoid organs. Lymphocyte development in both sites follows a similar sequence of progenitor proliferation under the influence of cytokines such as IL-7, gene segment rearrangement for the purpose of creating a diverse repertoire of antigen receptor-bearing cells, and selection of cells with useful antigen receptors (described in more detail below).

Following export to the blood from the primary lymphoid organs, mature naïve B and T cells on the lookout for their cognate microbial antigens home to peripheral or secondary lymphoid organs of the body, including the lymph nodes and spleen. Lymph, derived from plasma that has

leaked from blood vessels and contains debris from dying cells and antigens of any infectious organisms, drains from tissues via a network of lymphatic vessels. These vessels direct the lymph into regional lymph nodes where antigen is captured in T and B cell zones. In addition to antigen carried passively from infected tissues by lymph, it is also actively picked up and transported to the draining lymph nodes by mature DCs. It is therefore in the regional lymph nodes, as well as in the spleen, in which blood-borne antigen is filtered, where antigen is concentrated from larger regions of the body and first displayed to the lymphocytes that continuously home there. Mucosal epithelial surfaces, such as the small intestine, which are the portals of entry for the vast majority of infectious agents that invade the human body, have developed equally elaborate processes to surveil for the presence of pathogenic microbes. Specialized intestinal epithelial cells, called M cells, actively take up and transport antigens from the intestinal lumen to the underlying Peyer's patches, which consist of aggregates of macrophages, DCs, and circulating lymphocytes.

1.5.2 Lymphocyte Trafficking

Similar to the trafficking of neutrophils to sites of infection and inflammation, lymphocytes migrate to specific sites based upon their particular expression pattern of select homing and chemokine receptors. L-selectin and CCR7 are homing receptors found to be highly expressed by naïve T cells. Interaction between L-selectin and its ligand (PNAd) expressed by lymph node high endothelial venules (HEVs) initiates a low-affinity, transient interaction along the local endothelium (Rosen 2004). CCL19 and CCL21 chemokines, which are produced in the paracortical T cell areas of the lymph node, bind to the CCR7 receptor, which triggers a conformational change in the LFA-1 integrin allowing it to firmly bind to its endothelial ligand, ICAM-1, thereby arresting the lymphocyte. Collectively, these events allow the naïve T lymphocyte to enter the lymph node which will now follow the CCL19 and CCL21 gradient to the structure's T cell area (Cyster 1999, 2000). In a beautifully choreographed interaction, DCs carrying antigen captured from regional tissue sites and also bearing the CCR7 chemokine receptor will be equally drawn in by the CCL19 and CCL21 gradients to the T cell zone, thereby allowing for the DC presentation of captured antigen to the circulating T cells. Alternatively, circulating naïve B cells, which localize to the follicles of the lymph node cortex, express the chemokine receptor CXCR5, which specifically recognize and follow the CXCL13 chemokine produced only in the follicles (Cyster et al. 2000). In this way, naïve T and B cells localize to specific areas of the lymph node to test their antigen receptors against antigen originating from surrounding tissues. As we will see, a fully functional B cell response to an antigen requires signals provided by CD4 T cells. To facilitate this interaction, a cohort of the activated B and CD4 T cells will "flip" their chemokine receptor expression causing the CD4 T cells to move toward the follicles and B cells to move toward the paracortical T cell areas.

It is estimated that each of the body's 1×10^{12} lymphocytes passes through each lymph node about once a day in search of their cognate antigen (Abbas et al. 2012). In the absence of an antigen-recognition event, naïve lymphocytes will exit the lymph node via the efferent lymphatic and enter the next lymph node in the chain, surveilling for foreign antigen before eventually returning to the blood by way of the thoracic duct. Recognition of foreign antigen triggers the activation of transcription factors and genes that drive the clonal expansion and differentiation of the particular lymphocyte into effector cells. As part of this program of expansion and differentiation, the activated cells will decrease expression of the cell surface molecules responsible for recirculation through the peripheral lymphoid organs (CCR7 and L-selectin) and instead increase those ligands (E- and P-selectin ligand) and chemokine receptors (e.g., CXCR3) that will allow them to traffic to the site of infection. At the same time, TNFα and IL-1 produced at the site of infection will activate the local endothelium to express the complementary selectins and cell adhesion molecules which, along with local chemokine production,

will efficiently draw in the powerful effector cells required to fight the infection.

A more recent advancement in our understanding of the mechanisms that control lymphocyte circulation is the elucidation of the role that the molecule termed phospholipid sphingosine 1-phosphate (S1P) and its receptor plays in the egress of T cells from the lymph node (Cyster and Schwab 2012). S1P's influence on T cell's trafficking behavior is due to its high level of expression in the blood and lymph and low level inside the lymph node. In response to the high level of S1P in the blood, circulating naïve T cells express low levels of the S1P receptor. Upon entering the lymph node, where the S1P level is lower, naïve T cells begin to upregulate the receptor, thereby becoming more sensitive to its gradient, causing the T cell to leave the node through the efferent lymphatic. T cell recognition of antigen in the lymph node will delay the increased expression of the S1P receptor, thereby causing the cell and its progeny to be sequestered in the lymph node during the clonal expansion and differentiation phase of the T cell response. Upon completion of this process, the level of S1P receptor on the effector cells is allowed to increase, thereby drawing the cells back into the lymph and blood after which they will selectively traffic to the site of infection (Cyster and Schwab 2012).

1.5.3 Antigen and Antigen Receptors

Pathogen recognition by cells of the innate immune system is accomplished through PRRs that detect common motifs shared among broad groups of pathogens such as lipopolysaccharide and double-stranded viral RNA. It is therefore outside the scope of the function of the innate immune system to differentiate between closely related organisms or to mount an immune response tailored to the characteristics of a unique pathogen. The adaptive immune system, however, is designed for such tasks. As discussed, naïve T and B cells first encounter their cognate antigen as they circulate through the peripheral lymphoid organs of the body. Recognition of antigen occurs through antigen receptors which triggers the activation of the lymphocyte on which the receptor is expressed. As we will see, this activation leads to the transcription and translation of genes that encode cytokines and other effector molecules that allow the lymphocyte to divide, differentiate, and mediate its effector function. The activation signal is delivered through invariant accessory molecules associated with the antigen receptors, including the CD3 complex and CD4 and CD8 molecules for T cells, and the immunoglobulin alpha and beta (Igα and Igβ) proteins for B cells.

B and T cells recognize different types of antigen. B cell antigen receptors can recognize the three-dimensional structure of a variety of microbe-derived macromolecules, including polysaccharides, nucleic acids, lipids, and proteins. These may be present on the microbe's cell surface or be in soluble form (e.g., a secreted microbial toxin). The antigen receptors of most T cells, however, recognize peptide fragments from microbial protein antigens that have been broken down and displayed to the cells in the context of MHC proteins. Because a fully functional B cell response requires activation signals that can only be provided by antigen-stimulated CD4 T cells, foreign protein antigens are most effective at eliciting all functions of cellular and humoral immunity and are referred to as T-dependent antigens. Large macromolecular antigens may contain multiple different epitopes, which are the precise parts of the macromolecule recognized by different antigen receptors. A macromolecule with multiple identical epitopes is referred to as poly- or multivalent, an example of which are the long-chain polysaccharides of some bacteria capsules. The repeating sugar subunits of these polysaccharide chains engage multiple B cell antigen receptors of a cell at once, thereby generating a strong activation signal. Such antigens can activate a limited B cell response independent of T cell help and are therefore called T-independent antigens. Clinically, this is very significant because capsular polysaccharide vaccines induce protective immunity against encapsulated bacteria such as *Streptococcus pneumoniae* and *Haemophilus influenzae* by eliciting opsonizing antibodies that promote phagocytosis and killing of the microbe. Newborns mount poor T-independent responses,

and, therefore, pure capsular polysaccharide vaccines fail to induce protective immunity in this population. The development of conjugated vaccines, whereby bacterial polysaccharides are conjugated to foreign proteins thereby creating a T cell-dependent antigen, has dramatically decreased morbidity and mortality in newborns and infants caused by infection from encapsulated bacteria (Klein Klouwenberg and Bont 2008).

An additional significant difference between T and B cell antigen receptors is that T cell antigen receptors are only found in a membrane-bound form and do not serve any additional role beyond recognition of peptide antigen displayed by MHC. In contrast, the B cell antigen receptors are a membrane-bound form of antibody which is secreted prodigiously by fully differentiated plasma cells as the principle effector molecule of the humoral immune response. This antibody may be produced as one of five different "isotypes." While all secreted antibody must bind to its target antigen to contribute to the immune response, the mechanism by which it contributes will vary depending upon the isotype. Antibody effector functions include activation of the classical complement pathway, opsonization of pathogens for enhanced phagocytosis, mast cell sensitization, mucosal immunity, and pathogen/toxin neutralization.

1.5.4 Properties of MHC

The MHC gene was first identified for its role in the immunological rejection of tissue transplanted between genetically disparate individuals, whereby, in experimental mouse models, skin graft transplants were only accepted if the recipient and donor strains exhibited the same MHC genes (Rosenberg and Singer 1992). Today, we understand that MHC molecules are membrane proteins whose physiological function is to display peptides derived from protein antigens to T lymphocytes and that their significance in the setting of tissue transplantation is because of the polymorphic nature of the MHC genes across the population. The presented peptides may be derived from either microbial or self-proteins; however, normally only microbial peptides will be recognized by T cell antigen receptors. In humans, the MHC proteins are called human leukocyte antigens (HLA) and are encoded on chromosome 6, where two sets of genes are found, called the class I and class II MHC genes.

The MHC class I locus includes three HLA genes: HLA-A, HLA-B, and HLA-C. Each of the genes displays extensive polymorphism across the population, as evidenced by over 2600 known HLA-B alleles (Murphy and Weaver 2017). Each MHC class I molecule consists of an alpha chain covalently bound to a β2-microglobulin molecule. The class II locus includes the HLA-DP, HLA-DQ, and HLA-DR genes, each of which encodes an alpha chain and a beta chain that together form an MHC class II molecule. HLA-DR is the most polymorphic of the class II genes, represented by over 1200 different alleles (Murphy and Weaver 2017). MHC class I molecules are expressed by all nucleated cells. This is in contrast to MHC class II molecules, which are expressed mainly by antigen-presenting cells, which are dendritic cells, B cells, and macrophages.

Both MHC class I and class II gene products demonstrate a tertiary protein structure that includes a peptide-binding cleft accommodating peptides of 8–10 and 10–30 amino acids in length, respectively. Many of the polymorphic differences between unique MHC class I and class II alleles translate into structural differences in the molecules' peptide-binding clefts determining the complementary array of antigenic peptides that are presented by each MHC. The existence of many different MHC alleles is therefore beneficial at the level of the population as it provides the capability to display a vast array of peptide antigens within the group, thereby ensuring that members will be able to display and mount effective responses to the diversity of microbes in the environment. This is further ensured at the level of each individual by the fact that MHC genes are codominantly expressed, meaning that alleles inherited from both parents are transcribed and translated. This maximizes the number of different MHC molecules in an individual, thereby expanding the breadth of antigenic peptides presented.

1.5.5 Antigen Processing and Presentation

Different microbes may establish infections in different locations inside the host. For example, bacteria such as *Haemophilus influenza* and *Staphylococcus pneumoniae* replicate outside of host cells, while viruses, including rabies, hepatitis B, and HIV, establish infections inside of host cells where they utilize different components of the cell's own machinery to create new viral particles. Microbial antigen may, therefore, originate in either extracellular or intracellular locations within the host. This becomes significant as the extra- or intracellular habitat of the microbe not only has implications for how antigen is processed by host cells and presented to T cells but also for what mechanisms the immune system must use to clear the infection. Accordingly, antigen derived from organisms such as bacteria, fungi, and parasites that originate outside of host cells will be taken up by antigen-presenting cells (macrophages and dendritic cells) and enzymatically digested in the cell's phagolysosomes. The resulting microbial peptide fragments will be loaded onto MHC class II molecules as they are transported to the cell surface from the endoplasmic reticulum, where they are synthesized (Guermonprez et al. 2002). Once at the cell surface, the MHC class II-peptide complexes are surveyed for recognition by circulating CD4 T cells. On the other hand, antigen produced in the cytoplasm of virally infected cells is digested by the proteasome. The resulting peptide fragments are then shuttled into the endoplasmic reticulum by way of the transporter associated with antigen presentation (TAP), where they are loaded onto MHC class I molecules as they are being synthesized (Williams et al. 2002). The stable MHC class I-peptide complex then makes it way to the cell surface via the exocytic pathway. Once at the surface, the peptide-MHC complexes are interrogated for recognition by CD8 T cells.

The physical interaction of the T cell antigen receptor with the MHC-peptide complex spans both the peptide and the MHC molecule. As a result, T cell antigen receptors can only recognize peptide antigens when presented in the context of one's MHC class I or II molecules, a concept called MHC restriction. Antigen recognition above a threshold affinity triggers a cascade of intracellular signaling events that leads to the activation of the lymphocyte on which the receptor is expressed and the development of effector functions that are specific to the type of pathogen encountered. Therefore, CD4 T cells activated by microbial antigen taken up in phagosomes and presented by MHC class II may respond by producing cytokines (e.g., IL-17 and IFNγ) that enhance the recruitment and killing ability of phagocytes, whereas CD8 T cells activated by viral antigen produced in the cytosol and presented by MHC class I will respond by producing perforin and granzyme and the expression of Fas ligand (FasL) which trigger the induction of apoptosis of the virally infected cell (Murphy and Reiner 2002; Russel and Ley 2002).

1.5.6 Molecular Structure of Antigen Receptors

The molecular structure of B and T cell antigen receptors is similar in that they both include variable and constant regions. The variable region is so named because of the extent to which antigen receptors from different B and T cell clones demonstrate amino acid sequence variability in this area. Within each variable region, variability of the amino acid sequences is concentrated in what are termed hypervariable regions, also known as complementarity determining regions (CDRs), as these are the regions of the receptor that determine antigen specificity based upon their complementary interaction with antigen. On the other hand, the constant region of the B and T cell antigen receptors demonstrates minimal variability between different clones. This region is required for structural integrity and, in the case of secreted antibody, their specific protective function.

The B cell receptor is built from four polypeptide chains, two identical larger (heavy) chains and two identical smaller (light) chains. Each chain has a variable region and a constant region. The assembled antibody molecule has a "Y" shape with two antigen-binding sites at the top,

each of which is formed by the association of one heavy chain and one light chain variable region. The lower portion of the "Y" is built from the constant region of the heavy chains, which consists of three to four constant domains. As a membrane-bound antigen receptor, it is this C-terminal end of the heavy chain that is anchored in the plasma membrane; however, activated B cells will produce antibodies that lack the membrane anchor and are therefore produced as a secreted protein. Early investigation into antibody structure and function identified the portion of the antibody responsible for antigen binding as the Fab (fragment, antigen binding) fragment and that portion responsible for its biologic activity as the Fc (fragment, crystalline) fragment (Porter 1991). Therefore, each antibody has two identical Fab fragments and a single Fc fragment. As we will see, the phagocytosis of antibody-coated microbes is facilitated through neutrophil and macrophage recognition of antibody via a number of different Fc receptors.

Antibody heavy chains contain one of five different constant regions, termed μ, δ, γ, ε, and α. Antibodies produced with the different heavy chain constant regions are grouped together into classes or isotypes named according to their heavy chain: IgM, IgD, IgG, IgA, and IgE. Each of the different isotypes is characterized by its specialized role(s) in providing immunological protection to the host. IgM and IgD are remarkable because these are the isotypes specifically used by naïve B cells as membrane-bound antigen receptors (Abney et al. 1978). Once activated, B cells will produce secreted IgM which is characterized by its pentameric form and low affinity for antigen. Cooperation between CD4 T cells and B cells responding to the same microbe will result in CD4 T cell-derived activation signals that lead to full B cell activation and switching to the production of either IgG, IgA, or IgE.

The most common form of the T cell receptor is built from two polypeptide chains, termed the α and β chains. Each chain contains a single variable and constant region, with the antigen-binding site formed by the association of the alpha and beta chain variable regions. As mentioned already, the T cell antigen receptor recognizes antigenic peptide displayed by one's MHC molecules, a feature known as "MHC restriction" of the TCR. Thus, portions of the TCR interact with the MHC, while others interact with the antigenic peptide. Remarkably, a T cell response can occur as a result of the TCR recognizing as few as 1–3 amino acid residues of the bound antigenic peptide (Sant'Angelo et al. 1996). Additionally, not all of the potential epitopes of a complex antigen will be recognized to stimulate a T cell response. Those that do trigger an immune response are referred to as "immunodominant epitopes" (Kjer-Nielsen et al. 2003).

1.5.7 Development of T Cells and B Cells

As mentioned earlier, development of B cells in the bone marrow and T cells in the thymus follows a sequence of progenitor proliferation, recombination of antigen-receptor gene segments, and selection of cells with useful antigen receptors. Developing lymphocytes are characterized according to their stepwise progression through this process. The early proliferation of lymphocyte progenitors driven by cytokines such as IL-7 gives rise to a large number of progenitors called pro-B and pro-T cells. Generation of such a large number of cells is critical because only a fraction will fully mature to competent lymphocytes. It is during the pro-B and pro-T cell stage when gene segment recombination begins in order to create the genetic code for each cell's unique antigen receptor, beginning with the immunoglobulin (Ig) heavy chain and TCR β chain, respectively. Prior to this recombination, the "germline" configuration of these loci includes multiple adjacent gene segments belonging to the variable (V), diversity (D), and joining (J) families. For example, on the Ig heavy chain locus, there are about 45 different V gene segments, 23 D segments, and 6 J segments, among which is the potential for a million of different V-D-J combinations, each of which yields a unique Ig heavy chain variable domain (Abbas et al. 2016). In addition, the heavy chain locus also includes a number of constant (C) region genes which encode for the heavy

chain constant domains that specify the different antibody isotypes. The germline TCR β chain locus is similarly constructed, however, with a different number of V, D, and J segments and fewer constant region genes.

Genetic recombination during the pro-B and pro-T cell stage includes the random selection of one each of the V, D, and J DNA segments which are spliced together to create an in-frame V-D-J coding exon of the Ig heavy chain or TCR β chain DNA loci, respectively, which then undergo gene transcription (Early et al. 1980; Shinkai et al. 1992). It is at the level of the RNA transcript that the recombined antigen-receptor variable region is connected to the heavy chain or β chain constant (C) region gene, thereby creating a complete set of RNA instructions for the first half of the B cell and T cell antigen receptor. For pro-B cells, this RNA splicing always occurs between the recombined heavy chain variable region and the mu (μ) constant region RNA. As a result, Ig recombination during the pro-B cell stage results in the production of a heavy chain of the IgM isotype (i.e., the μ heavy chain), a central feature of B cell development (Goding et al. 1977). Translation of the recombined μ heavy chain and TCR β chain proteins marks the progression of the developing lymphocytes from the pro- to the pre-B and pre-T cell stage, at which point an almost identical process of random genetic recombination and subsequent expression occurs at the Ig light chain and TCR α chain loci. Successful expression of the fully recombined IgM B cell receptor and TCR marks advancement to the immature lymphocyte stage.

For B cells, the final step to full maturity may take place in the bone marrow or the spleen and involves the co-expression of both IgM and IgD isotype antigen receptors (Abney et al. 1978). Immature T cells express both the CD4 and CD8 co-receptor (referred to as "double-positive" thymocytes) and have the potential to terminally differentiate into either subset, a fate determined by which self-MHC molecule the randomly generated TCR recognizes (von Boehmer et al. 1989). As a result of this process, called positive selection, *double-positive thymocytes* that recognize peptide antigen presented by one's own MHC class II molecules become CD4 T cells, while those that recognize peptide antigen presented by MHC class I molecules become CD8 T cells. Importantly, only cells that recognize peptide/MHC complexes with low to moderate affinity will become positively selected to either the CD4 or CD8 subset. Cells that do not recognize either MHC would not be helpful during an immune response in that individual and therefore die by apoptosis. On the other hand, double-positive lymphocytes that bind with high affinity to self-peptides in the thymus presented by either MHC class I or class II pose a significant threat to the individual because of the likelihood of becoming activated by self-antigens and initiating an autoimmune response. Therefore, these cells are also removed from the maturation process, either by apoptosis or redirection of their development into regulatory T cells, a population of CD4 T cells identified by their constitutive expression of CD25 (Shortman et al. 1990; Jordan et al. 2001). Regulatory T cells enter the peripheral tissues and function to control T cell reactivity to self-antigens through the production of inhibitory cytokines IL-10 and TGF-β, and expression of CTLA-4 (Sakaguchi et al. 2008; Saraiva and O'Garra 2010). This process of purging potentially autoreactive immature lymphocytes from the repertoire is called negative selection. Immature B cells are also screened against self-antigen found in the bone marrow; however, developing B cells that bind to self-antigen at this site have the opportunity to create a different light chain (an event called receptor editing) and thus change the specificity of the antigen receptor.

This elaborate process of building antigen receptors from randomly selected gene segments spliced together from the germline DNA creates a tremendously diverse repertoire of millions of different antigen receptors, a concept termed "combinatorial diversity." The diversity of antigen receptors is further enhanced by a process whereby nucleotides are randomly deleted and added from the V-D-J sites of recombination, thereby expanding many times the number of unique antigen receptors generated during the process of lymphocyte development. This so-called "junctional diversity" increases the

number of unique antigen receptors by a million fold or more. The incredible number of different antigen receptors generated as a result of this complex process ensures that the immune system has the capacity to recognize and respond to any infectious threat it may encounter.

The genetic recombination process requires a lymphoid-specific enzyme called VDJ recombinase that is composed of the recombinase-activating gene 1 and 2 proteins, termed RAG 1 and RAG 2 (Jung et al. 2006). The critical role of these proteins in the development of B and T cells is highlighted by the fact that mutation in the RAG genes is responsible for an autosomal recessive form of severe combined immune deficiency (SCID), characterized by a deficiency in T and B cell numbers.

1.5.8 T Cell Activation

After reaching full maturity and export from the central lymphoid organs, naïve B and T cells will begin a pattern of circulation, discussed earlier under Lymphocyte Trafficking, which facilitates the antigen receptor–mediated screening of the antigens concentrated in the peripheral lymphoid organs. Our attention now turns to the molecular interactions involved in T and B cell activation and the effector mechanisms brought to bear by these cell types during the immune response, beginning with T cells.

As already established, activation of naïve T cells during an immune response depends upon their recognition of foreign antigen by way of their T cell antigen receptor (TCR). Antigen is displayed to T cells within the context of MHC class I and class II molecules, which are presented on the surface of antigen-presenting cells. DCs are the most critical APCs for the activation of naïve T cells as they are either transporting antigen to the regional lymph nodes from the peripheral tissues or capturing antigen in the lymph nodes that is carried there by the flowing lymph (Banchereau and Steinman 1998). A complementary interaction between the TCR and the MHC-peptide complex that is of high enough affinity and long enough duration will lead to the biochemical signals needed to activate a T cell response. The strength of the interaction is assisted by integrins, such as LFA-1, on the T cell binding to integrin ligands, such as ICAM-1, expressed by the DCs (Friedl and Brocker 2002). As seen earlier, under resting conditions, integrins such as LFA-1 are in a low-affinity conformation and only bind to their ligands with high affinity under the influence of chemokines, as well as, in this case, antigen recognition.

If antigen recognition occurs, then T cell activation is achieved as a result of a biochemical signaling cascade involving the CD3 complex and its associated ζ chains, as well as the CD4 and CD8 co-receptors (described below). The activation of naïve T cells also requires a "costimulatory" signal delivered to the T cell when its cell surface CD28 molecule engages either of its ligands, B7-1 and B7-2 (Bour-Jordan and Bluestone 2002). Because B7-1 and B7-2 are only expressed by DCs which have become activated through innate recognition of pathogens via their pathogen recognition receptors, this co-stimulation requirement for naïve T cells to become activated serves as a checkpoint to help ensure that T cells are responding to foreign, and not self, antigens. T cells whose receptors engage self-antigen in the absence of costimulation may become unresponsive to antigen stimulation going forward, a condition referred to as anergy. Cells can be maintained in the anergic state by the T cell expression of CD28-like molecules that deliver an inhibitory (rather than costimulatory) signal, such as cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) or programmed death protein1 (PD-1) (Schneider et al. 2008). While CTLA-4 and PD-1 prevent the response to self-antigens and the development of autoimmunity, they are also seen to suppress potentially helpful immune responses against tumor cells, an area of study that led to the development of drugs termed "checkpoint inhibitors" that block the immunosuppressive function of CTLA-4 and PD-1, thereby unleashing the immune system to more aggressively attack developing and established tumors. So significant was this body of work that it earned immunotherapy pioneers James Allison and Tasuku Honjo the 2018 Nobel Prize in Medicine (Peggs et al. 2009).

Successful T cell antigen recognition and costimulation will result in a cell-signaling cascade initiated by the Lck tyrosine kinase, which is associated with the cytoplasmic domain of the CD4 and CD8 co-receptors. The Lck kinase phosphorylates tyrosine residues of the CD3 ζ chains, which become docking sights for another tyrosine kinase, Zap-70, which also becomes activated when phosphorylated by Lck (Au-Yeung et al. 2009). The activation of ZAP-70 leads to the activation of the transcription factors NFAT, NFκB, and AP-1, which move into the nucleus and activate genes required for T cell proliferation, cytokine production, and effector function (Brownlie and Zamoyska 2013). Key among these genes are those that encode the cytokine IL-2 and the IL-2 receptor. IL-2 is important early during the T cell response as it stimulates the clonal proliferation and survival of activated T cells, thereby expanding many fold the number of antigen-specific cells capable of responding to current infectious threat.

1.5.9 T Cell Effector Functions

It is critical at this point to recognize the diversity of the different kinds of pathogens that the immune system must be able to protect against, including bacteria that survive in phagosomes, viruses that replicate in the cytoplasm, and parasites that infect the lumen of the gut. The immune response to these different types of infections must be tailored to their unique features and vulnerabilities. To provide this capability, activated T cells differentiate under the influence of signals, some of which were generated during the innate immune response, into specific effector cell populations capable of mounting an effective immune response to the particular offending pathogen. We will begin this discussion with the different subsets of activated CD4 T cells and the pathogens that they defend against (Table 1).

Once activated by antigen, CD4 T cells differentiate into different subsets of effector cells that are primarily defined by the cytokines that they produce. These cytokines are the critical factors responsible for recruiting and/or activating unique effector functions of the immune system that are optimal for responding to different pathogens. The first CD4 T cell subsets to be defined were referred to as T helper subsets 1 and 2 (Th1 and Th2). Subsequently, a third, Th17, subset was identified. Today, we understand that Th1 cells are critical for the immune response to intracellular microbes, Th2 cells are most protective against parasitic helminth infections, and Th17 cells are best at combating extracellular bacteria and fungal infections (Annunziato and Romagnani 2009).

CD4 T cells differentiate into Th1 cells under the influence of the cytokines produced during the innate immune response to intracellular bacteria and viruses. These cytokines include IL-12 produced by DCs and interferon γ (IFNγ produced by NK cells. At the molecular level, this Th1 differentiation is driven by the activation of the transcription factors STAT1, STAT4, and T-bet that occurs in response to the early secreted IL-12 and IFNγ (Murphy and Reiner 2002). By this mechanism, naïve CD4 T cells which recognize antigens of these microbes will be triggered by IL-12 and IFNγ to differentiate into Th1 cells. IFNγ is not only important for the differentiation of the Th1 cells, but it is also the principal effector cytokine produced by this CD4 T cell subset and is critical in their role of enhancing macrophage killing of microbes that have been phagocytosed (Annunziato and Romagnani 2009). Th1 cell-derived IFNγ works in concert with a molecule found on the surface of Th1 cells, called CD40L. The CD40L receptor, CD40, is expressed by macrophages and B cells, and this ligand-receptor interaction is necessary for Th1-mediated help during the immune response, as evidenced by the cellular and humoral immunodeficiency observed when CD40L is not sufficiently expressed (Kamanaka et al. 1996). The enhanced ability of Th1-activated macrophages to kill phagocytosed microbes is due to their increased production of reactive oxygen species, nitric oxide, and damaging lysosomal enzymes. Th1 cells also enhance the antigen-presenting cell function of macrophages by inducing their expression of MHC class II and the B7-1/B7-2 costimulatory molecules (Annunziato and Romagnani 2009).

Whereas pathogens such as intracellular bacteria and viruses induce strong innate immune

Table 1 T cell differentiation and effector mechanisms

Effector T cells	Inducing cytokines/ factors	Signature effector molecules	Immune mechanisms	Host defense	Pathological mechanisms
Th1	IL-12, IFNγ	IFNγ	Enhanced macrophage killing and antigen presentation; opsonizing antibodies; promotes Th1; inhibits Th2 and Th17	Intracellular microbes	Tissue injury caused by cytokines elicited by activated macrophages during autoimmune responses and chronic infection
Th2	IL-4	IL-4, IL-5, IL-13	IgE production; eosinophil activation; alternative macrophage activation; promotes Th2	Helminth parasites	Allergic responses
Th17	IL-1, IL-6, IL-23, TGF-β	IL-17, IL-22	Neutrophil and monocyte recruitment; epithelial barrier	Extracellular bacteria, fungi	Tissue injury caused by recruited neutrophils and monocytes during autoimmune responses
CTL	IL-2, IL-12, type I IFNs	Perforin/ granzymes, FasL	Target cell apoptosis	Viruses	Cytolytic injury during cell-mediated autoimmune responses

responses that drive the production of inflammatory cytokines, parasitic helminths are much less of a trigger for the innate immune response. In the absence of these strong inflammatory signals, it appears that antigen-activated CD4 T cells may default to producing low levels of the cytokine IL-4, which activates the transcription factors GATA-3 and STAT6 that promote the differentiation to the Th2 subset (Paul and Zhu 2010). As noted above, Th2 cells are especially protective against helminth infections, which is achieved via a number of different mechanisms. To begin with, committed Th2 cells are strong producers of IL-4 and IL-5, which trigger B cells to class switch to the IgE antibody isotype and promote eosinophils responses, respectively. Eosinophils and mast cells express high levels of the Fc receptor for IgE (FcεR1) and, therefore, will be activated through these receptors by IgE-coated helminths. Once activated, eosinophils release their granule contents which destroy the helminths. IL-4, along with another Th2 cytokine, IL-13, induce intestinal mucus secretion and peristalsis, which also contribute to helminth expulsion (Anthony et al. 2007). Another effect of the IL-4/IL-13 cytokine pair is that they promote the development of so-called alternatively activated macrophages that have anti-inflammatory and tissue repair functions (Van Dyken and Locksley 2013).

The most recent Th cell subset to be described are the Th17 cells. Th17 cells are characterized by secretion of the cytokines IL-17 and IL-22. IL-17 is most well-known for promoting the recruitment of phagocytes, mainly neutrophils, to the site of an infection and, therefore, are important contributors to defense against extracellular bacteria and fungal infections (Littman and Rudensky 2010). Differentiation of Th17 cells requires a number of different cytokines, including TGF-β and the inflammatory cytokines IL-1 and IL-6 (McGeachy and Cua 2008).

A fundamental feature of CD4 T cell responses is the extent to which the balance between the production of Th1, Th2, and Th17 cytokines impacts the outcome of the immune response. This is because many of the cytokines produced by one subset are inhibitory to the others. For example, IFNγ produced by Th1 cells inhibits the development of Th2 and Th17 responses, while IL-4, IL-10, and IL-13 produced by Th2 cells inhibit the killing ability of macrophages, thereby suppressing Th1-mediated cellular immunity (Murphy and Reiner 2002; Annunziato and Romagnani 2009). This can be demonstrated

experimentally using different strains of mice with either a Th1 or Th2 predisposition, but it is most profoundly demonstrated in different populations of people infected with *Mycobacterium leprae.* This pathogen has the capacity to survive and replicate in phagosomes once taken up by macrophages. Control of the infection requires macrophage activation by a dominant Th1 response. If this occurs, the result is the tuberculoid leprosy form of disease, characterized by localized infection and low infectivity. On the other hand, *Mycobacterium leprae* infection of an individual who mounts a more dominant Th2 response that impedes macrophage activation and strong cellular immunity results in the more severe lepromatous leprosy, characterized by unchecked growth of mycobacterium, disseminated infection, and high infectivity (Modlin 1995).

As opposed to bacteria and fungi that originate outside of host cells and, therefore, can be phagocytosed and killed, opsonized, neutralized, or lysed, viruses that replicate in the cell's cytoplasm are comparatively more difficult to reach. CD8 T cells have evolved to meet this challenge. As described earlier, viral antigen synthesized in the cytoplasm during the viral replication is presented to CD8 T cells via MHC class I molecules. Antigen recognition by CD8 T cells will result in their activation and expression of cell membrane and secreted proteins which will be used to induce apoptosis in the infected cell, thereby preventing the production of new virons. The CD8 T cell membrane protein is called Fas ligand (FasL), which binds to its receptor, called Fas, on the infected cell. This receptor-ligand interaction will trigger the activation of caspases in the infected cell, resulting in its apoptosis. Target cell apoptosis can also be induced through the CD8 T cell release of the granule proteins: granzyme B and perforin. Granzyme B is the protein responsible for the activation of caspases and induction of apoptosis, while perforin is required to facilitate entry of granzyme B into the infected cell (Russell and Ley 2002).

The final phase to the T cell response to infection will be the contraction of effector T cell numbers and the establishment of a much smaller number of long-lived memory T cells, which will surveil for the re-occurrence of infection. Memory cells, which can be found in lymphoid organs or the peripheral tissues, do not continue to exhibit their effector functions during this period of surveillance but are poised to rapidly expand and re-establish effector function upon re-encounter with their target antigens. The survival of memory CD4 and CD8 T cells does not require antigen stimulation; however, their maintenance is dependent on stimulation by the cytokines IL-7 and IL-15 (Murali-Krishna et al. 1999; Seddon et al. 2003).

1.5.10 B Cell Activation

While different types of B cells have been described, such as marginal zone B cells and B-1 B cells that uniquely reside in certain areas of the spleen and mucosal tissues and respond to polysaccharides and lipids, the discussion on B cell activation and effector function in this chapter will focus on follicular B cells that are the source of high-affinity class-switched antibodies, the principal mediators of humoral immunity. Follicular B cells reside in and circulate through the lymphoid follicles and become activated by protein or protein-associated antigen that has been transported to and concentrated here. We will see that antigen recognition is just the first step in the activation of follicular B cells that also involves interaction with helper CD4 T cells responding to the same microbial antigens.

Similar to the CD3 complex on T cells, the Igβ and Igα chains associated with the B cell antigen receptor serve important roles in the cascade of signaling events induced upon B cell recognition of antigen. The phosphorylation of Igβ and Igα tyrosine residues, recruitment of kinases, and activation of adaptor proteins lead to the activation of transcription factors that control genes involved in B cell proliferation and differentiation. As seen with T cells, B cells also benefit from innate costimulatory signals during the activation process, provided by complement receptors such as CR2 and TLRs which engage components of the microbe (Pasare and Medzhitov 2005). Collectively, these

events induce the early phase of the B cell response, characterized by increased survival and proliferation and functional changes that will facilitate the B cell-T cell interaction that will occur next. These changes include the B cell's transition into an antigen-presenting cell, accomplished by the internalization of the receptor-bound antigen and the increased expression of MHC class II and B7-1/B7-2 costimulatory ligands. The activated B cell will also increase its expression of the CCR7 chemokine receptor at the same time that activated helper T cells in the paracortex are increasing expression of CXCR5 (Okada and Cyster 2006). Recall that the CCR7 and CXCR5 chemokine receptors direct leukocyte trafficking to the T cell and B cell areas of the lymph node, respectively. Therefore, the outcome of this flip in chemokine receptor expression will be that B and helper CD4 T cells responding to antigen will migrate toward each other. At this point, the B cell is functioning as a professional antigen-presenting cell, expressing high levels of MHC Class II/peptide complexes and costimulatory ligands. If CD4 T cell recognition of antigen presented by the B cell occurs, the CD4 T cell will provide activating signals through its secretion of cytokines and expression of CD40L, which will bind to CD40 expressed by the activated B cell (Meng et al. 2018). As a result, the fully activated B cell will undergo clonal expansion and antibody synthesis and secretion. Following this T-B cell interaction, a smaller number of activated CD4 T and B cells will be drawn into the B cell follicle. These CD4 cells, referred to as follicular helper T cells, provide signals to the B cells that induce their rapid division, creating clusters of dividing B cells referred to as germinal centers (Crotty 2014). A sequence of somatic mutation of the B cell Ig genes followed by selection of those clones producing the antibody with highest affinity or antigen now occurs, a process referred to as affinity maturation. The selected high-affinity clones will differentiate into long-lived antibody-producing plasma cells and memory B cells.

As noted earlier, antibodies are produced in a number of different forms called isotypes. The isotype of an antibody is significant as different isotype antibodies have different immunological functions. While the first antibody produced during a primary B cell response is always IgM, isotype class switching during the immune response, and subsequent exposures to the antigen (secondary response), will lead to the production of larger amounts of other isotypes, including IgG, IgA, and IgE. This isotype class switching is under the control of the cytokines produced by follicular helper T cells providing help to germinal center B cells (Crotty 2014). For example, IFNγ, the signature Th1 cytokine, causes isotype switching to the IgG1 and IgG3 isotypes. During the immune response to extracellular bacteria, these isotypes are notable for their role as effective opsonins, which work in concert with IFNγ−activated macrophages that have enhanced phagocytic and killing ability. In contrast, the IL-4 produced by Th2 CD4 T cells stimulates class switching to IgE, which works together with eosinophils to eliminate helminths (Anthony et al. 2007).

The ability of B cells to class switch from IgM to other Ig isotypes, as directed by the CD4 T cells, allows the humoral response to be optimized to fight a particular infection (Davies and Metzger 1983). At the molecular level, the isotype is determined by the unique constant region (μ, δ, γ, ε, or α) incorporated into the antibody's heavy chain. Isotype class switching, therefore, requires recombination of the heavy chain DNA such that the variable region is combined with the appropriate constant region. The importance of isotype class switching is underscored by the occurrence of X-linked hyper-IgM syndrome, an immune deficiency caused by a mutation in the gene encoding the T cell CD40L molecule (Meng et al. 2018). In this syndrome, activated B cells receive early activation signals through their antigen receptor but do not get help from CD4 T cells because of the CD40L mutation, therefore preventing class switching from occurring. Patients of this disease produce mainly low-affinity IgM that has limited protective function and therefore suffer from recurrent infections with pyogenic bacteria due to reduced opsonizing IgG. Importantly, these people also experience reduced cell-mediated immunity because of the important role

of CD40L in providing CD4 T cell help to macrophages, as described in Sect. 5.9 of this chapter.

1.5.11 Antibody Effector Function

The importance of antibody to the immunological protection of the host is illustrated by the increased frequency of infectious disease in those individuals with compromised B cell development. These individuals commonly suffer from recurrent respiratory infections by pyogenic bacteria, such as *Streptococcus pneumonia* and *Haemophilus influenzae*. The main virulence factor of these encapsulated bacteria is their polysaccharide capsule that protects them from phagocytosis. The B cell response to antigens of the polysaccharide capsule results in the production of antibody that when bound to the capsule facilitates the effective phagocytosis of the bacteria by neutrophils and macrophages (Klein Klouwenberg and Bont 2008). Antibodies that facilitate phagocytosis of coated microbes are referred to as opsonins. When bound to the microbe, the Fc portion of the antibody extends away from the microbe's surface. Antibodies of the IgG (IgG1 and IgG3) isotype are the most effective opsonins because their Fc region readily binds to a high-affinity Fc receptor, called FcγR1, expressed by phagocytes. This interaction between the Fc receptor and its ligand triggers the phagocytosis of the coated microbe.

Antibodies of the IgM and IgG isotypes that have coated a microbe can also indirectly facilitate its phagocytosis by the activation of the complement system, discussed in detail during the section on innate immunity (Diebolder et al. 2014). It is the classical complement pathway that is activated by antibody bound to a microbe, resulting in the deposition of the C3b complement protein on the microbial cell membrane, a potent opsonin recognized by the CR1 complement receptor, expressed on phagocytes. In addition to the deposition of the C3b opsonins, activation of complement also results in the production of factors chemotactic for neutrophils (C3a and C5a) and the formation of the bactericidal MAC.

IgG antibodies may also coat host cells during the course of an infection with enveloped viruses, such as influenza. In this situation, antibodies are binding to viral glycoproteins that are embedded in the host cell membrane as part of the viral life cycle. These IgG isotype antibodies can be recognized by FcγRIII, an Fc receptor expressed uniquely by NK cells. When engaged these receptors generate signals that activate the cytolytic function of NK cells resulting in the induction of apoptosis of virally infected cell, a process called antibody-dependent cell-mediated cytotoxicity (ADCC) (Chung et al. 2009).

Individuals with humoral immune deficiencies are also susceptible to infections by viruses which are normally neutralized by antibody, such as the enteroviruses (e.g., poliovirus and coxsackievirus). Neutralization refers to an antibody's capacity to block the infectivity of a microbe by binding to and neutralizing microbial surface molecules required to establish infection. Antibodies can also attach to microbial toxins, thereby preventing them from mediating their dangerous effects. This is exemplified by the use of the tetanus vaccine, where recipients are vaccinated with an inactivated version of the tetanus toxin (toxoid) in order to induce production of antibodies capable of binding to and neutralizing the toxin. Although any isotype antibody can neutralize, most neutralizing antibodies in the blood and tissue are IgG (Ward and Ghetie 1995). In the mucocal organs, this job is performed by IgA, the principal class of antibody produced in mucosal tissues (Suzuki et al. 2004). The vast majority of infectious agents invade the human body via the mucosal organs, underscoring the importance of strong immunological protection at these sites. The plasma cells responsible for the production of mucosal IgA are found in the lamina propria, beneath the mucosal epithelium. Once secreted by the plasma cell, the dimeric IgA is ferried across the mucosal epithelium into the organ lumen by a special Fc receptor called the poly-Ig receptor (Lamm 1998). Once released into the lumen, the IgA will neutralize would-be pathogens, preventing them from crossing the epithelial barrier and establishing an infection. In the lactating mother, dimeric IgA binds to the same poly-Ig receptor to get transcytosed across the

glandular epithelium and released into the breast milk, thereby providing an important measure of immunological protection against intestinal and respiratory infection in the newborn.

Whereas antibody coating a bacterial cell may facilitate its phagocytosis, most helminths are too large to be taken up by a macrophage or neutrophil. The immune response to such parasites depends upon the activation of eosinophils. The recruitment and activation of eosinophils to the infection require the production of IgE isotype antibody, the principal isotype produced in response to a helminth infection. As described earlier, B cells class switch to IgE under the direction of IL-4 produced during a dominant Th2 helper CD4 T cells response to the helminth. IgE bound to the helminth will activate the eosinophils through the high-affinity Fc receptor for IgE, called FcεR1, expressed on the eosinophil surface. In response the eosinophils release granules containing major basic protein and eosinophilic cationic protein, which are toxic to parasites. Mast cells also express FcεR1 and therefore will also become activated and participate during the anti-helminth response (Anthony 2007).

1.5.12 Immunological Tolerance

As we have discussed, the B and T cells of the adaptive immune system are created with a tremendous capacity to discern the presence of any of the many microbes with which we share our environment. Of course, creating the diverse repertoire of antigen receptor–bearing B and T cells that makes this possible comes with the risk that some of those cells will bear receptors with an affinity for normal molecules expressed by the host, otherwise referred to as self-antigens. The concept of Immunological Tolerance refers to the fact that although the immune system would appear to walk a fine line between highly sensitive surveillance for foreign microbes and mistaking a harmless self-antigen as a threat, it does so successfully because of multiple built-in mechanisms and checkpoints. These mechanisms include the active process of removing developing lymphocytes that express receptors found to strongly bind self-antigen in the bone marrow and thymus, a mechanism referred to as central tolerance. On the other hand, peripheral tolerance refers to mechanisms that prevent activation by self-antigens in the periphery.

The underlying concepts of central tolerance were discussed earlier in Sect. 5.7. Essentially, lymphocytes at the immature stage of development found to interact strongly with self-antigen are directed to undergo apoptosis, a process referred to as negative selection. Negative selection is an active process in that self-antigens must be displayed to developing lymphocytes in order to identify and delete those with potentially autoreactive antigen receptors. One potential challenge, therefore, is establishing central tolerance to antigens only expressed in certain specialized peripheral tissues, for example, those of endocrine organs. The protein called AIRE (autoimmune regulator) assists in this regard by activating the expression of these peripheral tissue genes in the thymus. In doing so, AIRE assures that peptide derived from these self-proteins will be presented to developing T cells and that cells with antigen receptors that bind with high affinity to these peptides when presented by host MHC will be removed. The importance of AIRE is underscored by the development of autoimmune polyendocrine syndrome (APS) type I, a disorder caused by a defective AIRE gene and characterized by a constellation of autoimmune assaults on tissues of the endocrine system (Anderson et al. 2005).

Importantly, not every immature B and T cell that encounters self-antigen during development will undergo apoptosis. For example, CD4 T cells with high affinity for self-antigens may be triggered to differentiate into regulatory T cells, a unique and specialized population of CD4 T cells that will help maintain peripheral tolerance, as described below. Additionally, immature B cells that recognize self-antigens in the bone marrow may go through a process called receptor editing, whereby the cell re-expresses the RAG genes for the purpose of recombining a second light chain. Replacement of the original with the newly recombined light chain will alter the

antigen receptor such that a new antigen-binding site will be created. If the edited B cell receptor still recognizes self-antigen with high affinity, the cell will die by apoptosis.

Despite the intricate mechanism of negative selection and function of proteins such as AIRE, the thymus and bone marrow are sources of autoreactive B and T cells that enter the periphery. The evidence for this are the multiple mechanisms designed to prevent the activation of circulating mature lymphocytes by self-antigens (peripheral tolerance), and the unfortunate autoimmune diseases that develop when those mechanisms are deficient in some way. These mechanisms include the functional inactivation and deletion of autoreactive cells, as well as their suppression by regulatory T cells or other inhibitory elements.

As discussed earlier, the activation of naïve T cells requires not only antigen recognition through the TCR but also engagement of the CD28 costimulatory receptor with its ligand B7-1 and B7-2 expressed by the dendritic cell. Because B7 is expressed when the dendritic cell is activated by a microbe through a pathogen recognition receptor, or by the local production of inflammatory cytokines (also an indication of an infectious threat in the region), this costimulation requirement assures naïve T cell activation occurs as a result of recognizing microbial antigen. It is therefore likely that T cells engaging antigen presented in the absence of costimulation are recognizing peptide derived from self-proteins. Since these T cells represent a potential autoimmune threat, they are functionally inactivated, a state that is referred to as anergy. Anergic T cells survive but are unresponsive to antigen going forward. This unresponsiveness is believed to be due to expression of molecules such as CTLA-4 and PD-1, which deliver inhibitory signals to the T cell. CTLA-4 may also suppress the T cell responses by binding to and removing the B7 costimulatory molecules from the surface of APCs. The importance of CTLA-4 to peripheral tolerance is underscored by the fact that the development of autoimmune diseases such as Grave's disease and Hashimoto's thyroiditis is associated with polymorphisms in the CTLA-4 gene, which potentially impact its function (Ueda et al. 2003). In addition to becoming anergic, T cells that recognize self-antigen presented without costimulation may be triggered to undergo apoptosis. This is because costimulation normally induces the production of anti-apoptotic proteins, protecting fully activated T cells from induced cell death. Recognition of self-antigens in the absence of costimulation would therefore fail to stimulate this increase in anti-apoptotic proteins and be more likely to lead to apoptosis of the autoreactive T cell. Anergy and apoptosis are also potential outcomes for self-reactive B cells. The main determining factor in this case is whether or not an antigen-engaged B cells receives adequate help from CD4 T cells. A B cell activated by recognition of self-antigen may fail to elicit CD4 T cell help, in which case the tolerogenic mechanisms of anergy and apoptosis are more likely to follow.

Another important mediator of peripheral tolerance are regulatory CD4 T cells. Although regulatory T cells may develop as a result of negative selection mechanisms in the thymus, as already discussed, they are also thought to arise in the periphery following CD4 T cell recognition of self-antigen. Regulatory CD4 T cells are phenotypically identified by their constitutive expression of the IL-2 receptor α chain, CD25, a hint to the important role that IL-2 plays in the survival and function of these cells, along with the cytokine TGF-β. The transcription factor FoxP3 is required for the development and function of regulatory T cells, a finding that has contributed to our appreciation of their importance to maintaining peripheral tolerance, as mutations in the FoxP3 gene is known to result in the development of an aggressive autoimmune syndrome called IPEX, for *i*mmune *d*ysregulation, *p*olyendocrinopathy, *e*nteropathy, *x*-linked syndrome (Wildin et al. 2001). Regulatory T cell control over the immune response is accomplished via several mechanisms, including expression of CTLA-4 and the secretion of IL-10 and TGF-β, cytokines known for their inhibitory effect on T cells, B cells, macrophages, and dendritic cells (Sakaguchi et al. 2008).

1.6 Introduction to Allergy and the Immunological Mechanisms of Hypersensitivity

Although all of the mechanisms of innate and adaptive immunity and tolerance discussed above are constantly functioning in the background, we don't often think about the day-to-day activity of the immune system until it seems to not be working quite right. While congenital or acquired immune deficiencies are indicated clinically by an abnormally high frequency of infections, hypersensitivity reactions in many ways represent the opposite problem, injury caused by excessive or dysregulated immune responses. This may occur as a result of aberrant responses to environmental or self (auto)-antigens when the mechanisms of tolerance discussed above are not fully functional. Utilizing the basics of immunology described in this chapter, this final section will provide an overview of the mechanisms of hypersensitivity reactions, with a focus toward the type I hypersensitivity reaction, otherwise known as the allergic response (Table 2).

Hypersensitivity reactions, whereby the immune system causes injury to host tissues, are classified based upon the immunopathogenic mechanism responsible for the disease. Four principle hypersensitivity mechanisms are usually described. The type I hypersensitivity reaction underlies the response to harmless environmental antigens which trigger diseases such as allergic asthma, hay fever and food allergies. As we will discuss in more detail below, diseases caused by hypersensitivity mechanisms II–IV often involve the aberrant immune responses to self-antigens and, therefore, are the mechanistic basis for autoimmunity.

1.6.1 Introduction to the Allergic Response

The immediate type I hypersensitivity (allergic) response is triggered by an apparent excessive response to harmless environmental antigens, referred to as allergens. These may include pollen, dust mites, insect venom or animal dander. Before a clinically significant allergic response can occur, an individual must be sensitized to the allergen. During sensitization, individuals who develop allergies default to a strong Th2 CD4 T cell response when exposed to the allergen (Fahy 2015). As discussed in the T and B Cell Effector Function sections, Th2 cells are principally characterized by the production of the cytokines IL-4, IL-5, and IL-13. At this point, IL-4 and IL-13 are the critical players as they instruct the allergen-specific B cells to class switch to IgE (Gould and Sutton 2008). The IgE antibodies with specificity for the offending allergen will coat the surface of

Table 2 Mechanisms of hypersensitivity

Hypersensitivity	Mediators	Pathogenic mechanisms	Diseases
Immediate hypersensitivity (type I)	Th2 CD4 T cells; IgE; mast cells; eosinophils	Th2 response to environmental antigens; IgE sensitization and allergen activation of mast cells; recruitment of eosinophils; vasoactive amines, lipid mediators	Allergic rhinitis; allergic asthma; food and drug allergies; anaphylaxis
Antibody mediated (type II)	IgM; IgG; complement; neutrophils	Physiological impairment of target tissue; complement activation; opsonization; neutrophil recruitment and activation	Myasthenia gravis; Graves' disease; Goodpasture's syndrome, immunohemolytic anemia
Immune complex mediated (type III)	IgG or IgM complexed to circulating antigen; complement; neutrophils	Vascular deposition of immune complexes; complement activation; neutrophil recruitment and activation	Systemic lupus erythematous; post-streptococcal glomerulonephritis
T cell mediated (type IV)	Th1 and Th17 CD4 T cells; CD8 T cells	Leukocyte recruitment and activation; cytokine mediated inflammation; direct cytolytic killing	Type I diabetes; allergic contact dermatitis; multiple sclerosis

mast cells located in connective and subepithelial tissues throughout the body. Mast cells bind the IgE via their cell surface FcεRI, resulting in the antigen-binding regions of the antibody oriented away from the cell surface (Gould and Sutton 2008). The mast cells are now said to be sensitized against the offending allergen. Re-exposure to the sensitizing allergen will cause cross-linking of the IgE on the mast cell surface by the allergen, which will stimulate the mast cell's activation and release of the chemical mediators of the allergic response (Gould and Sutton 2008).

The chemical mediators released from the mast cell include histamine, which is preformed and stored in cytoplasmic granules (Gandhi and Wasserman 2009; Smuda and Bryce 2011). Histamine's biological effects include dilation of blood vessels, increased vascular permeability, and transient contraction of smooth muscles (Gandhi and Wasserman 2009; Smuda and Bryce 2011). Mast cell activation also stimulates the rapid synthesis and secretion of eicosanoids, including prostaglandins and leukotrienes, both of which are derived from arachidonic acid. Leukotrienes have effects similar to those of histamine; however, molecule-for-molecule leukotrienes are much more powerful stimulants of smooth muscle contraction (Gandhi and Wasserman 2009). The final set of mediators released by the mast cells are cytokines that mobilize and recruit inflammatory cells, including eosinophils and neutrophils, to the site of allergen exposure. These cytokines include TNFα, IL-5, IL-4, and IL-13 (Eifan and Durham 2016).

The earliest clinical effects of the allergic response can be experienced minutes after allergen exposure (hence the term immediate hypersensitivity reaction is used), reflecting the rapid release of histamine and synthesis of eicosanoids by activated mast cells (Eifan and Durham 2016). These effects include edema, mucus secretion, and smooth muscle spasm. For example, the classical wheal and flare response observed minutes after the subcutaneous injection of allergen to a sensitized individual is caused by histamine-mediated vasodilation and vascular leakage. Similarly, airway obstruction experienced during the immediate phase of the asthmatic response is caused by smooth muscle bronchoconstriction, mucus secretion, vasodilation, and increased blood vessel permeability.

As compared to the immediate hypersensitivity reaction, which is caused by mediators released from resident tissue mast cells, the later phase of the allergic reaction is caused by cells recruited to the site by the mast cell-derived cytokines. The infiltrate is heavy with eosinophils, as one might predict by the IL-5 produced by mast cells and Th2 cells. When activated, eosinophils produce two unique proteins called major basic protein and eosinophil cationic protein, which cause additional epithelial damage and more airway constriction (Costa et al. 1997).

The clinical manifestations of allergic responses vary with the anatomical site of the allergic reaction. For example, allergic rhinitis develops in response to inhaled allergens such as pollen that stimulate mast cells in the nasal mucosa, resulting in increased mucus secretion. On the other hand, allergic asthma is caused by the activation of bronchial mast cells and is characterized by airway obstruction caused by mucus secretion, inflammation, and bronchial smooth muscle contraction. The most severe form of allergy is anaphylaxis, caused by the systemic activation of sensitized mast cells. This may occur in response to bee stings or ingested nuts or shell fish, the allergens from which get absorbed into the circulation. The systemic reaction causes edema in many tissues, accompanied by a fall in blood pressure and bronchoconstriction, creating a potentially life-threatening situation.

It is unknown why some individuals originally mount the strong Th2 responses to environmental antigens that are the determining factor for the development of allergies. For certain, there is a genetic basis for the development of allergic disease, as evidenced by the large number of genetic polymorphisms that appear to associate with the development of disease. As one might expect, a number of the genes implicated are associated with CD4 T cell differentiation, cytokine signaling pathways, and the high-affinity IgE receptor (Holloway et al. 2010).

1.6.2 Antibody and T Cell-Mediated Hypersensitivity Reactions

Type II and type III hypersensitivity reactions are both mediated by antibodies directed against either tissue-bound antigens or antigens circulating in the blood or tissue fluid, respectively. Type II hypersensitivity diseases include autoimmune diseases such as Graves' disease, myasthenia gravis, and Goodpasture syndrome, whereby the autoantibody's attachment to a cell surface or extracellular matrix component (e.g., collagen) either disrupts normal physiological function of the target cell or elicits an inflammatory response via the activation of complement and recruitment of neutrophils. Once on the scene, neutrophils become activated by the bound antibody and complement (Binks et al. 2016). Type III hypersensitivity reactions are initiated by the binding of antibody to antigen circulating in the blood and tissue fluids. Such immune complexes are normally removed by the phagocytic cells of the spleen and liver. However, when phagocytic cells are not functional or are overwhelmed, or the immune complexes are of a certain size or electrical charge, the circulating immune complexes may be deposited in the walls of blood vessels. This especially happens in the kidney because of the high pressure at which blood flows though this organ. An inflammatory response ensues when the deposited immune complexes trigger the activation of complement, leading to the generation of C5a which effectively recruits neutrophils that become activated by the deposited immune complexes and complement. Systemic lupus erythematous (SLE) is a striking example of a type III hypersensitivity disease, characterized by the widespread deposition of immune complexes composed of autoantibody bound to a number of different nuclear autoantigens, most notably double-stranded DNA (Fairhurst et al. 2006).

Finally, type IV hypersensitivity reactions are mediated by CD4 or CD8 T cells activated by either self-antigens or persistent environmental or microbial antigens. Type I (autoimmune) diabetes is a classic example of a type IV hypersensitivity disease caused by the response of autoreactive CD4 and CD8 T cells to autoantigens expressed by β cells of the pancreas. As a result, the β cells are killed directly either by the infiltrating CD8 T cells or by the inflammatory cytokines produced by macrophages activated by the autoreactive helper CD4 T cells (Roep 2003).

1.7 Conclusion

This chapter endeavored to provide the reader with an overview of the principle mediators of the immune response as it has evolved to protect the host from multiple kinds of infectious threats. This included a discussion of the early acting innate immune response, which effectively functions to control the spread of an infection while the T and B cells of the adaptive immune system expand in number and differentiate into effectors specialized at clearing the current infection. We then discussed the different mechanisms by which the immune system can itself cause tissue injury, focusing on the allergic response. With this foundation of basic immunology knowledge, the reader is better prepared to understand the applied clinical immunology that follows in the proceeding chapters of this comprehensive text.

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Epidemiology of Allergic Diseases

2

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Abstract

Allergic diseases are a group of conditions categorized by aberrant IgE-mediated responses following allergen exposure. The prevalence of allergic disease is increasing worldwide. There are many proposed theories as to why the prevalence is increasing with a likely multifactorial etiology. Many allergic diseases including asthma, allergic rhinitis, allergic conjunctivitis, and atopic dermatitis share similar risk factors. Food allergies appear to have independent risk factors that differ from other allergic diseases. There has been much research completed on the prevalence and other epidemiological factors involved in allergic disease. There is, however, a significant amount of underreported and understudied allergic disease especially in developing nations which make the accuracy of the data from these areas more difficult to interpret.

Keywords

Epidemiology · Prevalence · Risk factors · Allergic disease

Abbreviations

AC Allergic conjunctivitis
AD Atopic dermatitis
AR Allergic rhinitis

2.1 Introduction

Atopy is the propensity to produce allergen-specific immunoglobulin E (IgE) after exposure to an allergen in genetically susceptible individuals (Jarvis and Burney 1998). Atopy is strongly associated with the development of allergic disease, which represents a spectrum of disorders including allergic rhinitis, allergic conjunctivitis, allergic asthma, food allergy, atopic dermatitis, and anaphylaxis. Allergic disease can develop in people of all ages, and approximately 25% of the population in developed countries is affected. The incidence appears to be increasing with some describing allergic disease as the "epidemic of the twenty-first century" (Pawankar et al. 2008). The complexity and severity of allergic diseases also appear to be increasing with the greatest burden being seen in children and young adults (Pawankar 2014). The social and economic burden of allergic disease is reflected in a higher loss of work and school, rising healthcare costs, and a reported lower quality of life in those suffering from allergic diseases (Jarvis and Burney 1998).

Environmental factors that contribute to the development of atopic diseases include allergen exposure, indoor and or outdoor air pollution, childhood infections, family size, and rural versus urban location (Pawankar 2014). It is important to note that the increasing prevalence trend has been found predominantly in developed countries, and despite this increase in the Western world, allergic diseases such as asthma and eczema continue to be uncommon in underdeveloped regions. The cause underlying the increase in atopic diseases is the subject of intense research, although the definitive answer has remained elusive.

Over the last century, theories have been proposed in an attempt to explain the increased prevalence of allergic disease. None of these theories have provided a single definitive cause to explain

the changes. Simple genetic factors are possible contributors, though they are not the exclusive explanation for increased prevalence. There are, however, environmental factors that may play a role in the genetics of the increased incidence of allergic disease over the past century (Schwartz 2009). Research data has shown that on a regional level, climate change, namely, season duration, temperature, and humidity, may contribute to the increase in allergic disease (Silverberg et al. 2015). There have been several variations of suggested hygiene hypothesis proposed. Hygiene theories are predicated on individuals living in cleaner environments with improved hygiene and decreased infectious exposure (Okada et al. 2010).

With the increase in the prevalence of allergic disease, research has begun exploring the effect of the human microbiome on the development of immune tolerance (Blázquez and Berin 2017). This emerging evidence is known as the microflora hypothesis or biodiversity hypothesis. It is considered to be an extension of the hygiene hypothesis (Stiemsma and Turvey 2017). Recent literature has suggested that multiple beneficial interactions occur between a human and their microbiome.

Microbial imbalance, known as dysbiosis, negatively affects the development of immune tolerance leading to allergic disease (Riiser 2015). The maturity of the gut microbiome can be influenced by the interactions of diet, antibiotics, and environment (Riiser 2015). Lifestyle changes in Western societies that affect these interactions lead to the depletion of bacteria that are necessary for the maintenance of mucosal homeostasis (Plunkett and Nagler 2017). The human microbiome is most influenced during the first 100 days of life and stabilizes by the age of 3 (Riiser 2015). Recent studies from animal models have demonstrated that dysbiosis that occurs early in life leads to susceptibility to the development of food allergies and asthma (Blázquez and Berin 2017; Stiemsma and Turvey 2017). This failure to stimulate protective tolerogenic pathways leads to the development of type 2 allergic responses (Plunkett and Nagler 2017). Further studies are ongoing to determine how manipulating the human biome during pregnancy or the first 100 days of life may prevent or cure allergic disease (Stiemsma and Turvey 2017).

With the incidence of allergic diseases increasing, it is important and necessary for clinicians to understand the epidemiology of allergic disease so that the implementation of successful treatment and prevention strategies can occur. This chapter will focus on the definition, prevalence, and risk factors for allergic rhinitis and conjunctivitis, allergic asthma, atopic dermatitis, and food allergies with the aim for a better understanding of the epidemiology of allergic diseases which will allow for a more successful management of these conditions.

2.2 Asthma

2.2.1 Definition

Asthma is a chronic respiratory disease that is defined by airway inflammation that causes reversible airway obstruction and often involves wheezing, shortness of breath, cough, and chest tightness (Gomez-Llorente et al. 2017). There are various types of asthma, the most common of which being allergic asthma (Mao et al. 2017). The epidemiology of this disease entity will be the focus of this section.

2.2.2 Prevalence

The prevalence of allergic diseases, including asthma, has been shown to be affected by migration (Garcia-Marcos et al. 2014). This principle is known as the "healthy immigrant phenomenon." This concept suggests that immigrants migrating to higher-income countries tend to be healthier than those born in that country. This protective phenomenon decreases reciprocally as the number of years residing in the high-prevalence country increases. Immigrants to these high-prevalence countries tend to develop asthma later in life as well as hypersensitivity to allergens (Garcia-Marcos et al. 2014).

As previously alluded, the prevalence of asthma between the Western and developing world differs significantly. Moradi-Lakeh et al. found that Saudi Arabia has a relatively low asthma prevalence of 4.05% (Moradi-Lakeh

et al. 2015). A study by Huang et al. performed in one of the largest cities in China, Shanghai, reported an asthma prevalence of 10.2% among its preschool children (Huang et al. 2015). The study noted that over the 20-year span (1990–2011), considerable modernization had taken place in Shanghai leading to some changes in environmental exposure. The study performed by Huang et al. demonstrated that following modernization, an increased asthma prevalence took place, specifically among preschool children. The prevalence increased from 1.79% in 1990 to 10.2% in 2011 (Huang et al. 2015). The United States, which has also undergone some level of modernization, also has increased asthma prevalence. According to Akinbami et al. (2012), the prevalence of asthma in the United States increased from 7.3% in 2001 to 8.4% in 2010 (Akinbami et al. 2012).

2.2.3 Risk Factors

Asthma is a common respiratory problem worldwide and has been shown to have various associations and risk factors. These include obesity, physical activity, environmental pollutants, and maternal and paternal smoking.

2.2.3.1 Environmental Allergens

Various environmental allergens have been found to increase the risk of developing asthma including dust mites, mold, and cockroaches. Follenweider and Lambertino reported that dust mite exposure which can occur by various routes plays a significant role in the development of asthma. Molds such as *Alternaria* are found in a myriad of places in the environment, which can increase the risk of asthma. Cockroaches are ubiquitous and often found in inner-city homes. Their fecal material and the exoskeletons which are shed are significantly allergenic. Accordingly, cockroaches have been found to cause an increase in the risk of developing asthma (Follenweider and Lambertino 2013). Environmental avoidance for a sensitized individual is important though this can be a difficult task due to the ubiquitous nature of these allergens.

2.2.3.2 Obesity

Obesity is a chronic condition that can be influenced by multiple factors. However, obesity has been shown to be a risk factor in patients diagnosed with asthma. Obese patients have an increased risk of developing asthma, as well as increased prevalence of asthma. Among patients with asthma, obesity may worsen the severity. The International Study of Asthma and Allergies in Childhood (ISAAC) found that wheezing can be related to body mass index (BMI). The study suggests that overweight and obese individuals wheezed more with exercise than their normal BMI counterparts (Weinmayr et al. 2014). This trend was found to be more pronounced in higher-income countries. Obese individuals seemingly have more severe symptoms, decreased asthma control, altered response to inhaled medication, and resistance to steroids (Gomez-Llorente et al. 2017).

Though the association between asthma and obesity has long been recognized, the underlying mechanism is still unknown. Various reasons have been postulated ranging from genetics to physical activity to microorganism exposure. The latter refers to the alteration of the gut microbiome by obesity. The gut microbiome is important for the development of the immune system. It has been found that obesity causes a microbial imbalance, which has been linked to asthma (Gomez-Llorente et al. 2017). The relationship between obesity and asthma is seemingly complex and much is yet to be known and understood about the intricacies of this relationship.

2.2.3.3 Physical Activity

Physical activity can influence asthma. Mitchel et al. found that a sedentary lifestyle corresponding to 5 h or more per day of television is associated with an increase in asthma symptoms in children. It was also noted that vigorous physical activity also increases asthma symptoms in adolescents, though the exact cause is not explicitly stated (Mitchell et al. 2013). Ironically, regular aerobic exercise decreases symptoms of asthma, improves quality of life, and may even protect against developing and manifesting asthma.

2.2.3.4 Pollutants

Air pollution has been reported to worsen asthma. In a study evaluating the impact of density of truck traffic on residential streets and asthma in the Republic of Macedonia, Vlaski et al. found that individuals exposed to truck traffic throughout the day had increased prevalence of asthma symptoms, including wheezing and nighttime cough (Vlaski et al. 2014).

2.2.3.5 Smoking

It has been a long-standing finding that smoking has a negative effect on respiratory health. Although it has not been confirmed that secondhand smoking, namely, maternal and paternal smoking, causes the onset of childhood asthma, Mitchell et al. found that parental smoking causes an increased risk of developing asthma. It was also found that maternal smoking has a greater impact on the development of asthma (Mitchell et al. 2013).

2.2.3.6 Microbiota

Recent studies have demonstrated a distinct difference in both the lung and gut microbiomes of healthy patients compared to asthmatic patients (Riiser 2015). Severe asthmatic patients were found to have a larger component of *Actinobacteria* and *Klebsiella* species in their lung microbiota when compared to healthy controls (Stiemsma and Turvey 2017). Severe asthmatic patients were also found to have a more significant amount of actinobacterial taxa and a decrease in the number of *Proteobacteria* when compared to those with moderate asthma (Stiemsma and Turvey 2017). Healthy patients were also found to have a higher proportion of *Bacteroidetes* when compared to asthmatic patients (Riiser 2015). In children with asthma, the bacterial load is also considerably higher than healthy control subjects (Riiser 2015). Further research is needed to determine the therapeutic potential of manipulating the human gut and lung microbiome in the prevention and treatment of asthma.

2.2.3.7 Additional Risk Factors

Additional risk factors for developing asthma include air pollution, specifically during pregnancy, gastroesophageal reflux (GERD), cardiovascular disease, dyslipidemia, and COPD. Deng et al. found that maternal exposure to air pollution during the second trimester of pregnancy increases the risk of developing asthma (Deng et al. 2016). In a study done by Panek et al. in Poland, GERD was found to be a risk factor for the development of severe asthma. Additionally, cardiovascular disease, hypertension, COPD, neoplastic disease, and dyslipidemia were all associated with decreased asthma control. This study also showed that the co-occurrence of another disease with asthma could be a marker for poor response to asthma treatment (Panek et al. 2016).

2.3 Food Allergy

2.3.1 Definition

Food allergy refers to a maladaptive immune response directed toward an otherwise innocuous food antigen (Sicherer and Sampson 2010; Vassallo and Camargo 2010) that can be life-threatening and is reproducible on exposure to the same food. Symptoms related to food allergy are immunoglobulin E (IgE) mediated and can occur within minutes to several hours after ingestion or exposure to the culprit food. Manifestations of food allergy classically involve the skin, gastrointestinal tract, and respiratory tract, but other systems can be involved. The severity of the reaction is dependent on the patient's sensitivity, amount of food ingested, co-ingestion of other foods, and whether or not the food is raw, cooked, or processed. In addition, the existence of other comorbidities, such as asthma and atopic dermatitis, can also impact the severity of the reaction (Burks et al. 2012).

Nearly any food protein can cause a food allergy, but the majority of food allergies are due to milk, egg, peanut, tree nuts, shellfish, fish, wheat, and soy (Sicherer and Sampson 2010) depending on the age of the individual. Prevalence of food allergy peaks in childhood with the highest incidence occurring in the first year of life (Steinke et al. 2007). The probability of having an

allergic reaction is correlated to the level of specific serum IgE for some food proteins. Most reported fatalities have been attributed to peanut and tree nut allergy as well as a delay in the administration of epinephrine. Additional factors that are associated with fatal or near-fatal reactions include a history of asthma, lack of skin symptoms, patient denial of symptoms, simultaneous intake of alcohol, or reliance on oral antihistamines to manage symptoms (Burks et al. 2012).

Adverse food reactions may also be non-IgE mediated. Adverse reactions that are not considered true IgE-mediated allergic responses include host-specific metabolic disorders such as lactose intolerance, galactosemia, and alcohol intolerance. In addition, an adverse response to pharmacologically active components such as caffeine, tyramine in cheese that can trigger migraines, and histamine in spoiled fish, which can result in scombroid poisoning, all can appear as an IgE-mediated response when in fact the mechanism is non-immunogenic (Sicherer and Sampson 2010).

2.3.2 Prevalence

Determining the prevalence of food allergies can be challenging as a result in differences of patient self-reporting and actual proven allergic reactions via either medical history and clinical testing or an oral challenge (Burks et al. 2012). Much of the data from published studies on food allergies come from patient self-reporting of symptoms. Due to the variation in patient understanding of the nature of true food allergy, self-reporting likely leads to an overestimate of the prevalence of a true IgE-mediated food allergy. A discrepancy in self-reported and oral food challenge may be found when in fact an individual did have a true IgE-mediated reaction to a food which resolved prior to when additional confirmatory testing was obtained (Sicherer 2011). In addition, many of the published studies that have evaluated the prevalence of food allergy do not include the gold standard for diagnosis, an oral food challenge (OFC), to confirm an IgE-mediated true allergic reaction.

There is a broad range of prevalence of food allergies in the United States and worldwide that has been reported in the literature (Fig. 2.1). A general consensus is that food allergies are thought to affect approximately 5% of children and 3–4% of adults in Westernized countries with the incidence of food allergies increasing (Sicherer and Sampson 2010).

The National Health and Nutrition Examination Survey (NHANES) surveyed 20,686 individuals in the United States between 2007 and 2010 found that the overall prevalence of self-reported food allergy was 6.53% in children and 9.72% in adults (McGowan and Keet 2013). A study performed by Sicherer et al. looked at 5300 US households finding that the self-reported prevalence of peanut, tree nut, or both was reported by 2.1% in those younger than 21 and 1.3% of adults (Sicherer et al. 2010). In Canada, the overall prevalence of self-reported food allergy is 8.07% with

Proposed risk factors and theories for the development of food allergies:
Hygiene hypothesis
Delivery by cesarean section
Changes in dietary fat content
Vitamin D deficiency and insufficiency
Darker skin tone
Use of antacids
Late introduction to food protein
Eczema
Family history of food allergy
Immigration to developed county during infancy

Fig. 1 Proposed risk factors and theories for the development of food allergies

residents of Quebec having the lowest rate of self-reported food allergy, followed by Ontario and Atlantic Canada and Western Canada (Soller et al. 2012).

It is estimated between 11 and 26 million people of the European population suffer from a food allergy (Mills et al. 2007). A systemic review and meta-analysis performed by Nwaru et al. found that the lifetime prevalence of a self-reported food allergy was 17% with a 6% point prevalence in Europe. When an oral food challenge was performed, food allergy was confirmed in 1% of patients studied. The study further documented that food allergy was higher among children than in adults and highest in Northwestern Europe than in other areas, while Southern Europe had the lowest prevalence (Nwaru et al. 2014). A study of 969 3-year-old children performed by Venter et al. in the United Kingdom found that there was an allergy to milk in 0.5%, egg in 1.4%, wheat in 1.3%, cod in 0.5%, peanut in 0.2%, and sesame in 1.4% (Venter et al. 2008).

A study performed by Osterballe et al. evaluated 1272 young adults aged 22 in Denmark by utilizing food allergy questionnaires. Twenty percent of respondents reported an unfavorable reaction to non-pollen-associated foods. In 42 cases an oral food challenge was completed which resulted in an actual prevalence of IgE-mediated food allergy of 1.7% (Osterballe et al. 2009).

Ho et al. provide one of the first surveys of self-reported food allergies in Hong Kong that studied children aged 14 and below finding an estimated prevalence of 4.8%. Shellfish was the most common allergen causing more than one-third of the reported reactions, whereas the prevalence of peanut allergy was only 0.3–0.5% (Ho et al. 2012).

A meta-analysis of 51 articles from various countries was performed by Rona et al. that examined the self-reported prevalence of allergy to the major food allergens. They found that the self-reported prevalence varied between 1.2% and 17% for milk, 0.2% and 7% for egg, 0% and 2% for peanut and fish, 0% and 10% for shellfish, and 3% and 35% for any food (Rona et al. 2007).

Much of the reported data are consistent with the increased prevalence of food allergy. In the United States, the prevalence of self-reported food allergy increased 18% from 1997 to 2007 in children less than 18 years of age. Outpatient visits in the United States for food allergy tripled between 1993 and 2006. In the United Kingdom, hospital admission for food allergy increased sevenfold from 1990–1991 to 2003–2004 (Lack 2012). Hu provided the first study in China to show the trend in food allergy prevalence and found that from 1999 to 2009 the prevalence of food allergy increased from 3.5% to 7.7% with egg and cow's milk being the most common food allergens (Hu et al. 2010).

There is no doubt that food allergy creates a social and economic burden on the patients affected and also on their caregivers. A study performed by Patel et al. demonstrated that the economic burden of food allergies was an estimated half a billion dollars (Patel et al. 2011). In the United States, 125,000 emergency room visits and 53,700 episodes of anaphylaxis have been attributed to food allergy (Sicherer and Sampson 2010), as well as resulting in 3,000 hospitalizations and 100 deaths per year (Atkins and Bock 2009).

The above studies highlight a trend in the increase of food allergies in developed countries with milk, egg, peanut, tree nuts, shellfish, fish, wheat, and soy being the most common food allergens. Further studies are needed with an oral food challenge, the gold standard to diagnose food allergy, for more precise prevalence data due to the wide variability in patient self-reported food allergy. In addition, further research in undeveloped countries is needed to supplement our knowledge of potential triggers versus possible protective features for the development of food allergies in the people of these countries when compared to the data already known (Table 2.1).

2.3.3 Risk Factors

The mechanisms behind the rise in food allergies are poorly understood, but with the increase in public awareness, numerous factors have been investigated (Fig. 2.1). Ongoing research is focused on examining the hygiene hypothesis

Table 1 Prevalence of self-reported food allergy by region

Region	Authors	Prevalence
United Stales	McGowan and Keet 2013	Overall 6.53% in children and 9.72% in adults
	Sicherer et al. 2010	Allergy to peanut and tree nut or both in 2.1% of those younger than 21
Canada	Soller et al. 2012	Overall 8.07% with Quebec having the lowest rate
Europe	Nwaru et al. 2014	Lifetime risk of 17% with highest rate in Northwestern Europe
United Kingdom	Venter et al. 2008	Allergy to milk in 0.5%, egg in 1.4%, wheat in 1.3%, cod in 0.5%, peanut in 0.2%, and sesame in 1.4%
Denmark	Osterballe et al. 2009	20% reported an unfavorable reaction to non-pollen-associated foods
Hong Kong	Ho et al. 2012	Overall 4.8% with shellfish being the most common
China	Hu et al. 2010	Overall 7.7% with egg and cow's milk being the most common

(Strachan 1989), changes in the dietary fat content (Devereux and Seaton 2005; Black and Sharpe 1997; Anandan et al. 2009), vitamin D deficiency (Vassallo and Camargo 2010), the use of antacids leading to exposure of more intact food protein (Untersmayr and Jensen-Jarolim 2008; Trikha et al. 2013), and delay in oral exposure to the food protein antigen (Du Toit et al. 2008; Du Toit et al. 2015) as potential explanations related to the increasing prevalence of food allergies. In addition, food allergies are commonly associated with other allergic diseases such as eczema (Allen and Koplin 2016; Brown et al. 2011; Maloney et al. 2011; Tan et al. 2012), and genetic factors are being explored (Sicherer et al. 2017; Hourihane et al. 1996). Investigators speculate that the rise in food allergies may be the second wave of the increase in allergic disease noted at the end of the twenty-first century, versus a new food epidemic that may be due to a distinctive set of factors (Allen and Koplin 2016).

2.3.3.1 Hygiene Hypothesis

It has been theorized that allergic diseases are associated with the Western lifestyle. The phrase "hygiene hypothesis" was coined after Strachan published data in 1989 demonstrating that declining family size, improvements in household amenities, and higher standards of personal cleanliness reduce the opportunity for cross infection in young families, resulting in more widespread atopic diseases, particularly eczema and allergic rhinitis (Strachan 1989). Investigators suggest that the lack of early childhood contact to infectious agents, gut flora, and parasites increases the susceptibility to all types of allergic diseases by modulating the immune system development (Lack 2012).

Factors such as methods of infant delivery have been suggested to play a role in the development of food allergy. Eggesbo et al. found that there was a sevenfold increase in parental-perceived reaction to eggs, fish, or nuts in children that were born by cesarean section (Eggesbø et al. 2003). In addition, Gil et al. reported that cesarean delivery was a risk factor for the development of cow milk allergy (Gil et al. 2017). It has also been postulated that early colonization of colonic microflora in infants protects against the development of allergic disease. This theory has led to the administration of either probiotics or prebiotics in an effort to lessen the likelihood of developing an allergic disease (Lack 2012). Some studies have shown that this protects against the development of eczema but have not demonstrated a reduction in allergen sensitization (Dotterud et al. 2010).

2.3.3.2 Maternal and Infant Diet

It is uncertain if the restriction of the maternal diet during pregnancy or lactation plays a role in the development or course of food allergy (Burks

et al. 2012). A review by Murano et al. which included 15 observational and 14 intervention studies found that breastfeeding for at least 4 months was linked with a reduced risk of cow's milk allergy over the first 18 months in high-risk infants (Muraro et al. 2004). It is important to note that none of these studies were randomized nor prospective. Other systematic reviews that have taken place have been unsuccessful in confirming that breastfeeding is associated with a decrease in food allergy (Kramer and Kakuma 2004; Silva et al. 2014). Conversely, studies by Saarinen et al. and Wetzig et al. have found that extended breastfeeding may increase the possibility of sensitization or food allergy development in infants who are deemed high risk (Saarinen et al. 1999; Wetzig et al. 2000). Based on conflicting data, the only recommended preventative strategy is to exclusively breastfeed until 4–6 months of age without any maternal diet restrictions (Burks et al. 2012; Vassallo and Camargo 2010).

There is evidence suggesting that the time of food protein introduction may impact the development of food allergies. A study by Du Toit et al. found that there to be a tenfold higher prevalence of peanut allergy in Jewish children in the United Kingdom versus Jewish children in Israel which was thought to be related to the difference in dietary practices in the two different populations of children. It was a common practice in Israel to introduce peanut into the diet of infants between the ages of 4 and 6 months, while in the United Kingdom, Jewish children had peanut introduced in their diet around age 3 based on the countries' guidelines at that time. The study found that children who had peanut introduced later were more likely to have a food allergy (Du Toit et al. 2008). Based on this observation, the Learning Early About Peanut Allergy (LEAP) trial randomized 640 children between the ages of 4 and 11 months with severe eczema, egg allergy, or both to either consume or avoid peanut-containing foods until they were 60 months of age. The LEAP trial found that the prevalence of peanut allergy was 35.3% in the avoidance group and 10.6% in the consumption group demonstrating that early introduction of the peanut food protein may be used as a preventative strategy in high-risk infants (Du Toit et al. 2015).

Additional studies have confirmed that early introduction of peanut is beneficial. Fleischer et al. and Togias et al. evaluated high-risk infants, defined as those with an allergy to egg or early-onset eczema, and found that early introduction of peanuts was protective for this population. The American Academy of Pediatrics (AAP) has subsequently endorsed the introduction of peanut proteins for high-risk infants as early as 4–6 months of age after applicable testing (Fleischer et al. 2015; Togias et al. 2017). With respect to foods other than peanuts, there is limited evidence as to the time of appropriate introduction. There are ongoing studies to address the topic of dietary avoidance throughout pregnancy and lactation and the idea of early versus delayed allergen exposure in the development of food allergy (Burks et al. 2012).

Various studies have also evaluated whether the quality or variety of food may play a role in the rise in food allergy. Roduit et al. examined 856 children from rural areas in five European countries and found that greater diversity in complementary foods introduced in the first year of life was associated with a reduced risk of diagnosed food allergy and food sensitization (Roduit et al. 2014). Grimshaw et al. found that children exposed to more fresh fruit and vegetables and home-prepared meals were found to have less challenge-proven food allergy at 2 years of age (Grimshaw et al. 2014).

2.3.3.3 Vitamin D Deficiency

It has been shown that vitamin D is critical in the development of tolerance, immune system defenses, and epithelial barrier integrity, and with the rise in vitamin D deficiency has come speculation that a deficiency of vitamin D may be a direct cause of increasing food allergies (Camargo et al. 2007; Vassallo and Camargo 2010). Camargo et al. were the first to hypothesize that vitamin D may impact the risk of food allergy and anaphylaxis after observing a strong north-south gradient in EpiPen prescription frequencies in the United States. The gradient was independent of socioeconomic status, longitude, and physician density

(Camargo et al. 2007), and it has been proposed that the increase in food allergy may be associated with the concomitant increase in the epidemic of vitamin D deficiency (Vassallo et al. 2010).

An association with increased pediatric admissions and ER visits has also been noted with increasing distance from the equator in children born in the autumn and winter (Vassallo et al. 2010; Mullins et al. 2011). Allen et al. found that infants with vitamin D insufficiency were three times more likely to have a peanut or egg allergy, and children with vitamin D deficiency were six times more likely to have a food allergy (Allen et al. 2013). Osborne et al. studied populations of children in Australia to inspect the associations of food allergy and latitude. They found that a latitude gradient was present for peanut and egg with a higher incidence being present in children residing furthest from the equator (Osborne et al. 2012).

This rising trend of vitamin D deficiency can be attributed to the changes in lifestyle with increased time spent indoors with less exposure to sunlight. To further support the vitamin D hypothesis, it has been shown that birth during seasons that are of low UVB intensity is more common in children with the diagnosis of food allergy. It has also been noted that those with darker skin tones are more likely to be vitamin D deficient and food allergy is highest among African Americans followed by Hispanics and then non-Hispanic whites (Vassallo et al. 2010).

Vassallo and Camargo proposed a "multi-hit" theory in which vitamin D deficiency in a developmentally critical stage increases the vulnerability to colonization with abnormal intestinal microbial flora and gastrointestinal infection. This contributes to abnormal intestinal barrier permeability and an inappropriate exposure of the immune system to dietary allergens. Vassallo and Camargo believed that the additional factor of vitamin D deficiency fosters a pro-sensitization immune imbalance that can compromise immunologic tolerance and can lead to food allergy (Vassallo and Camargo 2010).

It is thought that early correction of vitamin D deficiency during pregnancy and early childhood can stimulate tolerance, improve mucosal immunity, improve microbial flora, decrease gastrointestinal infections, and blunt the development of food allergy (Vassallo and Camargo 2010). Nwaru et al. found that maternal intake of vitamin D during pregnancy was correlated with a decrease in the risk of food sensitization (Nwaru et al. 2010). Further testing of this theory is needed to determine if vitamin D deficiency does, in fact, play a strong role in food allergy.

2.3.3.4 Dietary Fat

Studies have found that a decline in the consumption of animal fats with a corresponding increase in the use of margarine and vegetable oils has led to an increase in allergies. The fatty acids found in animal fats inhibit synthesis of prostaglandin E2 (PGE2), whereas the fatty acids found in margarine and vegetable oils increase the production of PGE2. PGE2 reduces the IFN-gamma production by T lymphocytes which results in an increased IgE production by B-cells (Devereux and Seaton 2005; Black and Sharpe 1997). A systematic review performed by Anandan et al. concluded that supplementation with omega oils was unlikely to play an important role in primary prevention for allergic disease (Anandan et al. 2009).

2.3.3.5 Antacids

The rise in food allergies has also been hypothesized to be associated with the increased use of acid-suppressive medications such a proton pump inhibitors and histamine-2 blockers (Untersmayr and Jensen-Jarolim 2008; Trikha et al. 2013). In US infants less than 1 year of age, the prevalence of gastroesophageal reflux disease (GERD) has been estimated to have tripled from 2000 to 2005 and to have increased by 50% in other pediatric age groups (Trikha et al. 2013). With this rise in prevalence and diagnosis of GERD in the pediatric population has come an increase in prescriptions for gastric acid-suppressive medications (Untersmayr and Jensen-Jarolim 2008, Trikha et al. 2013). Normal digestion by gastric acid reduces the potential for food proteins to bind specific IgE. It is thought that the increase in gastric pH from acid-suppressive medications alters the digestive function of the stomach leading to intact labile food protein during gastric transit. This leads to a greater quantity of food

protein that can bind IgE, lowering a threshold dose of allergens that is required to elicit symptoms of food allergies (Untersmayr and Jensen-Jarolim 2008). Sensitization due to gastric acid-suppressive medications is therefore thought to be a result of the presentation of undigested or improperly digested proteins by antigen-presenting cells in the intestinal epithelium. Trikha et al. performed the first large-scale retrospective cohort study to investigate this potential link. The trial compared 4724 children ages 0–18 years with the diagnosis of GERD and on gastric acid-suppressive medications with 4724 aged-matched controls without the diagnosis of GERD. They found that in comparison to the control group, the group of children with GERD who were receiving acid-suppressive medications had a 1.7-fold increase in the risk of developing at least one food allergy at 1 year of age when compared to those who were not on gastric acid-suppressive medication. The risk of developing food allergy was similar irrespective of whether a proton pump inhibitor or a histamine-2 blocker was used (Trikha et al. 2013).

2.3.3.6 Eczema

It has long been recognized that there is a strong association between eczema and food allergy. Children with eczema are five times more likely to develop IgE-mediated food allergy (Allen and Koplin 2016). Children with moderate-to-severe atopic dermatitis may have worsening skin involvement after the ingestion of a known food protein allergen (Maloney et al. 2011). The link between these two disease processes has caused researchers to speculate that the filaggrin gene, which is strongly associated with eczema, might independently increase the risk of developing food allergy (Allen and Koplin 2016). A study by Brown et al. demonstrated that this association could be true, while a study by Tan et al. determined that the filaggrin probably leads to an increased risk of food sensitization instead of leading to the actual food allergy itself (Brown et al. 2011; Tan et al. 2012).

The Lack hypothesis suggests that sensitization to food proteins could occur by the introduction of a low dose of food protein through the damaged skin barrier in a patient with a breakdown in the skin barrier in conditions such as eczema. Lack further proposes that oral ingestion of the allergens early in infancy can negate the development in desensitization but can instead lead to oral tolerance of the food protein leading to the prevention of food allergy (Lack 2012).

2.3.3.7 Family History

An increase in risk of developing food allergy has been noted if a sibling or parent is affected, suggesting a genetic component (Lack 2012). Hourihane et al. found that a child has a sevenfold increased risk of developing a peanut allergy if a parent or sibling is affected by a food allergy (Hourihane et al. 1996). Sicherer et al. reported that a monozygous twin had a 64% chance of developing a peanut allergy if the other twin sibling was affected (Sicherer et al. 2000). These studies likely suggest that there are genetic factors that increase one's predisposition if another family member is affected, but there have been no conclusive findings regarding specific loci (Sicherer et al. 2017).

2.3.3.8 Immigration Status

Studies have also suggested that immigration status may play a role in the risk of developing food sensitization. Keet et al. evaluated at 3550 subjects and compared the development of food sensitization between those that were US-borne versus foreign-born subjects. They reported that US-borne children and adolescents carried an increased risk of sensitization to any food. Within the foreign-born group, those that immigrated to the United States before the age of 2 had increased odds of food sensitization compared to those immigrants that arrived at the United States after the age of 2. Children of immigrants who were born in the United States were at the highest risk of developing food sensitization. The authors suggested that foreign-born children who immigrated during their infancy lost some of the protective effects of foreign birth possibly indicating that this early-life exposure to a developed country leads to an increased risk of food sensitization (Keet et al. 2012).

2.3.3.9 Microbiota

The gut microbiome has been the most thoroughly researched human microbiome thus far (Riiser 2015). Studies have shown that certain bacterial species are associated with the development of food allergy. One-year-old children who are sensitized to one or more food allergens have been found to have an elevated *Enterobacteriaceae/Bacteroidaceae* ratio as well as a lower gut microbiota richness (Riiser 2015). Clostridia species have also been found to be protective in the development of food allergy (Blázquez and Berin 2017).

Cesarean section is known to affect the development of the gut microbiome, and children who are born by cesarean section have been found to have a higher risk of becoming sensitized to egg and milk (Riiser 2015). With the emerging data, further research will be needed to recognize microorganisms that could be used therapeutically to prevent or to treat food allergy (Blázquez and Berin 2017).

2.3.3.10 Conclusion

Food allergy creates a significant medical and socioeconomic burden on both the patient and the family members who are involved in their care (Cummings et al. 2010). Deaths due to anaphylaxis from food allergy occur predominantly away from home highlighting the need to promote public awareness of this growing health concern (Atkins and Bock 2009). Due to this significant healthcare burden, it is clear that a better understanding of the epidemiology of food allergy may lead to successful prevention and treatment in the future. Research is ongoing to address this growing epidemic.

2.4 Allergic Rhinitis

2.4.1 Definition

Allergic rhinitis (AR) is defined as an inflammation of the nasal mucosa triggered by exposure to an allergen following previous allergic sensitization. Antigen-presenting cells recognized allergen within the nasal mucosa of allergic individuals (Chaplin 2006). With the antigen exposure, there is a cascade of immune cell response involving CD 4+ T helper cells (Th2) with a subsequent activation of B-cells. This B-cell activation induces class switching to produce antigen-specific immunoglobulin E (IgE). The antigen-specific IgE binds to high-affinity receptors on the mast cells which when cross-linked with an allergen produces an immune-mediated allergic response that leads to allergic symptoms within the mucosa (Broide 2010).

Major symptoms that characterize AR include nasal itching, sneezing, rhinorrhea, and nasal congestion (Bousquet et al. 2001). The symptoms of AR can have a significant effect on sufferers who experience a decrease in quality of life as well as productivity resulting from altered sleep habits, increased fatigue, and decreased mood (Meltzer 2001).

AR can be characterized by severity, duration, or seasonal pattern. AR is categorized based on symptoms typically divided into seasonal or perennial (Skoner 2001). Variation in timing of seasonal AR will vary based on location and climate. Seasonal variant of AR is most commonly caused by pollen from trees, grasses, weeds, and mold. Perennial variant of AR is often seen due to indoor allergens including dust mites, animal dander, and mold spores (Nathan et al. 1997).

2.4.2 Prevalence

Allergic rhinitis (AR) is considered one of the most prevalent chronic medical diseases of the respiratory tract although it is not often recognized as such likely due to its severity which is not associated with life-threatening consequences. Examining population prevalence of AR is difficult to accurately assess as much of the data that has been collected is by questionnaires and telephone surveys. It is thought the data collected in this manner may actually continue to underreport the disease (Skoner 2001).

The World Allergy Organization estimates that at least 400 million people across the world suffer from AR. The prevalence of AR is increasing throughout the world (Pawankar et al. 2013).

The onset of AR most commonly occurs early in life, and the prevalence steadily grows until age 20 at which time 80% of individuals who will have AR have developed symptoms consistent with the diagnosis (Skoner 2001). In the United States, AR affects nearly 60 million people or nearly one in every five individuals. It is a disease that continues to grow in prevalence (Meltzer et al. 2009; Nathan et al. 1997). In one study from Japan, Kusunoki et al. showed the prevalence of AR in pediatric patients to be 27.4%. This prevalence showed an increase by 7% over a 10-year period. In the study, they also noted there was also an increased symptomatic severity in their patients (Kusunoki et al. 2009).

AR was assessed throughout Europe and ranged from 17% in Italy to 29% in Belgium. Throughout Europe, the study showed an overall prevalence of AR to be 23%. Bauchau and Durham showed that despite the high prevalence of AR throughout Europe, the disorder often goes undiagnosed (Bauchau and Durham 2004).

The ISAAC Phase Three Study was a large, worldwide project examining the prevalence of allergic diseases. In this study, the overall prevalence of AR in pediatric patients around the world was between 8.5% and 14.6%. This data was beneficial as it showed a wide variability in prevalence not only by country but also within countries and different medical centers (Mallol et al. 2013).

Eriksson et al. in a recent study suggest that the prevalence of AR in Sweden may have reached a plateau. Their report showed that the prevalence of AR in Sweden was 28%. The results of this self-reported study showed a similar prevalence as compared to previous similar studies within the nation (Eriksson et al. 2012). It is still to be determined if the prevalence of AR in other countries has neared a plateau or will continue to rise with many contributing risk factors associated with the disease still present.

2.4.2.1 Variability of AR Among Economic Classes and Living Environments

Most rates of AR prevalence throughout the world have shown a steady increase (Pawankar et al. 2013). This phenomenon has been shown to be higher in urban areas and areas with lower allergen exposure. Sole et al. showed that living in a rural environment demonstrated a decreased prevalence of allergic rhinitis (Solé et al. 2007).

Lima et al. used previous research within Brazil to compare the prevalence of allergic disease among different socioeconomic classes. This study was completed within the municipality of Sao Paulo, Brazil, which is the third largest urban area in the world and considered to be one of the most polluted. Their data showed a lower prevalence of AR symptoms found in those living in the poorer areas of the city with more allergen exposure (Lima et al. 2007). The validity of prevalence when using questionnaires and surveys among different socioeconomic classes is questionable because of the concern for literacy and possible lack of survey understanding. However, other investigators looking at similar data confirmed, through both skin prick testing and IgE-mediated testing, that the prevalence of AR in individuals living in urban areas was higher when compared to those living in rural environments (Cingi et al. 2005).

2.4.3 Risk Factors

With the prevalence of AR increasing throughout much of the world, researchers have studied risk factors associated with this disorder. With the improvement of genetic study over time and the research that is being completed, it is apparent that the risk factors involved with AR are multifactorial. Many risk factors of AR are listed in Table 2.2 and are discussed below.

2.4.3.1 Pollution

Air pollution has been shown to be a risk factor for the development of AR. Morgenstern et al. completed a longitudinal birth cohort study, which

Table 2 Risk factors of allergic rhinitis

Increased risk	Decreased risk
Pollution	Early pet and animal exposure
Smoking	Large family size
Genetics (family members with allergic disease)	

examined the development of rhinorrhea and sneezing in young children. Their study showed that children living near major roads and highways had increased odds of developing rhinitis symptoms in the first year of life (Morgenstern et al. 2007). Similar results have been reported in Taiwan. Lee et al. found that younger individuals and males reported higher rates of AR following exposure to traffic-related air pollutants (Lee et al. 2003). Additionally, Hwang et al. studied 32,143 Taiwanese school children who have persistent exposure to nitric oxide, carbon monoxide, and sulfur dioxide. These gases are common traffic-associated air pollutants to the major cities in Taiwan. Their data shows that these pollutants are likely associated with an increased prevalence of AR (Hwang et al. 2006).

2.4.3.2 Smoking

A large meta-analysis found a very small association with smoking and allergic diseases including AR in adults. Likewise, among children and adolescents, direct smoking, as well as secondhand smoke exposure, showed a modestly increased risk of allergic disease (Saulyte et al. 2014).

2.4.3.3 Genetics

AR does not exhibit a Mendelian inheritance pattern, but it does have a hereditary component. It has been shown that having a parent with AR increases the risk of a child developing AR (Dold et al. 1992). Newer research techniques include the utilization of genome-wide association studies also known as GWAS. These techniques use single nucleotide polymorphisms or SNPs to look at portions of the patient's gene. Wang et al. used these techniques to look for genetic factors contributing to AR. Their research found possible involvement of IL-13 SNPs in the regulation of IgE production in response to allergens (Wang et al. 2003). Further research is ongoing to fully elucidate the genetic inheritance and components of AR.

2.4.3.4 Family Size

Family size and familial order have been shown to affect risk of developing AR. Strachan performed a longitudinal 23-year study in England which found that the first-born child was most likely to have AR. This study also noted that there was an inverse relationship to household sizes. Households with more children were less likely to be atopic and suffer from AR than those with fewer children (Strachan 1989). Matheson et al. also showed that the incidence of rhinitis decreased with the increased number of siblings in addition to sharing a bedroom with an older sibling (Matheson et al. 2011). It is thought that the larger family size and increased risk of early-life infections may be protective against the development of AR.

2.4.3.5 Pets and Animal Exposures

Studies indicate that early pet exposure, specifically cats and dogs, may induce tolerance and thereby reduce the risk of atopic AR. Multiple studies have shown being raised on a farm, with varied large animal exposure, is associated with a reduced incidence of rhinitis (Matheson et al. 2011; Waser et al. 2005).

2.5 Allergic Conjunctivitis

2.5.1 Definition

Allergic conjunctivitis (AC) is a broad term that is defined as the inflammation of the ocular conjunctiva. Multiple forms exist of which seasonal AC and perennial AC are most common. Both the seasonal and perennial forms of AC involve IgE-mediated hypersensitivity reactions that elicit mast cell activation and immediate allergic response (Bielory 2000). The presence of an allergen-specific IgE can be documented in nearly all cases of seasonal and perennial AC (see Fig. 2.2) (Bonini 2004). Individuals with AC may have a combination of watery, itchy, red/injected, painful, stinging, or swollen eyes (Bielory 2000).

Less common forms of allergic conjunctivitis include vernal keratoconjunctivitis (VKC) and atopic keratoconjunctivitis (AKC). VKC is more common in tropical climates and is most often IgE negative to common allergens (Jun et al. 2008). VKC is caused by chronic Th-2-mediated

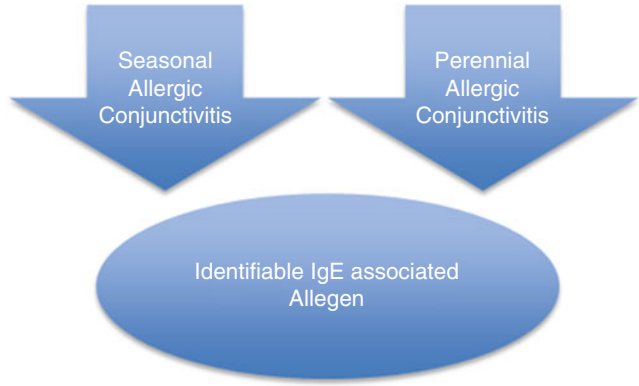

Fig. 2 Most common ocular allergies and allergen association

inflammation (Maggi et al. 1991). AKC is a chronic inflammation of the ocular surface as well as the eyelid. The inflammation is due to chronic mast cell degranulation as well as T-cell-mediated cytokines (Bonini 2004). Both VKC and AKC can develop into severe diseases without appropriate treatment. Results of untreated VKC and AKC can be vision loss (Tanaka et al. 2004).

2.5.2 Prevalence

The World Allergy Organization estimates that over one billion people worldwide suffer from AC. The prevalence of AC, like other allergic diseases, is increasing (Pawankar et al. 2013). Determining the exact prevalence of AC is difficult as there are few studies focused solely on the disease process. Isolated AC is less common than individuals having comorbid allergic disease processes like rhinoconjunctivitis.

In the United States, data shows that the prevalence of patients with at least one allergic ocular symptom event during their lifetime was approximately 36%. Of these individuals, 6.4% had only ocular symptoms, whereas 29.7% had both ocular and nasal symptoms. In this data review, ocular symptoms were highest during the midsummer months of June and July corresponding to the summer pollen season (Singh et al. 2010).

In a study to further explore the prevalence of AC in 3,210 Brazilian adolescents, Geraldini et al. determined the prevalence of AC to be 20.7% (Geraldini et al. 2013). Additionally, in one of the most populated cities in the world, Karachi Pakistan, 812 school-age children were studied to determine the prevalence of AC. The study showed that 19.2% of the children studied had AC. The study also reported that there was an increase in incidence which is correlated to the increasing age of the child (Baig et al. 2010). As is seen with other allergic diseases, the prevalence of AC is increasing throughout the world.

2.5.3 Risk Factors

The risk of AC is higher in those with other allergic diseases, specifically allergic rhinitis as they are commonly comorbid conditions. Allergic conjunctivitis symptoms are triggered by exposure to pollen, animals, molds, and dust mites. Individuals exposed to environments with high pollen loads are most likely to experience symptoms of AC.

Perkins et al. reported that farm exposure early in life was found to decrease the risk of AC as well as allergic rhinoconjunctivitis. This is thought to be secondary to the increase in allergic tolerance due to the early-life allergen exposure (Perkin et al. 2015).

Lois et al. showed that exposure to tobacco smoke whether active or passive could cause ocular irritation through disruption of the lipid layer of the tear film. This ocular irritation can worsen the symptoms of those with allergic conjunctivitis (Lois et al. 2008).

Overall, there is limited data on the specific predisposing factors associated with AC.

As with other allergic diseases, exposure to known allergens will produce symptoms of AC.

2.6 Atopic Dermatitis

2.6.1 Definition

Like asthma, atopic dermatitis (AD) or eczema is a chronic inflammatory disease of the skin that is associated with skin itching and dryness and can involve secondary infections (Civelek et al. 2011). Atopic dermatitis has various severities and can have a significant effect on quality of life (Sánchez 2017).

2.6.2 Prevalence

Like other allergic disorders, atopic dermatitis has been shown to be influenced by migration, which may act as a protective factor. Individuals seemingly carry the low prevalence of their originating location to the high-prevalence area of their migration. It is important to note, however, that this effect is only in one direction. Migration to low prevalence does not seem to have an effect. Silverberg and Simpson found that in the United States, AD has a prevalence of 12.97%. It was also reported that the severity of disease varied by region with the highest prevalence of the disease being in the Northeast and Midwest region (Silverberg and Simpson 2014). The prevalence of atopic dermatitis differs in various regions of the world. According to Dennis et al., Columbia has a prevalence of 14% (Dennis et al. 2012). Zhang et al. found that Shanghai, China, had an eczema prevalence of 3.48% (Zhang et al. 2015). Meanwhile, the Mediterranean country of Turkey has an eczema prevalence of 17.1% (Civelek et al. 2011). It has been reported that countries in the Mediterranean have a lower prevalence of atopic dermatitis than developed countries of other parts of the world. However, between countries within the Mediterranean itself, the prevalence is comparable (Civelek et al. 2011) (Table. 2.3).

2.6.3 Risk Factors

Atopic dermatitis has been found to have similar risk factors as asthma, such as air pollution, ethnicity, overweight, and obesity (Fig. 2.3). Similar to asthma, it has also found that watching 5 or more hours of television per day also increases AD symptoms in adolescents (Mitchell et al. 2013) (Fig. 2.3). Atopic dermatitis has also been found to be influenced by household income, parental education, and health (Silverberg and

Table 3 Prevalence of eczema in various parts of the world

Country	Prevalence (%)
United States	12.9
Columbia	9.3
Shanghai, China	3.48
Turkey	17.1

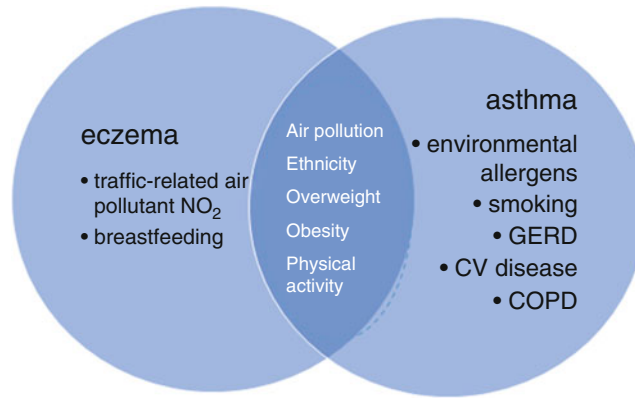

Fig. 3 Eczema and asthma risk factors

Simpson 2014). One difference with risk factors between asthma and eczema is that there was no association found between smokers in the home, living in a metropolitan area, and eczema severity (Silverberg and Simpson 2014). However, Deng et al. reported that maternal exposure to "traffic-related air pollutant NO_2" in the first trimester of pregnancy is associated with increased risk developing eczema (Deng et al. 2016). All the previously mentioned risk factors affect eczema severity, while the latter is simply associated with an increased risk of developing eczema. Another factor that has been found to influence the development of eczema is breastfeeding. According to Chiu et al., breastfeeding, either partial or exclusive, for greater than 6 months is associated with decreased risk of developing atopic dermatitis (Chiu et al. 2016). Although atopic dermatitis and other allergic disorders share similar pathophysiology, they differ in their risk factor associations.

2.7 Conclusion

The prevalence of all atopic disorders appears to be increasing worldwide. Multiple theories have attempted to explain this growth in prevalence. The hygiene hypothesis, first coined in 1989, likely plays an important role in the increase of atopic disease in the Western world. This is thought to be related to a decrease in allergen exposure leading to abnormal immune system activity. This aberrant immune response leads to a lack of development of tolerance to an otherwise innocuous antigen resulting in atopy. In addition, Westernized countries have an increasing amount of air pollution which has been shown to be a risk factor in the development of asthma, atopic dermatitis, allergic rhinitis, and allergic conjunctivitis. It appears that food allergies have a separate set of risk factors apart from allergic rhinitis, allergic conjunctivitis, atopic dermatitis, and asthma which some believe may be a separate second wave of increasing atopic disorders. Genetics likely also play a key role in the development of allergic disease with ongoing studies currently being undertaken to fully elucidate the genetics leading to susceptibility within families. Further research is needed in this area, which affects an estimated 25% worldwide (Wang et al. 2015) leading to a significant economic burden. Additional studies are needed in the underdeveloped countries, as these populations are grossly understudied in most of the current literature. We expect that the natural history of atopic disease will continue to expand and that new theories will continue to arise due to the ongoing research in this field.

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Definition of Allergens: Inhalants, Food, and Insects Allergens

3

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Abstract

The environment we live in and the food we consume on a daily basis contain numerous foreign antigens. During embryonic development and throughout our entire lives, the human body develops tolerance to many of these allergens in order that we do not suffer from the various maladies that result from an aberrant response to otherwise non-dangerous non-self-antigens. However, it is not always clear to the human immune system which antigens should be granted "immunity." For some pathogenic organisms, it is appropriate to protect ourselves against these invaders, as they may be harmful and cause disease or death. For other non-self-antigens, the immune system must develop tolerance to these proteins because they may be essential for our survival. On the other hand, the inability to develop tolerance to food, or to pollen, or to animal dander can lead to undesired biological consequences, which in many cases manifest in the form of an allergy. The molecules that cause symptoms are most often proteins or glycoproteins and lipoproteins. For many of them, their native function is known, but this is not always the case. There are also many allergenic substances which have not been well defined from either from a structural or functional perspective. The common mechanism for the development of IgE-mediated hypersensitivity involves the cross-linking of IgE antibodies on the surface of mast cells and the subsequent degranulation of preformed and newly synthesized mediators by the latter. Allergenic proteins can contain linear or conformational epitopes or be heat stable or heat labile. Food allergens can be modified by food processing or are affected by specific methods of cooking, which can denature the protein or, conversely, render a protein more allergic through various known chemical pathways such as the Mallard reaction. The end result is either a protein that is less or more allergic than the native protein. Pollens can be carried through biotic or abiotic means, but not all pollen allergens have been characterized. The peak season for pollens varies by the species, geography, and climate. This complex network of exposure is what the human immune system needs to navigate through to reach the balance where it knows exactly what to defend against and what to ignore. This is not always successful.

Keywords

Pollen · Allergenic determinants · Component-resolved diagnosis · Food allergy · Allergic rhinitis · Asthma · Eczema · Atopic dermatitis · Dust mite · Dander · Heat labile

3.1 Introduction

Allergic diseases, or the predisposition to develop allergic diseases known as atopy, have been on the increase both in the developed world

and in less affluent parts of the world (Bhattacharya et al. 2018; Gonzales-González et al. 2018; Leung et al. 2014a; Ojeda et al. 2018; Simonsen et al. 2018; Vrbova et al. 2018). Potential reasons for this increase include the "hygiene hypothesis" and the increased ability for people to travel and be exposed to a higher number of allergens, air pollution, climate change, the exposure to adjuvants such as those in air pollution, and many others. However, the common environmental allergens, for the most part, have remained the same. Indoor allergens mostly include dust mite and epidermals, with cockroach and mouse being increasingly blamed for inner-city allergies and asthma. Outdoor allergens include grass, tree, and weed pollens, and while the specific species may vary geographically and temporally, the primary culprits are somewhat consistent. Mold allergies can arise from the exposure in areas of high humidity or failures of water maintenance, but mold spores generally originate from outdoor environments. Since the proposal of the hygiene hypothesis in 1989, the scope of the "hygiene hypothesis" in allergic diseases has become a theory with diverse influence and of course includes the interaction of microbiome with the immune system (Alexandre-Silva et al. 2018; Von Mutius 2007).

The development of allergies arises not only via the respiratory tract. Sensitization can occur through any biological interface including the skin and the mucous membranes of the gut. For this reason, foods are a frequent trigger of both IgE- and non-IgE-mediated immune reactions. With respect to common foods that may cause anaphylaxis, the chief culprits worldwide still tend to be cow's milk, egg, soy, wheat, peanut, tree nuts, fish, and shellfish, though the primary offenders may vary from country to country, within countries, between cultures, and even within cultures (Loh and Tang 2018; Prescott et al. 2013). Some regions of the world may have specific food allergies related to their respective diet, such as buckwheat in Japan, sesame in the Middle East, and various legumes in India (Koike et al. 2018; Irani et al. 2011; Boye 2012; Verma et al. 2013a) (Fig. 1).

3.2 Nomenclature System for Allergens

Allergens are named using a standardized methodology that is maintained by the World Health Organization, International Union of Immunological Societies (WHO/IUIS) Allergen nomenclature subcommittee, which was established in 1984 for the purpose of classifying and defining allergens according to the genus and species from which they are derived (Pomés et al. 2018). But the idea apparently had been tossed around as early as 1980 (de Weck 1996). Other considerations in naming allergens include structure, function, order of discovery, and relationship with other allergens from similar species.

The name of an allergen contains the first three letters of the genus, a space, followed by the first letter of the species, a space, and finally a number. For example, the scientific name for the common household cat is *Felis domesticus*. The major allergenic protein in cat is known as *Fel d 1*. There may be other allergenic proteins, and they would normally be numbered in the order of their discovery, but the numbering may later be revised based on common functions in related species. Thus, all of the "Group 1" allergens of dust mite species have the same function. In some cases, the first three letters of two or more genus are the same, in which case a fourth letter may be added. An example of this would be *Can* for dog and *Cand* for candida. If two or more species of the same genus have the same first letter, then an additional letter can be added. An example would be *Ves v 1* and *Ves vi 1* for the allergens from *Vespula vulgaris* and *Vespula vidua*.

3.3 Types of Allergens

3.3.1 Allergenic Epitopes

Allergens can come in many forms. Most are proteins, although glycoproteins and lipoproteins can also trigger production of IgE (Xu et al. 2018; Jappe et al. 2018; Shahali et al. 2017). Other allergens are not proteins at all but may be

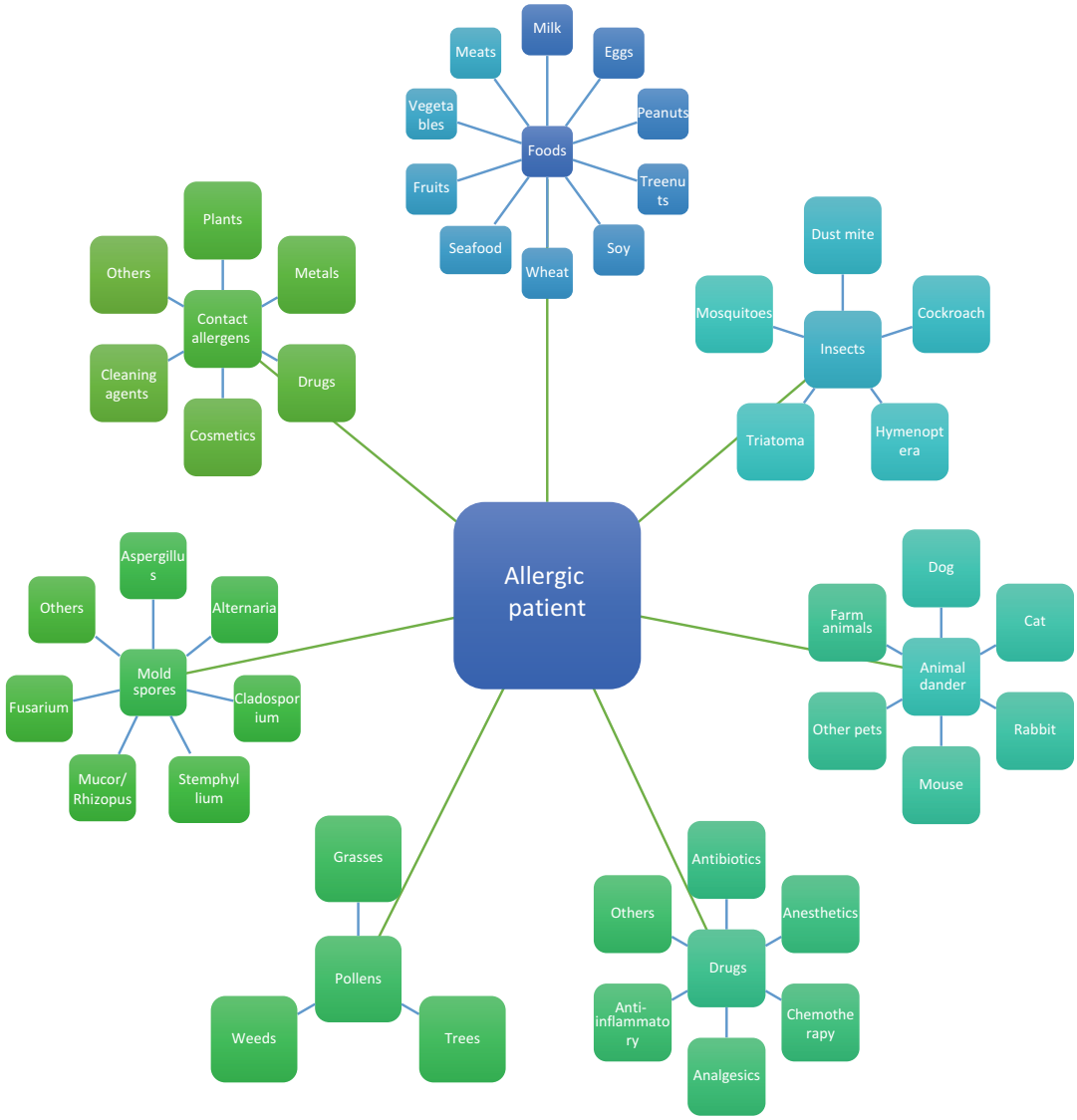

Fig. 1 Sources of allergens. Allergens can originate from many diverse environmental sources. Outdoor allergens include pollens from grasses, trees, or weeds, as well as mold spores. Failure to control indoor humidity means that mold spores can also originate indoors. Other indoor allergens include dust mites, cockroach, and pet dander. Any food can be a potential allergen, although the more common ones include cow's milk, egg, soy, wheat, peanut, tree nuts, fish, and shellfish, which account for 90% of all food allergies. Venom stings can produce allergic symptoms, as can latex and medications, which are not discussed in this paper. Contact allergy can result from a wide range of plants, metals, medications, and foods. Oral allergy syndrome can result from sensitization to a cross-reacting pollen allergen

polysaccharides, lipids, polysaccharides, or other molecules (Del Moral and Martinez-Naves 2017; Russano et al. 2008; Wieck et al. 2018). Proteins, however, are generally considered to be the most immunogenic or allergenic.

The human immunoglobulin repertoire is capable of generating antibodies with 10^{16}–10^{18} specificities, by undergoing somatic hypermutation and immunoglobulin VDJ gene rearrangements. An allergen can have many IgE antigenic determinants.

In general, a molecule must be of a certain size before it can illicit an immunological response. This size can vary but has been estimated to be in the range of 5–10 kD. If one assumes the average molecular weight of an amino acid is 110 daltons, then one would need a peptide or protein of at least 45 amino acids to generate an allergic response through binding of IgE. In fact, the process is not quite so simple, and smaller proteins do bind IgE either in their native or denatured forms.

Proteins are conventionally listed as primary sequences, starting from amino-terminal to the carboxyl-terminal. Biologically, protein structures are constrained by hydrogen bonds as specific secondary structures. Local interactions between secondary structures within a protein further generate tertiary structures which are defined biochemically by its atomic coordinates. Thus, proteins can fold into complex structures and possess multiple structural antigenic sites that can be targeted by antibodies. Most epitopes bind to IgE via a lock and key mechanism in which the antibody recognizes a secondary or tertiary structure of the protein, a so-called conformational shape. Conformational epitopes are formed from amino acids residues that are brought together by folding of the protein (Barlow et al. 1986). Conformational epitopes may be composed of either continuous or discontinuous amino acid sequences. Continuous amino sequences in a linear form can also elicit allergic responses through a variety of assistive mechanisms.

The allergens of many species have been studied extensively, while at the same time, we have very little information on the allergens of other species of animals or plants. Many allergens have been characterized and their function(s) defined. Some have even been characterized in terms of allergenic potential. Many allergenic proteins have been cloned, and the recombinant protein utilized in research to identify epitopes and developed vaccines for immunotherapy.

3.3.1.1 Conformational Epitopes Versus Linear Epitopes

Conformational epitopes can be envisioned as a lock and key model, in which the shape of the molecule, also known as secondary and tertiary structure, fits into the specific structure formed by the hypervariable region of the antibody molecule. The cross-linking of two or more IgE antibodies bound to antigen on the surface of mast cells leads to degranulation of mast cells, releasing preformed and newly synthesized mediators which can lead to allergic symptoms. Conformational epitopes generally require the antigen to be of a minimum size. This size has been thought to be at least 5 kD.

Linear epitopes are based upon the primary amino acid sequence of a portion of the protein. Accurate prediction of linear epitopes is a challenging task. Multiple algorithms are available for B-cell epitope prediction, with most of them based on limited epitope data sets (Larsen et al. 2006; Chen et al. 2007; Wang et al. 2011a; Söllner and Mayer 2006), and/or multi-algorithm parameters based on hydrophobicity, flexibility, accessibility, and biochemical properties of the amino acid side chains. However, their accuracy is unreliable (Sanchez-Trincado et al. 2017). Recently, new frameworks for linear B-cell epitope prediction, which are based on extensive immune epitope databases, have been reported (Lian et al. 2014; Manavalan et al. 2018).

Although most epitopes are conformational, progress in the prediction and mapping of conformational IgE epitopes are much impeded because such studies are technologically tedious (Breiteneder 2018) and often require detailed understanding of the three-dimensional structure of the molecule of interest, which is available for only a few allergens. To date, computational methods on predicting conformational epitopes have been largely based on spatial features of the protein with regard to solvent accessibility, physiochemical properties, and structural geometry. In addition, methods are also available for antibody-antigen-specific epitope prediction, which is largely based on a docking-like approach by analyzing interfaces of antigen-antibody 3-D structure to identify antibody-antigen recognition regions (Soga et al. 2010; Krawczyk et al. 2014; Sela-Culang et al. 2014). Despite many IgE epitopes prediction methods available, cross-validation with clinical samples will ensure such knowledge can be translated into clinical applications such as component-resolved diagnosis and vaccine design.

3.3.2 Component-Resolved Diagnostics

Component-resolved diagnosis is the analysis of individual allergenic proteins present in a particular environmental or food allergen. Previously, specific IgE testing quantified all antibodies directed against an allergen, and did not break it down based on individual proteins, let alone epitopes. Recently, however, antibody characterization has taken on a more precise mandate, and antibodies against individual allergenic proteins can be quantified in the evaluation of allergic patients. This is especially important with foods, where the differentiation of antibodies against various components in the food can affect treatment decisions. The most widely used example of this is with peanut allergen, where it has been found that the presence of IgE antibodies against the component Ara h 2 is more commonly associated with anaphylaxis, whereas the predominance of IgE antibodies directed against Ara h 9 is more commonly found in patients with oral allergy syndrome. Although not as widely used, component-resolved diagnosis can be helpful in the evaluation of pollen allergies as well.

3.3.3 Cross-Reactive Carbohydrate Determinants (CCDs)

Cross-reactive carbohydrate determinants are protein-linked carbohydrates that are being used to explain the high degree of cross-reactivity between allergens from foods, plants, and insects. It is believed that CCDs do not elicit clinical allergy symptoms; however, it has been suggested that these cross-reactive allergens may be the reason for oral allergy syndrome (Aalberse 1998; Ebo et al. 2004; van Ree 2002).

3.4 Environmental Allergens

3.4.1 Outdoor Allergens

There are numerous tree species in all regions of the world. Susceptibility to allergies in sensitized individuals depends on the pollinating seasons, which can vary from region to region. The predominance of tree species can also vary. Pollinating seasons vary for the same tree species depending on the region and climate. The majority of tree pollinating seasons begin in the springtime, although there are exceptions to this, such as a winter pollinating season for mountain cedar in the Southern United States. Some trees pollinate later in the year, and so there is a possibility that even a seasonal allergic rhinitis patient can suffer from symptoms throughout the year.

Grasses tend to pollinate in the springtime, but again the timing and duration of grass pollen season vary depending on climate. Rainfall and temperatures can affect grass pollen seasons. In some areas, grass is considered a perennial allergen. The grasses that are used in most lawns throughout the world tend to be a mixture of fairly common species, including fescue, Kentucky, perennial rye, and others. Other grasses can be found on the side of roads and can grow wild, such as Timothy grass or Johnson grass. Timothy grass can be found throughout the continental United States. It is native to Europe but not the Mediterranean region. Johnson grass is native to the Mediterranean region. It was and is considered an invasive weed and is used as a perennial forage crop in many states. Bahia grass is often found in lawns in the Southeastern United States.

Weeds tend to pollinate later in the year, and there are several species well known to be fall pollinators, including ragweed, which has a short but very intense season. Ragweed is native to North America. The family to which ragweed belongs is known as Compositae and also includes sage, marsh elder, mugworts, rabbitbrush, goldenrod, sunflower, marigolds, and zinnias.

The clinical impact of pollen also depends on the type of pollen itself, as some pollens tend to be more allergenic than others. It should also be noted that pollen exposure is a dynamic process. Changes in climate, especially due to global warming which can directly and indirectly affect pollinating seasons, and human introduction of new species can affect regional exposures. The presence of other extraneous material, such as diesel exhaust particles, can act as an adjuvant

and increase Th2 response to accentuate the effects of pollens. So where one lives or works or the road they travel to work can make a difference.

3.4.1.1 Tree Pollen

Acacia

The genus *Acacia* contains over 1000 species. Acacia trees are considered small and fast growing. Acacia is abundant in California and pollinates early in the season, even as early as February. It is a yellow pollen and covers the road surfaces and cars during heavy pollination. However, it has been deemed not to be an allergen, and thus some allergists do not test for it at all. Acacia has been cited as having a role in occupational disease of floriculturists (Ariano et al. 1991). In addition, gum arabic, a natural gum derived from hardened sap of various acacia tree species, such as *Acacia senegal*, has also been described as a cause of occupational allergy (Viinanen et al. 2011). The allergens of Acacia have not been characterized.

Alder

Grey alder can be commonly found in North America as well as in Europe. Adler allergens have been characterized, based on the study of European alder (*Alnus glutinosa*) (Hemmens et al. 1988). There are over 30 allergens that have been identified. But only three of these allergens have been characterized from *A. glutinosa*, although not from *A. incana* (Grey alder). These include *Aln g 1,* which is a 17 kd protein (Breiteneder et al. 1992) and which is homologous to Bet v 1 from the birch tree. Aln g 2 has been categorized as a profilin (Niederberger et al. 1998), while the Aln g 4 allergen has been characterized as being a two EF-hand calcium-binding protein of 9.4 kD molecular weight. Recombinant Aln g 4 has been shown to trigger basophil histamine release and in vivo skin reactions in alder-sensitized patients (Hayek et al. 1998).

Ash

Ash (genus *Fraxinus*) is closely related to olive trees. *Fraxinus* is widely distributed throughout the Northern Hemisphere, including Asia, Europe, and North America (Vara et al. 2016). The European species of ash is *Fraxinus excelsior*, of which multiple allergens have been characterized. In Europe, ash is a major allergen causing allergic rhinitis symptoms in the springtime (Imhof et al. 2014). The major allergen from *Fraxinus excelsior* cross-reacts with the same group allergen of other related trees, such as olive. Fra e 1 is a glycosylated protein of unknown function comprising 15 isoforms (Poncet et al. 2010). Fra e 2 is a profilin of about 14 kD molecular weight (Poncet et al. 2010), and Fra e 3 is a 9 kD protein thought to be a calcium-binding protein (Poncet et al. 2010). Fra e 9, which is homologous to the corresponding allergen from the related olive tree, Ole e 9, is a 1,3-beta-glucanase (Palomares et al. 2005), and finally, Fra e 12 is an isoflavone reductase (Castro et al. 2007).

White ash (*Fraxinus americana*) is native to North America but also present in Europe. Ash trees are medium to large trees. Ash pollen has a distinctive shape in that it is usually four-sided, making its identification by pollen counters fairly easy.

Birch

Birch trees are commonly found in the Northern Hemisphere, in temperate climates. The scientific name for the genus is *Betula*, and it is member of taxonomic order Fagales. Birch trees like cool and moist areas and are often found along the shores of rivers and lakes. Most birch trees are small to medium in size, but some species do grow to be quite large (e.g., yellow birch, *Betula alleghaniensis*). There are currently over 100 known taxa of birch. Birch is often used to make furniture or as firewood or kindling.

Birch pollen allergy is believed to affect some 100 million people globally (Ipsen and Løwenstein 1983; Wiedermann et al. 2001). Birch pollen is a particularly potent allergen, and data suggests that up to 50% of the population in some endemic areas may be allergic. People sensitized to birch pollens are often also sensitized to nuts (Uotila et al. 2016). The white birch tree (*Betula verrucosa*) is one of the more common

species and is the basis for the common allergens for birch. There are four common birch allergens. Bet v 1 is a 17 kd protein of unknown function, although it has been purported to act as a pathogenesis-related protein in plants, specifically PR-10, that is expressed during stress and illness in plants. There are multiple isoforms of Bet v 1, labeled from Bet v 1a to Bet v 1n. The protein possesses ribonuclease activity and shows homology and cross-reactivity with other tree species, including alder, hazel, and hornbeam. Bet v 1 also shows homology with various fruit, seed, and vegetable allergens, including apple, celery, cherry, and peanut, which is believed to be the root cause of oral allergy syndrome, whereby patients present with itchiness around the mouth and throat after eating such fruits, after having been sensitized to Bet v1. The PR-10 pathogenesis-related proteins are believed to have RNase enzymatic activity as well as the ability to bind cytokines (Swoboda et al. 1996; Bufe et al. 1996; Bantignies et al. 2000).

Among the other birch allergens, Bet v 2 is a profilin, Bet v 4 is a polcalcin, and Bet v 6 is an isoflavone reductase. These minor allergens are rarely sole sensitizers but may contribute to cross-reactivity between birch and foods in oral allergy syndrome.

Cedar

The genus known as Cedar includes a variety of small to large evergreen, coniferous trees. Cedars are related to firs and produce a very pleasant scented wood. Most cedars can withstand cold and have been transplanted from their Mediterranean and Western Himalayan origin to other regions with more temperate climates, such as Western Europe, North America, Australia and New Zealand. Cedars are quite hardy as they are able to withstand cold temperatures down to −25 °C, with some species such as the Turkish cedar able to survive even at lower temperatures.

A common species of cedar, white cedar or *Libocedrus decurrens*, is actually a member of the family Cupressaceae. On the other hand, Japanese cedar (*Cryptomeria japonica*) is a member of the Taxodiaceae family. *Libocedrus* is also related to the genus *Thuja*. *Thuja* includes Western red (*Thuja plicata*) and Eastern white (*Thuja occidentalis*) cedars.

In the Southern United States, such as Texas, mountain cedar (*Juniperus ashei*) is well known as a species that pollinates in the wintertime (December–January). Many allergens have been defined in Japanese cedar. But Cry j 1 and Cry j 2 are the most common. Cry j 1 is a glycoprotein similar to pectate lyase. Cry j 2 is a polygalacturonase. Both have molecular weights about 45 kD. Another major allergen of Japanese cedar, Cry j 3, is a smaller protein of 19–27 kD and is a thaumatin-like protein. Other allergens found in Japanese cedar include chitinases, isoflavone reductase-like proteins, and lipid transfer proteins (Fujimura and Kawamoto 2015). Studies on desensitization to Japanese cedar using oral immunotherapy are ongoing (Wakasa et al. 2013).

Cypress

Arizona cypress (*Cupressus arizonica*) is native to the southwest United States and Mexico, but it has also been exported to Europe. It thrives in dry soil, requiring only 10–12 inches of water annually. Arizona cypress is a medium-sized tree that grows to up to 60 feet high. Allergens of cypress include Cup a 1, considered a major allergen of 43 kD molecular weight (Di Felice et al. 1994; Di Felice et al. 2001). Other allergens are mostly glycoproteins and include Cup a 2 (Di Felice et al. 2001); Cup a 3, a 21 kDa protein (Palacín et al. 2012); and a calcium-binding protein, Cup a 4 (de Coaña et al. 2010). The Italian cypress (*Cupressus sempervirens*) allergen Cup s 1 is a pectate lyase (Arilla et al. 2004), and Cup s 3 is homologous to other pathogenesis-related group 5 (PR-5) proteins (Togawa et al. 2006).

Elm

There are six genera of the elm family (Ulmaceae), with *Ulmus*, *Zelkova*, and *Planera* (Weber 2004) being more common. *Ulmus* is the most common elm genus in the United States. Elm is native to the United States and Europe (Torri et al. 1997; Kosisky and Carpenter 1997), although there are also transplanted species, such as Chinese elm, which is native to China, Korea, and Japan. Elm trees grow by streams and in damp

places of regions of temperate climate. Flowers develop in winter and early spring, and the season may vary from region to region. There is a report on the association of increase hospitalizations for asthma with daily increase in elm pollen counts in urban Canada (Dales et al. 2008). The individual allergenic proteins in elm are currently not commercially analyzed by component-resolved diagnostics.

Eucalyptus

Eucalyptus are large trees that grow quickly; a common species is *Eucalyptus globulus*. Eucalyptus is known to be able to cause asthma exacerbations (Galdi et al. 2003). The commonly used Eucalyptus oil is extracted from the fresh leaves of this species and can cause toxicity (Darben et al. 1998; Schaller and Korting 1995). Symptoms can include slurred speech, muscle weakness, and ataxia which may progress to loss of consciousness. It can also cause contact dermatitis (Gyldenlove et al. 2014). No allergens from this plant have yet been characterized.

Mango

Allergens from the mango tree, *Mangifera indica*, include Man i 1, a major allergen 40 kD in size which functions as a glyceraldehyde 3-phosphate dehydrogenase (GAPDH). It shares 86.2% homology in amino acid sequence with the wheat GAPDH. This particular allergen has been cloned. Other allergens include a 30 kD protein named Man i 2 (Dube et al. 2004) and a minor allergen, Man i 3, which is a profilin (Song et al. 2008). An additional 27 kD protein has been associated with anaphylactic reactions to mango (Renner et al. 2008). Low-abundance mango allergens have been shown to be cross-reactive with banana species (Cardona et al. 2018). Mango is an evergreen tree with a long history. It is in the same family as cashew, pistachio, and sumac.

Maple/Box Elder

Box elder is related to the maple family and belongs to the genus *Acer*. The scientific name for box elder is *Acer negundo*. Maples in general are abundant in northern, temperate climates. There are over 125 species of Acer. Box elder is a medium-sized tree and is fast growing. It is a known trigger for exacerbations of asthma and allergic rhinitis (Sousa et al. 2012). To date no allergens have been characterized (Ribeiro et al. 2009). Maple is considered to be a major allergenic tree in many locales.

Mulberry

There are about ten species of mulberries. Mulberries can be either a tree or a shrub and can be either monoecious or dioecious. Mulberries originated from Asia but can be found all over the world now. There are two species found native to North America. Mulberry trees are medium trees, with a light bark and a wide, round canopy. Flowers are small, as are the pollen grains. While leaves from white mulberries (*Morus alba*) can be used as food for silkworms, the red mulberry (*Morus rubra*) is cultivated for its fruits. Mulberry is an important allergen that causes significant symptoms of allergic rhinitis, allergic conjunctivitis, and asthma (Navarro et al. 1997; Targow 1971). Like sumac, the leaves of the mulberry tree have been reported to cause a form of contact urticaria (Muñoz et al. 1995). No allergens from this plant have yet been characterized.

Oak

Oak belongs to the order Fagales, the family Fagaceae, and the genus *Quercus*. *Quercus* is a very large genus with over 500 species. Some of the more common species for which allergenic extracts have been developed include Virginia live oak, California black oak, Oregon white oak, and Valley oak.

Oak can be either trees or shrubs. The widespread sensitization to oak observed throughout many regions of the world reflects the near ubiquitous presence of various oak species, whether they be native to a particular region or transplanted. For example, Virginia live oak is native to the Southeastern United States but can also be found in Cuba and Mexico. White oak is even more common than live oak. Oak sensitization has been found to occur in Europe, Asia, and South Africa. *Quercus alba* is a common species found in many locales. Oak pollen allergies may

cross-react with birch allergens Bet v 1, 2, and 4 (Egger et al. 2008). Recently, a major allergen from Mongolian oak, which is found in Korea, was characterized. The allergen, Que. m 1 (from the species *Quercus mongolica*), has been reported to be homologous to pathogenesis-related 10 (PR-10) like protein (Lee et al. 2017).

Olive

Olive is a very important allergen that is widely cultivated in many parts of the world. It belongs to the family Oleaceae. This family includes olive (*Olea*), ash (*Fraxinus*), privet (*Ligustrum*), and lilac (*Syringa*). Olive is native to the Mediterranean area, but it is grown widely in other parts of the world, including Northern California, and in the dry climates of the Western States. It is a well-characterized allergen, and over 20 specific allergens have been identified. The pollination season varies depending on the region, but the further north one goes, the later the season seems to last. *Olea europaea* is the main species of olive tree of which Ole e 1, Ole e 4, and Ole e 7 are considered major allergens. Ole e 1 is a trypsin inhibitor, and Ole e 7 is a lipid transfer protein (Villalba et al. 1990). Ole e 9, a 1,3 beta-glucanase, is also a major allergen of olive (Castrillo et al. 2006; Duffort et al. 2006; Palomares et al. 2006a; b). Ole e 1 is homologous to Fra e 1, and patients exhibit cross-reactivity between the two (Palomares et al. 2006c).

Pine

Pinus radiate is a common species of the pine tree, from the family Pinaceae. Other pine species include *Pseudotsuga taxifolia* and *Picea excelsa* and *Pinus strobus*, corresponding to the well-known trees Douglas fir, spruce, and white pine. All of these are commonly harvested for Christmas trees so they make their way into homes and other indoor environments. Certain species of pine, including white pine, are native to North America, but there are over 100 species distributed throughout both hemispheres. Five allergenic proteins of 82 kD, 67 kD, 54 kD, 44 kD, and 38 kD have been identified from pine trees (Fountain and Cornford 1991). As an allergen, pine is not considered to be one of the more prevalent or more potent allergens (Freeman 1993; Bousquet et al. 1984).

Sycamore

Maple leaf sycamore (London plane tree or hybrid plane) is *Platanus acerifolia*, a hybrid of Oriental plane tree (*P. orientalis*) and American sycamore (*P. occidentalis*) (Weber 2004). They are planted along the streets in London and in Philadelphia. The tree can reach 30 meters in height. Several allergens that have been characterized from *Platanus acerifolia*, including Pla a 1, an invertase inhibitor of molecular weight 18 kD (Asturias et al. 2006). Other allergens include Pla a 2, a polygalacturonase of 43 kD (Asturias et al. 2002), a 10 kD lipid transfer protein Pla a 3 (Asturias et al. 2002), and a profilin with the designation Pla a profilin (Enrique et al. 2004). Sycamore maple belongs to the maple family, and its scientific name is *Acer pseudoplatanus*.

Walnut

Walnut trees belong to the genus *Juglans*, a member of the family Juglandaceae. They are found throughout the United States and other regions including Asia, the Middle East, and Western and Eastern Europe. Walnut trees generally pollinate between April and June, but the season can begin earlier in the year in the Southeastern United States. The spores can be circular or triangular and are generally between 30 and 40 microns in diameter. Two walnut species, *Juglans regia* and *Juglans nigra*, are common in the human diet and can be food allergens as well. Five allergens have been identified in *J. regia*. Jug r 1 is a 2S albumin, Jug r 2 is a vicilin, Jug r 3 is a non-specific lipid transfer protein, Jug r 4 is a legumin, and Jug r 5 is a profilin. Two allergens have been identified in *J. nigra.* Jug n 1 is a 2S albumin, and Jug n 2 is vicilin. All except Jug r 5 have been shown to cause severe and systemic allergic reactions (Costa et al. 2014). Two allergens, Jug r 1 (a storage protein) and Jug r 3 (a lipid transfer protein), have been identified to cause food allergy reactions including anaphylaxis (Sato et al. 2017).

Willow

Willow is a member of the family of trees known as Salicaceae. Salicaceae actually includes poplars, cottonwood, aspen, and willow trees. Willow belongs to the genus *Salix*, which also includes 400 species of shrubs and trees including willows, osiers, and sallows. Willows like to grow in the Northern Hemisphere in colder regions. From a seasonal standpoint, willow trees are early bloomers, sometimes heralding the arrival of early spring. While willow is an important allergenic tree, the specific allergens have not been characterized. Willow pollen is anemophilous, or wind borne, and is small, between 18 and 21 microns in diameter, depending on the species. Wind-borne pollens, as opposed to insect borne or entomophilous pollens, tend to be more relevant as triggers of allergies because they travel for longer distances.

3.4.1.2 Grass Pollen

Grass allergy is one of the more common types of seasonal allergy. Symptoms include rhinorrhea, nasal congestion, sneezing, itching of the eyes and nose, and eye inflammation and drainage. There are thousands of grass pollen species throughout the world. Grass pollen seasons tend to be short, lasting 2–3 months, but this can vary significantly with climate, and longer seasons can be present in areas where there is a lot of rainfall. A study in the Netherlands showed that patients tend to have more severe symptoms early in the grass pollen season (de Weger et al. 2011). This can have an impact on the timing of studies done to assess effectiveness of treatment. There are three major families of grass pollen with a high degree of cross reactivity within each family.

The Poaceae Family

Pooideae is the largest subfamily with the Poaceae family, comprising 3850 species. Members of this family include Timothy grass, sweet vernal grass, meadow fescue, perennial rye, June grass, Kentucky bluegrass, orchard grass, redtop grass, velvet grass, canary grass, and the cereal grains including wheat, rye, and barley. The second family is Chloridoideae, which includes Bermuda grass, lovegrass, and the prairie grasses, including salt grass, grama grass, and buffalo grass. The third family is called Panicoideae. This is the second largest family of *Poaceae* and comprises over 3250 species. Members of this family include Johnson grass, Bahia grass, sugarcane, and corn. There is less cross-reactivity within members of this group compared to members of the other two groups. Other subfamilies of Poaceae can also be important from a geographical perspective. For example, pampas grass, a member of the Danthonioideae subfamily, is endemic to South America and is a very attractive grass but is invasive as well and often takes over flower beds. It can also be found in Florida.

Bahia

Bahia grass, or *Paspalum notatum*, is a perennial grass considered to be a Southern subtropical grass. A major allergen of Bahia grass is Pas n 1 (Davies et al. 2011a; Drew et al. 2011). It has been cloned and sequenced. Recombinant Pas n 1 shows 85% homology to the maize pollen group 1 allergen. rPas n 1 can activate basophils and competitively inhibit serum IgE activity with a 29 kD band of the grass pollen extract. It can also react with IgE from Bahia allergic patients (Davies et al. 2008). Another study reported a 55 kD protein allergen, designated Pan n 13, that cross-reacts with the group 13 allergens of maize pollen and Timothy grass (Davies et al. 2011b).

Bermuda

Bermuda grass, or *Cynodon dactylon*, is an evergreen perennial grass that is found in many regions around the world, especially in regions with warm climate. Three allergens have been characterized to date. Its major allergen is Cyn d 1 (Han et al. 1993) which is a group 1 glycoprotein allergen belonging to the β-expansin family (Drew et al. 2011). Another major allergen is a 12 kD allergen, designated as Cyn d 7 (Suphioglu et al. 1997) that shares sequence similarity with other pollen allergens such as Bet v 4 from birch. A profilin, Cyn d 12, is the third identified allergen that also shares some epitopes with sunflower profilin (Asturias et al. 1997a). Bermuda grass is often used on greens of golf courses, the other grass being Bentgrass. Bentgrass is preferred in

cooler climates, but Bermuda is more heat tolerant and is often found in warmer regions.

Johnson

Johnson grass, or *Sorghum halepense*, is a perennial grass that generally grows as a weed along with multiple crops and is considered to be one of the more invasive weeds in the world (Holm et al. 1977). Johnson grass was originally cultivated in South Asia, Southern Europe, and North Africa. Among those characterized, major allergens include a group 1 grass allergen known as Sor h 1 (Smith et al. 1994), a calcium-binding protein known as Sor h 7 (Vallier et al. 1992a; Wopfner et al. 2007), and a profilin identified as Sor h 12 (Yman 1981). Johnson grass allergens have also been shown to have cross-reactivity with some Bermuda grass allergens (Smith et al. 1994).

Meadow Fescue

Meadow fescue, or *Festuca pratensis*, is primarily used as a pasture grass, but it can also be a turf grass. It is native to Western Asia and Northern Europe and grows alongside roads and in meadows, hence its name. It is a relatively short grass and is used in lawns worldwide. Fes p 1 is a Group 1 grass allergen (Hiller et al. 1997) and is identified as the major allergen for meadow fescue. Other identified allergens include a group 4 and 60 kD grass allergen, Fes p 4 (Gavrović-Jankulović et al. 2000), Fes p 5 which is a ribonuclease and a Group 5 grass allergen (Matthiesen and Løwenstein 1991), and finally, Fes p 13 which is a polygalacturonase and a Group 13 grass allergen (Petersen et al. 2001). Meadow fescue usually enjoys temperate climates.

Orchard

Dactylis glomerata, commonly known as cocksfoot or orchard grass, is a perennial grass found in temperate regions of Africa, Australia, North America, and South America. It is also used as a forage grass. Dac g 4 is a major 59 kD allergen (Leduc-Brodard et al. 1996). Other characterized allergens include Dac g 1 (Mourad et al. 1988), Dac g 2 (Roberts et al. 1992), Dac g 3 (Guérin-Marchand et al. 1996), and Dac g 5 (van Oort et al. 2001). Orchard grass also shares epitopes with group I (Mourad et al. 1988) and group II grass allergens (Roberts et al. 1992) of perennial rye.

Perennial Rye

Lolium perenne, commonly known as perennial rye or just ryegrass, is native to Europe and is highly valued for its erosion control properties and as a forage grass. Perennial ryegrass is one of the predominant grass pollens causing allergic rhinitis, allergic conjunctivitis, and asthma. Ryegrass is the pollen that is mainly attributed to "thunderstorm asthma," a condition whereby thunderstorm downdrafts drive ruptured ryegrass pollen particles of approximately 3 microns in diameter to ground, breathing zone level, mimicking conditions during an allergen challenge study, and leading to rapid progression of allergic and asthma flares (Thien et al. 2018). Lol p 1 (Perez et al. 1990) and Lol p 2 (Tamborini et al. 1995) have been characterized as major allergens of perennial ryegrass. Other allergens include Lol p 3 (Ansari et al. 1989), Lol p 4 (Jaggi et al. 1989), Lol p 5, Lol p 9 (Blaher et al. 1996), Lol p 10 (Ansari et al. 1987), and Lol p 11, which is a soybean trypsin inhibitor (van Ree et al. 1995). Studies show that Lol p 5 has two isoforms, identified as Lol p 5A and Lol p 5C, respectively (Suphioglu et al. 1999; Klysner et al. 1992).

Timothy

Timothy grass, or *Phleum pratense*, is one of the most common grasses and is often considered the representative grass of the Pooideae subfamily, especially when conducting investigations for immunotherapy (including sublingual immunotherapy). It is native to Europe, with the exception of the Mediterranean region, as well as Northern Asia and North Africa (Gavrović et al. 1997). It is considered a pasture grass, having been introduced to the New World regions in America and Australia, and is a very highly used fodder for animals, including small pets such as bunnies. It is therefore most commonly found in meadows or fields but is also commonly seen on roadsides. The proteins in Timothy grass pollen have been characterized in detail. Allergens characterized to date include Phl p 1, a major group 1 allergen

(Suck et al. 1999); Phl p 4 (Fischer et al. 1996); Phl p 5, which is a major group 5 allergen (Flicker et al. 2000); a 11–12 kD protein identified as Phl p 6 (Vrtala et al. 1999); a calcium-binding protein known as Phl p7 (Niederberger et al. 1999); a profilin identified as Phl p 12 (Asturias et al. 1997b); and finally, Phl p 13 (Suck et al. 2000). The group 13 grass pollen allergens are polygalacturonases. The group 11 allergen Phl p 11 is a 20 kD protein that has been characterized and shown to have allergenic activity (Marknell DeWitt et al. 2002). Many of the grass allergens, including Timothy, have been standardized for skin testing and have also been developed as sublingual immunotherapy that is commercially available and FDA approved, such as Grastek® and Oralair®.

Redtop

Redtop is one of the common names of *Agrostis stolonifera*. As with Bermuda grass, red top is actually a type of Bentgrass (see above) and therefore is used on golf course greens and lawns and as turfs. It is a very hearty grass and can grow in a variety of soil conditions and climates. No allergens from this plant have been characterized yet, although a group 5 allergen (Agr s 5) has been identified.

The list of grasses described above is by no means comprehensive. Other common grasses include Kentucky bluegrass, June grass, and salt grass. In most cases, these grasses will cross-react within the same group, so not all grasses needed to be tested for or included in an immunotherapy mix.

3.4.1.3 Weeds

Cocklebur

Cocklebur, or *Xanthium commune*, is an annual weed that grows to about 1.5 meters tall. It is native to the Northern Hemisphere, having been found in Asia, Europe, and the North and Central Americas. Cocklebur flowers are monoecious, and the plant is self-fertilizing. Pollinating seasons usually begin in April and continue through October. Cocklebur belongs to the family Asteraceae and therefore is related to ragweed. However, there doesn't appear to be much allergenic cross-reactivity with ragweed. Allergens have not been characterized, although two, designated as Xan lb. and Xan Vla, have been identified.

English Plantain

English plantain, ribwort or *Plantago lanceolata*, is an erect perennial with a base of leaves. The plants are found mostly in temperate regions but can actually grow anywhere. Pollen season for English plantain ranges from April to about August. Plantains are commonly found on roadsides as flat leaves at the base of a stalk that will grow to be 0.3–0.5 m tall. The major allergen for English plantain is Pla l 1, a 17–20 kD protein, which acts as a trypsin inhibitor. Trypsin inhibitors are considered to be pathogenesis-related proteins (PR) (Calabozo et al. 2001). Other allergens include Pla l cytochrome C (Matthews et al. 1988a) and Pla l CBP, which are a calcium-binding protein (Grote et al. 2008). English plantain is a significant allergen in many parts of the world, causing seasonal allergic rhinitis and conjunctivitis as well as asthma exacerbations (Garcia-Gonzalez et al. 1998; Matthews et al. 1988b; Spieksma et al. 1980; Wuthrich and Annen 1979).

Mugwort

Mugwort is a common weed which originated from Europe and Asia. It often grows on roadsides and by old buildings and invades nurseries and lawns. Mugwort belongs to the family Asteraceae (Compositae). The Latin name for mugwort is *Artemisia vulgaris*. Mugwort is related to sagebrush (*A. tridentate*), wormwood (*A. absinthium* or *A. annua*), and tarragon (*A. dracunculus*) (Yman 1981; Katial et al. 1997; Hirschwehr et al. 1998; Leng and Ye 1987). Allergens from mugwort that have been characterized include Art v 1, which is a defensin of size 28 kD (Oberhuber et al. 2008a), Art v 2 (Arilla et al. 2007), Art v 3 (Gadermaier et al. 2007), Art v 4 (Oberhuber et al. 2008a), Art v 5 (Wopfner et al. 2005), Art v 6 (Wopfner et al. 2005), Art v 60 kD (Lombardero et al. 2004), and Art v 47 kD (Nilsen and Paulsen 1990). Interestingly, artemisinin, the active

ingredient in sweet wormwood (*Artemisia annua*), has been used successfully in the treatment of malaria. This treatment has been credited with saving over five million lives worldwide and won its discoverer the Nobel Prize in Physiology or Medicine in 2015 (Andersson et al. 2015).

Nettle

Nettle can be found worldwide and likes to grow in nitrate-rich soils. Like mugwort, it is often used in herbal remedies. It is fast growing and is dioecious and wind pollinated. The nettle pollen season is between April and October. The scientific name of Nettle is *Urtica dioica*, and it belongs to the family Urticaceae. It is a frequent cause of allergic rhinoconjunctivitis and asthma (Wuthrich and Annen 1979). Allergens from nettle have not yet been characterized.

Pigweed

Common pigweed or *Amaranthus retroflexus* is a member of a large family of weedy herbs consisting of 40 genera and up to 475 species (Wurtzen et al. 1995). It is widely distributed worldwide and is a significant trigger of asthma and allergic rhinoconjunctivitis (Calabria et al. 2007; Calabria and Dice 2007). Allergens of pigweed have not been characterized although two allergens of 14 kD and 35 kD have been reported. Pigweed cross-reacts with lamb's-quarter, or *Chenopodium album (*Lombardero et al. 1985*)*.

Ragweed

Ragweed is a group of weeds that are commonly found throughout the world. Common ragweed, also known as short ragweed or annual ragweed, scientific name *Ambrosia elatior* or *Ambrosia artemisiifolia*, is native to North America. It is one of the more common causes of allergic rhinitis and asthma in Europe, Asia, and the United States. Ragweed is one of only a handful of allergens with a commercially available, FDA-approved sublingual immunotherapy agent, while the others being grass mixture, Timothy grass, and dust mite (Creticos and Pfaar 2018; Nelson 2018; Pfaar and Creticos 2018). *Ambrosia* is nearly ubiquitous, mostly seen by roadsides, woodlands, dry fields, and pastures. The ragweed season in the Eastern United States is generally from August to October, but there is a very short peak from mid-August to September. The highest pollen counts for ragweed are in the middle of the day. Ragweed pollen constitutes an abundant, potent allergen which is one of the most important allergens among atopic individuals with allergic rhinitis or asthma (Pollart et al. 1989).

The allergens of ragweed have been extensively studied and characterized. These include Amb a 1, which is a pectate lyase of 38 kD in size (Wopfner et al. 2008; Oberhuber et al. 2008b); Amb a 2, also 38 kD, and another pectate lyase (Kuo et al. 1993); Amb a 3 (Kurisaki et al. 1986; Atassi and Atassi 1986); and Amb a 5 (Pilyavskaya et al. 1995; Mole et al. 1975; Zhu et al. 1995; Huang and Marsh 1991; Huang et al. 1991; Ghosh et al. 1991; Marsh et al. 1991; Zwollo et al. 1991), small proteins of 9 kD and 5 kD in size, respectively. Amb a 6 is also a small protein of 10 kD and is a lipid transfer protein (Marsh et al. 1987). The other proteins are also small proteins and function as profilin, calcium-binding proteins, and a cystatin protein inhibitor (Vallier et al. 1992b; Liebers et al. 1996; Rogers et al. 1993). Allergens from ragweed have been found to cross-react with each other and with pollens from mugwort or *Artemisia vulgaris*. Plant profilin is considered a panallergen, and on this basis, ragweed does cross-react with other pollens that have allergens functioning as profilins. Ragweed pollen also cross-reacts with yellow dock or sheep sorrel (Shen et al. 1985a).

Ragweed pollen is a common sensitizer in oral allergy syndrome, leading to mouth itching and tingling associated with ingestion celery, mango, carrot, watermelon, and other fruits (Paschke et al. 2001; Dechamp and Deviller 1987; Enberg et al. 1987; Caballero and Martin-Esteban 1998). Ragweed can also act as a skin sensitizer, causing a type of contact dermatitis (Fisher 1996).

Russian Thistle

Russian Thistle (or Saltwort), is *Salsola kali*, Russian Thistle has a widespread distribution, favors semiarid to arid climates and places such as sandy shores or beaches. It can even grow in the desert and is prevalent in dry climates such as the Middle

East. Several allergens have been identified from Russian thistle. Sal k 1 is a major allergen, of 43 kD in size, and functions as a methylesterase (Carnés et al. 2003). While reactivity to Sal k 1 is observed in most people allergic to Russian thistle, this is not the case for some of the lesser allergens, including Sal k 2 (Civantos et al. 2002), Sal k 3 (Assarehzadegan et al. 2011), Sal k 4 (Assarehzadegan et al. 2010), and Sal k 5 (Castro et al. 2008). Sal k 2 has been characterized as a protein kinase, while Sal k 3 is a methionine synthase. Sal k 4 is a profiling of 14 kD in size, while Sal k 5 is related to Ole e 1. Russian thistle, like many other trees, weeds, or grasses, has been implicated in oral allergy syndrome. The dried tumbleweed that one may see rolling around in the wind is derived from Russian thistle, among other weeds.

Sage

Sage is an herbal plant with the scientific name *Salvia officinalis*. Sage is the basis for the common spice which is used to flavor food. Sage has also been used in soaps and perfumes. *Salvia officinalis* is a small herbaceous shrub which originated from the Mediterranean (Yman 1981; Daniela 1993). But *Salvia divinorum* or sacred sage is native to Central America. Allergens from sage have not been characterized, but sage has been implicated in oral allergy syndrome or latex-fruit syndrome.

Scotch Broom

Scotch broom belongs to the family Fabaceae. The scientific name for Scotch broom is *Cytisus scoparius*. It is native to Europe and introduced into other countries such as the United States, South Africa, and the Southern Pacific. It is a small shrub and considered an invasive plant. The allergens from sage have not yet been characterized.

Sheep Sorrel

A common perennial herbal plant that originated in Asia and Europe, sheep sorrel or *Rumex acetosella*, is an invasive weed that has been transplanted to the United States. The plant is wind pollinated in the fall. It is commonly found in lawns and pastures and even on roadsides. It is known as a significant trigger for allergic rhinoconjunctivitis and asthma (Gniazdowska et al. 1993; Solomon 1969; Larenas et al. 2009; Dursun et al. 2008; Liang et al. 2010). Allergens from sheep sorrel have not been characterized, but sheep sorrel is an important allergen in the Northern Hemisphere.

Yellow Dock

Yellow dock (*Rumex crispus*) belongs to the family Polygonaceae. Therefore it is related to sheep sorrel. Pollination season is from June to October. Although several allergenic proteins have been identified, with molecular weights of 40, 38, 24, and 21 kD, none of these allergens have been fully characterized (Shen et al. 1985b).

3.4.1.4 Molds

Fungi, with the exception of mushrooms, are collectively called molds. Molds are saprophytes in nature, living on the decomposition of organic materials and are also occasional human pathogens. Molds can be found indoors and outdoors under moist environment. Molds that are known to cause allergies include the phylum Ascomycota such as *Aspergillus* and *Penicillium*, the phylum Zygomycota such as *Mucor* and *Rhizopus*, and the phylum Basidiomycota such as *Rhodotorula* and *Ustilago* (Levetin et al. 2016).

Phylum Ascomycota

The phylum *Ascomycota* is highly diverse and includes unicellular organisms to well-defined fruiting bodies that produce ascospores. Although aerial ascospore count is higher after the rain or during the season of high humidity, no ascospore allergens have been characterized.

Alternaria

Alternaria is a genus of ascomycete fungi. It is generally considered a saprophyte and plant pathogen. Although it is mainly an outdoor fungus and is considered a dry air spora, *Alternaria* allergens have been detected indoor (Peters et al. 2008). *Alternaria alternata* is known to be associated with severe asthma (Bush and Prochnau 2004). To date, 17 IgE-reactive *Alternaria alternata*

proteins of diverse biochemical and functional properties have been identified, of which Alt a 1 is considered a major airborne fungal allergen and a marker of primary sensitization to *Alternaria alternata (*Postigo et al. 2011*)*. The other *Alternaria* allergens include heat shock protein 70 (Alt a 3), disulfide isomerase (Alt a 4), ribosomal protein P2 (Alt a 5), enolase (Alt a 6), flavodoxin YCP4 protein (Alt a 7), mannitol dehydrogenase (Alt a 8), aldehyde dehydrogenase (Alt a 10), acid ribosomal protein P1 (Alt a 12), glutathione transferase (Alt a 13), manganese superoxide (Alt a 14), and vacuolar serine protease (Alta 15) (Gabriel et al. 2016). Alt a NTF2 is identified as nuclear transport factors, and Alta TCTP is identified as translationally controlled tumor proteins. The functions of the other *Alternaria* allergens (Alt a 2, Alt a 9, Alt a 70 KD) are unknown.

Aspergillus

Aspergillus belongs to the phylum of Ascomycota and is ubiquitous in nature. Several species of *Aspergillus* have been shown to be allergenic; they include *Aspergillus fumigatus*, *Aspergillus flavus*, *Aspergillus niger*, and *Aspergillus oryzae*.

Aspergillus fumigatus, also known as the common mold, is a major cause of allergic bronchopulmonary aspergillosis (ABPA). Currently, over 20 allergens of *A. fumigatus* have been reported. Five recombinant aspergillus allergens (rAsp f1-f4 and f6) are commercially used for diagnosis of allergic aspergillosis. *Aspergillus* is also a common culprit in allergic fungal sinusitis (AFS). These patients have peanut butter like mucous in their sinuses which is difficult to clear.

Aspergillus flavus, also known as cereal mold, is a saprophyte that grows on cereal grains, tree nuts, and legumes. It can also be found in soil. *Aspergillus flavus* is notorious for its production of a toxin called aflatoxin which causes acute hepatitis and liver cancer. Asp fl 13, a 34 KD alkaline serine protease, has been identified as a major allergen (Chou et al. 1999).

Aspergillus niger, also known as black mold, is ubiquitous in nature. It can be found in many different habitats such as soil, rotting fruits, and decaying substances. To date, three *Aspergillus niger* allergens have been identified. Asp n 14 is a beta-xylosidases of about 105 KD (Sander et al. 1998), Asp n 18 is a vacuolar serine protease of 34 KD, and Asp n 25 is 3-phytase B of 66–100 KD.

Aspergillus oryzae, also known as rice mold, has been widely used in the fermentation of soybeans in making soya sauce and rice to make sake. Two *Aspergillus oryzae* proteins, the 34 KD alkaline serine protease (Asp o 13) and the 53 KD TAKA-amylase A (Asp o 21), have been reported as allergens (Baur et al. 1994; Shen et al. 1998).

Phylum Basidiomycota

Basidiomycota is the second largest phylum of fungi and are best characterized by their fruiting bodies that produce sexual spores called basidiospores which are released to the air during high humidity. The mushrooms described below under food allergens are part of this group of plants. *Basidiospores* have strong asthma-environmental association, with spikes in emergency department visits. Two basidiospore allergens have been described in *Rhodotorula mucilaginosa*, one is an n enolase, and the other is a serine protease (Chang et al. 2002; Chou et al. 2005). In addition, *Ustilago* is a smut fungus that produces airborne smut spores. Allergic reactions to grain smuts and corn smut (*Ustilago maydis*) extract have been reported (Santilli Jr. et al. 1985).

Cladosporium

Cladosporium is commonly found in areas with moisture, humidity, and water damage, producing spores that are easily spread in the air. The scientific name is *Cladosporium herbarum*. The old name of *Cladosporium* was *Hormodendrum*. Two proteins Cla c 9 of 36 KD and Cla c 14 of 36.5 KD molecular weight have been identified as *Cladosporium cladosporioides* allergens. Cla c 9 is a vacuolar serine protease, and Cla c 14 is a transaldolase. Ten allergens have been identified in *Cladosporium herbarum*: Cla h 5 is an acid ribosomal protein P2, Cla h 6 is an enolase, Cla h 7 is a YCP4 protein, Cla h 8 is a mannitol dehydrogenase, and Cla h 9 is a vacuolar serine protease (Achatz et al. 1995; Pöll et al. 2009; Simon-Nobbe et al. 2006). The molecular

identities of Cla h1, Cla h 2, Cla h 3, Cla h 10, and Cla h 12 remain unknown (Bowyer and Denning 2007; Kurup and Vijay 2008).

Epicoccum

Epicoccum purpurascens is a fungus which is a frequent sensitizer for allergies and asthma. It is an important outdoor mold and is considered a dry air spora. It is often found on dying substrates, including spoiled vegetables and fruits, compost, and even human skin or sputum. The allergens in *Epicoccum* have not been characterized (Lehrer 1983; Chapman and Williams 1984; Karlsson-Borgå et al. 1989; Guill 1984).

Fusarium

No allergens have been functionally characterized, but a few allergens of molecular weight 14, 19, 35, 45, 50, and 70 kD occur commonly among three *Fusarium* species: *F. solani*, *F. equiseti*, and *F. proliferatum* or *F. moniliforme* (Horner et al. 1995). *Fusarium* is a large genus with over 100 species (Verma and Gangal 1994; Pumhirun et al. 1997). It is a soil fungus that can be found on decaying plants and grains worldwide. Fusarium is a significant allergen and a trigger for asthma and allergic rhinitis (Mohovic et al. 1988; Enríquez et al. 1997). In addition, it is a known culprit for onychomycoses (Ninet et al. 2005).

Helminthosporium

A common mold found on cereals, grains, sugarcane, and soil is *Helminthosporium*. These spores are found worldwide and are considered a dry air spora, which release on dry days. In a study of 110 pediatric asthmatic and/or allergic rhinitis subjects in the Mid-Atlantic United States, 38% had positive skin testing to *Helminthosporium* (Hendrick et al. 1982; Al-Doory and Domson 1984). A common species is *H. halodes*. The allergens of *Helminthosporium* have not been characterized.

Mucor

Mucor is a large genus. *Mucor racemosus* was identified in soil samples nearly 140 years ago. It is found worldwide, growing on animal waste, decaying vegetables, and grains. It can be found at high elevations. *Mucor* are also found indoors and has been isolated from dust samples. It is a significant trigger of allergy symptoms (Mohovic et al. 1988; Dezfoulian and De la Brassinne 2006). The allergens of *Mucor* species have not yet been characterized.

Penicillium

Penicillium is of industrial importance in food and drug production. Penicillium represents the genus, and there are multiple varieties on the food staple, such as *P. herbarum*, *P notatum*, etc. The most well-known species is *P. chrysogenum* which produces penicillin, a molecule that is used as an antibiotic. Penicillia are ubiquitous soil fungi that prefer cool and moderate climates. *Penicillium* species can also be found in the air and dust of homes and public buildings. The following allergens have been identified from *P. chrysogenum*: Pen ch 13, a 32 kD protein is an alkaline serine protease (Lai et al. 2004); Pen ch 18, a 34 kD protein is a vacuolar serine protease (Shen et al. 2003); and Pen ch 20, a 68 kD protein is a N-acetylglucosaminidase (Shen et al. 1992).

Rhizopus

Rhizopus nigricans also known as bread mold is one of the more common *Rhizopus* species found worldwide. Its spores are released in hot, dry weather. It feeds on old food, decaying fruits and vegetables, and is also found in soil. Interestingly, it is also found in storage facilities and libraries (Zielińska-Jankiewicz et al. 2008). The spores contain allergenic proteins with 31 distinct allergens (Bush et al. 2006). However, no allergens have been characterized. In addition, a heat shock protein, Hsp70, has been isolated (Černila et al. 2003). *Rhizopus* is often blamed for occupational asthma in sawmills and food handlers of strawberries, peaches, corn, and peanuts (Zhang et al. 2005; O'Connell et al. 1995; Wimander and Belin 1980; Belin 1987; Belin 1980; Hedenstierna et al. 1986; Rydjord et al. 2007).

Stachybotrys

Stachybotrys chartarum and *S. alternans* is the black mold found in homes on substrates with a

high cellulose content, such as Sheetrock, wood, and ceiling tiles. It is usually found in areas of high humidity. Contrary to folklore, there is no such thing as toxic black mold or any human disease that has been blamed on mycotoxins. Mycotoxins have to be ingested in large quantities to be harmful to humans. There is no good scientific evidence that demonstrates that airborne *Stachybotrys* causes any of the vague symptomatology associated with the so-called toxic mold syndrome or sick building syndrome (Rudert and Portnoy 2017). *Stachybotrys* species have not been shown to be a significant allergen.

Stemphylium

Stemphylium herbarum is a mold which is common in subtropical and temperate regions of the world. Other members of the genus *Stemphylium* include *S. solari* and *S. botryosum.* They grow on vegetables and plants and are thus a plant pathogen. They can be commonly found on tomatoes and decaying vegetations in forested areas. The allergens of *Stemphylium* have not been characterized, but it is known that they share cross-reactivity with *Alternaria*, *Curvularia*, and *Aspergillus* species (Agarwal et al. 1982; Schmechel et al. 2008; Schumacher et al. 1975; Wijnands et al. 2000; Bonilla-Soto et al. 1961). *Stemphylium* are known to be a significant inducer of asthma and allergy symptoms in sensitized individuals (Karlsson-Borgå et al. 1989; Prince et al. 1971). Angioedema has been reported from exposure to *Stemphylium* (Gaudibert 1971).

Ulocladium

Ulocladium chartarum is a mold that is related to *Alternaria* and is found in soil and on decaying vegetation. It is ubiquitous and can function as food spoilers or plant pathogens. It has been demonstrated to be a significant allergen in inner-city, low socioeconomic areas with high population density. Allergens of *Ulocladium* have not been characterized. Like *Fusarium*, *Ulocladium* has also been blamed for skin fungal infections (Hilmioğlu-Polat et al. 2005; Altmeyer and Schon 1981; Teresa Duran et al. 2003; Badenoch et al. 2006).

Phylum Zygomycota

There are approximately 1000 species within this phylum. The subphylum *Mucoromycota* is known for producing airborne sporangiospores.

3.4.2 Indoor Allergens

3.4.2.1 Dust Mites

Dust mites of the family Pyroglyphidae are microscopic bugs that feed on dead skin shed from animals, including humans. They are members of class Arachnida, which include spiders, and can be found in beddings, carpets, and upholstered furniture. They are also more abundant in humid climates, and certain species in particular thrive on high humidity. Dust mites require moisture in the air to propagate.

The major allergenic dust mites include *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, *Euroglyphus maynei*, and *Blomia tropicalis*. House dust mite allergy can trigger rhinitis, asthma, and even eczema (Miller 2018).

Dermatophagoides

In *Dermatophagoides pteronyssinus*, three allergens with protease activity have been identified. They are Der p 1, Der p 3, and Der p 6. Other *Dermatophagoides pteronyssinus* allergens with identified functions include Der p 4 (amylase), Der p 7 (a bactericidal permeability increasing like protein), Der p 8 (glutathione S-transferase), Der p 9 (collagenolytic serine protease), Der p 10 (tropomyosin), Der p 11 (paramyosin), Der p 14 (apolipophorin), and Der p 20 (arginine kinase). Der p 2 is a protein of the NPC2 family, and Der p 23 is identified as a peritrophin-like protein domain (Asturias et al. 1998; Caraballo et al. 1998; Lin et al. 1994; Lynch et al. 1997; Mills et al. 1999; Pittner et al. 2004; SHEN et al. 1996; Tsai et al. 2005).

Similar to *Dermatophagoides pteronyssinus,* there are three protease allergens in *Dermatophagoides farinae*. They are Der f 1, Der f 3, and Der f 6. Der f 2 is a protein of the NPC2 family. Der f 7, Der f 10, Der f 11, and Der f 14 are proteins with bactericidal permeability,

tropomyosin, paramyosin, and apolipophorin, respectively. In addition, Der f 13 is a fatty acid-binding protein, Der f 15 is a chitinase, Der f 17 is a calcium-binding protein, and Der f 18 is a chitin-binding protein (Thomas 2015). Recently, a cofilin-related molecule has been identified as a novel *Dermatophagoides farinae* allergen Der f 31 (Lin et al. 2018). *Dermatophagoides farinae* seems to favor drier climates compared with *D. pteronyssinus*.

Dust mites may also play a role in sensitization in patients with atopic dermatitis or even eosinophilic esophagitis. The allergens of dust mite are found in the feces of dust mites. There are several important allergens, and they have been regrouped so that each group share common attributes between dust mite species.

Euroglyphus Maynei and Blomia Tropicalis

Euroglyphus maynei is found in areas of high moisture. These dust mites contain many individual allergens, but only a few have been fully characterized, including Eur m 1, which is a thiol cysteine protease; Eur m 3, a Group 3 allergen; and Eur m 4 or vitellogenin.

Blomia tropicalis is a storage mite that is found both in indoor environments and occupational setting in agricultural facilities. It is a mite that flourishes in tropical and subtropical climates, because of its requirement for moisture. *Blomia tropicalis* belongs to the family Glycyphagidae. Multiple allergens from *B. tropicalis* have been characterized. Blo t 1 is a homologue of the group 1 *Dermatophagoides* allergens, as is the case for Blo t 2 (Cheong et al. 2003a; Mora et al. 2003; Fonseca-Fonseca and Díaz 2003; Tsai et al. 2003). Blo t 3 is a trypsin-like protease (Flores et al. 2003; Cheong et al. 2003b; Yang et al. 2003), and Blo t 4 is an alpha-amylase. In total, there are over 30 allergens from *Blomia tropicalis*. Sensitization to *Blomia tropicalis* has been reported in North America, South America, and Asia, and it can be a significant trigger for asthma (Croce et al. 2000; Simpson et al. 2003; Fernandez-Caldas et al. 1993; Chew et al. 1999; Mariana et al. 2000; Fernández-Caldas et al., n.d.; Müsken et al. 2000; Arruda and Chapman 1992; Aranda et al. 2000; Montealegre et al. 1997; Rizzo et al. 1997).

3.4.2.2 Cockroach

Cockroach is one of the most common household pests worldwide. Cockroaches' allergen is an important cause of asthma. Two cockroach species, *Blattella germanica* and *Periplaneta americana*, are the focus of cockroach allergy research. *Blattella germanica* predominates in the temperate regions where the climate is cool and dry; *Periplaneta americana* predominates in the tropical areas where the climate is hot and humid.

Blattella germanica, also known as the German cockroach, usually infests unsanitary environment in restaurants and homes. German cockroaches are resistant to a broad range of pesticides. Currently, there are ten *Blattella germanica* allergens (Bla g 1, 2, 3, 4, 5, 6, 7, 8, 9, and 11) listed by the World Health Organization's International Union of Immunological Society as *Blattella germanica* allergens. Bla g 1 and Bla g 2 are used as markers to measure cockroach allergen exposure. Multiple *Blattella germanica* allergens have been defined at the molecular level. While Bla g 1 is a 46 kD protein of unidentified function, Bla g 2 is identified as a 36 kD inactive aspartic protease (Gustchina et al. 2005; Wunschmann et al. 2005), Bla g 3 is a 79 KD hemocyanin, Bla g 4 is a 21 kD lipocalin (Tan et al. 2009), Bla g 5 is a 23 kD glutathione S-transferase (Arruda et al. 1997; Jeong et al. 2008), Bla g 6 is a 17 kD troponin C (Hindley et al. 2006), Bla g 7 is a 33 kD protein tropomyosin (Jeong et al. 2003), Bla g 8 is myosin light chain (Hindley et al. 2006), Bla g 9 is a 40 kD arginine kinase, and Bla g 11 is a 57 kD alpha-amylase. (www.allergen.org).

Periplaneta americana, also known as the American cockroach, is not native to North America but is present worldwide. *Periplaneta americana* are most commonly found near food-processing and storage areas and sewers, particularly around pipes and drains. They spend most of their time in crevices for safety and feed on almost anything. To date, the *Periplaneta americana* allergens characterized include Per a 1, a 13–45 kD transmembrane protein (Schou et al. 1990); Per a 2, a 36 kD aspartic protease (Lee et al. 2012); Per a 3, a 72 or 78 kD a species-specific arylphorin (Wu et al. 2003); Per a 4, a

21 kD calycin (Tan et al. 2009); Per a 5, a glutathione-S-transferase homologue (Pan et al. 2006); Per a 6, a 18 kD calcium-binding protein (troponin) (Khantisitthiporn et al. 2007); Per a 7, a 33–37 kD tropomyosin (Yang et al. 2012); Per a 8, a myosin; Per a 9, a 43 kD arginine kinase (Tungtrongchitr 2009); Per a 10, a 28 kD serine protease (Sudha et al. 2008); Per a 11, a 55 kD alpha-amylase; and Per a 12, a 45 kD chitinase (Fang et al. 2015). Other *P. americana* allergens are Per a FABP, a fatty acid-binding protein; Per a trypsin, a trypsin; and Per a cathepsin.

3.4.2.3 Epithelial

Dog

The common species of dog is *Canis familiaris* and thus the allergen nomenclature of Can f 1. Dogs were the earliest domesticated animals and have been found in human households as early as 12,000 years ago. Can f 1 is a 25 kD lipocalin that is found in dog serum, dander, saliva, hair, and pelt. Dog dander is defined as the material shed into the environment from dog hair and dandruff. The dander itself consists of very small particles of less than or equal to 2.5 microns MAD. Therefore, dog dander, like cat dander, can be carried on clothing and spread very easily.

Contrary to popular belief, there is no such thing as a hypoallergenic dog. A study of Can f 1 levels in homes comparing those with hypoallergenic and non-hypoallergenic dogs showed no difference in levels. Similarly, characteristics of the breed such as those with "hair" versus "fur" also show no significant difference. The concept of the hypoallergenic pet is one that was introduced and perpetuated by dog breeders with limited to no knowledge of allergens.

Cat

The scientific name for cat is *Felis domesticus*. The major cat allergen is Fel d 1, and this accounts for allergic responses to cat in about 80% of cat allergic individuals (Leitermann and Ohman Jr 1984; Ohman et al. 1977). Cat allergen is very "sticky" and is carried on clothes, thus facilitating transfer into cat-free environments, including classrooms and homes without cats (Enberg et al. 1993). Clothing is a carrier of cat allergens (D'amato et al. 1997). Cat (Fel d 1), dog (Can f 1), and horse allergen can easily disperse in public environments over time (Egmar et al. 1998). Studies on cat allergen (Fel d 1) levels on school children's clothing and in primary school classrooms in Wellington, New Zealand (Patchett et al. 1997), and others suggest that school can be a risky environment for children allergic to cats and a site for transfer of cat allergen to homes (Almqvist et al. 1999).

Fel d 1 is present in sebaceous glands, anal glands, and salivary and lacrimal glands of cats. It is a tetrameric glycoprotein of molecular weight 36 kD, consisting of two heterodimers of chain 1 and 2, which are encoded by the genes *CH1* and *CH2*. The function of Fel d 1 is unknown, although it shares homology with uteroglobin, which is a member of the secretoglobin super family (Kaiser et al. 2003).

Rabbit

The scientific name for rabbit is *Oryctolagus cuniculus*. Rabbit belongs to the family Leporidae. The two major allergens of rabbit are Ory c 1 and Ory c 2. These proteins are between 18 and 38 kD in molecular weight and belong to the lipocalin family of proteins. They are found in hair, saliva, urine, and dander. Serum albumin is another minor allergen (Bush et al. 1998; Wood 2001; Warner and Longbottom 1991; Price and Longbottom 1986; Price and PLongbottom 1988). Rabbit may be an important contributor to allergic symptoms in the homes where they are kept as pets or in an occupational setting such as in laboratories or pet stores. Rabbit allergy may cross-react with deer allergy, and allergy to rabbit meat has been reported, with some cross-reactivity to bovine.

Mouse

Native to Asia, house mice are now ubiquitous. They exist in all climates and are routinely found both indoors and out. They are also prevalent in fields and often can be detected in homes in new developments. Major allergens were found in mouse skin, serum, and urine. Mouse has been

found to be a major allergen in inner city or urban environments with high population density. Sensitization to mouse allergens has been shown to be strongly associated with asthma outcomes (Ahluwalia et al. 2013). Two mouse allergens have been characterized. The major mouse allergen is Mus m 1, a prealbumin of 19 kD in molecular weight found in hair, dander, and urine (Lorusso et al. 1986). The other mouse allergen (Mus m 2) is a 16 kD glycoprotein found in hair and dander.

Rat

Rattus norvegicus is also known as the house rat, Norway rat, or brown rat. *Rattus norvegicus* has many relatives, and the major allergens, like other animals, tend to belong to the lipocalin class of molecules (Mäntyjärvi et al. 2000). Allergy to rat is a common cause of occupational allergies or asthma (Gordon et al. 1992; Thulin et al. 2002; Baur et al. 1998).

Guinea Pig

Guinea pigs (*Cavia porcellus*) are popular household pets and are also raised for meat in some countries. They belong to the family Caviidae. Guinea pig allergens are derived from their hair, dander, urine, saliva, and pelts. Five guinea pig allergens have been characterized to date, Cav p 1, Cav p 2, Cav p 3, and Cav p 6, and are identified as members of the lipocalin family, and Cav p 4 is serum albumin (Bush et al. 1998; Swanson et al. 1984; Fahlbusch et al. 2002).

Other Household Pets

None of the allergens from other household pets, such as gerbils or hampsters (*Cricetus cricetus*), have been characterized, but there have been reports of allergy to small animals (Berto et al. 2002; Horiguchi et al. 2000; McGivern et al. 1985; Muljono and Voorhorst 1978; Osuna et al. 1997).

Horse

Horses (*Equus caballus*) are domesticated animals. They are found in almost all regions of the world. Previously serving as a means of transportation, they are now more widely used for entertainment, recreation, and/or sport. Allergens are found in horse dander and horse serum protein. The allergens of horses are primarily glycoproteins. Equ c 1, Equ c 2, and Equ c 4 are lipocalin proteins of 25 kD, 17 kD, and 18.7 kD, respectively (Mäntyjärvi et al. 2000; Botros et al. 2001), and Equ c 3 is a 67 kD serum albumin (Botros et al. 1998).

Cattle

Domestic cattle (*Bos domesticus*, *Bos taurus*) is composed of many breeds and is the source of domestic beef and dairy cattle worldwide. Cattle allergy is mostly reported in cattle farmers or veterinarians due to occupational exposure. Early studies determined cow hair and dander as the source of allergens. Lipocalins (Bos d 1 and Bos d 2) are considered the major allergens (Mäntyjärvi et al. 1996). Other allergens present in cow hair and dander extracts include the Ca-binding s-100 homologue Bos d 2 (11 kD), alpha-lactalbumin (14 kD), Bos d 5 beta-lactoglobulin (18 kD), serum albumin Bos d 6 (67 kD), and IgG Bos d 7 (160 kD). Bods d 8, Bos d 9, Bos d 10, Bos d 11 and Bos d 12 are caseins (20–30 kD) (Bernard et al. 1998; Zahradnik et al. 2015). Cow allergens may cross-react with deer allergens (Spitzauer et al. 1997). There is about a 20% chance of cross-reactivity between cow dander allergens and cows' milk allergens (Valero Santiago et al. 1997).

Sheep

Sheep are used for their fur in the production of wool clothing. Cheese can be produced from sheep's milk. There are no characterized allergens from sheep.

3.4.2.4 Feathers

Chickens

The scientific name for chicken is *Gallus domesticus*. However, the allergens that are named for this species, namely, Gal D x, are generally representative of hen's egg allergy. Chickens are bred almost worldwide for food. The allergens of chicken (not hen's egg) have

not been characterized, but proteins between 20–30 kD in size and 67 kD have been identified through IgE immunoblots (Tauer-Reich et al. 1994). There does appear to be some cross-reactivity between chicken and other fowl and bird species including duck, goose, parrot, and others. There also seems to be some cross-reactivity between allergens in chicken feathers and hen's egg. It is the levitins that provide this cross-reactivity (de Blay et al. 1994; Mandallaz et al. 1988; Nevot Falco and Casas Ramisa 2003).

Duck and Goose

While no allergens have been characterized, there is likely some allergenic cross-reactivity among bird species. The Latin name for duck is *Anas platyrhyncha* and that for goose is *Anser anser*.

Canary

The scientific name of canary is *Serinus canarius*. Canaries, parrots, and budgerigars may contain similar proteins that cross-react with other bird species including chicken, duck, and goose (Tauer-Reich et al. 1994).

3.5 Food Allergens

The allergens in grains, egg, milk, and coffee are summarized in Table 1.

3.5.1 Grains

3.5.1.1 Rice

The genus *Oryza* contains about 20 rice species that grow in shallow water, swamps, and marshes. *O. sativa*, also known as the Asian rice, is one of the most important food crops cultivated worldwide, which constitutes a major dietary portion of half of the world population. Asthma, rhinitis, conjunctivitis, atopic dermatitis, and anaphylaxis due to the ingestion of rice or inhaling boiling rice vapors have been reported (Orhan and Sekerel 2003). The rice allergens that have been identified are Ory s LTP, a 14 kD lipid transfer protein (Poznanski et al. 1999; Enrique et al. 2005; Asero et al. 2007; Asero et al. 2002; Asero et al. 2001a); Ory s aA/TI, a 16 kD alpha-amylase/trypsin inhibitor (Izumi et al. 1999; Adachi et al. 1993; Alvarez et al. 1995a; b; Izumi et al. 1992; Nakase et al. 1996; Nakase et al. 1998; Tada et al. 1996; Yamada et al. 2006); Ory s Glyoxalase I, a glyoxalase (Enrique et al. 2005; Usui et al. 2001; Kato et al. 2000; Urisu et al. 1991); and Ory s 12, a profilin (van Ree et al. 1992). In addition, Ory s 1 (beta-expansin), Ory s 2, Ory s 3, Ory s 7, Ory s 11, Ory s 12, and Ory s 13 have been characterized in rice pollen and contribute to asthma, allergic rhinitis, and allergic conjunctivitis as a result from exposure to rice pollen. Ory s 12, a profilin, has been detected in both rice seed and rice pollen. There is some evidence that buckwheat may cross-react with rice.

3.5.1.2 Rye

Rye (*Secale cereale*) is a cereal grain grown primarily in Central, Eastern, and Northern Europe. It is also grown in North and South America, Australia, New Zealand, and Northern China. Like wheat and barley, rye contains gluten; thus people who have gluten related disorders should avoid rye consumption. The allergens isolated include Sec c 12, a profilin (van Ree et al. 1992); Sec c 20, a secalin (Rocher et al. 1996); and Sec c a A TI (renamed as Sec c 38), a 13.5 kD alpha-amylases/trypsin inhibitor (García-Casado et al. 1995; García-Casado et al. 1994). Sec c 1, Sec c 2, Sec c 4, Sec c 5, Sec c 12, and Sec c 13 are additional allergens that have been characterized. Some of these pollens are present in both rye pollen and rye seed. The panallergen profilin is heat labile, and Sec c 12 has been identified to be a profilin.

3.5.1.3 Oat

Although the allergens of oats have not been characterized, the allergic symptoms of oats, including atopic dermatitis, result from exposure to the seed storage protein (Varjonen et al. 1995). Oat contains gluten-like allergens, but these allergens including alpha 2, gamma 3, and gamma 4 avenins generally do not cause significant symptoms in patients with celiac disease (Hallert et al. 1999). Oat cross-reacts with grass pollen allergens, as well as other grains such as maize, rice,

Table 1 Allergens in grains, milk, eggs, and coffee

Identified function/ family	Allergen name
Lipid transfer protein	Ory s LTP (rice) Tri a 14 (wheat) Hor v LTP (barley)
Alpha-amylase/trypsin inhibitor	Ory s aA/TI (rice) Sec c a A TI (renamed as sec c 38) (rye) Tri a aA/TI (wheat)
Glyoxalase	Ory s Glyoxalase I (rice)
Profilin	Ory s 12 (rice) Sec c 12 (rye) Tri a 12 (wheat) Hor v 12 (barley)
Beta-expansin	Ory s 1 (rice) Sec c 1 (rye)
Secalin	Sec c 20 (rye)
Group 5 grass pollen allergen	Sec c 5 (rye)
Avenins	Alpha 2 (oat) Alpha 3 (oat) Alpha 4 (oat)
Hevein-like protein	Tri a 18 (wheat)
Chitinase	Tri a chitinase (wheat)
Thioredoxin	Tri a 25 (wheat)
Gluten	Tri a gluten (wheat) Tri a 26 (wheat) Tri a LMW Glu (wheat)
Peroxidase	Tri a Bd3 6 K (wheat) Tri a peroxidase (wheat)
Germin	Tri a germin (wheat)
Triosephosphate isomerase	Tri a TPIS (wheat)
Alpha-amylase	Hor v 15 (barley) Hor v 16 (barley)
Beta-amylase	Hor v 17 (barley)
Hordein	Hor v 20 (barley) Hor v 21 (barley)
Expansin	Hor v 1 (barley)
Alpha-lactalbumin	Bos d 4 (cow's milk)
Beta-lactoglobulin	Bos d 5 (cow's milk)
Bovine serum albumin	Bos d 6 (cow's milk)
Immunoglobulin	Bos d 7 (cow's milk)
Casein	Bos d 8 (cow's milk)
Ovomucoid	Gal d 1 (eggs)
Ovalbumin	Gal d 2 (eggs)
Ovotransferrin	Gal d 3 (eggs)
Lysozyme	Gal d 4 (eggs)
Serum albumin	Gal d 5 (eggs)
YGP42 protein	Gal d 6 (eggs)
Chitinase	Cof a 1 (coffee)
Cysteine-rich metallothionein	Cof a 2 (coffee) Cof a 3 (coffee)
Gliadin	Tri a alpha-beta-gliadin (wheat) Tri a alpha-gliadin (wheat) Tri a beta-gliadin (wheat) Tri a gamma-gliadin (wheat) Tri a omega-2 gliadin (wheat)
Lactoferrin	Bos d Lactoferrin (cow's milk)
Lactoperoxidase	Bos d lactoperoxidase (cow's milk)
Undefined function	Ory s 2 (rice) Ory s 3 (rice) Ory s 7 (rice) Ory s 11 (rice) Ory s 13 (rice) Sec c 2 (rye) Sec c 4 (rye) Sec c 13 (rye) Tri a Bd 17 K (wheat) Hor v Z4 (barley) Hor v 2 (barley) Hor v 4 (barley) Hor v 5 (barley) Hor v 13 (barley)

and barley. Oat allergens have also been reported to be a common solid food cause of food protein-induced enterocolitis syndrome (FPIES) (Nowak-Wegrzyn et al. 2003; Sicherer 2005).

3.5.1.4 Wheat

Wheat is a staple food crop for many populations worldwide. *Triticum aestivum* is the most commonly cultivated wheat variety for human consumption. Wheat is an important source of carbohydrates, essential amino acids, and dietary fiber. However, because wheat is rich in gluten, it can also trigger celiac disease in susceptible individuals. To this date, there are 19 wheat allergens which have been identified and characterized. Among these, Tri a 12 is a profilin (Thulin et al. 2002), Tri a 14 is a lipid transfer protein and (Horiguchi et al. 2000), and Tri a 18 is a hevein-like protein (Weichel et al. 2006). Other common wheat allergens include Tri a Gluten (Morita et al. 2003), Tri a Chitinase, a chitinase (Diaz-Perales et al. 1999), Tri a Bd

17 K (Kimoto 1998), Tri a 25, a thioredoxin (Brant 2007), Tri a 26, a glutenin, Tri a aA/TI, an alpha-amylase/trypsin inhibitor (Buonocore et al. 1985), Tri a Bd3 6 K is a peroxidase (Yamashita et al. 2002), Tri a LMW Glu, a glutenin (Morita et al. 2003), Tri a Germin, a germin (Jensen-Jarolim et al. 2002), Tri a Peroxidase, a peroxidase (Watanabe et al. 2001), and Tri a TPIS, a triosephosphate isom-erase (Rozynek et al. 2002). Other allergens include Tri a alpha-beta-gliadin (Bittner et al. 2008), Tri a alpha-gliadin (Sandiford et al. 1997), Tri a beta-gliadin (Sandiford et al. 1997), Tri a gamma-gliadin (Sandiford et al. 1997), and Tri a omega-2 gliadin (Sandiford et al. 1997). Wheat is a common cause of food-dependent exercise-induced anaphylaxis (Fiedler et al. 2002). Occupationally, wheat allergens are a cause of Baker's asthma (Sander et al. 1998; De Zotti et al. 1994; Prichard et al. 1984; Valero Santiago et al. 1988).

3.5.1.5 Barley

Barley (*Hordeum vulgare*) is a major cereal grain grown in temperate climates. Like wheat and rye, barley contains gluten which makes it an unsuitable grain for consumption by people with gluten sensitivity. Multiple allergens for barley have been characterized: Hor v 15, a 16 kD protein (Armentia et al. 1993); Hor v 16 is an alpha-amylase (Perrocheau et al. 2005); Hor v 17 is a beta-amylase; Hor v 20 and Hor v 21 function as hordein, a form of storage protein (Palosuo et al. 2001); Hor v LTP, a 10 kD protein, a lipid transfer protein (Palosuo et al. 2001); and Hor v Z4, a 45 kDa protein (Palosuo et al. 2001). A few other allergens have been reported from Barley pollen as well. These include Hor v 1, which is an expansin, Hor v 2, Hor v 4, Hor v 5, Hor v 12, and Hor v 13. Group 2, 4, and 5 allergens show cross-reactivity to grasses (Nandy et al. 2005).

3.5.2 Milk

3.5.2.1 Cow's Milk

Cow's milk is the most consumed form of milk in the Western world. Cow's milk is one of the more common allergens worldwide. Aside from cattle, the other livestock also provides milk for human consumption, with goat and sheep milk being the second and third most commonly consumed. Cow's milk allergy usually presents early on in life, but many with cow's milk allergy will outgrow their allergy by adolescence. Cow's milk is one of those allergens that has been associated with food protein-induced enterocolitis syndrome. There is a slight (10%) chance of cross-reactivity to beef.

Cow's milk contains 30–35 grams of protein per liter, with 80% bound in the form of casein micelles. Besides casein, milk contains other proteins, which are more soluble than casein and are collectively known as whey proteins. However, whey proteins are not so easily digested in the intestine. Cow's milk has a higher casein/whey ratio than human milk. Lactoglobulin and lactalbumin are the most common whey proteins. Milk also contains several carbohydrates. Lactose intolerance can also cause symptoms that mimic cow's milk allergy.

Seven allergens have been characterized to date. Bos d 4 is an alpha-lactalbumin (Wal 2002), and Bos d 5 is a beta-lactoglobulin (Wal 2002). Bos d 6, a 67 kD protein, is a bovine serum albumin, also present in dander, muscle, and serum (Wal 2002). Bos d 7 is an immunoglobulin (Ayuso et al. 2000), Bos d 8 is a casein (Wal 2002), and two other allergens, Bos d lactoferrin (Wal 2002) and Bos d lactoperoxidase (Indyk et al. 2006), have been identified.

3.5.2.2 Sheep's Milk

The milk of sheep and other animals can cross-react with cow's milk. Clinically, respiratory symptoms have been reported in patients sensitized to sheep's milk (Vargiu et al. 1994).

3.5.2.3 Goat's Milk

There appears to be cross-reactivity between cow's and goat's milk. However, data on this is limited (Bernard et al. 1992). In one study, about 88% of cow's milk allergic patients also had IgE to goat milk (Dean et al. 1993). The cross-reactivity between the milk of these two species appears to be due to homology in the serum albumin and casein sequences of the two species (Spuergin et al. 1997).

3.5.3 Eggs

After cow's milk, hen's egg allergy is the second most common food allergy in infants and young children in many countries, though regional difference may exist (Caubet and Wang 2011). Eggs from chickens or hens weigh anywhere from 30 to 90 grams. About 10% of the weight is in the shell. Much of the weight of the egg white is from protein. Egg allergy can develop in response to proteins in egg whites or yolks. People with allergic reactions to chicken eggs may also be allergic to other types of eggs, such as goose, duck, turkey, or quail. Egg allergy may be defined as an adverse reaction of immunological nature induced by egg proteins and includes IgE antibody-mediated allergy as well as other allergic syndromes such as atopic dermatitis and eosinophilic esophagitis. Six allergenic proteins from the egg of the domestic chicken (*Gallus domesticus*) have been identified (Heine et al. 2006). Ovomucoid (Gal d 1, 11%), ovalbumin (Gal d 2, 54%), ovotransferrin (Gal d 3, 12%), and lysozyme (Gal d 4, 3.4%) (Bernhisel-Broadbent et al. 1994) are from the egg white. Serum albumin (Gal d 5) (Quirce et al. 2001) and YGP42 protein (Gal d 6) (Amo et al. 2010), a fragment of the vitellogenin-1 precursor, are from the egg yolk.

Although ovalbumin (OVA) is the most abundant protein comprising hen's egg white, ovomucoid (OVM) has been shown to be the dominant allergen in egg (Caubet and Wang 2011; Miller and Campbell 1950; Bleumink and Young 1971; Cooke and Sampson 1997). Ovomucoid is heat stable and therefore is not denatured by baking. Thus, patients who can tolerate baked egg products, but not baked milk products, are more likely to be allergic to ovalbumin rather than ovomucoid.

3.5.4 Fruits

The allergens in fruits are summarized in Table 2.

3.5.4.1 Citrus

Citrus allergy was thought to be much more common in the past. It is possible that in the past, its acidic nature led to more of an irritant dermatitis rather than a true allergy. However, there are still some people who develop allergy to citrus. Cross-reactivity among fruits is based on similarities in amino acid sequence and secondary and tertiary structures. Molecules that serve common functions across the different fruits are likely to be cross-reactive (Table 1).

3.5.4.2 Orange

The scientific name for orange is *Citrus sinensis*. Three orange allergens have been identified at the biochemical level. Cit s 2 is a natural profilin. An unexpectedly high reactivity to Cit s 2 was found in vivo (78% of positive SPT responses) and in vitro (87% of sera from orange-allergic patients had specific IgE to Cit s 2). The purified allergen inhibited around 50% of the IgE binding to an orange pulp extract (Lopez-Torrejon et al. 2005). Cit s 1 is a germin-like glycoprotein. Specific IgE to Cit s 1 was detected in 62% of 29 individual sera from orange-allergic patients, whereas positive SPT responses to the purified allergen were obtained in only 10% of such patients. Deglycosylation of Cit s 1 resulted in a loss of its IgE-binding capacity indicating carbohydrate is involved in its IgE epitope (Ahrazem et al. 2006). Cit s 3 is identified as a non-specific lipid transfer protein (Ahrazem et al. 2005), and recently the gibberellin-regulated protein has been reported as a novel orange allergen. Twelve of 14 subjects with orange allergy were positive by either ELISA, basophil activation tests, or skin prick tests (Inomata et al. 2018).

3.5.4.3 Lemon

Lemon (*Citrus limon*) is commonly grown for culinary and non-culinary purposes in households and also commercially. Cit l 1 is a germin-like protein (Pignataro et al. 2010). The N-terminal sequence of the lemon allergen (nCit l 3) is identical to the orange allergen Cit s 3 in 18 out of 20 amino acids, with lipid transfer protein characteristics and approximately 9.6 kD in molecular weight (Ahrazem et al. 2005).

Table 2 Allergens in fruits

Identified function/family	Allergen name
Lipid transfer protein	Cit s 3 (orange) nCit l 3 (lemon) Fra a 3 (strawberry) Pru av. 3 (cherries) Rub i 3 (raspberry)
Profilin	Cit s 2 (orange) Fra a 4 (strawberry) Pru av. 4 (cherries) Cit la 2 (watermelon) Cuc m 2 (melon)
Triosephosphate isomerase	Cit la TPI (watermelon)
Germin-like glycoprotein	Cit s 1 (orange)
Germin-like protein	Cit l 1 (lemon)
Bet v 1 homologue	Fra a 1 (strawberry) Pru av. 1 (cherries) Rub i 1 (raspberry)
Thaumatin-like protein	Pru av. 2 (cherries)
Malate dehydrogenase	Cit la MDH (watermelon)
Plant serine protease	Cuc m 1 (melon)
PR1 protein	Cuc m 3 (melon)

3.5.4.4 Grapefruit

The scientific name of grapefruit is *Citrus paradisi*, and it belongs to the family Rutaceae. Specific IgE reactivity to grapefruit has been detected in patients with atopic dermatitis, allergic rhinitis, bronchial asthma, and even food-dependent exercise-induced anaphylaxis (Matsumoto et al. 2009). However, the molecular identities of grapefruit allergens are unknown.

3.5.5 Berries

Berries include a variety of popular fruits such as strawberries, cherries, raspberries, blackberries, and blueberries. They are commonly used in cakes, shakes, and juices.

3.5.5.1 Strawberry

Strawberry (*Fragaria ananassa*) is a perennial herbaceous plant of the family Rosaceae, characterized by the distinct shape of its leaves, white flowers, and also by its fruits. "Strawberry" is not a true berry but a fleshy receptacle with multiple one-seeded fruits that do not split open when ripen. Strawberry is a common allergen in children (Eriksson et al. 2004; Zuidmeer et al. 2008). Three allergenic proteins have been identified. Fra a 1 is a Bet v 1 homologue with molecular weight 18 kD (Karlsson et al. 2004), Fra a 3 is a lipid transfer protein of 9 kD (Yubero-Serrano et al. 2003), and Fra a 4 is a profilin of 13 kD (Zuidmeer et al. 2006).

3.5.5.2 Cherry

The scientific name of cherry is *Prunus avium*. Cherry is a fast-growing deciduous tree of the family Rosaceae. The cherry plant is not self-fertilizing. Oral allergy syndrome and urticaria are common allergic reactions to cherries (Asero 1999; Pastorello et al. 1994). Four cherry allergens have been characterized. Pru av. 1 is a 18 kD Bet v 1-homologue, Pru av. 2 is a thaumatin-like protein of 23.3–29 kD (Inschlag et al. 1998), Pru av. 3 is a 15 kD lipid transfer protein, and Pru av. 4 is a profilin of 15 kD molecular weight (Wiche et al. 2005).

3.5.5.3 Raspberry

The scientific name of raspberry is *Rubus idaeus*. It is a member of the Rosaceae family. Allergens from raspberry include Rub i 1, a Bet v 1 homologue, and Rub i 3, a lipid transfer protein (Marzban et al. 2008), both isolated from the red raspberry, *Rubus idaeus*. In addition, two other IgE-reactive raspberry proteins, a chitinase and a cyclophilin, have also been identified (Marzban et al. 2008). Besides the allergens isolated and/or characterized, raspberry also appears to contain high-molecular-weight proteins which appear to be allergenic (Marzban et al. 2005). Occupational asthma due to raspberry has also been reported (Sherson et al. 2003). Raspberry cross-reacts with other berries in the genus *Rubus*.

3.5.5.4 Blackberry

The scientific name of Blackberry is *Rubus fruticosus*. It is in the family Rosaceae. Blackberries grow in the wild and are invasive, and they are protected by their thorny branches. To date, there is no blackberry allergens identified at the biochemical level, but a Mal d 1 homologue has been reported from blackberry (Marzban et al. 2005). As mentioned above, there is extensive cross-reactivity within the *Rubus* genus.

3.5.5.5 Blueberry

The scientific name of blueberry is *Vaccinium myrtillus*, and it belongs to the family Ericaceae.

Blueberry has been shown to contain a lipid transfer protein, but no blueberry allergens have been characterized. Blueberry cross-reacts with other plants as its lipid transfer protein shows homology with many of the stone fruits. Another member of the *Vaccinium* genus is cranberry (*Vaccinium oxycoccos*).

3.5.6 Melons

3.5.6.1 Watermelon

The scientific name of watermelon is *Citrullus lanatus*. Watermelon belongs to the family Cucurbitaceae. Allergic reactions to watermelon are commonly presented as oral allergy syndrome. Three allergenic proteins have been defined: they are Cit la 2, a 13 kD protein which is a profilin; Cit la MDH, a malate dehydrogenase; and Cit la TPI, a triosephosphate isomerase (Pastor et al. 2009). Although watermelon is largely composed of water and the protein content is rather low, individuals sensitized to profilins can be allergic to watermelons.

Other melons (honeydew, cantaloupe, winter melon) are a diverse group of fruits with varying sizes, colors, and flavors. They belong to the family Cucurbitaceae and genus *Cucumis.* A number of allergens have been characterized from *Cucumis melo*, including Cuc m 1, a plant serine protease (Cuesta-Herranz et al. 2003); Cuc m 2 (López-Torrejón et al. 2005), a profilin of molecular weight 13 kD; and the 16 kD molecular weight Cuc m 3, which is a PR1 protein (Asensio et al. 2004). In addition, Cuc m LTP is a lipid transfer protein. Melons are often considered a culprit in oral allergy syndrome, with cross-reactivity to Bet v 2, the birch tree profilin (Asero et al. 2003).

3.5.7 Tree Nuts

Among foods causing allergic reactions in children, tree nuts (i.e., walnut, hazelnut, Brazil nut, pecan) have attracted considerable attention for several reasons. Allergies to these foods are common and account for severe and potentially fatal allergic reactions (Sicherer and Sampson 2000). The many allergens in tree nuts can be categorized based on their function (Table 3).

3.5.7.1 Almond

Almonds are fruits of the almond tree (*Prunus amygdalus)* with two major varieties: the sweet (*Prunus amygdalus* var. *dulcis*) and the bitter (*Prunus amygdalus* var. *amara*) almonds. Bitter almond is not approved for sale in the United States because it contains amygdalin, which is toxic.

Almonds are widely consumed as a food item and are also processed for their oil content. The almond fruit measures about 4 cm in length and is an important ingredient in many cuisines around the world. Allergens characterized to date include Pru du 3, Pru du 4 which is a profilin (Sathe et al. 2002), Pru du 5 which is an acidic ribosomal protein (van Ree et al. 1992), and Pru du 6. The 2S albumin Pru du 2S albumin cross-reacts with many other nuts, including Ara h 2 from peanut.

3.5.7.2 Brazil Nut

The Brazil nut is the seed of the *Bertholletia excelsa* tree that primarily grows in South America's Amazon forest, along the banks of Amazon River. Allergic reactions including anaphylaxis to Brazil nuts have been reported (Arshad et al. 1991; Senna et al. 2005). Characterized allergenic proteins of Brazil nut include Ber e 1 which is a 9 kD 2S storage albumin and is resistant to digestion by pepsin (Alcocer et al. 2002) and Ber e 2 which is a 11S globulin seed storage protein (Guo et al. 2007).

3.5.7.3 Cashew

The cashew nut is harvested from the cashew nut tree (*Anacardium occidentale*). Cashew tree belongs to the Anacardiaceae family. Cashew nuts are consumed popularly as roasted snacks and are also an important ingredient in baked goods. Allergens include Ana o 1 which is a 7S vicilin-like protein (Teuber et al. 2002); Ana o 2 which is a legumin-like protein of molecular

Table 3 Allergens in tree nuts

Identified function/family	Allergen name
Profilin	Pru du 4 (almond) Cor a 2 (hazelnut) Jug r 7 (walnut) Ana o (cashew)
Bet v 1 homologue	Cor a 1 (hazelnut)
Acidic ribosomal protein	Pru du 5 (almond)
Storage albumin	Ber e 1 (Brazil nut)
Globulin seed storage protein	Ber a 2 (Brazil nut) Cor a 9 (hazelnut)
Vicilin-like protein	Ana o 1 (cashew) Car i 2 (pecan) Pis v 3 (pistachio) Cor a 11 (hazelnut) Jug r 2 (walnut) Jug r 6 (walnut)
Legumin-like protein	Ana o 2 (cashew)
2S albumin	Pru du 2S albumin (almond) Ana o 3 (cashew) Cor a 14 (hazelnut) Pis v 1 (pistachio) Car i 1 (pecan) Jug r 1 (walnut)
Isoflavone reductase homologue	Cor a 6 (hazelnut)
Luminal binding protein	Cor a 10 (hazelnut)
Oleosin	Cor a 12 (hazelnut) Cor a 13 (hazelnut)
Legumin seed storage protein	Car i 3 (pecan)
11S globulin subunit	Pis v 2 (pistachio) Pis v 5 (pistachio) Jug r 4 (walnut) Pru du 6 (almond)
Magnesium superoxide dismutase	Pis v 4 (pistachio)
Non-specific lipid transfer protein	Cor a 8 (hazelnut) Jug r 3 (walnut) Jug r 8 (walnut) Pru du 3 (almond)
PR-10	Jug r 5 (walnut)

weight 33 kD (Garcia et al. 2000); Ana o 3, a 12.6 kD 2S albumin (Robotham et al. 2005); and Ana o profilin. Cashew shows cross-reactivity primarily with pistachio, but the IgE epitopes of the vicilin allergen of many nuts are structurally similar.

3.5.7.4 Hazelnut

Hazelnuts belong to the Betulaceae or Corylaceae family. The scientific name of hazelnut is *Corylus avellana*. They grow in clusters on hazel trees which are found primarily in temperate zones of the world, such as in much of Europe. Hazelnuts are an important ingredient in a variety of dessert preparations around the world. Characterized allergens include Cor a 1 which is a 17 kD protein and a Bet v 1 homologue (Hirschwehr et al. 1992), Cor a 2 which is a profiling of molecular weight 14 kD (Hirschwehr et al. 1992), Cor a 6 which is a isoflavone reductase homologue, Cor a 8 which is a non-specific lipid transfer protein of molecular weight 9.4 kD (Pastorello et al. 2002), Cor a 9 which is a 40 kD 11S storage globulin (Beyer et al. 2002), Cor a 10 which is a 70 kD luminal binding protein, and Cor a 11 which is a 48 kD 7S vicilin-like seed storage globulin (Hansen et al. 2009). Cor a 12 and Cor a 13 are oleosins (Akkerdaas et al. 2006), and Cor a 14 is a 2S albumin (Masthoff et al. 2013). The latter three all range from 13 to 17 kD in size.

3.5.7.5 Pecan

The pecan tree (*Carya illinoinensis*) is an important source of timber and also known for its edible nuts. They are native to southern and southeastern North America. Pecan allergens characterized to date include Car i 1 which is a 16 kD 2S seed storage albumin (Barre et al. 2005; Jacquenet and Moneret-Vautrin 2007), Car i 2 which is a 55 kD vicilin-like protein, and Car i 3 which is a legumin seed storage protein. Pecan is closely related to walnut and hickory.

3.5.7.6 Pistachio

Pistachios nuts are green, edible seeds from pistachio trees *(Pistacia vera*). Pistachio nuts are widely used in ice creams and cakes or eaten as a roasted snack. Pistachio is in the cashew family of nuts. Although pistachio allergy is not so common, hypersensitive reactions to pistachio are similar to other nut allergies, and cases of food-dependent exercise-induced anaphylaxis to pistachio have been reported (Porcel et al. 2006). Allergens characterized to date include Pis v 1 which is a 2S albumin (Jacquenet and Moneret-Vautrin 2007; DÍaz-Perales et al. 2000), Pis v 2 which is a

11S globulin subunit, Pis v 3 which is a vicilin-like protein, Pis v 4 which is a magnesium superoxide dismutase, and Pis v 5 which is also a 11S globulin subunit.

3.5.7.7 Walnut

Walnuts are in the family Juglandaceae. Walnut is cultivated for its rich oil content that is used in pastas or salads. It is also consumed as a roasted snack. Allergens characterized for English walnut (*Juglans regia*) to date include Jug r 1 which is a 15–16 kD 2S albumin seed storage protein (Roux et al. 2003); Jug r 2 which is a 44–48 kD vicilin seed storage protein (Barre et al. 2005); Jug r 3 which is a 9 kD non-specific lipid transfer protein (Roux et al. 2003); Jug r 4 which is a 11S globulin seed storage protein (Wallowitz et al. 2006); Jug r 5, Jug r 6, and Jug r 7 which are a profilin (Wallowitz et al. 2006), and Jug r 8 which is also a 9 kD non-specific lipid transfer protein.

3.5.8 Vegetables

3.5.8.1 Legumes

IgE-binding proteins have been identified in the majority of legumes. Overall, allergenicity due to consumption of legumes in decreasing order may be peanut, soybean, lentil, chickpea, pea, mung bean, and red gram (Verma et al. 2013b).

3.5.8.2 Peanut

Peanut (*Arachis hypogaea*) is a member of the Fabaceae family. They grow close to the ground, and their fruits are produced underground. In the United States, peanuts are mainly consumed after being processed as peanut butter. However, they are also widely consumed as a snack or used as an ingredient in baked goods. There are 17 peanut allergens that have been characterized. These include Ara h 1, a 64 kD protein vicilin seed storage protein (Burks et al. 1991); Ara h 2, a 17 kD protein conglutin seed storage protein and a trypsin inhibitor (Burks et al. 1998); Ara h 3, a 60 kD protein and a 11S globulin seed storage protein (Burks et al. 1998); Ara h 4 (Boldt et al. 2005); and Ara h 5, a 15 kD protein and a profilin (Kleber-Janke et al. 1999). Ara h 6 and Ara h 7 are both 2S albumin and heat- and digestion-stable proteins (Kleber-Janke et al. 1999). Ara h 8 is a 17 kD protein that found to be a Bet v 1-homologous allergen (Mittag et al. 2004). Other characterized peanut allergens include non-specific lipid transfer proteins (Ara h 9 (Asero et al. 2000), Ara h 16, and Ara h 17), oleosins (Pons et al. 2002) (Ara h 10, Ara h 11, Ara h 14, and Ara h 15), and defensins (Ara h 12 and Ara h 13).

3.5.8.3 Soybean

Soybean is one of the world's most important legumes because of its wide use as a source of animal and human nutrition. It can be used fresh and processed into soybean flour, into oil, or into soy milk. The scientific name of soybean is *Glycine max*. A number of soybean allergens have been characterized. Major allergens of soybean include Gly m 1, a lipid transfer protein; Gly m 2 (Helm et al. 1998); Gly m 3, a profilin (Ogawa et al. 1991); Gly m 4, a bet v 1 homologue (Ogawa et al. 1991); Gly m 5, a 7S globulin or vicilin; Gly m 6, an 11S globulin called legumin (Natarajan et al. 2006); Gly m 7; and Gly m 8, a 2S albumin (Inomata et al. 2007).

3.5.8.4 Sesame

The scientific name of sesame is *Sesamum indicum*. Technically not a legume, sesame contains several allergens, including Ses i 1, Ses i 2, Ses i 3, Ses i 4, Ses i 5, Ses i 6, and Ses i 7. Ses i 1 is a 2S albumin and is heat stable and digestion. Ses i 3 is a vicilin-type globulin which is also a seed storage protein and is a major allergen. Another seed storage protein is Ses i 2, which is also a 2S albumin.

3.5.9 Leafy Green Vegetables

The allergens in vegetables are summarized in Table 4.

3.5.9.1 Spinach

Spinach is *Spinacia oleracea*, a member of the Chenopodiaceae family. Native to the Middle

Table 4 Allergens in vegetables

Identified function/family	Allergen name
Lipid transfer protein	Ara h 9 (peanut) Ara h 16 (peanut) Ara h 17 (peanut) Gly m 1 (soybean) Bro o 3 (cabbage) Lac s 1 (lettuce) Dau c 3 (carrot) Lyc e 3 (tomato) Broccoli (no allergens specified)
Profilin	Ara h 5 (peanut) Gly m 3 (soybean) Spi o 2 (spinach) Dau c 4 (carrot) Sol t 8 (potatoes) Lyc e 1 (tomato) Cap a 2 (chili pepper)
Chitinase	Lyc e chitinase (tomato)
Peroxidase	Lyc e peroxidase (tomato)
Bet v 1 homologue	Ara h 8 (peanut) Gly m 4 (soybean) Dau c 1 (carrot)
Thaumatin-like protein	Cap a 1 (chili pepper)
2S albumin	Ara h 6 (peanut) Ara h 7 (peanut) Gly m 8 (soybean) Ses i 1 (sesame) Ses i 2 (sesame)
Vicilin-like seed storage globulin	Ses i 3 (sesame) Ara h 1 (peanut)
11S globulin subunit	Ara h 3 (peanut) Gly m 6 (soybean) Ses i 6 (sesame) Ses i 7 (sesame)
Protein conglutin seed storage protein	Ara h 2 (peanut)
Trypsin inhibitor	Ara h 2 (peanut)
Heat- and digestion-stable protein	Ara h 6 (peanut) Ara h 7 (peanut)
Oleosin	Ara h 10 (peanut) Ara h 11 (peanut) Ara h 14 (peanut) Ara h 15 (peanut) Ses i 4 (sesame) Ses i 5 (sesame)
Defensins	Ara h 12 (peanut) Ara h 13 (peanut) Gly m 2 (soybean)
7 s globulin or vicilin	Gly m 5 (soybean)
PRP-like protein	Dau c 1.02 (carrot)
Glycosylated beta-fructofuranosidase	Lyc e 2 (tomato)
Glucanase	Lyc 3 (tomato)
Seed biotinylated protein	Gly m 7 (soybean)
Patatin	Sol t 1 (potato)
Cathepsin D inhibitor (PDI)	Sol t 2 (potato)
Cysteine protease inhibitor	Sol t 3 (potato)
Serine protease inhibitor	Sol t 4 (potato)
LTP	Aspa o 1.01 (asparagus) Aspa o 1.02 (asparagus)

East, it is now grown all over the world. Spi o 2 is a profilin. Among the protein bands that show up in spinach extract are 20 kD and 25 kD and several minor 14–18 kD proteins. Spinach cross-reacts with other leafy green vegetables. It is a rare allergen, with cases described mostly in the context of occupational asthma (Schuller et al. 2005).

3.5.9.2 Cabbage

Cabbage (*Brassica oleracea*) is vegetable crop characterized by its dense multilayer leafy head of either green, purple, or white in color. It is a member of the Brassicaceae family. It is valued for its vitamin C, vitamin K, and dietary fiber. Allergy to cabbage is uncommon (Dolle et al. 2013). Bra o 3, a 9 kD cabbage IgE-binding protein, was identified as a lipid transfer protein, and IgE from patients allergic to cabbage can also cross-react with mugwood pollen and peach (Palacin et al. 2006).

3.5.9.3 Lettuce

Lettuce is a common food, and there are many varieties. The scientific name for fresh lettuce is *Lactuca sativa*. There are many varieties of *Lactuca sativa*, as in *L. sativa* var. *capitate* (head lettuce). Only one allergen from lettuce has been characterized, Lac s 1, which is a lipid transfer protein of molecular weight 9 kD. Lettuce cross-reacts within its own family, the *Asteraceae* family, including chicory, endive, and romaine. It is an uncommon food allergen, although it has been reported in the occupational setting (Alonso et al. 1993; Fregert and Sjoborg 1982; Paulsen and Andersen 2016; Veien et al.

1983) or in the context of food-dependent exercise-induced anaphylaxis (Romano et al. 1995).

3.5.10 Inflorescent Vegetables

3.5.10.1 Broccoli

The scientific name of broccoli is *Brassica oleracea* var. *italica* and is a member of the family *Brassicaceae*. IgE-mediated reactions to broccoli are uncommon with occasional occupational contact dermatitis and other forms of allergies (Sanchez-Guerrero and Escudero 1998). Non-specific lipid transfer protein has been implicated as an potential allergen in broccoli (Pyee et al. 1994). Broccoli cross-reacts with other members within its family.

3.5.10.2 Mushrooms

Mushrooms are a large group of edible fungi. They are characterized by an exposed fruiting body. The mushroom is the reproductive part of the plant. They have been cultivated in multiple regions and used extensively as a food substance. Some common varieties that are commonly eaten are the oyster mushroom (*Pleurotus*), the shiitake mushroom (*Lentinus*), the white wood ear (Chinese translation, *Auricularia*), the champignon (*Agaricus bisporus*), and the maitake (*Grifola*). Certain varieties of mushrooms may also contain poisons or toxins or may have psychogenic properties when eaten (Chang 1996; Holsen and Aarebrot 1997). The actual allergens in mushrooms as well as their cross-reactivity have not been well studied, although enolases are considered a panallergen of mushroom (Breiteneder et al. 1992; Herrera-Mozo et al. 2006). There may be cross-reactivity to some of the environmental molds and edible mushrooms on skin testing. Mushroom can also be responsible for oral allergy syndrome (Dauby et al. 2002). Mushrooms can also be an occupational allergen and a cause of hypersensitivity pneumonitis in people who work on mushroom farms (Hoy et al. 2007; Kamm et al. 1991; Miyazaki et al. 2003; Takaku et al. 2009; Tanaka et al. 2000, 2002; Tsushima et al. 2000, 2005).

3.5.10.3 Artichoke

The scientific name of artichoke plant is *Cynara scolymus*. It is a member of the Compositae family. The lobed scale-like leaves of the immature flower heads is edible. Although mostly cultivated in the Mediterranean Basin, it is also grown in Northern California. Food allergic reactions to artichoke are rare among consumers. However, there are several case reports of occupational urticaria, rhinitis, and asthma in vegetable workers (Miralles et al. 2003; Quirce et al. 1996; Romano et al. 2000).

3.5.10.4 Cauliflower

Cauliflower is a member of the family *Brassicaceae*, and together with a number of other vegetables such as broccoli, kale, cabbage, and Brussels sprouts, they are all within the species *Brassica oleracea*. The scientific name of cauliflower is *Brassica oleracea* var. *botrytis.* Cauliflower can come in different colors, such as purple, green, orange, and white depending on the pigments each contains. No allergens from cauliflower has been identified. However, individuals allergic to other plant lipid transfer proteins may cross-react with cauliflower LTPs, and there was a case report of anaphylaxis to cauliflower (Hernandez et al. 2005).

3.5.11 Bulb Vegetables

3.5.11.1 Onion

Onion (*Allium cepa*) is a member of the family Amaryllidaceae, which also include leek, garlic, and chive commonly used in the human diet. Onion plants are cultivated for their underground bulbs, which are actually underground stems surrounded by fleshy leaves. Yellow, red, and white onions are the most common varieties available in the market. Young onion plants whose bulbs are not yet formed are also harvested and sold as scallions. Eye irritations caused by fresh cut onions are not allergic reactions to onion. Food allergy to onions is not common. A case report of systemic urticaria/angioedema after eating raw onions indicated that lipid transfer protein and another onion protein of 43 kD were IgE

reactive (Asero et al. 2001b). On the other hand, the onion lipid transfer protein is implicated as a contact allergen (Arochena et al. 2012; Enrique et al. 2007).

3.5.11.2 Garlic

The scientific name of garlic is *Allium sativum*. It belongs to the family Alliaceae or Liliaceae. Garlic has been around for some time now and is used as a spice in many cultures of the world. It is also a natural antibiotic and was called the Russian penicillin during the Second World War. Besides its antibiotic properties, garlic also has been demonstrated to have antiplatelet activity and anticancer activity. There are multiple protein bands in garlic extract, and these are thought to include activities such as a mannose-binding lectin (Smeets et al. 1997) and an alliin lyase (Kao et al. 2004). Garlic cross-reacts with other members of the Alliaceae family, including leek and chives. As a food allergen, it is considered relatively uncommon, though reports of asthma contact dermatitis and anaphylaxis have been reported (Perez-Pimiento et al. 1999; Asero et al. 1998; Ma and Yin 2012; Pires et al. 2002; Yagami et al. 2015).

3.5.12 Stalk Vegetables

3.5.12.1 Celery

Celery is a plant belonging to the family Apiaceae. The Latin name for celery is *Apium graveolens*. The edible form of celery resulted from breading the bitterness out of wild celery or smallage. Celery is an important allergen because it is responsible for oral allergy syndrome. At least one of its allergenic proteins contains cross-reactive carbohydrate determinants (Bublin et al. 2003; Fotisch et al. 1999).

3.5.12.2 Asparagus

Asparagus (*Asparagus officinalis*) is a flowering perennial plant of the Liliaceae family. They are commonly available in the market as asparagus shoots. Asparagus can cause contact dermatitis (Rieker et al. 2004; Yanagi et al. 2010), urticaria, as well as occupational rhinitis and asthma (Eng et al. 1996; Escribano et al. 1998; Lopez-Rubio et al. 1998; Sanchez et al. 1997).

Two LTPs designated as Aspa o 1.01 and Aspa o 1.02 were identified as asparagus allergens (Tabar et al. 2004). Profilin and some glycoproteins in asparagus are also likely relevant allergens (Diaz-Perales et al. 2002).

3.5.12.3 Fennel

Fennel is often used as a spice. It can be found in Southern Europe, the Middle East, Asia, and other tropical or Mediterranean climates. The scientific name is *Foeniculum vulgare*, and it belongs to the family Apiaceae, which also contains carrot (see below), caraway, parsley, and anise. Possible allergens include a lipid transfer protein and other molecules that are cross-reactive to Bet v 1. Fennel has been reported to cause oral allergy syndrome and may cross-react with pollens from birch and hazelnut (Asero 2000). An allergy to the spices of the Apiaceae family is relatively rare (Moneret-Vautrin et al. 2002).

3.5.13 Root Vegetables

3.5.13.1 Carrot

Carrot is a common root vegetable of the Umbelliferae plant family (Apiaceae). The scientific name of carrot is *Daucus carota*. Wild carrot is native in Eurasia. Domesticated carrot (*Daucus carota* subspecies *sativus*) is cultivated, and the taproots are harvested for food. Carrots are valued for carotene and are widely used in the human diet. Although most carrots in the market are orange, they can be of a variety of colors such as purple, yellow, and red. Although carrot itself is rarely involved in food allergies, systemic allergic reactions including occupational asthma and anaphylaxis due to carrots have been reported (Moreno-Ancillo et al. 2005; Fernandez-Rivas et al. 2004; Kawai et al. 2014). Dau c 1, a 16 kD Bet v1 homologue, has been identified as a carrot allergen (Hoffmann-Sommergruber et al. 1999), Dau c 3 is a lipid transfer protein, and Dau c 4 is a profilin (Asero et al. 2000; Ballmer-Weber et al.

2005). The carrot cyclophilin and Dau c 1.02, a Dau c PRP-like protein, have also been identified as IgE-reactive carrot proteins (Fujita et al. 2001; Wangorsch et al. 2012).

3.5.13.2 Turnips

The scientific name for turnip is *Brassica rapa*. It is a root vegetable widely cultivated in temperate climate and its white taproot harvested for human diet. A 2S albumin from turnip was reported be an IgE reactive to sera from subjects with positive skin prick test to turnip rape (Puumalainen et al. 2006).

3.5.13.3 Beets

Beets or beetroot is indeed a bulbous root that is usually bright red (there are other colors) and commonly used in salads. The scientific name for beetroot is *Beta vulgaris craca*, in the family Chenopodiaceae. It is extremely rare to have a food allergy to beetroot. But it can cause urine to turn red due to the pigment betalain.

3.5.14 Nightshade Vegetables

The nightshade family consists of a variety of vegetables including eggplant, tomatoes, green peppers, and potatoes. These plants belong to the family Solanaceae.

3.5.14.1 Potatoes

Potatoes are a staple food in the Western world. It has a long history and interestingly was introduced back to Europe by the Invas (circa 1500s AD). The scientific name is *Solanum tuberosum*. Characterized allergens include Sol t 1, with molecular weight of 43 kD, Sol t 2–4, and Sol t 8, which is a profilin. Although potato consists mostly of starch and other complex carbohydrates, the allergens are proteins, and potato allergy has been reported (Eke Gungor et al. 2016; Nater and Zwartz 1967; Nater and Zwartz 1968; Pearson 1966).

3.5.14.2 Tomato

Tomato is *Lycopersicon esculentum* in Latin. There are many varieties of tomato. It is used in the cuisine of almost every culture. It is a great source of vitamin C. Like other plants, tomato has a profilin (Lyc e 1, 14–16 kD) and a lipid transfer protein (Lyc e 3, 8–10 kD) (Westphal et al. 2004; Le et al. 2006). Lyc e 2 is a glycosylated beta-fructofuranosidase (Westphal et al. 2003). Some of the other allergenic proteins characterized function as enzymes, e.g., Lyc e chitinase, Lyc e peroxidase, and Lyc 3 glucanase. Tomato possesses cross-reactive carbohydrate determinants (CCDs). Like many other fruits and vegetables, tomato is not an unusually powerful antigen but can precipitate oral allergy syndrome or auriculotemporal syndrome (Sicherer and Sampson 1996).

3.5.14.3 Chili Pepper

The chili pepper we are discussing here is *Capsicum frutescens*, of the family Solanaceae. This is not white or black pepper of the family Piperaceae. Chili peppers may contain several allergens, including Cap a 1 and Cap a 2. Cap a 2 is the profilin, while Cap a 1 is a thaumatin-like protein. A Bet v 1 homologue has been isolated from some peppers. Other allergens may include a chitinase, an ascorbic acid oxidase, a 1,3-beta-glucanase, and a beta-1,4,-glucanase (Ebner et al. 1998; Jensen-Jarolim et al. 1998; Wagner et al. 2004). None of these allergens have been characterized, but there is cross-reactivity to panallergen profilins and Bet v 1. Sweet pepper has been reported to cause rhinitis and contact dermatitis (Anliker et al. 2002; Meding 1993; Niinimaki et al. 1995). Chili peppers can be involved in an oral allergy syndrome (Wagner et al. 2004).

3.5.14.4 Eggplant

Eggplant originated in India and Africa and spread to the rest of Asia and Europe and then to the Americas. The scientific name for eggplant is *Solanum melongena*. This species is the East Indian aubergine. Another name for eggplant is aubergine. Eggplant is in the family Solanaceae. There are many varieties of eggplant. Eggplant seems to cross-react with latex (Lee et al. 2004). However, like other plants, eggplants possess proteins that are known to cause allergies, such as profilin and lipid transfer proteins (Pramod and

Venkatesh 2004; Pramod and Venkatesh 2008). Recently, two proteins of 64 kD and 71 kD with polyphenoloxidase activities were demonstrated to react with IgE from eggplant allergic subjects (Harish Babu et al. 2017).

3.5.15 Other Plants

3.5.15.1 Cacao

The scientific name of cacao is *Theobroma cacao*. It belongs to the family Sterculiaceae. Cacao is used for the production of cocoa and chocolate. A 2S seed albumin storage protein of molecular weight 9 kD has been identified as coming from the cacao plant and characterized (Kochhar et al. 2001). It shows homology with other plant 2S albumin allergens. Theobromine is found in young plants, while caffeine is in higher concentrations in the mature plant. It is not known if cacao is a significant allergen, as many of the reported reactions were case reports (Perfetti et al. 1997).

3.5.15.2 Coffee

Coffee, scientific name *Coffee arabica*, is derived from a small tree that produces dried seeds. These coffee beans are then roasted, ground up, and then brewed to form one of the most consumed drinks throughout the world. Allergic reactions to coffee are rare and mostly described as case reports (Francuz et al. 2010; Jelen 2009). Cof a 1, a chitinase and two cysteine-rich metallothioneins, Cof a 2, and Cof a 3 have been identified as coffee allergens (Peters et al. 2015).

3.5.16 Meats

Allergy to meats, such as chicken, beef, pork, and lamb, is relatively uncommon. However, two conditions have brought attention to meat allergy. The first is an allergy to galactose-alpha-1,3-galactose or alpha-gal as it is commonly called (Mabelane et al. 2018). Alpha-gal is a carbohydrate present in mammalian cell membranes. The second condition is cat-pork syndrome, or pork-cat syndrome, describing an allergen cross-reactivity between two animals based on the similarities of their albumin protein structure (Wilson and Platts-Mills 2018).

Table 5 Allergens in seafood

Identified function/family	Allergen name
Parvalbumin	Gad m 1 (cod) Sal s 1 (salmon) Gad c 1 (cod)
Beta-enolase	Sal s 2 (salmon)
Aldolase	Sal s 3 (salmon)
Tropomyosin	Met e 1 (shrimp) Pen a 1 (shrimp) Pen i 1 (shrimp) Pen m 1 (shrimp) Lit v 2 (shrimp) Cha f 1 (crab) Pan s 1 (lobster) Hom a 1 (lobster) Clams (no allergens specified) Cra g 1.03 (0yster) Per v 1 (mussel) Chl n 1 (scallop) Hal m 1 (abalone)
Arginine kinase	Pen m 2 (shrimp)
Myosin light chain	Cra c 5 (shrimp)
Troponin C	Cra c 6 (shrimp)
Triosephosphate isomerase	Cra c 8 (shrimp)
Sarcoplasmic calcium-binding protein	Cra c 4 (shrimp)
Hemocyanin	Shrimp
Actin	Clams
Undefined function	Gad m 45 kD (cod)

3.5.17 Seafood

There are allergens common within the fish group and within the shellfish group. Crustaceans usually cross-react with other crustaceans and mollusks with other mollusks. This is not always the case however. The allergens found in seafood are summarized in Table 5.

3.5.17.1 Fish

In human diet, fish is a valuable source of essential amino acids, polyunsaturated fatty acids, and lipid-soluble vitamins. In addition to the parvalbumins, several other fish proteins such as enolases, aldolases, and fish gelatin seem to be important allergens (Kuehn et al. 2014).

3.5.17.2 Tilapia

Tilapia is a freshwater fish known for high protein and vitamins but low on fat content. The Nile or Black tilapia (*Oreochromis niloticus*), Blue tilapia (*O. aureus*), and Mozambique or red tilapia (*O. mossambicus*) are the three most common tilapia in the fish market. Fish allergens have been identified in many species, but there is more to be known about freshwater fish. Some of the allergens identified include parvalbumin, collagen, fructose-biphosphate aldolase, enolase, and tropomyosin. The tilapia tropomyosin has been identified as an allergen (Liu et al. 2013).

3.5.17.3 Cod

Cod is a common fish used for food. Cod is known for its protein, phosphorus, niacin, and vitamin B-12 content. Two cod species are commonly harvested for human consumption. The Atlantic cod is of the family Gadidae. Two allergens have been identified from the Atlantic cod (*Gadus morhua*) (Kuehn et al. 2014). The first is Gad m 1, a parvalbumin that is similar to Gad c1 from the Baltic cod (*Gadus callarias*), as well as a calcium-binding protein that has a molecular weight of 12.3 kD (Aas and Elsayed 1969; Aas 1966). The second allergen of the Atlantic cod, Gad m 45 kD, has an unknown function (Ebo et al. 2010). The allergens of the Baltic cod are similar, as mentioned above (Elsayed et al. 1971; Untersmayr et al. 2006; Elsayed and Bennich 1975). Gad c 1 is a 41 kD protein (Galland et al. 1998).

3.5.17.4 Salmon

Salmon is a popular human food because it is high in protein content and rich in vitamin D and omega-3 fatty acids. Atlantic, Chinook, Chum, Coho, Pink, and Sockeye salmon are popular in the US diet. About one third of the salmon consumed in the United States are wild caught. In addition to wild caught and farmed salmon, the FDA has approved genetic engineered salmon for human consumption in 2015. Genetic engineered salmon is the first genetic engineered animal in the food market. Salmon allergens for *Salmo salar* (Atlantic salmon) (Kuehn et al. 2014) include Sal s 1 (beta-parvalbumin 1, 12 kD), Sal s 2 (beta-enolase, 47.3 kD), and Sal s 3 (aldolase A, 40 kD).

3.5.17.5 Tuna

The Latin name for tuna is *Thunnus albacares*. The allergens in tuna are less cross-reactive than those of cod, salmon, and pollock (Van Do et al. 2005). There also has been data showing that the parvalbumin content in tuna is lower than other fish. It has been shown that canned tuna is less reactive than fresh tuna, illustrating the lability of antigens in the context of food processing (Sletten et al. 2010; Kelso et al. 2003).

Not all fish are discussed in this paper. The panallergen for fish is parvalbumin, which shows cross-reactivity between fish species.

3.5.17.6 Shellfish

Crustaceans

Seafood allergens belong to a group of muscle proteins, namely, the parvalbumins in codfish and tropomyosin in crustaceans (Leung et al. 1999). In shellfish, crustaceans, and mollusks, the protein tropomyosin (TM) seems to be the major allergen responsible for allergic reactions (Leung et al. 2014b). Tropomyosin belongs to the family of actin filament-binding proteins with different isoforms (Rahman et al. 2012).

Shrimp

Shrimp is one of the most common allergenic food. IgE reactivity to tropomyosin from many shrimp species have been demonstrated and designated as Met e 1 (*Metapenaeus ensis*) (Shanti et al. 1993), Pen a 1 (*Penaeus aztecus*) (Daul et al. 1994), Pen I 1 (*Penaeus indicus*) (Shanti et al. 1993), Pen m 1 (*Penaeus monodon*) (Leung et al. 1994), and Lit v 2 (*Litopenaeus vannamei*) (Samson et al. 2004). Arginine kinase (40 kD) and an unidentified component of 16.5 kD have also been reported and might be additional cross-reacting allergens playing a role in allergy to crustaceans (Shanti et al. 1993; Daul et al. 1994; Leung et al. 1994; Leung and Chu 1998). Pen m

2 from *Penaeus monodon* is identified as arginine kinase (Yu et al. 2003). Other shrimp allergens reported are sarcoplasmic calcium-binding protein (Cra c 4), myosin light chain (Cra c 5), troponin C (Cra c 6) and triosephosphate isomerase (Cra c 8) from *Crangon crangon (*Bauermeister et al. 2011*)*, and hemocyanin from *Macrobrachium rosenbergii* (Yadzir et al. 2012). Interestingly, food-dependent exercise-induced anaphylaxis associated with consumption of shrimp has been reported (Matsumoto et al. 2009).

Crab

There are multiple genera of crab. Crab is of the order Brachyura, and there are nearly 7000 species in nearly 100 families of crab. Some are extinct. Some common species of crab consumed as food are the *Charybdis feriatus*, the brown crab (*Cancer pagurus*), the blue or red swimming crabs (*Portunus pelagicus* and *haanii*, respectively), Shanghai hairy crab or Chinese mitten crab, and the European crab (*Pilumnus hirtellus*). The Dungeness crab is *Metacarcinus magister* or *Cancer magister*. The hermit crab can but is not commonly eaten. Crab is a potent allergen, sometimes causing dramatic manifestations. It may also be considered an occupational allergen for workers in the food industry. Cross-reactivity between crab, crayfish, shrimp, and lobster have been identified (Daul et al. 1992; MALO et al. 1997). The crab tropomyosin from *Charybdis feriatus* has been identified an allergen and designated as Cha f 1 (Leung et al. 1998a).

Lobster

Patients who are allergic to lobster often are also allergic to other crustaceans such as crab and shrimp (Halmepuro et al. 1987). The lobster allergens that have been identified as tropomyosin include Pan s I in the spiny lobster (*Panulirus stimpsoni*) (Leung et al. 1998b) and Hom a I in the American lobster (*Homarus americanus*) (Leung et al. 1998b).

Mollusks

Tropomyosin has been identified as the major allergen among various common edible mollusks (Leung and Chu 1998; Leung et al. 1996) such as clam, oyster, abalone, mussel, and scallop.

Clam

The mollusks tend to be cross-reactive with each other but also with crustacean tropomyosin. There are more than 150 species of clams consumed in the human diet worldwide. From a nutritional standpoint, clams are low in fat and rich in protein and minerals. In the case of clam, cross-reactivity can occur between krill and oyster (Eriksson et al. 1989). Recently, Mohamad et al. reported that tropomyosin and actin as allergens in the carpet clam (Mohamad Yadzir et al. 2015).

Oysters

Although there are more than 200 species of oysters, the two common oysters consumed in the US diet are the Eastern oyster (*Crassostrea virginica*) and the Pacific oyster (*Crassostrea gigas*).

Exercise-induced anaphylaxis may occur after ingestion of smoked oysters (Maulitz et al. 1979). The oyster tropomyosin (Cra g 1.03) has been identified as an allergen (Leung and Chu 2001).

Abalone

The scientific name of Abalone is *Haliotis midae*, and it belongs to the class Gastropoda. Lopata et al. reported five patients with RAST responses to abalone whose serum bound to two major allergens of 38 and 49 kD molecular weight. The designation Hal m 1 was assigned to the 49 kD protein, while the 39 kD protein is a tropomyosin identified from *Haliotis diversicolor.*

(Lopata et al. 2002; Lopata et al. 1997; Chu et al. 2000). The heat shock protein from *H. discus* was also reported as an allergen (Lu et al. 2004; Wang et al. 2011b).

Mussels and Scallop

The blue mussel, *Mytilus edulis*, shows cross-reactivity to oyster. The mussel tropomyosin of *Perna viridis* (Per v 1) and scallop tropomyosin of *Chlamys nobilis* (Chl n 1) have been identified as shellfish allergens (Chu et al. 2000).

Squid and Octopus

Octopus is *Octopus vulgaris* of the family Octopodidae, and squid is *Loligo edulis* or *Loligo vulgaris* of the Loliginidae family. Squid are more aggressive than octopods.

Contrary to what might be expected, squid shows more cross-reactivity to crustaceans rather than octopus or other mollusks, with the exception of oyster (Leung et al. 1996; Carrillo et al. 1992).

3.6 Special Categories

3.6.1 Stinging Insect Allergens

In the context of allergy testing and treatment, there are five important species of stinging insects, including honey bee, yellow jacket, yellow hornet, white-faced hornet, and paper wasp. In addition, reactions to the fire ant have been described, and while this is technically not a sting, it is often discussed in conjunction with the five stinging insects. Mosquito allergy has been reported but is much rare. The most common reaction from a mosquito bite is a local, usually small wheal around the bite site.

The Latin names and allergens present in stinging insects are illustrated in Table 6. In general, it is believed that bumble bees (*Bombus terrestris*) are not aggressive and also differ from honey bees in that their stinging action is not suicidal, because it possesses a retractable stinging apparatus.

3.6.2 Latex

Latex from *H. brasiliensis* contains proteins, lipids, amino acids, nucleotides, cofactors, and abundant *cis*-1,4-polyisoprene. It is the last product that is purified and cross-linked (vulcanized) with use of heat and sulfur to make rubber (Palosuo et al. 1998). The finished product contains about 2–3 percent protein (Slater 1989; Slater 1991; Sussman et al. 1991).

3.6.3 Oral Allergy Syndrome (OAS)

OAS occurs in patients with a prior cross-reactive aeroallergen sensitization and clinically presents with initial oral-pharyngeal symptoms after ingestion of a triggering fruit or vegetable. Although controversial, these symptoms may progress to systemic symptoms outside the gastrointestinal tract in 8.7% of patients and anaphylactic shock in 1.7% (Webber and England 2010).

3.7 Summary and Conclusions

This chapter describes a number of common and environmental allergens that people with allergies may be exposed to. This is in no way meant to be a complete list, but it does cover most of the common allergens. It is clear that all forms of allergic diseases have been increasing in incidence over the past 50 years, but the causes for this increase is unknown, despite the proposed "hygiene hypothesis." The identification and evaluation of food allergies have become more precise with the development of component-resolved diagnostics, and patients with a true food allergy versus oral allergy syndrome can sometimes be distinguished by measuring the levels of the distinct protein allergens in certain foods such as peanut. However, obtaining a detailed and accurate allergy history and physical remains a critical part of the management of an allergic patient. The assimilation and consideration of all types of information, including history, physical examination, and improved laboratory strategies and analysis allow us to offer directed management advice to patients, ranging from avoidance of the suspect allergen, treatment with medications, and immunotherapy (Table 7). Well-informed communication between patients, family members, and care providers is critical to optimize patient care (Scurlock and Jones 2018).

Immunotherapy has been around for over a hundred years. Our understanding of the immunologic changes that accompany immunotherapy has improved, but we still do not know why some people respond better than others (Arasi et al. 2018; Virkud et al. 2018; Scurlock 2018). The twenty-first century brings

Table 6 Stinging insect allergens

Common name	Latin name	Primary allergen (s)	Type of molecule	Size (kD)	Comments
Honey bee	*Apis mellifera*	Api m 1	Phospholipase A2	16	Differs from vespid phospholipase
		Api m 2	Hyaluronidase	39	Cross-reacts between honey bees and *Vespula* but not *Polistes*
		Api m 3	Acid phosphatase	43	
		Api m 4	Melittin	3	
Yellow jacket	*Vespula* spp.	Ves v 1	Phospholipase A1	35	
		Ves v 2	Hyaluronidase	42	
		Ves v 3	Dipeptidyl peptidase	100	
		Ves v 5	Antigen 5	25	
		Ves v 6	Vitellogenin	200	
Paper wasp	*Polistes* spp.	Pol d 1	Phospholipase A1	34	
		Pol d 4	Serine protease	33	
		Pol d 5	Antigen 5	23	
White-faced hornet	*Dolichovespula maculata*	Dol m 1	Phospholipase A2	37	
		Dol m 2	Hyaluronidase	43	
		Dol m 5	Antigen 5	23	Significantly cross-reactive among *Dolichovespula* spp., *Vespula* spp., and *Polistes* spp.
Yellow hornet	*Dolichovespula arenaria*	Similar to white-faced hornet			
Bumble bee	*Bombus terrestris*	Bom t 1	Phospholipase A2		
		Bom t 4	Serine protease		
European hornet	*Vespa crabro*		Phospholipase A		Not a particular aggressive vespid
			Hyaluronidase		
			Antigen 5		
Fire ant	*Solenopsis invicta*	Sol i 1	Phospholipase	37	
		Sol i 2		26	
		Sol i 3	Antigen 5	24	

a number of new advances in immunotherapy, ranging from oral immunotherapy to foods and to the development of antigens that will be safer and more effective (Wai et al. 2017). The antigens may be recombinant peptides derived from the amino acid sequence of the allergenic epitope or may be accompanied with immune response modifiers. Other strategies include alternate routes of administration and the design of allergen polymers. All of these are being studied now, with the promise of safer and more effective ways to minimize the impact that allergens may have on patient's quality of life.

Table 7 Clinical trials of immunotherapy

Food allergy	How	Dose	Results
Egg allergy (Tan et al. 2017)	This experiment was conducted in infants from 4 to 6 months that had a risk of developing the allergy. Risk of allergy was determined upon whether the infants had at least one relative that had the allergy to egg. A skin prick allergy test was conducted on these infants in response to egg white. Those who reacted with a reaction less than 2 mm were given either whole-egg powder (experimental) or rice powder (control) until they were 8 months old. No other eggs were provided in the diet	The dose was either an incorporation of whole-egg powder or rice power (control) in the infants' diet	If an infant who is high risk for allergy development is introducing whole-egg powder into their diet, their sensitization will be reduced
Maize and rice pollen (Ramavovololona et al. 2014)	Pollen extracts from maize and rice were detected for their IgE and IgG reactivity		Sensitization resulting from high levels of maize and rice pollen is related
Food and inhalant allergens in Turkey (Parlak et al. 2016)	The sera of undiagnosed patients were tested with an IgE test kit. Once tested, specific IgE was found among allergens on cats, dogs, grass, *Dermatophagoides pteronyssinus*, and *Aspergillus fumigatus*	Sera for IgE test classification	The most frequent allergen was related to the high consumption of milk
Dust mites and mugworts (Kim et al. 2018)	Patients who had allergy symptoms received subcutaneous immunotherapy for the allergens HDM or mugwort. BAT (basophil activation test) was done to see the response of the stimulation from the allergen before the immunotherapy was started and 3,6,12, and 24 months after beginning immunotherapy. Personal allergy symptoms were later evaluated using a survey given to the patients	Subcutaneous (specifics not mentioned)	Significant drop in BAT to mugwort after 2 years of immunotherapy. The survey showed no association to actual relief of clinical symptoms. The change in BAT for HDM correlated to the change in non-specific basophil activation
Subcutaneous pollen allergoid (Bozek et al. 2017)	Patients underwent allergen-specific immunotherapy (SIT) for pollen. The rhinitis symptom score and asthma symptom score were measured after SIT was		25% of patients showed complete relief of allergies and did not need allergy relief medication during pollen season. SIT's long-term effect did not

(*continued*)

Table 7 (continued)

Food allergy	How	Dose	Results
	finished. Patients' outcomes were grouped into three groups: (A) no symptoms or intake of medication during the treatment period, (B) no symptoms during the analysis period but there could have been medication intake, and (C) at most one mild symptom during the analysis period		significantly depend on the duration of immunotherapy against pollen
Long-term follow-up of SLIT peanut allergy trial (Burks et al. 2015)	40 patients ranging from 12- to 40-year-olds were collected were collected to test an oral dose of 10 g peanut powder after doing SLIT for 2–3 years. After 3 years of being on SLIT, those patients were also given peanut butter to test their reaction toward it	10 g peanut powder oral dose for 2–3 SLIT patients; open feeding of peanut butter for 3-year SLIT patients	98% of study members tolerated the administered doses without adverse reactions; 4/37 patients had complete and continuous desensitization and unresponsiveness to the peanut powder
Oral immunotherapy of children with anaphylactic peanut allergy (Nagakura et al. 2018)	22 peanut allergy patients underwent oral immunotherapy. Overtime, the patients increased their ingestion of peanut protein until reaching 795 mg of peanut protein per day. Once they reached 795 mg, they would maintain that dose daily. Once 3 months had passed with no symptoms displayed, they would stop their daily ingestion of the 795 mg of peanut protein for 2 weeks and retest their tolerance afterward. A second food tolerance test was given after 2 years	Increasing daily dosage of peanut protein until 795 mg is reached; food dose test was also 795 mg of protein powder	All patients had reached desensitization after 8 months of trying oral immunotherapy. For the 2-year food tolerance test, 15/22 patients had no outstanding reaction to the peanut powder
Oral immunotherapy with AR101 for peanut allergies (Bird et al. 2017)	A double-blind experiment was conducted with subjects ranging from 4 to 26 years old who were sensitive to 143 mg of peanut proteins. Subjects were assigned either daily dosages of AR101 or the placebo whose dosages went up from 0.5 to 300 mg per day. Once they reached the maximum dosage, patients were tested to see how they handled over 443 mg of peanut protein (goal was to have mild to no symptoms)	Raising dose of 0.5–300 mg of protein powder for immunotherapy; for final test, they tested for reactions toward 443 mg	For the final test, 23/29 were able to tolerate the 443 mg of peanut protein, while 18/23 were able to tolerate over 1043 mg. In the placebo group, only 5/26 were able to tolerate above 443 mg, while 0 were able to tolerate 1043 mg

(*continued*)

Table 7 (continued)

Food allergy	How	Dose	Results
Epicutaneous immunotherapy for peanut allergies (Sampson et al. 2017)	They randomly assigned patients to receive different concentrations of peanut proteins in a patch or to receive a placebo patch. After 12 months of daily patch use, the patients took a food challenge to test their tolerance toward peanuts	Concentrations of patches included 50ug, 100ug, and 250 ug	93.7% of patients were able to do the challenge. The 250ug patch and the placebo had largest difference of response rate. 100ug patch and placebo patch had a negligible difference (therefore, 50ug has negligible results too)
SLIT therapy for peaches and peanuts (Gomez et al. 2017)	48 patients who were allergic to peaches were classified into subcategories based on their peanut sensitivity (A, allergic; B, sensitized; C, tolerant). SLIT's effects were tested with skin prick tests and food challenges		After 1 year of being on SLIT, the reaction of the skin prick test decreased outstandingly, and patients had a higher tolerance to peaches. Those in group A had a significant decrease in skin prick reaction and increase in peanut tolerance. Group B and C were not mentioned in results

Comments: With oral immunotherapy and epicutaneous immunotherapy clinical trials for peanuts, there has been a higher threshold noticed for children. Oral immunotherapy has been seen to provide a larger change in threshold than epicutaneous immunotherapy, but oral immunotherapy has had more adverse reactions that occur in patients. Oral immunotherapy, epicutaneous immunotherapy, and SLIT have been noted to change the immune response toward foods (Parrish et al. 2018)

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Part II

Allergic Upper Airway Disease

Allergic Ocular Diseases

4

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Contents

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Abstract

The ocular surface may exhibit a wide variety of immunologic responses resulting in inflammation of the conjunctiva and cornea. Diagnosis of allergic conjunctivitis is generally made by thorough history and careful clinical observation. The presence of an antigen triggers the allergic cascade, and, thus, avoidance of the offending antigen is the primary behavioral modification for all types of allergic conjunctivitis (Takamura et al., Allergol Int 66:220–229,

2017; Takamura, J Jpn Ophthalmol Soc 114:831–870, 2010). In the diagnosis of allergic conjunctival diseases, it is required that type I allergic diathesis is present, along with subjective symptoms and objective findings accompanying allergic inflammation (Singh et al., J Allergy Clin Immunol 126:778–783, 2010).

Keywords

Allergic conjunctivitis · Atopic keratoconjunctivitis (AKC) · Giant papillary conjunctivitis (GPC) · Perennial allergic conjunctivitis (PAC) · Seasonal allergic conjunctivitis (SAC) · Vernal keratoconjunctivitis (VKC)

4.1 Introduction

Allergic conjunctival disease is defined as "a conjunctival inflammatory disease associated with a type I allergy accompanied by some subjective symptoms and objective findings." The traditional classification for hypersensitivity reactions is that of Gell and Coombs and is currently the most commonly known classification system (Table 1). Conjunctivitis associated with type I allergic reaction is considered allergic conjunctival disease even if other types of inflammatory reactions are involved (Takamura et al. 2017; Takamura 2010). The most common causes of allergic conjunctivitis are seasonal allergens such as pollen and mold spores. People with seasonal allergic rhinitis (hay fever) normally notice their symptoms worsen when they go outdoors on days with high pollen counts. Indoor allergens such as dust mites and pet dander can also cause eye allergies year-round. If you suffer from this type of allergy, you may notice your symptoms worsen during certain activities such as cleaning your house or grooming a pet. The commoner conditions are mild and do not affect the cornea. The rare diseases involve the cornea and can be sight-threatening. Allergic conjunctivitis is a very common condition that occurs with allergic rhinitis and contributes to burden of disease and QOL.

Table 1 Gell and Coombs classification system for various immunologic hypersensitivity reactions (Singh et al. 2010)

Type I: Anaphylaxis type (or immediate type) reactions
Immediate hypersensitivity reactions occur when a sensitized individual comes in contact with a specific antigen. Immunoglobulin E (IgE) has a strong affinity for mast cells, and the cross-linking of two adjacent IgE molecules by the antigen triggers mast cell degranulation. The mast cell's degranulation releases various preformed and newly formed mediators of the inflammatory cascade
Type II: Antibody-mediated cytotoxic type reactions
It is this type of reaction that autoantibodies bind to self-tissues and complements activated by the binding of autoantibodies injury their tissues
Type III: Immune complex-mediated type reactions
Hypersensitivity reactions result in antigen-antibody immune complexes, which deposit in tissues and cause inflammation. A classic systemic type III reaction is the Arthus reaction, and ocular type III hypersensitivity reactions include Stevens–Johnson syndrome and marginal infiltrates of the cornea. These type III reactions can often induce a corneal immune (Wessely) ring that disintegrates as the inflammatory reaction subsides
Type IV: Delayed type reactions
Hypersensitivity reactions, also known as cell-mediated immunity, are interceded by T lymphocytes. This inflammatory cell-driven reaction is also referred to as delayed-type hypersensitivity, since its onset is generally after 48 h, in contrast to the type I reaction, which is an immediate hypersensitivity. Also, type IV hypersensitivity reactions imply immunocompetence on the part of the individual since an intact immune system is required to mount the cell-mediated response. Ocular examples of type IV hypersensitivity include phlyctenular keratoconjunctivitis, corneal allograft rejection, contact dermatitis, and drug allergies
Type V: Stimulating antibody type reactions
Additional type that is sometimes (especially in the UK) used as a distinction from type II. It is a feature of this reaction that autoantibody binds but does not involve tissue damage. Instead of binding to cell surfaces, the antibodies recognize and bind to the cell surface receptors, which either prevents the intended ligand binding with the receptor or mimics the effects of the ligand, thus impairing cell signaling. These conditions are more frequently classified as type II, though sometimes they are specifically segregated into their own subcategory of type II

4.2 Classification

Allergic conjunctival disease is classified into multiple disease types according to the presence or absence of proliferative changes, complicated atopic dermatitis, and mechanical irritation by foreign body. Allergic conjunctivitis may be divided into five major subcategories: (i) Allergic conjunctivitis without proliferative change. Allergic conjunctivitis is subdivided into seasonal allergic conjunctivitis (SAC) and perennial allergic conjunctivitis (PAC) according to the period of onset of the symptoms. Whereas symptoms of SAC are occurring during one season, symptoms of PAC are occurring throughout all seasons (Singh et al. 2010); (ii) Atopic keratoconjunctivitis (AKC), complicated with atopic dermatitis (Hogan 1953; Chen et al. 2014); (iii) Vernal keratoconjunctivitis (VKC) with proliferative changes (Kumar 2009); and (iv) Giant papillary conjunctivitis (GPC) induced by irritation of a foreign body (Allansmith et al. 1977; Aswad et al. 1988). Allergic conjunctival diseases are also classified in Table 2.

4.2.1 SAC and PAC

Allergic conjunctival diseases without proliferative changes in the conjunctiva include SAC where symptoms appear in a seasonal manner and PAC where symptoms persist throughout the year. These are commonly grouped together. These common IgE-mediated diseases are related to seasonal or perennial allergens. They are characterized by symptoms of ocular itching, watering and redness, and signs of hyperemia and edema of the tarsal conjunctival surfaces. There is frequently an association with allergic rhinitis. SAC is intermittent in nature, and in temperate regions, follows exposure to pollen allergens in sensitized individuals. PAC is a mild, persistent form of allergic conjunctivitis resulting from continuing exposure to persistent allergens such as house dust mites. Allergic rhinitis is often accompanied by multiple ocular symptoms. There is an increase in the frequency of symptoms in those younger than 50 years in the populations of subjects with ocular and nasal symptoms combined and isolated nasal symptoms ($P < 0.001$) (Singh et al. 2010). Ocular symptoms are more frequent than nasal symptoms in relation to animals ($P < 0.001$), household dust ($P < 0.001$), and pollen ($P < 0.001$).

Table 2 Classification of allergic conjunctival diseases

Allergic conjunctivitis without involvement of the cornea (Singh et al. 2010)
(i) Seasonal allergic conjunctivitis (SAC)
(ii) Perennial allergic conjunctivitis (PAC)
Upper palpebral conjunctival with involvement of the cornea
(iii) Atopic keratoconjunctivitis (AKC) (Hogan 1953; Chen et al. 2014)
(iv) Vernal keratoconjunctivitis (VKC) (Kumar 2009)
Papillary conjunctivitis induced by irritation of a foreign body
(v) Giant papillary conjunctivitis (GPC) (Allansmith et al. 1977; Aswad et al. 1988)

4.2.2 AKC

This is a severe disease which is associated with atopic dermatitis. The condition is lifelong, starting in the third of fourth decade (Fig. 1). AKC is a chronic allergic conjunctival disease that may occur in patients with facial atopic dermatitis. In 1952, Hogan described this disease as a bilateral conjunctivitis occurring in five male patients with atopic dermatitis (Hogan 1953). Originally

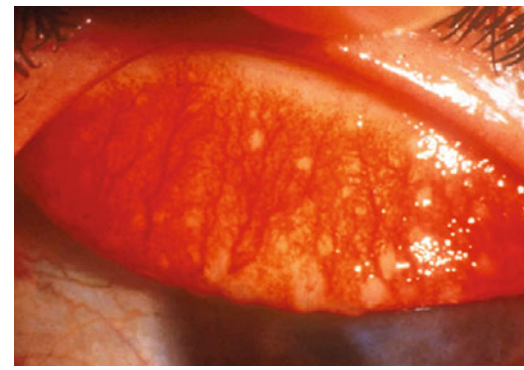

Fig. 1 Atopic keratoconjunctivitis (AKC). Upper palpebral conjunctival findings in AKC. Hyperemia, opacity, and subconjunctival fibrosis are present. Giant papillae may be present although many AKC cases have no proliferative changes

reported to flare with worsening dermatitis, atopic keratoconjunctivitis in some patients evolves independent of dermatitis (Chen et al. 2014). Atopy affects 5–20% of the general population. Atopic keratoconjunctivitis not only occurs in 20–40% of individuals with atopic dermatitis but it is also associated with a 95% prevalence of concomitant eczema and an 87% prevalence of asthma. This condition is more prevalent in men than in women, and the peak age of incidence is in persons aged 30–50 years (range, late teens to 50 years). Giant papillae may be present although many AKC cases have no proliferative changes. Upper palpebral conjunctival findings in AKC. Hyperemia, opacity, and subconjunctival fibrosis are present. IgE-mediated mechanisms may be implicated. The symptoms are perpetual ocular itching, soreness, impaired vision, and a sensation of dryness. Signs include chronic lid margin infection, chronic cicatrizing conjunctivitis, eczema of the eyelids, tear abnormality, and progressive scarring and vascularization of the cornea.

4.2.3 VKC

This is a severe inflammatory disease which may be intermittent or, less frequently, persistent (Fig. 2). VKC is, in about 60% of cases, associated with IgE-dependent hypersensitivity (Allansmith et al. 1977). Many VKC cases accompany atopic dermatitis, and atopic conditions of the external ocular surface. It characteristically affects young males in hot dry climates in a seasonal manner; however, this is not always the rule. VKC is characterized by conjunctival proliferative changes such as papillary hyperplasia of the palpebral conjunctiva or its enlargement, and swelling or limbal gelatinous hyperplasia. The symptoms are ocular watering, stickiness, itching, and difficulty with opening the eyes on awaking. If the cornea is involved, pain, blurred vision, and photophobia are experienced. The signs are giant papillary hyperplasia of the upper tarsal conjunctival surfaces, erosion of the corneal epithelium, and inflammation at the limbus. Corneal lesions with various severities including superficial punctate keratitis, corneal erosion, persistent corneal epithelial defect, corneal ulcers, or corneal plaque have been observed in VKC. Upper palpebral conjunctival findings in VKC. Conjunctival hyperemia, conjunctival edema, eye discharge, and formation of giant papillae are present.

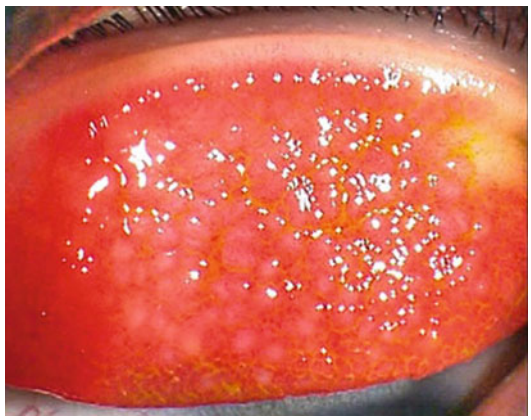

Fig. 2 Vernal keratoconjunctivitis (VKC). Upper palpebral conjunctival findings in VKC. Conjunctival hyperemia, conjunctival edema, eye discharge, formation of giant papillae are present

4.2.4 GPC

This is not a true ocular allergy but rather an repetitive mechanical irritation, often in due to contact lenses, that is aggravated by concomitant allergy (Fig. 3). This disease, also known as foreign body associated papillary conjunctivitis, results from trauma caused by contact lens edges, ocular protheses, or postoperative sutures. It may also evolve from spontaneous lid eversion resulting in conjunctival rubbing against the pillow, the so-called floppy eyelid syndrome. Upper subtarsal papillae, not always giant in size (> 1 mm), is the hallmark sign of the disease. GPC is conjunctivitis that accompanies proliferative changes in the upper palpebral conjunctiva induced by mechanical irritations such as contact lenses, ocular prosthesis, or surgical sutures. Contact lenses have become so familiar that both patients and physicians are likely to think of them as innocuous objects. They are widely prescribed for cosmetic reasons as well as to correct a variety of conditions that impair sight. But even the best tolerated contact lens is a prosthetic device on the surface of the eye and, like all

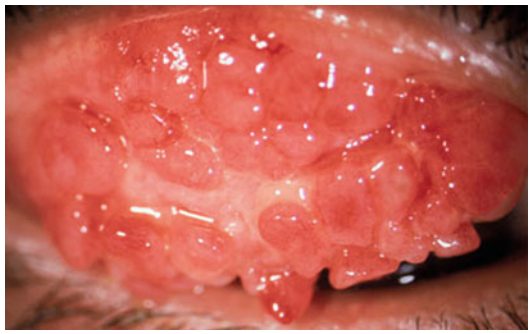

Fig. 3 Giant papillary conjunctivitis (GPC). Upper palpebral conjunctival findings in GPC. Hyperemia and dome-like giant papillae are present

prostheses, is foreign to the body. The tissues of the eye and its adnexa therefore mobilize normal responses to foreign bodies. For many contact lens wearers, the result may be minor inconvenience and relatively inconsequential problems with lens tolerance. For others, however, erythema, itching, increased mucus production, and formation of giant papillae on the upper tarsal conjunctiva may make prolonged wearing of contact lenses impossible. This disease related to wearing contact lenses and other ocular prostheses is now recognized as GPC. Hyperemia and dome-like giant papillae are present. Patients who develop GPC secondary to their wearing contact lenses for purely cosmetic reasons could, albeit reluctantly, change from contact lenses to wearing eyeglasses. But the proper care of patients who must wear contact lenses (e.g., in the event of keratoconus of high myopia) requires a range of hygienic and medical interventions to manage the possible adverse reactions to wearing contact lenses and to prevent the onset of GPC. There is no evidence that generally IgE-sensitized individuals are at greater risk of developing the disease. The cornea is rarely involved.

4.3 Causes

4.3.1 SAC

Seasonal, intermittent, allergic conjunctivitis is triggered by the same allergens responsible for intermittent allergic rhinitis. In the Northern Hemisphere these are tree pollens in April/May, grass pollens in June/July, and mold spores and weed pollens in July/August.

4.3.2 PAC

Perennial, persistent, allergic conjunctivitis is triggered by house dust mites, molds, and animal allergens, which may be present year round, although the symptoms do show some seasonal variation.

4.3.3 VKC

The majority of cases of VKC are intermittent and can occur during the high pollen season, although persistent cases do occur in warm subtropical or desert climates. Published reports of the association with IgE-mediated atopic disease vary between 15% and 60%. While there is a relationship between the condition and positive skin tests, the relationship is not necessarily causal.

4.3.4 AKC

AKC is a perennial disease which, when associated with the IgE-mediated subgroup of atopic eczema, may be exacerbated by contact with specific allergens such as house dust mites, mold spores, animal danders, and rarely foods.

4.3.5 GPC

Giant papillary conjunctivitis occurs in the presence of foreign bodies in the eye, such as contact lenses or ocular prostheses. Papillae develop on the upper tarsal conjunctiva along the line of contact with the source of mechanical trauma, e.g., the lens edge. The upper eyelid may be traumatized with each blink of the eye, which occurs between 10,000 and 12,000 times daily, and the area of trauma may serve as an entrance for antigen possibly derived from altered proteins or chemicals in contact lens solutions, although no

single causative allergen has been identified in this condition to date.

4.4 Epidemiology

Allergic conjunctivitis occurs very frequently and is seen most commonly in areas with high seasonal allergen and pollen counts. Allergic conjunctivitis is one of the most common forms of conjunctivitis. In a report from the National Health and Nutrition Examination Survey studying the epidemiology of allergic conjunctivitis, 6.4% and 29.7% of 20,010 patients reported ocular symptoms and combined ocular and nasal symptoms, respectively. Forty percentage of the population reported experiencing at least one occurrence of ocular symptoms in the past 12 months (Singh et al. 2010). On the other hand, in Japan, the proportion of persons with allergic conjunctival diseases diagnosed by ophthalmologists was 12.2% in children and 14.8% in adults. From these results, the proportion of persons with allergic conjunctival diseases in the entire population is estimated to be about 15–20%. A research group on allergic ocular disease of the Japan Ophthalmologists Association conducted epidemiologic surveys of all patients with allergic conjunctival diseases that were treated at 28 facilities (7 university attached hospitals, 5 general hospitals, and 16 ophthalmic hospitals and clinics) all over Japan during the period from January 1, 1993 to December 31, 1995 (Takamura et al. 2017). They found that female patients with SAC or PAC outnumbered male patients by 2:1, whereas male patients with VKC outnumbered female patients by 2:1. The number of patients with allergic conjunctive disease was maximum at the age of 10 and the incidence decreased with aging. The main subjective symptoms were an ocular itching, ocular hyperemia, eye discharge, and a foreign body sensation in each disease type. In SAC, symptoms of allergic rhinitis such as sneezing, rhinorrhea, nasal blockade were found in many cases.

AKC is a relatively uncommon but potentially blinding ocular condition. It occurs predominantly between the late teenage years and fifth decade of life. In 1953, Hogan described this disease as a bilateral conjunctivitis occurring in five male patients with atopic dermatitis (Hogan 1953). Originally reported to flare with worsening dermatitis, atopic keratoconjunctivitis in some patients evolves independent of dermatitis (Kumar 2009). Atopy affects 5–20% of the general population. Atopic keratoconjunctivitis not only occurs in 20–40% of individuals with atopic dermatitis but it is also associated with a 95% prevalence of concomitant eczema and an 87% prevalence of asthma. This condition is more prevalent in men than in women, and the peak age of incidence is in persons aged 30–50 years (range, late teens to 50 years). Other than atopic keratoconjunctivitis, common ocular atopic phenomena include allergic conjunctivitis, giant papillary conjunctivitis, and vernal keratoconjunctivitis.

VKC occurs predominantly in areas with tropical and temperate climates, such as the Mediterranean, the Middle East, and Africa. The limbal form of VKC commonly occurs in dark-skinned individuals from Africa and India. Also, VKC has a significant male preponderance, typically affecting young males. The onset of VKC generally occurs in the first decade and persists throughout the first two decades. Symptoms usually peak prior to the onset of puberty and then subside.

4.5 Pathophysiology

The pathological conditions of allergic conjunctival disease with lesions in the conjunctiva are assumed to be caused by interactions between various immune system cells and resident cells, which are mediated by physiologically active substances (e.g., histamine and leukotriene), cytokines, and chemokines. Eosinophils are the main effector cells in allergic conjunctival disease. Various cytotoxic proteins released from eosinophils infiltrating locally into the conjunctiva are thought to cause keratoconjunctival disorders such as severe AKC and VKC. It is also speculated that keratoconjunctival resident cells may be involved in the etiology of allergic conjunctival disease by

cytokine-stimulated production of chemokines such as eotaxin and thymus and activation-regulated chemokine (TARC) which cause eosinophil and Th2 cell migrations from the circulation, respectively.

4.5.1 SAC and PAC

The general idea is that there is an allergic response in the conjunctivitis to an allergen. The allergen causes cross-linkage of membrane-bound IgE that causes mast cells to degranulate. This causes a release and cascade of allergic and inflammatory mediators, such as histamine. Since the conjunctiva is a mucosal surface similar to the nasal mucosa, the same allergens that trigger allergic rhinitis may be involved in the pathogenesis of allergic conjunctivitis. Common airborne antigens, including dust, molds, pollen, grass, and weeds, may provoke the symptoms of acute allergic conjunctivitis, such as ocular itching, redness, burning, and tearing. The main distinction between SAC and PAC, as implied by the names, is the timing of symptoms. Individuals with SAC typically have symptoms of acute allergic conjunctivitis for a defined period of time, that is, in spring, when the predominant airborne allergen is tree pollen; in summer, when the predominant allergen is grass pollen; or in fall, when the predominant allergen is weed pollen. Typically, persons with SAC are symptom-free during the winter months in cooler climates because of the decreased airborne transmission of these allergens. Seasonal allergic conjunctivitis can manifest itself through tear film instability and symptoms of eye discomfort during the pollen season. One study found that outside the pollen season, allergic inflammation did not cause permanent tear film instability. In contrast, individuals with PAC may have symptoms that last the year round; thus, PAC may not be caused exclusively by seasonal allergens, although they may play a role. Other common household allergens, such as dust mite, cockroach dust, cigarette smoke, airborne allergens, molds, and pet dander, may be responsible for the symptoms of PAC.

4.5.2 VKC

VKC is a chronic bilateral inflammation of the conjunctiva, commonly associated with a personal and/or family history of atopic diseases. More than 90% of patients with VKC exhibit one or more atopic conditions, such as asthma, eczema, or seasonal allergic rhinitis. Corneal complications and conjunctival scarring frequently occur, particularly in more severe cases and in patients whose VKC onsets at a very young age. A personal or family history of atopy is seen in a large proportion of VKC patients. VKC was originally thought to be due to a solely IgE-mediated reaction via mast cell release. It has now been shown that IgE is not enough to cause the varied inflammatory response that is seen with VKC. Activated eosinophils are thought to play a significant role and these can be shown consistently in conjunctival scrapings; however, mononuclear cells and neutrophils are also seen. Additional attention has been given to the CD4 T-helper-2 driven type IV hypersensitivity with immunomodulators such as IL-4, IL-5, and basic fibroblast growth factor (bFGF). Thought has been given to a possible endocrine method as well as there is a decrease in symptoms and prevalence after puberty. A hereditary association has been suggested, but no direct genetic associations have been made. VKC is seen more often in patients who have atopic family histories, but no clear correlation with specific genetic loci has been elucidated (Kumar 2009).

4.5.3 AKC

The pathophysiological mechanism of disease is not fully understood. However, evidence suggest the involvement of various cells within the conjunctiva, specifically eosinophils, fibroblasts, epithelial cells, mast cells, and TH2 lymphocytes. Allergens activate these various cells creating an inflammatory response. AKC is a bilateral inflammation of conjunctiva and eyelids, which has a strong association with atopic dermatitis. It is also a type I hypersensitivity disorder with many similarities to VKC, yet AKC is distinct in a number

of ways. In 1953, Hogan first described the association between atopic dermatitis and conjunctival inflammation (Hogan 1953). He reported five cases of conjunctival inflammation in male patients with atopic dermatitis. Atopic dermatitis is a common hereditary disorder that usually first appears childhood; symptoms may regress with advancing age. Approximately 3% of the population is afflicted with atopic dermatitis, and, of these, approximately 25% have ocular involvement (Chen et al. 2014). Again, more advanced cases may result in significant conjunctival cicatrization, severe dry eye, and loss of corneal clarity through chronic or acute keratitis.

4.5.4 GPC

Because GPC is a common complication of contact lens wear, it has been called contact lens-induced papillary conjunctivitis. Spring first described giant papillary conjunctivitis in association with contact lens use, which is hypersensitivity-related inflammation of the ocular tarsal palpebral conjunctivae (Aswad et al. 1988). Prior to the popularization of hydrogel (soft) contact lenses over the past four decades, such reactions were primarily seen as immunoglobulin E (IgE)-mediated ocular allergies: allergic conjunctivitis or VKC, which occasionally becomes severe and leads to shield corneal ulcers and other complications. However, GPC related to contact lens wear never leads to the severe tissue morbidity of VKC. Giant papillary conjunctivitis symptoms and signs, such as papillary changes in the tarsal conjunctiva, have been associated with the use of all types of contact lenses (e.g., rigid, hydrogel, silicone hydrogel, piggyback, scleral, prosthetic) (Henriquez et al. 1981). A combination of type I and type IV hypersensitivity reactions may be responsible for the pathogenesis of GPC (Allansmith et al. 1977). The immediate hypersensitivity is mediated by specific IgE bound to mast cells in the conjunctival, but the nature of the specific antigen or antigens has not been discovered. The delayed inflammatory reaction is mediated by sensitized lymphocytes, reacting with antigen to release lymphokines, with resultant tissue inflammation and tissue damage. Cellular infiltration of the conjunctival epithelium with mast cells, eosinophils, basophils, and polmorphonuclear leukocytes, as well as an occasional lymphocyte, is regularly observed in GPC. Eosinophils are present in conjunctival scrapings in somewhat less than one-fourth of individuals with GPC. The involvement of mast cells, basophils, or eosinophils in abnormal positions in the conjunctival tissue reflects the disturbed nature of the immune apparatus in GPC. All GPC patients examined had one of the following abnormalities: mast cells in the epithelium, eosinophils in the epithelium or substantia propria, or basophils in the epithelium or substantia propria. It is believed that an antigen is present, in predisposed individuals, which stimulates the immunological reaction and the development of GPC. Prolonged mechanical irritation to the superior tarsal conjunctiva, of the upper lid, from any of a variety of foreign bodies may also be a contributing factor in GPC. Although contact lenses (hard and soft) are the most common irritant, ocular prostheses, extruded scleral buckles, elevated glaucoma shunts or filtering blebs, scleral shells, and exposed sutures following previous surgical intervention may also precipitate GPC.

4.6 Subjective

In seasonal and perennial allergic conjunctivitis, important features of the history include a personal or family history of atopic disease, such as allergic rhinitis, bronchial asthma, and/or atopic dermatitis. The most important feature in the clinical history is the symptom of itching, because even if tissue damage due to allergic inflammation is relatively mild, ocular injury can be large due to mechanical tissue destruction due to ocular scratching the eyes. Although anyone can endure the itching of the eyeball or eyelid while getting up, since everyone may unconsciously scratches the eyes against the itching without hesitation while sleeping, the patient education is necessary for prevention.

Without itching, the diagnosis of allergic conjunctivitis becomes suspect. Itching is the most

characteristic symptoms in allergic conjunctival disease, but some patients complain of a foreign body sensation instead. The foreign body sensation is frequently present in allergic conjunctival disease. Aside from cases where slight itching is felt as a foreign body sensation, it is very likely that when many conjunctival papillae sweep the cornea at the time of blinking, a foreign body sensation may occur. In allergic conjunctival disease, lymphocytes and eosinophils account for the majority of inflammatory cells, while neutrophils are few, serous and mucous discharge is often present, and the nature of the discharge differs from the purulent discharge associated with bacterial conjunctivitis and viscous and serous discharges found in viral conjunctivitis.

4.6.1 Subtype Specific Symptoms

4.6.1.1 SAC and PAC

Most people with allergic conjunctivitis have problems with both eyes. Symptoms may appear quickly, soon after the eyes have come into contact with the allergen. In other cases, as with some eye drops, symptoms may take from 2–4 days to appear. The following symptoms are most typical for allergic conjunctivitis:

- Eyes become red/pink
  By far the most common symptom. The eyes become irritated as the capillaries (small blood vessels) in the conjunctiva widen.
- Pain
  Some people have pain in one or both eyes. If the eyes are very red and painful, it is important to see a doctor. Any patient with painful, red eyes, and has become sensitive to light (photophobia), and feels his/her vision is affected should see a doctor straight away.
- Itchiness
  As the eyes are irritated they may itch, the itch may worsen if you keep rubbing them.
- Swollen eyelids
  The eyelids may puff up when the conjunctiva becomes inflamed or if the sufferer has been rubbing them a lot.
- Soreness
  The inflammation may make the whole area feel sore and tender. Some people say the soreness feels like burning.

People with seasonal allergic conjunctivitis will experience symptoms at certain times during the year, usually from early spring, into summer, and even into autumn. Those with perennial allergic conjunctivitis are susceptible at any time of year and may find certain times of the day are worse than others. If the eyelids are red, cracked, and/or dry, it is an indication that the patient most likely has contact conjunctivitis (Allansmith et al. 1977).

4.6.1.2 VKC

VKC is characterized by symptoms coined the term "morning misery" which described the active disease state of patients with severe itching, photophobia, foreign body sensation, mucous discharge (often described as "ropy"), tearing, blepharospasm, mucous discharge leaving them incapacitated upon awakening and "frequently resulting in lateness for school" and blurring of vision. It is typically bilateral but may be asymmetric in nature. While VKC is typically seasonally recurrent (hence the name vernal meaning springtime), 23% of patients may have a perennial form of them disease and many may have recurrences outside of the springtime (Kumar 2009). VKC is a severe allergic conjunctival disease with proliferative lesions in the conjunctiva. The proliferative lesion has giant papillae at the upper palpebral conjunctiva, limbal proliferation (limbal gelatinous hyperplasia and Horner-Trantas dots), and corneal lesions at high rates and easily becomes severe. Photophobia due to chronic keratitis is also common. Characteristic corneal lesions include exfoliated superficial punctate keratitis, shield ulcer (shield-shape ulcer), and corneal plaque. Clinical diagnosis is easy because the symptoms are characteristic. Major single-causative antigens are house dust mite, and the reaction with multiple kinds of antigens such as pollens and animal scurf occurs frequently.

4.6.1.3 AKC

In AKC, unlike VKC, the symptoms are perennial. There may be seasonal variation, however,

with worsening symptoms during winter months. The single most common symptom is bilateral itching of the eyelids, but watery discharge, redness, photophobia, and pain may be associated. Ocular signs of VKC commonly are seen in the cornea and conjunctiva. In contrast to AKC, the eyelid skin usually is not as significantly involved (Chen et al. 2014; Kumar 2009).

4.6.1.4 GPC

Primary symptoms in GPC are ocular itching with a mucoid or ropy discharge, very similar to that seen in VKC. Another symptom of GPC may be persistent foreign body sensations when using contact lenses, resulting in a decrease wear time and potential reduction in the visual acuity. Contact lens intolerance is especially problematic in patients with keratoconus who are highly dependent on contact lenses for optimal visual function (Allansmith et al. 1977).

4.7 Objective

Conjunctival hyperemia with dilated conjunctival vessels is the most frequent conjunctival finding. Conjunctival swelling is a finding that is induced by circulatory failure of the palpebral conjunctival vessels and lymphatic vessels. And in many cases, conjunctival opacity is accompanied. A conjunctival follicle is a lymphoid follicle seen under the lower palpebral conjunctival epithelium. This finding can be discriminated from papillae by the condition of a smooth dome-like prominence, which is surrounded by vessels. Conjunctival papillae are originated from epithelial proliferation in response to inflammation, in which the epithelium itself is hypertrophic. A vascular network is present from the center of the prominence, although this network is seen at the upper palpebral conjunctival fornix physiologically. Papillae of 1 mm or more in diameter, called giant papillae, are fibrous proliferative tissues found typically in VKC and GPC, and a large number of inflammatory cells such as lymphocytes, mast cells, and eosinophils are observed under the epithelium. Conjunctival edema is caused by leakage of plasma components from the vessels. Horner-Trantas dots found at the limbal region are small prominences induced by degeneration of proliferated conjunctival epithelium, in which congregated eosinophils may be present. Corneal complications in severe cases include superficial punctate keratitis, which is a partial defect of the corneal epithelium, exfoliated superficial punctate keratitis, and shield ulcer (shield-shape ulcer), which is a prolonged corneal epithelial defect.

4.7.1 Clinical Evaluation Criteria of Objective Findings

Major objective symptoms in each site of the palpebral conjunctiva, bulbar conjunctiva, limbal conjunctiva, and cornea were graded for severity and the clinical evaluation criteria were made.

4.7.1.1 Palpebral Conjunctiva

The items evaluated in palpebral conjunctival findings are hyperemia, swelling, follicles, papillae, and giant papillae. The criteria in each item are the density of dilated blood vessels for hyperemia, the scale and the presence or absence of opacity for swelling, the number of follicles in either side inferior palpebral conjunctiva where more follicles are observed than in the other side for follicle. Papillae are evaluated according to their diameter.

GPC is an immune-mediated inflammatory disorder of the superior tarsal conjunctiva. The initially small papillae eventually coalesce with expanding internal collections of inflammatory cells. As the name implies, the primary finding is the presence of "giant" tarsal papillae, which are typically greater than 0.3 mm in diameter. The most salient feature of GPC is the presence of giant papillae on the upper tarsal conjunctiva. Giant papillae are arbitrarily defined as papillae with a diameter greater than 1.0 mm, the condition is referred to as giant papillary conjunctivitis. Macropapillae (papillae with a diameter of 0.3–1.0 mm) are also abnormal (Ebert 1990). Also in VKC, the papillar findings are also graded as severe. In case with papillae of 1 mm or more in diameter, it is regarded as giant papillae, which are evaluated according to the prominence range (Chen et al. 2014).

4.7.1.2 Bulbar Conjunctiva

The bulbar conjunctiva is evaluated according to hyperemia and chemosis. Since pathologic conditions are characterized by marked hyperemia, the grade of "severe" hyperemia is defined as entire vascular dilation. Chemosis is evaluated according to its shape.

4.7.1.3 Limbal Conjunctiva

The Horner-Trantas dots is evaluated according to the number of the dots seen over the entire limbal region, and the swelling is evaluated according to the range of the salmon pink swelling observed at the scleral side of the limbus.

4.7.1.4 Cornea

The severity of the corneal epithelial defect is used as evaluation criteria. It is assumed in corneal disorders that superficial punctate keratitis is mildest and exfoliated superficial punctate keratitis is the next grade, and corneal erosion and shield ulcer follow in severity. Degenerated epithelium and mucin are deposited on the surface of the cornea and are observed as corneal plaque when corneal epithelium disorder persists. Because the condition may persist even after the inflammation is alleviated, the presence or absence of defective epithelium was not included in the grading evaluation.

4.8 Examinations

The objective of clinical examinations is to prove a type I allergic reaction in the conjunctiva and in the whole body. Clinical test methods for proving type I allergic reactions in the conjunctiva include the identification of eosinophils in the conjunctiva, instillation provocation test, and total IgE antibody measurements in lacrimal fluid. Systemic allergy tests detect antigen specific IgE antibodies in the skin and serum (Allansmith 1977).

Nonspecific examinations for type I allergy:

- Blood count of eosinophils
- Serum total IgE antibody (RIST: radioimmunosorbent test)
- Total IgE antibody measurement in lacrimal fluid
- Identification of eosinophils in the conjunctiva

Specific examinations for type I allergy:

- Serum specific IgE antibody (RAST: radioallergosorbent test)
- Histamine releasing test
- Basophil activation test
- Instillation provocation test
- Intracutaneous test
- Scratch test
- Prick test

4.9 Pathology: Histologic Findings

Allergic keratoconjunctivitis is a group of distinctive clinical disorders that are largely IgE-mediated hypersensitivity reactions but have quite similar histopathology.

As seen in the photograph, the epithelium is thickened and spongiotic, which intercellular edema or as seen here separation of epithelial cells. There is significant hyperemia with numerous eosinophils in chronic inflammatory infiltrate. However, most important is the exocytosis of eosinophils within the epithelium. The surface shows a desquamation of epithelium and inflammatory cells. Limbal papillae may occur in vernal keratoconjunctivitis (Horner-Trantas dots).

4.9.1 AKC

Conjunctival scrapings of patients with AKC may demonstrate the presence of eosinophils, although the number is not as significant as that seen in VKC. Additionally, free eosinophilic granules, which are seen in VKC, are not seen in AKC. Mast cells also may be found within the substantia propria of the conjunctiva in greater numbers (Singh et al. 2010). There is an increased amount of IgE in the tears of patients with AKC. Although AKC is typically recognized as a type I hypersensitivity reaction, evidence has been found that supports some involvement of type IV hypersensitivity reaction, as is the case in VKC.

4.9.2 VKC

Conjunctival scrapings of the superior tarsal conjunctiva show an abundance of eosinophils. Conjunctival biopsy reveals that there are a large number of mast cells within the substantia propria. Histochemical analysis of mast cells, present in VKC, reveals neutral proteases tryptase and chymase. There is an enhanced fibroblast proliferation, which leads to the deposition of collagen within the substantia propria and, as a result, induces conjunctival thickening. B-cell and T-cell lymphocytes are present locally, which combine to produce IgE. Increased total IgE antibodies in serum and lacrimal fluid and positive results for serum antigen specific IgE antibody are detected at high rates. In addition, a high positive rate of eosinophils in the conjunctival smear is found. Consequently, the definitive diagnosis is easy. Specific IgE and IgG as well as the inflammatory mediators histamine and tryptase have been isolated from tears of patients with VKC. Although VKC is typically recognized as a type I hypersensitivity reaction, evidence has been found that supports some involvement of type IV hypersensitivity reaction (Singh et al. 2010).

4.9.3 GPC

Immediate hypersensitivity of IgE-dependent anaphylactic mechanisms alone cannot account for the histologic picture in GPC. Histologic findings in GPC consist of cellular infiltration of the conjunctiva by a number of cell types. Plasma cells, lymphocytes, mast cells, eosinophils, and basophils have been identified within the substantia propria. Mast cells also may be found in the epithelium. There is also elevated tear levels of immunoglobulin, especially IgE and tryptase also are elevated, as in AKC and VKC. The degree of mast cell degranulation and tissue edema and the increase in eosinophils seen in IgE anaphylactic reactions do not include such features of GPC as increased tissue mass, presence of many inflammatory cells, extensive infiltration with eosinophils, increased number of mast cells in the substantia propria and epithelium, and the presence of basophils. The cellular infiltrate of giant papillary conjunctivitis and vernal conjunctivitis suggests a common immunologic basis for the two diseases. The mechanism of GPC is probably a basophil-rich delayed hypersensitivity (similar to cutaneous basophilic hypersensitivity) with a possible IgE humoral component. In (genetically) predisposed individuals, irritation caused by the foreign body combined with grinding the antigen repeatedly against the conjunctiva is thought to trigger a hypersensitivity response (Ebert 1990). Mechanical trauma is important in the pathogenesis of GPC. The condition is nearly universally present in patients with ocular prosthesis in whom excess mucous production can be observed. Abrasion of the upper palpebral conjunctiva by exposed suture ends (suture barb giant papillary conjunctivitis) has been reported and resolves with removal or trimming of the offending sutures). Studies of the ultrastructure of tissues from GPC patients and vernal conjunctivitis patients disclosed that patients with vernal conjunctivitis have more mast cells in the epithelium and substantia propria of the conjunctiva than do patients with GPC and that the mast cells are more completely degranulated (Allansmith et al. 1977). The greater number of mast cells in vernal conjunctivitis can explain the further findings of greater mediator-associated changes: higher tear histamine levels, more eosinophils, greater itching and inflammation, and more corneal pathology.

4.10 Diagnosis

Diagnosis of allergic conjunctivitis generally is made by taking a thorough history and by careful clinical observation. In the diagnosis of allergic conjunctival diseases, it is required that type I allergic diathesis is present, along with subjective symptoms and objective findings accompanying allergic inflammation. The diagnosis is ensured by proving a type I allergic reaction in the conjunctiva. Frequent subjective symptoms are ocular itching, hyperemia, eye discharge, foreign body sensation, ocular pain, and photophobia. The ocular itching is the most common among all

inflammatory symptoms accompanying type I allergic reactions and is important as a basis for diagnosis. Other important symptoms are hyperemia, eye discharge, and lacrimation, although those symptoms are not specific for allergic conjunctival diseases. Foreign body sensations, ocular pain, and photophobia are symptoms accompanying corneal lesions and indicate the severity of the inflammation rather than its diagnostic significance. Giant papillae, limbal proliferation (limbal gelatinous hyperplasia, Horner-Trantas dot), and shield ulcer are important objective symptoms. Conjunctival edema and follicles, papillary hyperplasia, and corneal epithelial abrasion (corneal erosion and exfoliated superficial punctate keratitis) are "intermediately specific," and conjunctival hyperemia and superficial punctate keratitis are "poorly specific." However, the symptoms and findings that form the basis of diagnoses are slightly different among the diseases as shown in Fig. 5.

4.10.1 SAC

A clinical diagnosis can be made by subjective symptoms including ocular itching, lacrimation, hyperemia, and foreign body sensation and objective symptoms including conjunctival hyperemia, conjunctival edema, and conjunctival follicles, which are found annually during the same season. The most common and important symptom of SAC is the ocular itching. Since the majority of SAC cases are conjunctivitis caused by pollen antigens, complicated symptoms of rhinitis are observed in 65–70% of cases. A positive test for serum antigen specific IgE antibody or a positive skin reaction, even in quasi-definitive diagnoses, makes it highly probable that a definite clinical diagnosis can be made. The serum total IgE antibody may be normal or mildly increased. The positive agreement rate in the measurement of the total IgE antibody in lacrimal fluid is about 70%. The exposure to a large amount of antigens may induce acute bulbar conjunctival edema. Classic signs of allergic conjunctivitis include injection of the conjunctival vessels as well as varying degrees of chemosis (conjunctival edema) and eyelid edema. The conjunctiva often has a milky appearance due to obscuration of superficial blood vessels by edema within the substantia propria of the conjunctiva. Edema is generally believed to be the direct result of increased vascular permeability caused by release of histamine from conjunctival mast cells.

4.10.2 PAC

A multiseasonal or almost perennial ocular itching, lacrimation, hyperemia, and eye discharge are subjective symptoms of PAC and conjunctival hyperemia and papilla without proliferative change in the conjunctiva are objective symptoms. Most cases pass over chronically. The major antigens are house dust mite. Because it is very likely that the clinical symptoms are mild and characteristic objective symptoms are lacking, clinical diagnosis can be difficult in some cases, especially in elderly cases. Since the positive rate of eosinophils in the conjunctival smear is low, repetitive testing becomes necessary for the proof in some cases.

4.10.3 AKC

In AKC, the atopic dermatitis is complicated with facial lesions and conjunctivitis is perennially chronic with ocular itching, eye discharge, papillary hyperplasia, and corneal lesions. Proliferative lesions such as giant papillae and limbal lesions are present in some cases. Long-term chronic inflammation may result in fornix foreshortening and symblepharon. AKC may affect eyelid skin and lid margin, conjunctiva, cornea, and lens. Skin of the eyelids may exhibit eczematoid dermatitis with dry, scaly, and inflamed skin and the lid margins may show meibomian gland dysfunction and keratinization. Moreover, staphylococcal colonization of eyelid margins is very common in AKC and may result in blepharitis. Conjunctiva may show chemosis and typically a papillary reaction, which is more prominent in the inferior tarsal conjunctiva, in contrast to that seen in vernal keratoconjunctivitis. Fibrosis or scarring of the

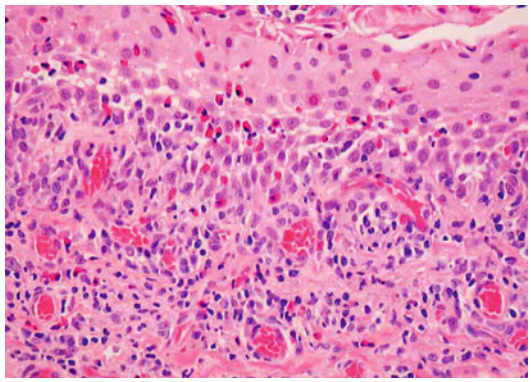

Fig. 4 Allergic keratoconjunctivitis and blepharitis inflamed by upper eyelid skin. Hematoxylin and eosin (H-E) staining. There is significant hyperemia with significant eosinophils in chronic inflammatory infiltrate. The epithelium of palpebral conjunctiva is thickened and spongiotic, which intercellular edema or as seen here separation of epithelial cells

conjunctiva may result in a shortened fornix or symblepharon formation with chronic inflammation. Corneal involvement ranges from PEK, early in the course of the disease, to neovascularization, stromal scarring, and possibly ulceration. There is also a strong association between AKC and herpes simplex labialis and herpes simplex viral keratitis. Increased total IgE antibodies in serum and lacrimal fluid and positive results of the serum antigen specific IgE antibody are found at high rates. As seen in VKC patients, the chronic eye rubbing of the cornea may contribute to the development of keratoconus. Characteristic lenticular changes in AKC include anterior or posterior subcapsular cataract formation. These slow progressing lens opacities are usually bilateral and present in the second decade of life. There is some reasonable speculation that the long-term use of topical corticosteroids can also induce the lenticular changes later in life (Fig. 4).

4.10.4 VKC

The classic conjunctival sign in palpebral VKC is the presence of giant papillae. VKC may be subdivided into two varieties as follows: palpebral and limbal. The papillae most commonly occur on the superior tarsal conjunctiva; usually, the inferior tarsal conjunctiva is unaffected. Giant papillae assume a flattop appearance, which often is described as "cobblestone papillae." In severe cases, large papillae may cause mechanical ptosis (drooping eyelid). The astute clinician's attention is always drawn to the everted upper tarsus, which reveals key telltale signs, including papillae, vascular abnormalities, conjunctival inclusion cysts, follicles, subconjunctival scarring, and entropion. A ropy mucous discharge may be present, which commonly is associated with tarsal papillae. Large numbers of eosinophils, indicating the presence of extended periods of inflammation, are present in the discharge. As the name implies, papillae tend to occur at the limbus, the junction between the cornea and the conjunctiva, and have a thick gelatinous appearance. They commonly are associated with multiple white spots (Horner-Trantas dots), which are collections of degenerated epithelial cells and eosinophils. Horner-Trantas dots rarely last longer than a week from their initial presentation and generally resolve rapidly with the initiation of topical corticosteroid therapy. While corneal vascularization is rare, the cornea may be affected in a variety of ways. Punctate epithelial keratopathy (PEK) may result from the toxic effect of inflammatory mediators released from the conjunctiva. The appearance of PEK may be a precursor for the characteristic shield ulcer, which is pathognomonic of VKC. PEK can coalesce, resulting in frank epithelial erosion and forming into a shield ulcer, which is typically shallow with white irregular epithelial borders. Although the pathogenesis of a shield ulcer is not well understood, the major factor in promoting development may be chronic mechanical irritation from the giant tarsal papillae. Some evidence suggests that the major basic protein released from eosinophils may also promote ulceration. Another type of corneal involvement is vernal pseudogerontoxon, which is a degenerative lesion in the peripheral cornea resembling corneal arcus. Keratoconus may be seen in chronic cases, which may be associated with chronic eye rubbing in predisposed individuals.

4.10.5 GPC

In cases of contact lenses, ocular prosthesis, or surgical sutures, clinical diagnosis of GPC is made when ocular itching, foreign body sensations, and eye discharge are present and conjunctival hyperemia, conjunctival edema, and papillary hyperplasia are found. GPC induced by contact lenses is called contact lens related papillary conjunctivitis. Early diagnosis is an essential component of the treatment of GPC. But, unfortunately, the earliest clues to the development of GPC in soft lens wearers are minor and are usually dismissed by patients as inconsequential: increased mucus in the nasal corner of the eye on arising and itching immediately after removing the lens. Patients, thinking that these minor signs and symptoms are "normal," may never report them to their physicians. In more severe stages of GPC, patients may complain of mild blurring of vision after hours of wearing the lens (from deposits on the lens and not corneal edema), readily apparent excess mucus, and movement of the lens on blinking. In advanced stages of GPC, patients cannot tolerate the foreign body sensation of pain associated with wearing the contact lens. Sheets or strings of mucus are present, sufficient sometimes to glue the eyes shut on waking in the morning. At this stage, the lenses are visibly clouded by mucus soon after they are inserted. Abnormal amounts of deposits on the soft lenses are a constant feature of the syndrome. Deposits on the lens are most easily seen by drying the lens slightly and looking through it against a light. Although some asymptomatic wearers of soft contact lenses may also produce heavy deposits on their soft lenses, all symptomatic wearers do. Usually, patients report the symptoms of GPC long before the appearance of definitive clinical signs. Furthermore, patients vary widely in how much ocular discomfort they will tolerate from various degrees of GPC. Some patients may continue wearing their soft contact lenses despite scores of giant papillae covering both upper tarsal plates. Other patients may stop wearing their soft contact lenses because of the itching and increased mucus, although the only definitive sign of GPC is conjunctival thickening. Such patients will complain of lens intolerance even though no giant papillae are apparent. Early in the clinical stage of GPC, the normally small papillae become obscured by more elevated ones. Small normal papillae do not enlarge to become giant papillae; new abnormal papillae begin to grow from the substructure of the deep conjunctival or tarsal area. At this point, there is a generalized thickening of the conjunctiva. The conjunctiva has a translucent rather than transparent appearance, and the vasculature of the plate becomes more visible. The conjunctiva may appear hyperemic. Giant papillary conjunctivitis represents the most severe cases, which present with giant papillae of 1 mm or larger in diameter. The involvement of type I allergy is unknown in some cases and positive results for serum antigen specific IgE antibody are not frequent. A positive rate of eosinophils in GPC is rarer than that in other allergic conjunctival diseases. Examination of superior tarsal conjunctiva reveals the presence of large cobblestone papillae, which are generally 0.3 mm or greater in diameter. In the more aggravated stage of GPC, the conjunctiva loses translucency to become more opaque (due to cellular infiltration), and it is possible to observe the earliest demarcations of macropapillae (0.3–1.0 mm) or giant papillae (1.0 mm or greater) (Ebert 1990). As the disorder progresses, giant papillae increase in size and elevation. The surface flattens to produce a mushroom appearance devoid of remnants of the small papillary pattern. As the number and size of giant papillae increase, they may almost completely cover zones 1 and 2 with papillae ranging in size from 0.6 to 1.75 mm in diameter, with most approximately 0.75–1.0 mm in diameter. Papillae and follicles resemble each other in some respects, and both are signs of active inflammation in the palperbral conjunctiva. Giant papillae are distinguished from follicles, however, by the presence of blood vessels in the centers of the follicles as well as around the edges. Follicles are more commonly observed in the inferior palpebral conjunctiva and the inferior fornix. Papillae are more commonly observed in the upper palpebral conjunctiva. The side walls of papillae are often perpendicular to the plane of the tarsal plate and not pyramidal-like follicles. Papillae may have

white heads resembling scars. These white, scar-like areas usually regress as the papillae regress. Some patients with GPC may have Horner-Trantas dots. A network of fine dilated blood vessels may be observed in GPC. The disease may also be confined to the limbus in some patients, with no infiltration of the lid.

4.11 Differential Diagnosis

Ocular itching is a cardinal symptom of allergic eye disease and in the absence of itching, an alternative diagnosis should be suspected. Allergic conjunctivitis must be differentiated from viral and bacterial conjunctivitis. Clinical features (e.g., recent exposure to an individual with infective conjunctivitis) may be helpful in this regard (Fig. 5). Infectious conjunctivitis such as viral, bacterial, Chlamydia, non-inflammatory conjunctival folliculosis, and dry eye are considered as differential diagnosis. Also, differential diagnosis is also necessary for ocular and conjunctival symptoms associated with contact dermatitis (Friedlaender 1998; Niederkorn 2008). The main distinction between seasonal and perennial allergic conjunctivitis, as implied by the names, is the timing of symptoms. Major differentiating factors between AKC and VKC, and other diseases are as references are shown in Table 2.

4.12 Treatments

Avoidance of the offending antigen is the primary behavioral modification for all types of allergic conjunctivitis. Perennial avoidance and elimination of antigens can be achieved by arranging the patient's daily living environment, especially their indoor environment. In contrast, the avoidance of pollen antigens is conducted mainly during the pollen-flying period, and it is necessary to take measures so that the daily activities of the patient will not be prevented by exposure to pollens. During pollen-flying period, goggle-type glasses are recommended to carry out daily activities such as riding a bicycle and having a stroll with a dog, although even glasses themselves can reduce

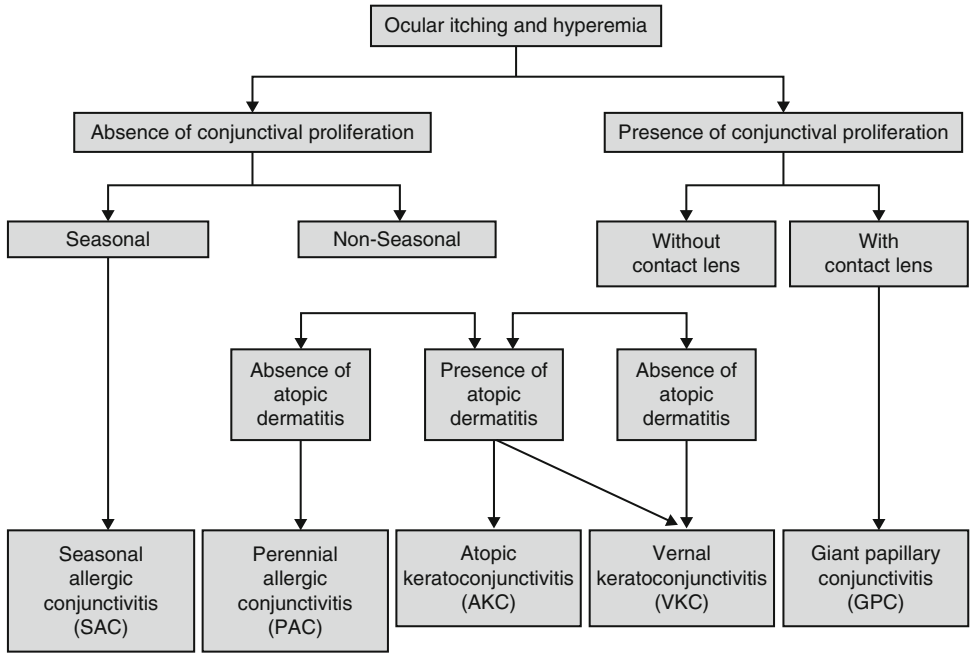

Fig. 5 Diagnostic flowchart of allergic conjunctival diseases. (Japanese Society of Allergology) http://www.allergologyinternational.com/article/S1323-8930(16)30173-3/fulltext#cebib0010

the amount of pollen flying into the ocular surface. In other respects, management of allergic conjunctivitis varies somewhat according to the specific subtypes. During the pollen-flying period, it is useful to stop inserting contact lenses as much as possible, changing to glasses to avoid antigens (Table 3).

In seasonal and perennial allergic conjunctivitis, superficial conjunctival scrapings may help to establish the diagnosis by revealing eosinophils, but only in the most severe cases, since eosinophils are typically present in the deeper layers of the substantia propria of the conjunctiva. Therefore, the absence of eosinophils on conjunctival scraping does not rule out the diagnosis of allergic conjunctivitis. Many investigators have described measurement of tear levels of various inflammatory mediators, such as IgE, histamine, and tryptase, as indicators of allergic activity (Bielory et al. 2012). Additionally, skin testing by an allergist may provide definitive diagnosis and pinpoint the offending allergen(s). Skin testing is now highly practical and readily available to all practicing ophthalmologists, as well as to optometrists in some states. Allergy-specific tear and conjunctival scraping laboratory tests are not currently available except in academic or commercial research settings. Similarly, impression cytology techniques are potentially enlightening yet available to only a few dedicated research centers and ophthalmology-specific diagnostic laboratories. Conjunctival scrapings can be sent to hospital cytology laboratories and may be useful if a pathologist with a particular interest in ocular diseases is readily available.

Drug treatment is the preferred treatment for allergic conjunctival diseases. The first option is antiallergic eye drops, which are the basic treatment for allergic conjunctivitis, followed by the differential use of steroid eye drops as necessary according to the severity. Pharmacologic intervention may be necessary to help alleviate the symptoms of acute allergic conjunctivitis. Various classes of medication may be effective against the symptoms of acute allergic conjunctivitis; each is directed at a specific point in the inflammatory and allergic cascade. Allergic conjunctivitis can be treated with a variety of drugs. These include

Table 3 Risk factors

Grouping	Type	Risk factors
Without corneal involvement	Acute	Environmental allergens, particularly if they are known; an example is cat dander
	Seasonal	Environmental allergens that are often associated with changes in seasons; examples include grass and weed pollens
	Perennial	Environmental allergens that occur throughout the year; examples include indoor allergens: dust mites, mold, animal dander
With corneal involvement	Vernal	Environmental allergens may incite an acute exacerbation. Most commonly present during the springtime with the associated increase in pollen. Increased presence in hot and dry environments with a decrease in inflammation and symptoms during the winter months
	Atopic	Genetic predisposition to atopic reactions with comorbid asthma and atopic dermatitis commonly present. Increased risk with positive family history. Environmental allergens may cause an acute exacerbation as well. No changes with seasons
	Giant papillary	Commonly seen in individuals wearing soft contact lens who infrequently replace their lenses, wear their lenses for prolonged periods of time, have poor lens hygiene, have poor contact lens fitting, or are allergic to the various contact lens solution. Similarly, irritation from exposed sutures or prostheses increases the risk for developing GPC

Citation: http://eyewiki.aao.org/Allergic_conjunctivitis. American Academy of Ophthalmology Eye Wiki, 2014

topical antihistamines, mast cell stabilizers, nonsteroidal anti-inflammatory drugs (NSAIDs), and corticosteroids. As always, care must be taken when using topical corticosteroids; pulsed regimen is recommended to minimize adverse reactions.

In VKC, conjunctival scrapings of the superior tarsal conjunctiva and of Horner-Trantas dots show an abundance of eosinophils. Conjunctival scrapings of patients with AKC may demonstrate the presence of eosinophils, although the number is not as significant as that seen in VKC. Additionally, free eosinophilic granules, which are seen in VKC, are not seen in AKC. For severe AKC and VKC, additional use of immunosuppressive eye drops, steroid oral medicines, subtarsal conjunctival steroid injection and surgical treatment such as papillary resection should be considered. Advanced point-of-service testing may soon become available through several diagnostic technology companies. Biomarkers such IgE, matrix metalloprotease-9 (MMP-9), or eosinophilic basic protein (EBP) may prove to be clinically useful surrogates for disease activity level and therapeutic response monitoring. Specimens can be obtained by tear sampling or conjunctival scraping techniques (Table 4).

4.12.1 Subtarsal Conjunctival Injection of Steroid Suspension

Triamcinolone acetonide or betamethasone suspension is injected to the subtarsal conjunctiva of the upper eyelid in intractable or severe cases. With caution for the elevation of intraocular pressure, it is desirable to avoid repeated use or the application to children aged less than 10 years.

4.12.2 Ophthalmic Lubricants

Lubricants act as humectants in the eye. Artificial tear, as mentioned below, substitutes provide a barrier function and help to improve the first-line defense at the level of conjunctival mucosa. The ideal artificial lubricant should be preservative-free; contain potassium, bicarbonate, and other electrolytes; and have a polymeric system to increase its retention time. Lubricating drops are used to reduce morbidity and to prevent complications. Lubricating ointments prevent complications from dry eyes. Ocular inserts reduce symptoms resulting from moderate to severe dry eye syndromes.

4.12.3 Artificial Tears: Altalube, Bion Tears, HypoTears, LiquiTears, Soothe, Systane, Tears Again, Viva-Drops

Artificial tears are used to increase lubrication of the eye. Nonpreserved artificial tears are recommended for use. Tears should be applied liberally throughout the day, and, if necessary, a lubricating ointment may be used at night. These agents help to dilute various allergens and inflammatory mediators that may be present on the ocular surface, and they help flush the ocular surface of these agents. Chilled tears, as well as any topical medication, provide an added degree of relief. Similarly, cold compresses can be extremely useful to avoid the customary irrational rubbing response to chronic or paroxysmal pruritus.

4.12.4 Antiallergic Eye Drops

Histamine H1 receptor antagonists block histamine H1 receptors, representative mediators released through the degranulation of mast cells, which results in suppression of hyperemia and ocular itching. Mast cell stabilizer inhibits the degranulation of mast cells and suppresses release of mediators (e.g., histamine, leukotriene, thromboxane A2), consequently, the early phase reaction to type I allergy is inhibited, and conjunctival local infiltration of inflammatory cells is curtailed, resulting in a reduction of the late phase reaction.

4.12.5 Antihistamines

These agents act by competitive inhibition of histamine at the H1 receptor and thus block the

Table 4 Differential diagnosis

Infectious conjunctivitis
A variety of microorganisms, such as viral, bacterial, and *Clamydia*, may infect the conjunctiva. Viral and bacterial conjunctivitis are quite contagious, easily passing from one person to another, or from a person's infected eye to the uninfected eye
Phlyctenular keratoconjunctivitis
Phlyctenular keratoconjunctivitis has been defined as a nodular inflammation of the cornea or conjunctiva that results from a hypersensitivity reaction to a foreign antigen, which is postulated to occur secondary to an allergic, hypersensitivity reaction at the cornea or conjunctiva, following reexposure to an infectious antigen that the host has been previously sensitized to
Toxic conjunctivitis
Typically, toxic conjunctivitis occurring with protracted use of topical ocular medications. Toxic ocular reactions are most frequently reported in patients with glaucoma, especially who are on lifelong therapy with multiple medications
Contact dermatitis
Contact dermatitis is not an IgE-mediated allergy and can be considered in a different category than the before mentioned allergic conditions (Molinari 1982). Allergens are generally simple chemicals, low molecular weight substances that combine with skin protein to form complete allergens. Examples include poison ivy, poison oak, neomycin, nickel, latex, atropine and its derivatives. Contact allergy involves the ocular surface, eyelids and periocular skin, although contact allergic reactions usually occur on the skin, including the skin of the eyelids, the conjunctiva may also support contact allergic reactions. Initial sensitization with a contact allergen may take several days. Upon reexposure to the allergen, an indurated, erythematous reaction slowly develops. The reaction may peak 2–5 days after reexposure. The delay in development of the reaction is due to the slow migration of lymphocytes to the antigen depot. The term "delayed hypersensitivity" is sometimes given to these reactions, in contrast to "immediate hypersensitivity," a term which emphasizes the rapid development of IgE antibody-mediated reactions. Contact allergic reactions are generally associated with itching. Treatment consists of withdrawing and avoiding contact with allergen. Severe reactions can be treated with topical or systemic corticosteroids. It is a type-IV delayed hypersensitivity response, that occurs through interaction of antigens with Th1 and Th2 cell subsets followed by release of cytokines (Kashima et al. 2014). It consists of two phases: sensitization at the first exposition to the allergen, with production of memory T-lymphocytes), and elicitation of the inflammatory response at the reexposure to the antigen, mediated by the activation of memory allergen-specific T-lymphocytes
Non-inflammatory conjunctival folliculosis
Conjunctival folliculosis is a fairly common benign, bilateral, non-inflammatory disorder characterized by follicular hypertrophy of the palpebral conjunctivae. Vessels are present at the edge of the follicle, in contrast to conjunctival papillae
Keratitis
Keratitis is an inflammation of the cornea sometimes caused by an infection involving bacteria, viruses, fungi, or parasites. Noninfectious keratitis can be caused by a minor injury, wearing your contact lenses too long, or other noninfectious diseases
Blepharitis
One of the most common ocular conditions characterized by inflammation, scaling, reddening, and crusting of the eyelid
Dry eyes syndrome
Dry eye syndrome is caused by a chronic lack of sufficient lubrication and moisture on the surface of the eye. Consequences of dry eyes range from subtle but constant eye irritation to significant inflammation and even scarring of the front surface of the eye
Ocular rosacea
Chronic inflammatory acneiform skin condition that leads to erythema of the skin on the face and neck. It is thought to represent a type IV hypersensitivity reaction **(**Table 1**)**
Episcleritis/scleritis
Episcleritis and scleritis are inflammatory conditions which affect the eye. Scleritis is much more serious and less common than episcleritis. Episcleritis affects only the episclera, which is the layer of the eye's surface lying directly between the clear membrane on the outside (the conjunctiva) and the firm white part beneath (the sclera). Scleritis affects the sclera and, sometimes, the deeper tissues of the eye. Both can be associated with other conditions such as rheumatoid arthritis and systemic lupus erythematosus (SLE), although this is more likely in the case of scleritis. Episcleritis does not cause scleritis, although scleritis can lead to associated episcleritis

(*continued*)

Table 4 (continued)

Angle closure glaucoma
Glaucoma is a nonspecific term used for several ocular diseases that ultimately result in increased intraocular pressure and decreased visual acuity. Primary angle closure is defined as an occludable drainage angle and features indicating that trabecular obstruction, which results in increased intraocular pressure, by the peripheral iris has occurred. The term glaucoma is added if glaucomatous optic neuropathy is present. The sudden and severe intraocular pressure elevation can quickly damage the optic nerve, resulting in acute angle-closure glaucoma

effects of endogenously released histamine. Systemic and/or topical antihistamines may be prescribed to relieve acute symptoms due to interaction of histamine at ocular H1 and H2 receptors (Gonzalez-Estrada et al. 2017). While systemic antihistamines often relieve ocular allergic symptoms, patients may experience systemic adverse effects, such as drowsiness and dry mouth.

- Emedastine difumarate (Emadine®)
  This agent is a relatively selective H1 receptor antagonist for topical administration. The 0.05% ophthalmic solution contains 0.884 mg/mL of emedastine difumarate.
- Epinastine (Elestat®)
  A direct H1 receptor antagonist, epinastine does not penetrate the blood–brain barrier and therefore should not induce adverse CNS effects. It is indicated for symptoms due to allergic conjunctivitis.
- Azelastine ophthalmic
  Azelastine, now available as a generic, competes with H1-receptor sites on effector cells and inhibits release of histamine and other mediators involved in the allergic response.
- Bepotastine besilate ophthalmic solution (Bepreve®)
  Bepotastine besilate is a topically active antihistamine that directly antagonizes H1-receptors and inhibits release of histamine from mast cells. It is indicated for itching associated with allergic conjunctivitis.
- Alcaftadine ophthalmic (Lastacaft®)
  An H1-receptor antagonist indicated for prevention of itching associated with allergic conjunctivitis, alcaftadine inhibits histamine release from mast cells, decreases chemotaxis, and inhibits eosinophil activation. It is available as a 0.25% ophthalmic solution.
- Cetirizine ophthalmic (Zerviate®)
  H1 receptor antagonist inhibits histamine release from mast cells, decreases chemotaxis, and inhibits eosinophil activation. Indicated for ocular itching associated with allergic conjunctivitis. It is administered twice daily.

Topical antihistamines competitively and reversibly block histamine receptors and relieve itching and redness but only for a short time. These medications do not affect other proinflammatory mediators, such as prostaglandins and leukotrienes, which remain uninhibited. A number of topical antihistamines are available, including epinastine (Elestat) and azelastine (Optivar®). Both are potent antihistamines that have a rapid onset and are effective in relieving the signs and symptoms of allergic conjunctivitis.

4.12.6 Mast Cell Stabilizers

Mast cell stabilizers inhibit the degeneration of sensitized mast cells when exposed to specific antigens by inhibiting the release of mediators from the mast cells (Finn and Walsh et al. 2013). The end result is a decrease in degranulation of mast cells, which prevents release of histamine and other chemotactic factors that are present in the preformed and newly formed state. Note that mast cell stabilizers generally do not relieve existing symptoms and are to be used on a prophylactic basis to prevent mast cell degranulation with subsequent exposure to the allergen. Therefore, they need to be used long term in conjunction with various other classes of medications. Common mast cell stabilizers include cromolyn sodium and lodoxamide (Alomide). Alcaftadine (Lastacaft), bepotastine (Bepreve®), olopatadine

(Patanol®), nedocromil (Alocril®), and ketotifen (Zaditor®) are also mast cell stabilizers with additional antihistamine properties and proactively inhibit histamine release while blocking subsequent distal pathway histamine receptors. These agents block calcium ions from entering the mast cell. Olopatadine is a relatively selective H1 receptor antagonist and inhibitor of histamine release from mast cells.

- Lodoxamide tromethamine (Alomide®)
  Lodoxamide is a mast cell stabilizer. The active ingredient in this product is 1.78 mg lodoxamide tromethamine.
- Olopatadine (Patanol®, Pataday®, Pazeo®)
  Olopatadine is a relatively selective H1 receptor antagonist and inhibitor of histamine release from mast cells. The active ingredient of Patanol is 1.11 mg olopatadine hydrochloride; Pataday is 2.22 mg olopatadine hydrochloride.
- Ketotifen (Zaditor®, Alaway®)
  Ketotifen is an over-the-counter (OTC) antihistamine eye drop. It is a noncompetitive H1-receptor antagonist and mast cell stabilizer. This agent inhibits release of mediators from cells involved in hypersensitivity reactions.
- Nedocromil ophthalmic (Alocril®)
  Nedocromil interferes with mast cell degranulation, specifically with release of leukotrienes and platelet activating factor.

4.12.7 Vasoconstrictors

Vasoconstrictors are available either alone or in conjunction with antihistamines to provide short-term relief of vascular injection and redness. Common vasoconstrictors include naphazoline, phenylephrine, oxymetazoline, and tetrahydrozoline. Generally, the common problem with vasoconstrictors is that they may cause dependency with resultant rebound conjunctival injection and inflammation. These pharmacologic agents are ineffective against severe ocular allergies and against other more severe forms of allergic conjunctivitis, such as atopic and vernal disease. They induce chemical tolerance and progressive tachyphylaxis, thereby adding continuously increasing medication and preservative toxicity to the clinical picture.

- Nonsteroidal Anti-inflammatory Drugs (NSAIDs)
  The mechanism of action of NSAIDs is believed to be through inhibition of the cyclooxygenase enzyme that is essential in the biosynthesis of prostaglandins, which results in vasoconstriction, decrease in vascular permeability and leukocytosis, and a decrease on intraocular pressure. NSAIDs act on the cyclooxygenase metabolic pathway and inhibit production of prostaglandins and thromboxanes. They have no role in blocking mediators formed by the lipoxygenase pathway, such as leukotrienes. Common NSAIDs that are approved for allergic indications include ketorolac tromethamine (Acular®).
- Ketorolac tromethamine (Acular®, Acuvail®)
  A member of the pyrrolo-pyrrole group of NSAIDs, ketorolac inhibits prostaglandin synthesis by decreasing activity of the enzyme cyclooxygenase, which results in decreased formation of prostaglandin precursors; in turn, this results in reduced inflammation. The active ingredient is 0.5% ketorolac tromethamine.

4.12.8 Corticosteroids

Corticosteroids have both anti-inflammatory (glucocorticoid) and salt retaining (mineralocorticoid) properties. Glucocorticoids have profound and varied metabolic effects (Abelson et al. 2015). In addition, these agents modify the body's immune response to diverse stimuli. Corticosteroids remain among the most potent pharmacologic agents used in the treatment of chronic ocular allergy. They act at the first step of the arachidonic acid pathway by inhibiting phospholipase, which is responsible for converting membrane phospholipid into arachidonic acid. By preventing the formation of arachidonic acid, corticosteroids effectively block both cyclooxygenase and lipoxygenase pathways, in contrast to NSAIDs, which act only on the cyclooxygenase pathway. Corticosteroids do have limitations, including

ocular adverse effects, such as delayed wound healing, secondary infection, elevated intraocular pressure, and formation of cataract. In addition, the anti-inflammatory and immunosuppressive affects are nonspecific. As a rule, topical steroids should be prescribed only for a short period of time and for severe cases that do not respond to conventional therapy. Severe forms of ocular allergy may require chronic steroid maintenance therapy to avoid permanent structural damage to the ocular surface and central corneal stroma. Corticosteroids exist in various forms and potencies. Relatively weak steroids, such as rimexolone, medrysone, and fluorometholone, tend to have less potency in the eye, with fewer ocular adverse effects. In contrast, agents such as prednisolone acetate and difluprednate are more potent and have a higher incidence of adverse effects.

Loteprednol etabonate (Lotemax® 0.05% and Alrex® 0.02%), is an ester steroid, which is rapidly metabolized once it enters the anterior chamber of the eye. Therefore, it is extremely useful in treating ocular surface and superficial corneal inflammations owing to its favorable safety profile and therapeutic index. Alrex has a specific indication for ocular allergy and has been shown in clinical studies to have fewer ocular adverse effects. Lotemax® is indicated and FDA approved for SAC and for GPC with concomitant contact lens use.

- Loteprednol etabonate (Lotemax®, Alrex®)
  This agent decreases inflammation by suppressing migration of polymorphonuclear leukocytes and reversing increased capillary permeability. It is a topical ester steroid eye drop that poses a decreased risk of glaucoma. It is available in 0.2% and 0.5% concentrations, as well as a gel formulation, a preservative-free ointment preparation, and in combination with tobramycin (Zylet®, Bausch & Lomb).

4.12.9 Immunotherapy

Immunotherapy is a mainstay in the systemic management of allergies. Traditionally, immunotherapy is delivered via subcutaneous injection (Wahn et al. 2012). However, sublingual (oral) immunotherapy (SLIT) is gaining momentum among allergists. Numerous articles have analyzed the effects of SLIT on allergic conjunctivitis. Preliminary indications are that SLIT may have a moderate effect on the signs and symptoms of allergic conjunctivitis, but further analysis is necessary. A 2012 study confirmed that SLIT may significantly reduce symptoms in children with grass pollen–allergic rhinoconjunctivitis. The preparation studied had significant effects on allergen-specific antibodies and was well tolerated.

4.12.10 Immunosuppressive Eye Drops

At present, two kinds of immunosuppressive eye drops (cyclosporine and tacrolimus) have been approved as treatment drugs for VKC. Immunosuppressive eye drops are expected to have equivalent or better effects than steroid eye drops. Cyclosporine enables the gradual reduction of the doses of steroid eye drops by combined administration with antiallergic eye drops and steroid eye drops. Tacrolimus itself also has effects on steroid-resistant severe cases (Ohashi et al. 2010).

4.13 Surgical Treatments

Severe cases of corneal shield ulcer may require superficial keratectomy to promote epithelial regeneration. This debridement also serves to obtain a direct culture specimen in the event that secondary infection ensues and helps guide prophylactic topical antimicrobial therapy. Generally, shield ulcers are chronic conditions that are often refractory to conventional therapy. There have been reports of excimer laser phototherapeutic keratectomy (PTK) being used to remove fibrin deposits on the Bowman layer and theoretically facilitate epithelial healing. Other surgical procedures, such as cryoablation of giant papillae or surgical removal of papillae with mucosal grafting, generally are not required, but they may

Table 5 Surgical therapies

Superficial keratectomy
Shield ulcer plaques, consisting of epithelial and inflammatory debris at the base of an ulcer, often are resistant to treatment with topical anti-inflammatory therapy. Superficial keratectomy may be required to remove plaques or debride shield ulcers and allow epithelialization. Medical treatment must be maintained until the cornea has reepithelialized in order to prevent recurrences
Excimer laser PTK
Excimer laser phototherapeutic keratectomy is an alternative to remove plaques or debride shield ulcers and allow epithelialization
Penetrating keratoplasty (full-thickness corneal transplant)
Corneal scarring and occasionally perforation may occur in severe cases and necessitate penetrating keratoplasty
Papillary resection
Papillary resection with or without mitomycin-C (MMC) application has been described as a method to reduce ocular surface inflammation
Surface maintenance/restoration procedures
Surface maintenance/restoration procedures may be required for severe persistent epithelial defects or ulceration. Various procedures may be
1. Amniotic membrane overlay grafting
2. Lamellar keratoplasty (partial-thickness corneal transplant)
3. Eyelid procedures such as botulinum toxin-induced ptosis or lateral tarsorrhaphy (surgical fusion of upper and lower eyelid margin to narrow the eyelid opening)
4. Gluing may be appropriate for focal ("punched-out") corneal perforations
Eyelid surgery
In advanced AKC, extensive scarring of the ocular surface and eyelid margins may necessitate eyelid surgery. This includes lid margin tightening and rotational procedures for lid mal-position, as well assymblepharon lysis and forniceal reconstruction for severe conjunctival scarring
Cataract surgery
Many patients will require cataract surgery at a relatively young age due to atopic and steroid-induced cataract development
Glaucoma surgery
A few patients may need glaucoma filtering surgery or valve placement if steroid-induced glaucoma develops
Stem cell transplantation
Patients who develop limbal stem cell deficiency may require ocular surface stem cell transplantation for visual rehabilitation. Associated systemic conditions should be treated as well. Uncontrolled dermatitis with vision-threatening complications requires systemic steroids. Any associated Herpes simplex keratitis should be treated with topical antiviral agents. Recurrent attacks of Herpes infection may require systemic antiviral also

be helpful in extremely advanced cases. Remember that since VKC is a self-limited disease, extensive reconstructive surgery may not have an acceptable risk-benefit ratio. Important surgical therapies are summarized in Table 5.

4.14 Complications

If you have seasonal or perennial allergic conjunctivitis, it is very rare to experience any serious complications. However, you may find your reoccurring symptoms frustrating. For example, if your conjunctivitis is caused by pollen, you may find it difficult to go outside during the spring and summer months without triggering your symptoms. This type of allergic conjunctivitis can affect your daily life and could make it difficult for you to concentrate at work or school, particularly if your eyes are severely irritated. Although this can affect your quality of life, it should not cause any long-term health problems.

4.14.1 VKC

Visual loss may be due to keratoconus and corneal scars, as well as complications of the

unsupervised use of topically administered corticosteroids.

4.14.2 GPC

Complications may arise if GPC is not treated. The complications could include:

- Prolonged discomfort, mental and emotional stress.
- Corneal damage, scar.
- Multiple damage to the eye conditions.
- Bacterial or viral (herpes simplex) infections can occur superimposed.

4.15 Prognosis

Since allergic conjunctivitis generally clears up readily, the prognosis is favorable. Complications are very rare, with secondary corneal ulcers or keratoconus occurring rarely. Although SAC, PAC, and GPC commonly reoccur, they rarely cause any visual loss. Conversely, VKC and AKC are frequently associated with significant risk of progressive corneal damage and resultant visual loss. In general, the prognosis of SAC and PAC is good despite significant discomfort and undesirable cosmetic consequences. Occasionally, individuals with chronic recurrences develop significant conjunctivochalasis or, less commonly, a corneal Dellen secondary to persistent limbal conjunctival chemosis. Conversely, AKC and VKC may lead to significant corneal complications such as ulceration and opacification, leading to permanent visual loss. Furthermore, significant chronic ocular surface disease places these patients at high risk for corneal transplantation complications and rejection. Lid involvement from any type of allergic conjunctivitis, particularly GPC, can significantly compromise contact lens tolerance. Medications used for allergic disease may lead to complications such as preservative toxicity and steroid-induced intraocular pressure (IOP) elevations or cataract. With proper treatment, you can experience relief or at least reduce your symptoms. Recurring exposure to allergens, however, will likely trigger the same symptoms in the future.

4.15.1 VKC

Generally, VKC is a rather benign and self-limiting disease that may resolve with age or spontaneously at puberty (Takamura et al. 2017; Takamura 2010). Nonetheless, the sometimes debilitating nature of this disease when it is active necessitates therapy to control symptoms. Complications typically arise from occasional corneal scarring and the unsupervised used of topical corticosteroids. In some patients, symptoms may persist beyond childhood, which in some cases may represent a conversion to an adult form of atopic keratoconjunctivitis. This persistence into adulthood has been shown to be as high as 12%.

4.15.2 AKC

AKC remains chronic for years, often persisting into old age, when it may resolve spontaneously. It may result in decreased vision or blindness from corneal complications, such as chronic superficial punctate keratitis, persistent epithelial defects, corneal scarring or thinning, keratoconus, cataracts, and symblepharon formation. Complications result from persistent surface keratopathy, corneal scarring or thinning, keratoconus, cataracts, and symblepharon formation. In addition, medical treatment with corticosteroids can further promote the development of cataracts, glaucoma, and secondary corneal infections. Proper prophylactic measures, prompt effective treatment of exacerbations, and well-timed elective surgical intervention can reduce the incidence of poor vision and blindness. Patients should be observed every few days or weeks until the ocular surface disease is stable. Moreover, when medically treating patients with steroids or immunosuppressants, a regular interval survey for drug-related adverse effects and complications is indicated. Patients should be observed frequently until the ocular surface disease is stable. Patients being treated with corticosteroids or

immunosuppressives should have regular examination for drug-induced adverse effects. Corticosteroids promote the development of cataract, glaucoma, and may lead to secondary corneal infections.

4.15.3 GPC

Functional prognosis of the GPC is good. Approximately, 80% of patients can return to comfortable contact lens wear with appropriate treatment. Ptosis of the upper lids and decreased contact lens tolerance can occur. Giant papillary conjunctivitis has been a common cause for temporary and permanent contact lens intolerance. The lids of some patients return to normal appearance following the resolution of giant papillary conjunctivitis, whereas other lids retain small, white, capped scars of the giant papillary lesions for long periods, sometimes indefinitely. Giant papillary conjunctivitis is not associated with mortality.

4.16 Home Care

Treating allergic conjunctivitis at home involves a combination of prevention strategies and activities to ease your symptoms. To minimize your exposure to allergens:

- Close windows when the pollen count is high.
- Keep your home dust-free.
- Use an indoor air purifier.
- Avoid exposure to harsh chemicals, dyes, and perfumes.
- To ease your symptoms, avoid rubbing your eyes.

Applying a cool compress to your eyes can also help reduce inflammation and itching.

Antigens flying into the ocular surface can be washed out by several drops of artificial tear. Because ordinary artificial tear contain preservatives, when instillation is repeated four or more times, an artificial tear without preservatives is recommended for safety. Since tap water reduces the stability of the layer of tears, frequent use of water for washing eyes should be avoided.

Cup-type eye washing tools are not recommended because skin blurs around the eyes and antigens attached to the skin touch the ocular surface. Furthermore, it pushes mites, bacteria, and other microorganisms spreading around the eyelids to the surface of conjunctiva and cornea. Such unsanitary and inappropriate cleaning operations are not medically recommended at all.

4.17 Prevention

Completely avoiding the environmental factors that cause allergic conjunctivitis can be difficult. The best thing you can do is to limit your exposure to these triggers. For example, if you know that you are allergic to perfume or household dust, you can try to minimize your exposure by using scent-free soaps and detergents. You may also consider installing an air purifier in your home. Early diagnosis and treatment will help prevent the rare complications that can occur with this disease.

4.17.1 SAC and PAC

Avoidance of the offending antigen is the primary behavioral modification; specific testing by an allergist, otolaryngologist, or eye care provider will identify the responsible allergen(s) and help the individual to establish a viable long-term strategy to avoid the allergen. Point-of-service 60-antigen regionally specific noninvasive fully reimbursable skin testing can readily be performed in the ophthalmologist's office, as well as the optometrist's office (in some states), with the Doctors Allergy Formula test kit (Bausch & Lomb), facilitating patient access and enhancing convenience. Contact reactions caused by medications or cosmetics are also treated best by avoidance.

4.17.2 VKC

As with most type I hypersensitivity disorders, allergen avoidance should be emphasized as the

first-line treatment. Although permanent relocation to a cooler climate is not feasible in many cases, it remains a very effective therapy for VKC. Maintenance of an air-conditioned environment and control of dust particles at home and work may also be beneficial. Local measures, such as cold compresses and periodic instillation of artificial tears, have also been shown to provide temporary relief. As with all allergic conditions, rubbing should be minimized through counseling, family engagement, cool compresses, chilled eye drops, and frequent handwashing to remove adherent pollen and bioadhesive allergens.

4.17.3 AKC

For optimal long-term prevention of AKC, reduce or eliminate the exposure to environmental allergen. The general principle for preventing all allergies is to avoid the triggers. Triggers for eye allergies can be avoided by (i) using sunglasses to act as a barrier for airborne allergens, (ii) using hypoallergenic bedding, (iii) washing sheets in hot water, and (iv) minimizing animal exposure, if animals are believed to trigger allergic symptoms. People who do not know what causes their allergic conjunctivitis may consider consulting an allergy specialist. The specialist may do allergy testing to find out what triggers the allergic symptoms. Mast cell stabilizers and antihistamines are the mainstay of prophylactic therapy. Reduction of environmental allergens along with oral and topical antihistamines helps in management of exacerbations.

4.17.4 GPC

Prevention of GPC involved reducing the possibility of getting your eyes irritated. If you are a contact lens wearer, the most important step of preventing GPC is to maintain the highest level of lens hygiene. Throw away whatever contact lenses you have been wearing as they may contain residues of the infectious agent. If disposing is impossible, disinfect them thoroughly using peroxide-based cleaning solutions and also some form of enzyme cleaning. Thoroughly clean and disinfect lenses between use. For soft lens wearers, use nonpreserved solutions when possible. Always rinse lenses in nonpreserved saline before inserting. Always remember wash your hands clean before handling contact lenses, and do remember to disinfect your lens storage also (Allansmith et al. 1977).

The goal of management is to allow the GPC patient to continue wearing contact lenses or to tolerate an ocular prosthesis with the benefit of the most effective and least obtrusive therapeutic program (Molinari 1982). Nonetheless, the treatment of GPC is complex, requires carefully sequenced clinical divisions, and can be both tedious and expensive for the patient and the physician. Six conditions favor the development or exacerbation of GPC: increased deposits on the lenses, increased time per day that lenses are worn, use of lenses consistently for months or years, individual reactivity to wearing a particular lens type, larger lens and therefore broader area of adhering antigenic material, and genetic constitution of the patient. The treatment of GPC depends on three therapeutic strategies: teaching the patient to clean the lens, finding the best tolerated lens, and treating the conjunctival inflammation.

4.17.5 Lens Care

Patients must clean the lens thoroughly, preferably using cleaning agents that are free of preservatives (e.g., thimersol). The lens should be rinsed and stored in fresh saline. Cold disinfecting solutions preserved with chlorhexidine should not be used. Three methods of sterilizing the lens are currently available: cold disinfection, heat disinfection, and treatment with hydrogen peroxide. In cold disinfection, the lenses remain overnight in the unheated disinfecting solution. Heat disinfection is effective, but the heat bakes the deposits on the surface of the lens. Hydrogen peroxide treatment depends on the disinfecting power of hydrogen peroxide, which is then neutralized by contact with a platinum disc. Of the three commercially available methods, treatment with hydrogen peroxide seems to be the best tolerated by the inflamed or potentially inflamed conjunctiva.

4.17.5.1 Deposits

Patients should clean their lenses with a proteolytic enzyme at least once a week. For some patients, daily cleaning with a proteolytic enzyme is recommended. Of the two enzyme preparations on the market – the proteolytic enzyme papain and a pancreatic enzyme containing lipases and proteolytic enzymes – the papain enzymatic cleaner seems to be more effective in removing deposits and quieting the GPC.

4.17.5.2 Type of Contact Lens

(i) Lens of the same design

In many patients, GPC can be controlled by reestablishing good cleaning practices, a new lens of the same design, and replacing the contact lenses every 6–12 months. The patient should then be instructed to clean the lens thoroughly and to use enzymatic cleaning as described above.

(ii) Lens of a different design

If proper care and cleaning of the lens and regular replacement do not resolve the GPC, a new contact lens of a different design should be prescribed. A lens of a different design and a polymer different from the one worn when the GPC developed (i.e., change manufacturers) should be prescribed. A lens of a lower water content also can be prescribed. We have initial evidence that non-hydroxyethylmethacrylate (HEMA) lenses may be better tolerated by patients with GPC than HEMA-containing lenses. Patients should be instructed to clean the new lens following the procedure described above.

(iii) Lenses of different design for each eye

A third maneuver in discovering a tolerable lens design is to prescribe lenses of different design for each eye. For example, one might prescribe a Hydrocurve lens for one eye and a CSI for the other, avoiding the polymer and design that had been associated with exacerbation of the GPC.

(iv) Rigid gas-permeable lens

A fourth option is to prescribe a rigid gas-permeable (RGP) lens rather than a soft (hydrogel) lens. RGP lenses are smaller and thus have less surface to hold deposits. The edge of a gas-permeable lens can be reshaped to be less traumatic to the conjunctiva. Finally, deposits are more easily removed from RGP lenses than from hydrogel lenses.

4.18 Current Research

Rebamipide acts by stimulating cells in the eye and altering the quality of the mucin or eye mucus which helps increase those cells known as goblet cells, to produce a more viable tear that protects the cornea (Kashima et al. 2014). Rebamipide eye drops attenuate giant papillae, suppress the inflammatory cytokines in human conjunctival epithelial cells, and downregulate the level of interleukin-8 (IL-8), eosinophil cationic protein (ECP), and total IgE level on the ocular surface in patients with allergic conjunctival diseases. Also another report investigate that the topical administration of rebamipide suppressed conjunctival allergic eosinophil infiltration in patients with allergic conjunctival diseases with giant papillae (VKC or AKC). These results revealed that the anti-inflammatory effects of rebamipide eye drops help to combat human ocular surface inflammation in patients with allergic conjunctival diseases. Moreover, rebamipide eye drops help in reducing the dependence on steroids for the treatment of allergic allergic conjunctival diseases.

4.19 Conclusion

Allergic conjunctival disease is defined as “a conjunctival inflammatory disease associated with a type I allergy accompanied by some subjective and objective symptoms.” Conjunctivitis associated with type I allergic reactions is considered allergic conjunctival disease even if other types of inflammatory reactions are involved. Classification of allergic conjunctival disease is as follows: (i) allergic conjunctivitis without proliferative change, (ii) atopic

keratoconjunctivitis (AKC) complicated with atopic dermatitis, (iii) vernal keratoconjunctivitis (VKC) with proliferative changes, and (iv) giant papillary conjunctivitis (GPC) induced by irritation of a foreign body. Allergic conjunctivitis is subdivided into "seasonal allergic conjunctivitis (SAC)" and "perennial allergic conjunctivitis (PAC)" according to the period of onset of the symptoms. The pathological conditions of allergic conjunctival disease with lesions in the conjunctiva are assumed to be caused by interactions between various immune system cells and resident cells, which are mediated by physiologically active substances (e.g., histamine and leukotriene), cytokines, and chemokines. Eosinophils are the main effector cells in allergic conjunctival disease. Various cytotoxic proteins released from eosinophils infiltrating locally into the conjunctiva are thought to cause keratoconjunctival disorders such as severe AKC and VKC. A clinical diagnosis can be made by subjective symptoms including ocular itching, lacrimation, hyperemia and foreign body sensation, and objective symptoms including conjunctival hyperemia, conjunctival edema, and conjunctival follicles, which are found annually during the same season. The most common and important symptom of SAC is the ocular itching. A positive test for serum antigen specific IgE antibody or a positive skin reaction, even in quasi-definitive diagnoses, makes it highly probable that a definite clinical diagnosis can be made. The serum total IgE antibody may be normal or mildly increased. The exposure to a large amount of antigens may induce acute bulbar conjunctival edema. Drug treatment is the preferred treatment for allergic conjunctival diseases. The first option is antiallergic eye drops, which are the basic treatment for allergic conjunctivitis, followed by the differential use of steroid eye drops as necessary according to the severity. For severe allergic conjunctival diseases (AKC and VKC), additional use of immunosuppressive eye drops, steroid oral medicines, subtarsal conjunctival steroid injection, and surgical treatment such as papillary resection should be considered.

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Allergic Rhinitis

5

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Contents

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Abstract

Allergic rhinitis is an allergen-induced response leading to inflammation of the nasal membranes. This is a common disorder increasing in prevalence in the Western Hemisphere and negatively impacts quality of life in affected individuals. Allergic rhinitis can significantly impair productivity and social functioning in both children and adults due to the bothersome symptoms of this disease. Indoor and outdoor exposures can lead to symptoms of allergic rhinitis. Pollens, mold spores, pet, and pest exposures are the cause of symptoms in most patients. Primary symptoms of allergic rhinitis are sneezing, rhinorrhea, nasal congestion, and itching. Allergy testing in the forms of skin test and in vitro blood test is necessary to confirm the diagnosis, keeping in mind that history-guided testing is essential. Treatment options vary depending on the patient age and preference. These options include allergen avoidance, pharmacotherapy, and allergen immunotherapy. Therefore, the goal is treatment directed toward improvement of symptoms and quality of life.

Keywords

Allergic rhinitis · Rhinitis · Immunotherapy · Histamine · Antihistamine · Allergy testing · AIT

5.1 Introduction

Rhinitis is inflammation of the nasal epithelium characterized by sneezing, itching, rhinorrhea, and congestion. Allergic rhinitis, also known commonly as hay fever, is caused by an allergic response mediated by immunoglobulin E (IgE). Approximately 10–25% of people suffer from allergic rhinitis, and it can be a debilitating disease due to the interference with quality of life (Corren 2014). Allergic rhinitis affected 60 million people in the United States in 2013, 40% of whom were in the pediatric population (Gentile et al. 2015). Each year, this affected population has 7 or more days of allergic rhinitis or conjunctivitis symptoms leading to loss of productivity and compromised quality of life. Socioeconomic costs are substantial (Borish 2016). Chronic nasal dysfunction results in impaired school performance and decreased productivity, as well as complications from the chronic inflammation leading to other disorders such as middle ear disease and sinusitis (Corren 2014). Children and adolescents are proportionally more commonly affected than adults, but symptoms and treatment are generally the same in both pediatric and adult groups (Marcdante and Kliegman 2015). Treatment options are varied and include avoidance, pharmacotherapy, and allergen immunotherapy. Allergic rhinitis can be well managed with proper guidance regarding precautions and treatment.

5.2 Epidemiology

The incidence and prevalence of allergic rhinitis has increased significantly, especially in Western countries, over the past few decades. Overall disease prevalence is 15–20%. However, accurate estimates around the world are difficult to obtain due to variability of geographic pollen counts and difficulty in recognizing the symptoms by both patient and physician. Peak prevalence occurs in early teen years, around 13–14 years of age. Most patients diagnosed with allergic rhinitis will exhibit symptoms before 20 years of age, with males tending to have an increased incidence in childhood although this equalizes later in adolescence. Studies have shown the incidence is higher in developed countries and in adolescents compared to children. However, allergic rhinitis decreases in prevalence with advancing age in adults (Ricketti and Cleri 2009). It is postulated that exposures in early childhood can result in an increased risk of allergic rhinitis development. Specifically, development of allergic rhinitis is associated with air pollution levels and maternal smoking history (Corren 2014). There is also a higher incidence in upper level socioeconomic groups, ethnicities other than Caucasian, those with greater exposure to high indoor allergen

concentrations, and patients with greater serum IgE concentrations (Ricketti and Cleri 2009). There is a decreased risk of developing allergic rhinitis in patients with a higher number of siblings, patients living in a farm environment, and those eating a Mediterranean diet (Corren 2014). About 50% of patients with allergic rhinitis have associated allergic conjunctivitis, both occurring as a result of an allergen trigger.

5.3 Anatomic and Allergic Pathophysiology

The clinical definition of allergic rhinitis is a nasal disorder induced by an IgE-mediated inflammatory reaction of the membrane of the nose after exposure to an allergen. Although seasonal allergic rhinitis can occur in infants, it is unusual due to an individual requiring two or more seasons of exposure to a seasonal antigen in order to develop an allergic response (Ricketti and Cleri 2009). Aeroallergen sensitization can occur in the first 2 years of life if there is a significant atopic family history, but classic seasonal allergic rhinitis symptoms such as pruritus, rhinorrhea, and congestion generally do not develop until 2–7 years of age (Garcia-Lloret 2011).

5.3.1 Nasal Anatomy and Pathophysiology

Six major functions of the nose differentiate it from other sensory organs of the body. It is an olfactory organ, but it is also an important part of speech and phonation, an airflow passageway, a way to humidify and warm inspired air and a noxious particle filter for inspired air. Significantly, the nose is also involved in allergic and immunologic responses (Ricketti and Cleri 2009).

Air is heated and humidified by the vascularized nasal turbinate mucosa as the air passes through the nasal airway. Large cavernous vascular sinusoids on the turbinates contribute to this heating and humidification of inspired air. When these sinusoids are dilated, they cause congestion. This can occur in both allergic and non-allergic types of disease (Scadding et al. 2012). These blood vessels are controlled by the autonomic nervous system. The sympathetic process leads to vascular constriction and decreased secretion, whereas the parasympathetic effect leads to vascular dilation and increased secretions. Due to the large amount of vasculature in the nasal mucosa, changes can lead to obstruction. The normal nasal cycle involves congestion and decongestion of the mucosa, but abnormalities in this cycle due to allergic symptoms lead to changes in this cycle and emphasize congestion (Ricketti and Cleri 2009).

The filtering role of nasal mucosa is also critical to overall health. Nasal secretions contain bacteriostatic enzymes that work at an optimal pH of 7, as do the cilia. In addition to enzymes, these secretions contain immunoglobulin A (IgA) and protein, providing lubrication and protection. Large particles are filtered by hairs within the nostrils. Cilia beat at a steady frequency leading to a streaming mucus blanket that contains the filtered materials, moving the captured debris toward the pharynx to be swallowed or expectorated (Ricketti and Cleri 2009). Mucus is secreted by goblet and serous cells in the epithelium and by nasal glands. The secretion is controlled by parasympathetic nerves, but sympathetic stimuli and reflexes can also enhance secretion (Scadding et al. 2012).

Nasal sensation is primarily through the trigeminal nerve, and sensory fibers are stimulated by inflammatory mediators like histamine and bradykinin. Stimulation leads to release of neuropeptides, therefore increasing vascular permeability and activating submucosal gland release. This results in sensations of itching, rhinorrhea, and burning involved in the rhinitis response (Joe and Liu 2015).

5.3.2 Nasal Allergic Pathophysiology

Allergen exposure in the mucus membranes affects the overall response because of immune involvement of the nose. Mediator release from nasal mast cells and basophils is an important part of the immediate-type allergic reaction. Allergic

rhinitis patients have IgE antibodies that bind to high-affinity receptors on mast cells and basophils; low-affinity receptors on other cells can also bind to IgE. Sensitization to an allergen is needed to trigger an IgE response, which occurs by the allergen interacting with an antigen-presenting cell (APC) such as a macrophage, dendritic cell, B cell, or epithelial cell. Most APCs process the allergen and fragments and are presented with class II major histocompatibility class (MHC) molecules to T-helper cells. This results in cytokine release by the T-helper cell. Switching from a type 1 T-helper cell (Th1) response to a type 2 (Th2) phenotype is an early event of the allergic sensitization process and is the initiating factor for allergic inflammation. Two major Th2 pathways that lead to this inflammation are cytokine secretion and isotype switching of B cells to secrete IgE and the secretion of eosinophil growth factor IL-5 (Ricketti and Cleri 2009).

After IgE antibodies specific for an allergen are secreted, they bind to high-affinity receptors on mast cells and basophils. The allergic response occurs when nasal reexposure to the allergen causes cross-linking of the specific IgE on the mast cell surface and inflammatory mediator release such as histamine, prostaglandins, and bradykinin. These cause the vasodilation, increased vascular permeability, increased secretion, and afferent nerve stimulation that lead to rhinitis symptoms (Ricketti and Cleri 2009). Cytokines are also generated in this response. Physical examination, therefore, would show swollen nasal mucosa with clear secretions consistent with the induction of these vasoactive mediators (Borish 2016).

Nasal mast cells are located in the nasal lamina propria as connective tissue mast cells, although some are epithelial and known as mucosal mast cells. Superficial nasal epithelium in patients with allergic rhinitis has significantly more mast cells and basophils when compared to non-allergic patients (Ricketti and Cleri 2009). The lamina propria is highly vascular with significant permeability amenable to access by pharmacologic agents. The capillary network is extensive and fenestrated, allowing for rapid fluid transit (Scadding et al. 2012). T-helper cells, eosinophils, neutrophils, and basophils accumulate with continued allergic response. Eosinophils release proteins that disrupt the respiratory epithelium leading to further mast cell mediator release and hyperresponsiveness. Eosinophils increase during seasonal exposure and correlate with the severity of disease in nasal scrapings. Basophils, lymphocytes, eosinophils, and neutrophils infiltrating the nasal cavity lead to the late-phase reaction of allergic rhinitis (Ricketti and Cleri 2009).

5.3.3 Early- and Late-Phase Response

The response to a triggering allergen includes an early and late phase. The early phase, also known as the immediate phase, lasts about 1 h and occurs immediately after exposure. The late phase then begins in 3–6 h with a peak at 6–8 h; it resolves in 12–24 h. Early-phase reactions are sneezing, pruritus, and rhinorrhea, whereas late-phase symptoms involve more nasal congestion. The late phase is exacerbated by factors promoted by the early-phase reaction, with release of inflammatory mediators and cell recruitment in the nasal mucosa (Lang 2010). The release of mediators in the early phase occurs by allergen contact with IgE on mucosal mast cells or basophils (Fischer 2007). Histamine is primarily involved in the early phase, whereas the late phase is associated with other mediators with inflammatory effects. Eosinophils play a large role in the late-phase response including release of leukotrienes which participate in the late-phase congestion. Separation of early- and late-phase responses can be difficult, and a perpetual late-phase response develops in sensitized patients during their allergic seasons or when exposed to perennial triggers (Lang 2010).

5.3.4 Hereditary Association

The influence of inherited and environmental factors in allergic disease continues to be studied. Atopy has been linked to genetic loci on particular chromosomes, identifying family history as a significant risk factor for allergic rhinitis. Risk is low for atopic disease in a patient with absence of

parental family history, increases with one parent or sibling affected, and nearly doubles with biparental family history (Ricketti and Cleri 2009). Identical monozygotic twins have a 40–50% concordance rate, with dizygotic twins having a 25% concordance rate. Studies to identify the specific genes involved are limited at this time, and findings are difficult to interpret due to lack of replication in separate population cohorts (Scadding and Kariyawasam 2012).

5.4 Allergens

Allergic rhinitis occurs due to hypersensitivity to outdoor pollens and mold spores as well as indoor mold spores and animal proteins. Seasonal symptoms are due to specific pollens and mold spores that vary by season, whereas perennial symptoms are associated with indoor mold spores and animal exposures that can occur throughout the year (Borish 2016). Another system to categorize allergic rhinitis involves the terms intermittent or persistent allergic rhinitis as opposed to seasonal or perennial allergic rhinitis. Intermittent allergic rhinitis is defined as symptoms less than 4 days a week or for less than 4 weeks, and persistent allergic rhinitis has symptoms present for more than 4 days a week and more than 4 weeks (Brozek et al. 2017). The specific pollens involved in causing symptoms of rhinitis are airborne, whereas plants depending on insect pollination such as many flowering plants are not involved in allergic rhinitis (Ricketti and Cleri 2009). Outdoor sources of seasonal aeroallergens are weeds, grasses, trees, and outdoor molds such as *Alternaria* spp. and *Cladosporium* spp. In contrast, indoor aeroallergens which are involved in year-round allergic symptoms include house dust mite; pests such as cockroaches, mice, and rats; indoor pets; and indoor molds such as *Aspergillus* spp. and *Penicillium* spp. (Ricketti and Cleri 2009).

Seasons of pollination depend on the particular plants and geographic location. Relative amounts of light determine the pollinating season, and the variability with light is a consistent factor. Variable factors include weather conditions which influence how much pollen is produced in that season (Ricketti and Cleri 2009). In general, trees pollinate in the spring, grasses in late spring to summer, and weeds in late summer to fall (Nelson). March is usually the earliest month in which pollens will appear in the Upper Midwest, Western, and Eastern United States, but again geographic location is critical in determining specific seasons (Ricketti and Cleri 2009). Pollens are able to travel hundreds of miles and result in symptoms remote from the locale of production (Marcdante and Kliegman 2015).

Ragweed is an important pollen because of its potency. It is a significant cause of allergic rhinitis symptoms in the eastern and midwestern portions of the United States, with severe and long-lasting symptoms when compared to symptoms from most other pollens. Symptoms usually begin as early as August in the Midwest, mid-Atlantic, and Southern United States for patients who are highly sensitized. These symptoms can last until a hard winter freeze (Ricketti and Cleri 2009).

Symptoms recur annually depending on the duration of pollination of the specific plant. Symptoms tend to be worse in the morning due to increased airborne pollen release after sunrise; weather factors such as rain can decrease symptoms due to removal of pollen from the air. Dry, windy weather leads to increased pollen distribution and worsening of symptoms. Intensity of symptoms follows the pollen season, although symptoms can persist following the end of pollination season depending on the patient. The lingering effect of the allergic rhinitis symptoms is due to a priming effect, leading to increased reactivity due to repeated exposure to pollen over the prior weeks (Ricketti and Cleri 2009). This is thought to be a nonspecific effect, meaning after disappearance of the pollen from the environment, the patient may react to another allergen that would not cause symptoms in absence of the priming effect. The mechanisms underlying priming are not completely understood, but are thought to be related to increased mast cell and eosinophil numbers with cytokine-induced inflammation (Gentile et al. 2015). Secondary infection can also worsen symptoms of allergic rhinitis, as can irritant effects on already inflamed nasal

membranes. Irritants that are known to cause clinical worsening in these patients are tobacco smoke, paint, newspaper ink, soap powder, and air pollutants.

Mold or fungus is another source of allergen that affects patients with allergic rhinitis and can be due to either indoor or outdoor mold spores. The most commonly identified mold species in the United States are *Alternaria* and *Cladosporium*, which are outdoor allergens that cause the majority of symptoms. Molds are most significant during warmer months, and outdoor molds are not present during winter in regions that develop a frost, due to the killing of the fungi, the source of the spores, in a hard freeze. However, they can begin to appear in the early springtime, which is the earliest some sensitized patients may begin to show symptoms. Mold can be present in damp or musty environments as well as in leaves, barns, moldy hay, or straw. Rarely, ingestion of certain foods such as beer, wine, melons, mushrooms, and certain cheeses with high mold content may also result in symptoms (Ricketti and Cleri 2009).

House dust mites are present in higher humidity environments and practically all climates, resulting in perennial symptoms in sensitized patients. This can be severe, since dust mites are present in bedding and require specific hot water cleaning to remove or pillow and mattress encasements to reduce dust mite allergen production. The chronic exposure to dust mite allergen, with mites found in almost all domestic rooms with fabric or carpet, can result in persistent, significant symptoms (Ricketti and Cleri 2009).

Cockroach infestation in inner city housing, especially apartments, is an important and often overlooked cause of allergic sensitization and symptoms. The allergens are identified in the cockroach's digestive secretions and body parts. Their presence also results in perennial symptoms in sensitized patients.

There are many other allergens involved in allergic rhinitis such as pets and rodents. These are considered perennial allergens like house dust mite and cockroach and will be discussed later in this chapter.

5.5 Classification and Differential Diagnoses to Consider

Allergic rhinitis can be classified into several categories, which are summarized in Table 1. These classifications are seasonal, perennial, intermittent, and persistent. Seasonal allergic rhinitis affects patients in a seasonal manner due to the aeroallergens known as pollen. Patients with seasonal symptoms can have spring, summer, or fall pollen sensitization. Depending on the geographic region, winter pollen exposure can also occur. Patients can have several pollen allergies, resulting in multiple affected seasons. Symptoms during the winter are suggestive of perennial allergen sensitization due to the lack of outdoor pollen during times of frost or freeze. However, in regions without frost or freeze, winter pollen exposure can occur as mentioned above. Perennial allergic rhinitis, in contrast to seasonal allergic rhinitis, occurs year-round without a seasonal preference. This is due to year-round allergens which are primarily indoor, specifically due to house dust mite, cockroach, mold, and pets (Marcdante and Kliegman 2015). Symptoms can acutely worsen with increased exposure to allergen (i.e., close pet contact, cleaning a dusty home). However, in many parts of the world, pollens as well as other allergens are perennial due to the climate. In addition, patients sensitized to multiple triggers may have year-round symptoms due to many seasonal sensitivities and geographic location; this can be confusing since the terms seasonal and perennial may not exclusively apply. These should be considered when classifying a patient. As described in a prior section,

Table 1 Classification of allergic rhinitis

Seasonal allergic rhinitis	Symptoms associated with particular pollen-associated seasons (spring, summer, fall)
Perennial allergic rhinitis	Year-round symptoms, due to non-pollen allergens that are present even in winter
Intermittent allergic rhinitis	Symptoms less than 4 days/week or for less than 4 weeks
Persistent allergic rhinitis	Symptoms more than 4 days/week and for more than 4 weeks

another classification strategy is to use intermittent or persistent allergic rhinitis as opposed to seasonal or perennial allergic rhinitis. Intermittent allergic rhinitis is defined as symptoms less than 4 days a week or for less than 4 weeks, and persistent allergic rhinitis has symptoms present for more than 4 days a week and more than 4 weeks (Brozek et al. 2017). This classification does not specify a particular season in which symptoms are greater or if symptoms are present year-round. Intermittent and persistent allergic rhinitis is also divided into mild, moderate, or severe categories. Mild symptoms do not cause sleep disturbance or an issue with quality of life, whereas moderate to severe symptoms cause interruption of sleep and daily activity, as well as a loss of productivity (Ricketti and Cleri 2009).

Another form of rhinitis is episodic rhinitis, which occurs with intermittent exposure to allergens, commonly indoor allergens encountered in occupational areas, schools, or homes other than the patient's.

5.5.1 Other Causes of Rhinitis

Non-allergic rhinitis is a form of rhinitis that has no relation to allergic triggers. A summary of these differential diagnoses, similarities among them, and common treatments is found in Tables 2 and 3. Incidence of non-allergic rhinitis increases with age, and many patients with allergic rhinitis have some component of non-allergic rhinitis (Joe and Liu 2015). This can be further divided into numerous groups, including infectious rhinitis, which is the most common cause of non-allergic rhinitis in children. Children have on average three to six common cold viruses a year, resulting in episodes of viral rhinitis that usually resolve within 7–10 days. This falls within the category of acute infectious rhinitis and can be identified with associated symptoms of sore throat, fever, poor appetite, and sick contacts (Marcdante and Kliegman 2015). Acute bacterial rhinosinusitis occurs with symptoms of facial pain, persistent purulent nasal discharge, and sometimes fever, often benefiting from treatment with antibiotics (Quillen and Feller 2006). This is in contrast to viral rhinitis, which is milder and is not affected by antibiotics. Chronic bacterial rhinosinusitis usually occurs in older children and adults. This condition has a more indolent course with more than 6 weeks of symptoms, which is also treated with anti-inflammatory therapy with or without antibiotics. Mucopurulent nasal discharge, often yellow or greenish, is usually necessary for the diagnosis. Associated symptoms include facial tenderness, headache, tooth and mouth pain, halitosis, and postnasal drip (Marcdante and Kliegman 2015).

Another form of rhinitis is chronic hyperplastic eosinophilic sinusitis, or CHES, which is an inflammatory disorder with accumulated eosinophils, mast cells, fibroblasts, and Th2 lymphocytes as well as goblet cell metaplasia and mucous gland hypertrophy. The eosinophilic accumulation is the diagnostic feature of this disease. Nasal polyps can complicate this disease. Aeroallergen sensitization may be present but the role of allergens in this disease is unclear. There is a high incidence of asthma in patients with CHES. Symptoms include nasal congestion, rhinorrhea, hyposmia, and facial or sinus pressure. These patients may require surgical treatment, especially if they have nasal polyposis, and patients with more eosinophilic infiltrate have a poorer prognosis (Borish 2016). However, surgery does not cure the disease, and relapse is inevitable without aggressive medical management.

Other infectious etiologies of rhinitis include tuberculosis, syphilis, and fungal infections. Primary nasal tuberculosis is rare, and symptoms involve crusting, occasional epistaxis, nasal congestion, and ulcerative lesions within the nares. Polyp development can also occur. Congenital syphilis can result in *snuffles*, which is the nasal symptom that occurs in infants. Allergic fungal rhinosinusitis involves atopic patients developing an allergic response to fungus growing within the nasal mucus, associated with nasal polyps. The fungus involved are those in the *Dematiaceae* family, for example, *Aspergillus* and *Rhizopus* species (Ricketti and Cleri 2009). The sinus mucosa develops a characteristic eosinophilic inflammation, and bone erosion can occur.

Table 2 Rhinitis differential and common treatments

	Patients affected	Treatment
Allergic rhinitis	All ages	Oral and intranasal antihistamines/decongestants, intranasal corticosteroids/cromolyn
Vasomotor rhinitis	All ages, generally not children	Intranasal corticosteroids, intranasal ipratropium
NARES	All ages, generally not children	Intranasal corticosteroids
Sinusitis (acute, chronic)	All ages	Antibiotics, nasal lavage
Atrophic rhinitis	More common in elderly	Nasal lavage, antibiotics. Avoid decongestants
Rhinitis of pregnancy	Pregnant patients	Intranasal budesonide/cromolyn, oral antihistamine, very brief use of intranasal decongestants
Rhinitis medicamentosa	Patients using intranasal decongestants	Discontinue intranasal decongestant
Occupational rhinitis	All ages (with allergen exposure at work)	Avoid inciting allergen, treat like allergic rhinitis
Physical rhinitis	All ages	Avoid inciting factor, can treat with intranasal ipratropium
Anatomic abnormality	More common in young children unless related to septum or polyps	Referral for potential surgical intervention
Oncologic abnormality	All ages	Referral to oncologic service and potential surgical intervention

Table 3 Common symptoms among the rhinitis differential

Symptoms	Allergic rhinitis	Vasomotor rhinitis	NARES	Sinusitis (acute, chronic)	Anatomic	Oncologic
Sneezing	+	+	+	–	–	–
Pruritus (nasal, oral, etc.)	+	–	+	–	–	–
Congestion	+	+	+	+	+	+/–
Epistaxis	–	–	–	–	+/–	+/–
Rhinorrhea	+	+	+	+	+	+
Bilateral nasal symptoms	+	+	+	+	+/–	+/–

Non-allergic noninfectious rhinitis is also known as vasomotor rhinitis. This is a common cause of rhinitis symptoms with patients presenting for assessment of potential allergic rhinitis. A greater number of patients with non-allergic rhinitis are female, and symptoms are usually perennial (Joe and Liu 2015). With vasomotor rhinitis, patients react to strong irritants such as dust particulates or volatile chemicals. Alcoholic beverages can also act as a trigger, as can barometric pressure changes and cold air. They can also react to strong fumes or odors, such as perfume, cigarette smoke, and chlorine. Symptoms include congestion, rhinorrhea, and limited sneezing with clear nasal discharge (Marcdante and Kliegman 2015).

Non-allergic rhinitis with eosinophils, also known as NARES, is associated with eosinophilia on a nasal cytology. This is seen less frequently in the pediatric population compared to adults. Clear nasal discharge is present in this disorder, as well as perennial symptoms of sneezing, itching, congestion, and occasionally hyposmia. Three stages of evolution appear to occur in NARES, with migration of eosinophils to secretions, retention of eosinophils in the mucosa, and development of nasal polyps (Ricketti and Cleri 2009). Some experts consider NARES an early or mild form of eosinophilic chronic rhinosinusitis discussed above.

Other forms of non-allergic and noninfectious rhinitis include physical rhinitis, gustatory

rhinitis, and reflex rhinitis. Skier's nose is an example of physical rhinitis with response to cold air. Gustatory rhinitis is a response to hot or spicy food, leading to a clear profuse rhinorrhea, sometimes without ingestion but exposure to the aroma. Reflex rhinitis is due to exposure to bright light, usually sunlight, causing a rhinorrhea response.

Atrophic rhinitis is a chronic condition with nasal crusting, purulent discharge, halitosis, and obstruction. This is due to atrophy of the nasal mucosa and underlying bone, leading to a patent nasal cavity with copious foul-smelling discharge. It is most common in areas with prolonged warm seasons such as South Asia and the Middle East; it also occurs more frequently in women. *Klebsiella* is an identified pathogen in this disorder in particular, and symptoms in atrophic rhinitis are severe congestion, altered sense of smell, and a constant malodorous smell. Secondary atrophic rhinitis is more likely to occur in patients with a history of nasal surgery In this case, it is referred to as "empty nose syndrome." It differs from primary atrophic rhinitis in that it is often associated with surgery, radiation, trauma, and chronic granulomatous disease (Corren 2014). This condition may be associated with systemic diseases discussed below.

Rhinitis associated with the workplace is also known as occupational rhinitis, resulting in nasal symptoms following exposures in a particular work environment. This can be allergic or non-allergic in etiology. Those at highest risk of developing occupational rhinitis are laboratory workers, furriers, and bakers due to their specific exposures. Symptomatic worsening during the workweek with improvement over the weekend or vacation away from the job leads to suspecting this diagnosis. Symptoms may persist outside of work when the trigger is absent if mucosal inflammation becomes more established. Depending on the trigger and mechanism, testing may be possible. Those working with irritants or aromatics, such as acids and perfumes, are classified as non-allergic. Allergy testing would not be indicated in this case, and exposure challenge would require an environmental chamber. However, for those exposed to allergic triggers such as grain flour and animal dander, testing can confirm the suspected diagnosis (Corren 2014). It should be noted that occupational rhinitis generally precedes or accompanies the development of occupational asthma, making early diagnosis and removal from the allergen important for asthma prevention as well as symptom improvement (Gentile et al. 2015).

Rhinitis of pregnancy, or hormonal rhinitis, is unrelated to allergic conditions. It was previously attributed to increased concentrations of hormones and mucus hypersecretion on mucosal surfaces in general, presumably for the protection of the cervix and vagina (Corren 2014). Newer data place a higher consideration on decreased alpha adrenergic tone in the venous sinusoids leading to increased vascular pooling of blood or edema caused by leakage of plasma from the vascular bed into the stroma (Ellegård 2006). Seven to thirty percent of pregnant patients will develop rhinitis of pregnancy, defined as new-onset nasal symptoms in absence of another known cause that lasts more than 6 weeks and resolve within 2 weeks after delivery (Ellegård 2006; Finkas and Katial 2016; Scadding et al. 2008). The primary symptom is clear or viscous secretions from the nose. It is often self-limiting, but the symptoms can be aggravating (Scadding et al. 2008). With nasal congestion and rhinorrhea, severe snoring can occur and increases the risk of gestational hypertension, preeclampsia, and intrauterine growth retardation. Rhinitis of pregnancy also increases the risk of obstructive sleep apnea in women predisposed to the disease (Ellegård 2006). Although there is data establishing a link between pregnancy and rhinitis symptoms, there is less information on the menstrual cycle link to rhinitis (Corren 2014). Pregnant patients may also have preexisting allergic rhinitis which can be difficult to distinguish from rhinitis of pregnancy in a patient who has not been previously evaluated.

Rhinitis medicamentosa is a disorder related to overuse of nasal decongestants that cause vasoconstriction due to alpha adrenergic effects, such as phenylephrine or oxymetazoline. This results in a paradoxical effect with continued use, with lessened decongestive benefit and increased sense

of nasal obstruction. The pathophysiology is not fully understood but is thought to be related to alpha adrenergic receptor downregulation, which makes the receptors less responsive to endogenous norepinephrine and exogenous vasoconstrictors (Lang 2010). Cocaine use can also cause this, and this disorder generally does not occur in the younger pediatric population due to limited use of these products. Symptoms are frequent sniffling and rhinorrhea, and physical exam shows red swollen nasal mucosa and minimal discharge. Symptoms will improve with treatment including discontinuation of the offending medication and potentially a short course of oral corticosteroids (Marcdante and Kliegman 2015).

There are also medications with rhinitis symptoms as a side effect including oral estrogens, alpha-blockers, and beta-blockers, as well as psychiatric medications such as benzodiazepines and tricyclic antidepressants. Often, discontinuation of these medications for a few days results in improvement. Aspirin and nonsteroidal anti-inflammatory drugs also may induce rhinitis, though some of the subjects affected have a mild or early development of aspirin-exacerbated respiratory disease (AERD). This condition is associated with development of CHES (see above).

Systemic diseases like cystic fibrosis, polychondritis, Kartagener syndrome or ciliary dysfunction, and hypothyroidism can cause symptoms mimicking allergic rhinitis. Granulomatous diseases such as granulomatosis with polyangiitis, sarcoidosis, and eosinophilic granulomatosis with polyangiitis (previously known as Churg-Strauss vasculitis) are other systemic disorders with rhinitis or nasal symptoms. Subjects with granulomatosis with polyangiitis or polychondritis can develop a depressed nasal bridge (saddle nose deformity) due to necrosis of the cartilage in the nasal septum. Purple discoloration of the nasal tip can be due to sarcoidosis. Hereditary hemorrhagic telangiectasia can present with epistaxis and may be confused with symptoms of allergic rhinitis (Scadding and Scadding 2016). Gastroesophageal reflux can be associated with rhinitis and recurrent ear infections. Cerebrospinal fluid (CSF) rhinorrhea may also mimic allergic rhinitis. This may occur after surgery or a traumatic event and should be ruled out by obtaining beta-2 transferrin levels from the nasal discharge. Beta-2 transferrin is an isomer of transferrin found almost exclusively in CSF. If the fluid is positive for beta-2 transferrin, the patient should be evaluated by neurological specialties immediately to repair the leak and prevent meningitis. Spontaneous, nontraumatic CSF rhinorrhea can also occur and is often persistent, mimicking more common forms of rhinitis (Ricketti and Cleri 2009). Beta-2 transferrin assay of nasal secretions is diagnostic for this condition as well.

Other issues that can cause symptoms similar to allergic rhinitis include anatomic abnormalities. In young children, the most common anatomic abnormality is adenoid hypertrophy leading to obstruction and increased susceptibility to nasopharyngeal infection. Persistent rhinitis can therefore occur, with or without infectious signs and symptoms similar to rhinosinusitis. In infants, congenital choanal atresia may present with signs of congestion and rhinorrhea, especially if distress is noted while feeding. Bilateral choanal atresia generally presents in the neonate with cyanosis occurring in cycles, since infants preferentially breathe nasally. This cyanosis will resolve with crying, since that involves mouth breathing. Choanal atresia can be associated with CHARGE syndrome (coloboma, congenital heart disease, choanal atresia, retardation, genitourinary defects, and ear anomalies). Evaluation for CHARGE syndrome should be considered in any infant with choanal atresia. Unilateral choanal atresia, in contrast, may not present until later in life and may appear as a foreign body due to unilateral discharge and obstruction (Marcdante and Kliegman 2015). Nasal polyps are rare in the pediatric group younger than 10 years of age, but any occurrence in children warrants an evaluation to rule out cystic fibrosis. Another diagnosis to be excluded with a finding of nasal polyps in children is primary ciliary dyskinesia. Polyps can be identified on examination as bilateral gray to white glistening masses that protrude into the nasal airway (Marcdante and Kliegman 2015). They can be associated with clear or purulent nasal discharge as well as a widened nasal bridge and symptoms of congestion or obstruction (Scadding and Scadding 2016). If a

patient presents with changes in the sense of taste or smell, polyps should be considered as well as chronic sinus disease. A foreign body should always be considered in a child, particularly a toddler, due to the tendency of young children to place objects such as food, small toys, and stones in the nose. Symptoms generally include foul smelling, unilateral discharge with purulence. The foreign body can often be noted on examination (Marcdante and Kliegman 2015). Another form of obstruction that can cause symptoms similar to allergic rhinitis is a nasal septum abnormality, such as a deviated septum. In pregnant women, nasal granuloma gravidarum or pregnancy tumor should be considered. This is a rapidly growing benign tumor causing nasal obstruction, which in contrast to rhinitis of pregnancy, is mostly unilateral and causes recurrent nosebleed. It may protrude and be seen from the outside, and it can also resolve without intervention after delivery (Ellegård 2006).

Oncologic causes should be considered in cases of chronic non-allergic rhinitis, especially with other concerning symptoms. Both benign and malignant nasal tumors can cause similar symptoms to allergic rhinitis (Fischer 2007). Encephaloceles are a neoplasm that can occur within the nasopharynx or the nose itself; they are generally unilateral and can have a pulsating quality. They increase in size with any process that increases the pressure in the cerebrospinal fluid, such as crying or straining. Other cancerous lesions can imitate nasal polyps and usually bleed with manipulation, such as carcinomas and sarcomas. Inverted papillomas are a friable and vascular tumor that can involve the nasal septum in addition to the lateral wall of the nose. Angiofibromas are also highly vascular tumors that can arise in the posterior choana of the nasopharynx, especially in preadolescent boys. Without treatment, all of these oncologic processes can result in erosion into surrounding regions (Ricketti and Cleri 2009).

5.6 Diagnosis and Evaluation

Allergic rhinitis is diagnosed by history, physical examination, and allergy testing via skin prick testing or laboratory blood panel. The skin prick testing and laboratory blood panel are best obtained by a clinician with expertise in performing and interpreting these tests, such as an allergist. Obtaining a history with recognition of symptom patterns and associations is the primary factor leading to a diagnosis of allergic rhinitis (Henke 2009).

5.6.1 History, Clinical Symptoms, and Physical Examination

Taking a history in patients with suspected allergic rhinitis is essential to help confirm the diagnosis. All patients may not have all symptoms of the typical allergic patient such as sneezing, rhinorrhea, nasal pruritus, and congestion. Important differentiations need to be made regarding onset and duration of symptoms as well as relation to location (i.e., school, work environments vs. home environment) in order to identify other potential factors such as occupational exposure. Other provoking factors should also be elicited from the patient (Lang 2010). Life events are important, such as acquiring a new pet or moving into a new home. History should be obtained regarding potential allergic conjunctivitis which can be associated with allergic rhinitis. Timing of the symptoms should also be identified regarding a particular season that is worse for the patient than others or if the symptoms are present year-round. Comorbidities should also be identified, such as atopic dermatitis, sleep apnea, gastroesophageal reflux disease, and asthma. A family history of atopic disease should also be sought. A medication list should be reviewed in order to rule out rhinitis as a medication side effect or rhinitis medicamentosa.

Sneezing is the most characteristic symptom of a patient with allergic rhinitis, and rapid succession sneezes are most characteristic. These episodes can be spontaneous or preceded by nasal pruritus and irritation. The nasolacrimal reflex commonly results in ocular symptoms such as tearing. In a sensitized patient, irritant or physical factors can cause frequent sneezing episodes without direct exposure to pollen. For example, a cold air draft can result in local nasal response and a

sneezing paroxysm. Rhinorrhea also occurs and is typically thin, clear discharge. This can be copious, resulting in local skin irritation due to continued production. If purulent discharge is identified, this is unlikely secondary to allergic rhinitis. However, epistaxis can occur since mucus membranes are friable due to the inflammation, and repeated forceful nose blowing or nose picking, especially in children, can lead to recurrent epistaxis. Nasal congestion due to swollen nasal turbinates also occurs and, depending on severity of the congestion, can lead to sinus ostia narrowing with sinus obstruction. Eustachian tube dysfunction can also occur secondary to congestion resulting in earache, decreased hearing, or crackling in the ears. Congestion may be the sole complaint in children, as opposed to symptoms such as rhinorrhea and sneezing. Changes in taste and smell occur with ongoing chronic congestion as well. Cough due to postnasal drip can occur, and this can be a productive or nonproductive cough. Ongoing drainage also leads to constant throat clearing. Nasal pruritus also occurs with partial relief by vigorous rubbing, particularly vertical displacement of the nasal tip. Pruritus is a common theme in allergic rhinitis, and the ears, throat, palate, and face are also frequently affected (Ricketti and Cleri 2009). Allergic conjunctivitis is associated with allergic rhinitis, with ocular signs and symptoms such as erythema, pruritus, and lacrimation. Additional symptoms may include weakness, fatigue, anorexia, and nausea, the latter likely due to postnasal drip and swallowing mucus.

The physical examination should include an evaluation of eyes, ears, nose, throat, and chest. A skin examination should also be performed to assess for rashes with features of atopy such as atopic dermatitis. It should be noted that these findings can be subtle, especially if the patient is affected with seasonal allergic rhinitis, and abnormalities may only be present during acute stages. Findings on eye examination can include "allergic shiners," which are dark periorbital swollen areas often of bluish-purple color possibly caused by venous congestion. Swollen or puffy eyelids from frequent rubbing of the eyes, lacrimation, and conjunctival injection also may occur. Ear examination may demonstrate retracted tympanic membranes or serous otitis media from eustachian tube dysfunction. Classic nasal findings are pale, blue, or gray nasal turbinates that can also be swollen and boggy causing nasal obstruction and mouth breathing with clear rhinorrhea. A transverse nasal crease can be noted across the lower nasal bridge due to frequent rubbing the nose upward and outward with the palm of the hand. This rubbing motion is referred to as the "allergic salute" (Marcdante and Kliegman 2015). Patients may also show a characteristic open mouth breathing pattern due to nasal obstruction reducing nasal breathing. This is sometimes termed the "allergic gape" (Finkas and Katial 2016). Examination of the throat may reveal postnasal drip with clear or white mucus drainage and swollen, non-erythematous tonsils. Direct visualization of the adenoid tissue with pharyngeal mirror or fiber-optic rhinolaryngoscope typically shows a papular appearance of the mucosa, termed cobblestoning, with enlargement of the adenoid tissue. Skin examination should be performed for rashes, typically eczema preferentially on flexor or extensor surfaces of joints, depending on the patient's age. There may be physical findings including residual lichenification, xerosis, or variable pigmentation. Older patients may have had eczema as infants or children, and this would be important history to obtain (Marcdante and Kliegman 2015). All of these findings may not be present during asymptomatic intervals or non-allergic seasons.

Unique findings in children may include a clucking sound from "itching" the soft palate with the tongue due to palatal pruritus. Children are also more likely to suffer from orthodontic abnormalities due to prolonged periods of mouth breathing secondary to nasal congestion. Skin and chest examination are especially important in children with an initial presentation for suspected allergic rhinitis, as they may have an undiagnosed atopic dermatitis or asthma which are more likely with atopy (Marcdante and Kliegman 2015).

Perennial allergic rhinitis and seasonal allergic rhinitis generally present similarly, but due to the chronicity of perennial symptoms, they may seem

more severe, particularly the nasal congestion. Children may have a more constant eye and nose rubbing, mouth breathing, and broadening of the midsection of the nose due to the chronic congestion and rubbing. The transverse nasal crease is generally present in patients with severe, perennial allergic rhinitis. Undiagnosed nasal polyps should be considered in patients with chronic symptoms, but this cannot be specifically related to allergic rhinitis as non-allergic patients develop polyps as well. Nasal secretions in patients with polyps may be more mucoid than clear, and narrowing and elevation of the arch of the palate results in the palatal "Gothic arch" in patients affected early in life (Ricketti and Cleri 2009).

5.6.2 Laboratory Evaluation

Confirmatory testing is not always necessary, and empiric treatment can be started in patients who have mild symptoms (Ferri 2017). Allergy testing often is reserved for those with more severe symptoms or unclear diagnosis; however, it is a consideration in any patient. Specific allergen testing would be needed if immunotherapy is being considered as a treatment option (Quillen and Feller 2006). Testing for allergic rhinitis can be performed by percutaneous skin prick testing (percutaneous testing), intradermal skin testing, or in vitro serum testing. Skin prick testing and intradermal testing provide immediate results; skin testing is generally preferred due to lower cost and immediate results (Lang 2010). There is, however, a concern that intradermal testing does not identify clinical allergy due to greater sensitivity and less specificity. Studies do not show correlation with allergen challenge and intradermal aeroallergen testing; thus, many clinicians do not routinely recommended intradermal testing as part of allergy skin testing. Skin prick testing is a more specific form of allergy testing (Marcdante and Kliegman 2015). The performance of the serum specific IgE testing is similar to skin prick testing, although results are delayed. In vitro specific IgE testing is necessary if skin disease, such as severe eczema or widespread psoriasis, limits opportunity for testing or medications that interfere with histamine response cannot be discontinued.

Saline and histamine controls are necessary for interpretation of skin prick and intradermal testing by providing, respectively, a negative and positive control. If a patient has a positive saline control or a negative histamine test, blood-specific IgE testing should be considered. If a patient has a negative histamine control, it is likely the patient is taking a medication with antihistamine properties. Positive allergen skin prick tests consistently correlate with allergen provocation challenges (Marcdante and Kliegman 2015). There is reproducibility on repeat skin prick testing which makes it a reliable method of diagnosis (Ricketti and Cleri 2009). However, aeroallergen skin testing is not recommended in pregnant patients due to the remote risk of anaphylaxis. This population would be better served with serum testing or returning for skin prick testing after delivery (Finkas and Katial 2016).

A serum test is recommended in patients with abnormal skin conditions that would interfere with the interpretation of the skin test, with history or high risk for anaphylaxis, with residence in areas where good quality extracts for skin testing are not available, and with treatment using medications that would interfere with skin testing. If patients have falsely positive saline controls, serum testing is also indicated (Ricketti and Cleri 2009). There are disadvantages to the blood test such as cost, prolonged time to result, and decreased sensitivity compared to skin prick testing, although the significance of the difference in sensitivity is debatable. There are different tests available for assessing serum IgE to allergens, although radioallergosorbent testing (RAST) is no longer commonly used (Ferri 2017). RAST was the first technique used to measure serum-specific IgE prior to the development of the newer enzyme-labeled anti-IgE. Enzyme assays are now preferred. It is important to note that all laboratory results should be correlated with symptoms. A positive allergen test in a patient with no allergic symptoms is considered sensitization without symptomatic involvement. Therefore, testing in an asymptomatic individual is not recommended (Marcdante and Kliegman 2015).

Specific IgE testing may be positive for allergens that are not clinically important, and it is important to correlate the testing with symptoms. Standardized extract use is desirable for diagnostic purposes. Clinicians should use allergen extracts based on symptoms and seasonality for optimal results (Gentile et al. 2015). Factors as simple as distance between the placements of allergen extract on the skin can affect results. Other factors that affect both results and interpretation are application site, the type of device used for testing, the season, and the extract qualities which can depend on expiration dates and storage conditions (Ricketti and Cleri 2009). Although skin testing can be performed in patients of any age, infants less than 1 year of age may not display a positive reaction due to less overall IgE produced in young children and differences in the skin. The skin differences also apply to elderly patients and subjects with sun damage (Gentile et al. 2015). Serum assays can be used as a supplement to skin testing, as skin testing is considered the diagnostic test of choice by allergy practice parameters. If the skin test is inconclusive, serum-specific IgE tests for confirmation can be performed. However, skin testing with high-quality extracts and proper technique remains the preferred method.

Measurement of serum IgE or blood eosinophils is not routinely recommended in patients undergoing evaluation for allergic rhinitis. Mean concentrations of total serum IgE and blood eosinophils are increased in allergic rhinitis, but there is a significant degree of overlap with values in asymptomatic patients, so the utility of this testing is limited (Corren 2014). A nasal smear with eosinophils via Hansel's stain suggests an allergic diagnosis, but this can also be found in patients with non-allergic rhinitis with eosinophils (NARES) and other non-allergic disorders (O'Connell 2017). However, eosinophilia on nasal smear is often a good predictor of clinical response to nasal corticosteroid therapy (Marcdante and Kliegman 2015). A summary of the common laboratory testing in allergic rhinitis is listed in Table 4.

Table 4 Laboratory evaluation for allergic rhinitis

Specific IgE (pollens, molds, pets, cockroach, house dust mite)	Elevated levels indicate sensitization, must correlate with symptoms for diagnosis
Total IgE	Can be elevated, but nonspecific for allergic rhinitis
Nasal eosinophil smear	Nasal eosinophilia noted in allergic rhinitis but also most nasal polyposis, allergic fungal rhinosinusitis, NARES, local allergic rhinitis
Peripheral eosinophils	Can be elevated, but nonspecific for allergic rhinitis

Radiographic imaging is not necessary for a diagnosis of allergic rhinitis. Computed tomography scan or magnetic resonance imaging may be helpful if an anatomic abnormality is suspected but is not recommended for evaluation of allergic rhinitis (O'Connell 2017). Patients with symptoms unresponsive to medical therapy and atypical for allergic rhinitis may benefit from a computed tomography scan of the paranasal sinuses, which probably is the most accurate test for evaluating inflammation of the sinuses. Standard x-ray imaging is not recommended for sinusitis because of poor sensitivity and specificity (Standring 2016). Findings on any of the abovementioned imaging modalities in allergic rhinitis would be minimal to none (Corren 2014). It is also important to note that radiographs are not necessary to diagnose sinusitis, and the importance of inflammation affecting these images is unclear.

Fiber-optic rhinolaryngoscopy is a procedure utilized for visualization of the nasal airway. This can help rule out other possibilities on the differential for allergic rhinitis and is usually reserved for patients with atypical symptoms or inadequate treatment response. Flexible scopes provide a view of superior and posterior nasal regions such as the septum, nasal turbinates, middle meatus, sphenoethmoid recess, adenoids, and eustachian tube orifices. While flexible scopes are used by most clinicians, rigid scopes are used primarily by otorhinolaryngologists for diagnosis as well as nasal or sinus surgery (Corren 2014). Other

procedures, such as peak nasal inspiratory flow, acoustic rhinometry, and rhinomanometry, can assess nasal airway patency, but the interpretation and reproducibility of results are limiting, and these are not commonly performed except in research (Scadding and Scadding 2016).

A subset of patients may suffer from local allergic rhinitis, or entropy, which is a potential reason for lack of specific IgE findings in the blood or positive skin prick testing but symptoms and signs consistent with allergy. Local allergic rhinitis has specific IgE identified only in the nose. These patients require a nasal allergen challenge to clinically confirm the diagnosis, which is performed in research settings (Corren 2014). The barriers in performing safe, reliable nasal allergen challenges limit the applicability of this procedure for clinical diagnosis.

5.7 Management and Treatment

Medical treatment can ameliorate the symptoms of allergic rhinitis and significantly improve quality of life. Success of the treatment depends on the patient's willingness to adhere to the regimen since deviation can result in recurrence. Other forms of treatment include immunotherapy and environmental control measures. The primary method of management and treatment of allergic rhinitis is avoidance of the offending allergen but requires life style changes that may not be acceptable or affordable.

5.7.1 Avoidance and Environmental Control

Directing avoidance based on results of skin testing or specific IgE blood testing can substantially reduce symptoms and the need for medications. Treatment of allergic rhinitis will be significantly more effective with limiting exposure to the allergen and maximizing control of the environment of the patient. However, in many cases of allergic rhinitis, complete avoidance is not possible due to the broad distribution of the allergens. For example, avoiding outdoor activity in a patient with pollen allergies would be detrimental to social functioning (Gentile et al. 2015). Complete avoidance results in a cure only when there is a single allergen with limited and defined distribution that can be easily controlled, such as an allergy to a household pet. Avoidance of animal allergens, house dust mite, and indoor molds can be accomplished more easily than avoidance of outdoor mold spores and pollens.

The only effective measure for minimizing exposure to animal allergens is removal of the animal from the home. The reason for this is the allergen, derived primarily from the cat or dog saliva and skin gland secretions not the hair or fur, can remain airborne for an extended time after the pet's presence in a particular room or location in the house. Furthermore, the mammalian allergens are sufficiently small to distribute throughout the home via the central heating and air-conditioning system despite standard filtration. However, due to the emotional attachment and personal choice to have a family pet, most households are not willing to take this step. This should still be discussed with the allergic patient's other health issues taken into consideration. Even after a pet's removal from the home, the allergen can persist for several months (Lang 2010). At the very least, pets should be kept out of the allergic patient's bedroom and preferably outside the house. Helpful interventions may include high efficiency particulate air (HEPA) filters, carpet or upholstery removal, frequent washing of bedding, and washing of the animal (Corren 2014).

Indoor mold or fungal growth usually occurs in areas of water intrusion in the living areas. Areas of the home that promote mold growth, such as shower stalls and basements, should be examined and cleaned to reduce exposure to mold spores in allergic subjects. The kitchen and cooking areas are also potential sources of fungal growth. Avoidance of damp, poorly ventilated areas is also recommended; for example, a patient with mold allergy should ideally not reside in a basement or attic (Ricketti and Cleri 2009). HEPA filtration may decrease exposure to allergens and is a consideration if sources cannot be controlled.

House dust mites commonly grow in locations with a humidity greater than 45–50%. Dust mites

are found on all continents except Antarctica; they survive best in warm, humid areas. For patients with house dust mite allergy, it is most practical to focus on making the bedroom as dust mite allergen-free as possible. The microscopic dust mites are found in highest concentrations in carpeting, pillows, mattresses, and upholstered furniture. Mite allergen proteins are large and heavy; therefore, it is less likely that they are transferred long distance via air. Mattress, box spring, and pillow allergen-proof, woven covers to seal against movement of dust mites coupled with frequent washing of bed linens in hot water may be beneficial in reducing exposure and possibly symptom improvement. HEPA filters are ineffective for dust mite allergic rhinitis (Corren 2014). Using foam pillows as opposed to down or feather pillows for patients with a dust mite allergy is also recommended by some experts, although this is unlikely to be relevant with woven encasements placed on the pillows. Regular vacuuming or steam cleaning of carpet, dusting, and floor cleaning may also be helpful. Removing dust-containing fixtures such as stuffed animals is another consideration. If possible for the family, removal of carpeting in favor of hardwood or tiled floors would be preferable to decrease the dust mite burden. High humidity is essential for the growth of the dust mite population, and therefore maintaining the absolute humidity at or below 45–50% in the home is optimal; this may be helpful for mold prevention as well (Ferri 2017). Wearing a mask while cleaning the house may be helpful to prevent exacerbating symptoms due to the movement of dust mite allergen that will be inhaled during the process. Air conditioning may decrease both mold spore and dust mite allergen levels, but the effectiveness depends upon the ambient heat and humidity (Lang 2010).

Cockroach allergy avoidance is potentially difficult depending on the housing situation, as most of the patients with cockroach infestations in their homes reside in apartments. Eliminating suitable environments for the cockroaches is the key to controlling symptoms. Highest allergen levels are found in kitchens and bathrooms due the need for a cockroach to be around food and water. Eating in living or sleeping areas potentially increases the inhalation exposure to cockroach. Insecticides and gel formulations of the insecticides, which are odorless and safe for indoor use, can be placed in the affected rooms, but extensive cleaning after extermination is needed due to the continued presence, even after the living insects have died, of the allergen in cracks and crevices of the home. Behavioral change to reduce the chances of reinfestation is critical to prevent recurrence of symptoms (Ricketti and Cleri 2009).

Avoidance of outdoor molds, and to some extent pollens, can be accomplished by remaining indoors when possible and closing windows and doors to avoid contact with outdoor allergens. Limiting outdoor activity during peak pollen hours, which are late morning to early afternoon, can be helpful in some patients. For those with allergy to outdoor triggers, however, pharmacotherapy or immunotherapy may be the best option.

Avoidance of smoke and secondhand smoke also will help avoid worsening the baseline inflammation present in a patient with allergic rhinitis and help to decrease symptoms. Irritants, such as smoke from burning outdoor vegetation or diesel particles from vehicles, may enhance symptoms and susceptibility to allergic sensitivity. General environmental pollution due to combustion products containing nitrogen and sulfur and particulates is also a concern; thus it is advisable for affected subjects to be aware of outdoor air quality assessments. Outside activities may need to be reduced during peak pollution periods. Indoor combustion products from fireplaces and natural gas appliances are potential sources of indoor pollutants.

5.7.2 Pharmacotherapy

Pharmacotherapy of allergic disease improves quality of life but does not modify the disease itself. There are multiple options for medical therapy with intranasal corticosteroids as the most effective treatment for allergic rhinitis. However, other medications can also improve symptoms.

5.7.2.1 Intranasal Corticosteroids

Intranasal corticosteroids (INCS) are the most effective single therapy for allergic rhinitis with high quality of evidence to indicate efficacy (Wallace and Dykewicz 2017). They treat nasal congestion, rhinorrhea, sneezing, and itching via regulation of the inflammation, edema, and mucus production in the nose. Mechanisms of action of INCS include vasoconstriction, inhibition of mediator release, eosinophil apoptosis, mucosal mast cell reduction, and suppression of cytokine release. INCS have some effect on allergic conjunctivitis usually associated with allergic rhinitis, but significant allergic ocular symptoms often require use of allergy eye drops. There can be an improvement in asthma as well with regular use of INCS, due to the relationship between asthma and allergic rhinitis. Benefit with treatment of allergic rhinitis occurs due to the anatomic connections between the nose and throat, as well as symptomatic improvement leading to less labored breathing and enhanced nasal breathing.

There are multiple types of INCS, such as beclomethasone, fluticasone, and mometasone. These medications have minimal systemic absorption and side effects. INCS can also be used for non-allergic rhinitis due to their general suppression of intranasal inflammation and mucous production. The local activity of the corticosteroid is critical when topically administered, due to affecting cellular activities and inflammation more effectively than systemic corticosteroids, with limited side effects (Ricketti and Cleri 2009). Delayed onset of action of INCS, generally 5–7 days after initiation, is generally expected, although many patients have clinical improvement within the first day of use. For most patients, regular use is needed for optimal effectiveness. Patients with severe congestion may require topical decongestants prior to administering an INCS, or even a course of oral corticosteroids to allow proper delivery of this nasal spray. The use of systemic corticosteroids should be only for severe cases that cannot be controlled by routine measures and not on a chronic basis (Ricketti and Cleri 2009).

Improper technique with INCS can result in local adverse effects. Pointing the nasal spray into the nasal septum may lead to bleeding due to epithelial thinning and decreased integrity of small blood vessels. Rarely, septal perforation is reported, which is why technique demonstration is important prior to prescribing the medication. Proper technique involves directing the nasal spray laterally, away from the septum. Other adverse effects include burning and local irritation as well as sneezing from the spray itself, and these can occur in up to 10% of patients (Marcdante and Kliegman 2015). The taste or smell of the INCS itself can be unpleasant, affecting patient adherence. Occasionally subjects with non-allergic rhinitis or mixed allergic/non-allergic rhinitis will complain of aggravation of symptoms by the odor of certain aqueous sprays, particularly those containing phenylethyl alcohol. Development of aqueous formulations have reduced local irritation and therefore increased the use of these sprays, including in children. Systemic side effects are rare if the INCS is used at the recommended dose, and evaluation of the hypothalamic-pituitary-adrenal axis as well as peripheral eosinophilia and osteocalcin (a marker of bone turnover) showed no effect by a variety of INCS (Ricketti and Cleri 2009). The development of candidiasis due to the use of INCS is rare, but with excessive mucosal drying it has occurred, usually on the septum or anterior inferior turbinate (Henke 2009). Some studies have shown the use of INCS results in increased intraocular pressure with reductions after discontinuation. Monitored use of INCS by a physician or other health professional is recommended, especially if other corticosteroids are being used or prolonged therapy is necessary (Ricketti and Cleri 2009). Long-term use does not result in adverse changes in nasal mucosa.

Intranasal corticosteroid injection is infrequently used since the advent of newer, safer INCS. Previously the injections were used for patients with both allergic and non-allergic conditions, especially nasal polyposis. It was thought that the injections could decrease the need for surgical intervention and associated complications in patients with polyps. Turbinate injections, however, have higher rates of systemic absorption and potential corticosteroid emboli leading to

transient or permanent visual loss; these are not concerns with INCS (Ricketti and Cleri 2009).

5.7.2.2 Oral and Intranasal Antihistamines

Another option for treatment is antihistamine therapy, although their effect on nasal congestion is less helpful than INCS. Antihistamines are a cornerstone of symptomatic therapy, used for over 50 years. Primarily, they help with nasal and ocular pruritus, sneezing, and rhinorrhea. Histamine acts through four receptors, and stimulation of the first receptor leads to most symptoms of allergic rhinitis. Antihistamines are inverse agonists of the H1 receptor, leading to the antihistaminic effects (Marcdante and Kliegman 2015). First-generation antihistamines are lipophilic and cross the blood-brain barrier, and these agents affect other neural receptors. The result is these agents have stronger sedation effects than second-generation antihistamines (Waller et al. 2014). Commonly used first-generation antihistamines are diphenhydramine and hydroxyzine. Their onset of action is within minutes, and they can be taken on an as needed basis. Generally, regular use of first-generation antihistamines is not recommended, especially in children or the elderly, due to effects on cognition and mobility. In children in particular, a deleterious effect on academic performance occurs with regular first-generation antihistamine use. A paradoxical stimulatory reaction also occurs in children. Other side effects are anticholinergic, resulting in blurred vision, urinary retention, dry mouth, tachycardia, and constipation. These effects can be severe, and the sedation effects can be profound as well: therefore the use of heavy machinery or driving a motor vehicle is relatively contraindicated. Large doses of these first-generation antihistamines can lead to cardiac abnormalities such as torsades de pointes. Other populations in addition to the children and the elderly that should use first-generation antihistamines with caution are those taking more than one antihistamine, patients on diuretic medications with history of hypertension, patients with electrolyte abnormalities, or those on antiarrhythmic medications or a history of arrhythmia. There is also a potentiating effect of alcohol and other drugs that affect the central nervous system, such as sedatives (Marcdante and Kliegman 2015). First-generation antihistamines are on the American Geriatrics Society Beers Criteria list of inappropriate medications for older adults (American Geriatrics Society 2015).

Second-generation antihistamines, in contrast, are more hydrophilic and do not as readily cross the blood-brain barrier (Waller et al. 2014). They are less likely to cause a significant sedative effect although this can occur, particularly at higher doses. They do not cause anticholinergic side effects like the first-generation medications and have longer half-lives allowing less frequent dosing. The young and elderly populations, therefore, are able to better tolerate these antihistamines. Cetirizine and loratadine are common over-the-counter second-generation antihistamines used for treatment of allergic rhinitis. Others include desloratadine and levocetirizine, derivatives of loratadine and cetirizine, respectively, which have been referred to as "third-generation antihistamines." Also included in this category is fexofenadine. The description of third-generation antihistamine is used to differentiate these medications, which were designed to have fewer central nervous system effects than second-generation antihistamines. However, this decreased central nervous system effect is not confirmed. Second- and third-generation antihistamines have a rapid onset of action that allows them to be taken on an as needed basis, which is similar to the first-generation antihistamines (Marcdante and Kliegman 2015). It should be noted that combination therapy of oral antihistamine and INCS has not shown additional benefit when compared to INCS use alone (Brozek et al. 2017). For any oral antihistamine, prophylactic administration, 2–5 h before a known allergen exposure, provides the best symptom control (Gentile et al. 2015).

Azelastine and olopatadine are intranasal antihistamine sprays that can be used as needed due to fast onset of action and used regularly for chronic symptoms (Marcdante and Kliegman 2015). Azelastine is a selective histamine receptor antagonist. In addition to histamine blocking, it inhibits inflammation. It does not commonly

cause drowsiness or psychomotor impairment, but these adverse effects can occur. Intranasal azelastine may synergize when combined with an INCS for optimal symptom control. Olopatadine spray is similar to azelastine and also uncommonly causes drowsiness. Both azelastine and olopatadine can have an unpleasant taste, which is commonly noted as a side effect (Ricketti and Cleri 2009). Both antihistamine nasal sprays act within 15–30 min and result in significant reduction of congestion, itching, sneezing, and runny nose (Corren 2014). Azelastine is FDA approved for treatment of non-allergic rhinitis.

5.7.2.3 Oral and Intranasal Decongestants

Oral or intranasal decongestants can be used for nasal congestion treatment, and oral decongestants are frequently combined with antihistamines. Commonly used oral decongestants are pseudoephedrine and phenylephrine, and intranasal are oxymetazoline and phenylephrine; these are sympathomimetic drugs that are vasoconstrictors via alpha adrenergic receptor activation resulting in improved nasal patency (Gentile et al. 2015). The efficacy of pseudoephedrine is confirmed but that of phenylephrine is questioned. Edema is reduced by either topical or systemic use of decongestants; however chronic topical use is associated with rebound congestion or worsening of the condition. Decongestants are aided in their benefits for allergic rhinitis by combining with an antihistamine. Adverse effects with oral decongestants can be significant, including insomnia, irritability, and palpitations. They can also increase intraocular pressure and cause urinary obstruction symptoms; decongestants should be avoided in patients with glaucoma or benign prostatic hypertrophy. The combination of first-generation antihistamine and a decongestant is particularly prone to cause side effects. In large doses, oral decongestants can result in hypertension as well (Ricketti and Cleri 2009). Purchase of decongestants may be limited depending on state laws, due to the use of these medications for illegal methamphetamine manufacturing. There are restrictions in use associated with certain sports teams, which should be considered for older children. Intranasal decongestant sprays can be used for acute relief of nasal congestion, but overuse is associated with rebound congestion and rhinitis medicamentosa. It is therefore recommended to limit daily use of this medication to 3–5 days (Corren 2014). Rhinitis medicamentosa involves the intranasal use of these medications followed by a rebound phenomenon leading to more congestion and edema, which is self-treated by increasing doses of the nasal spray. Discontinuation of the offending spray is the main treatment for rhinitis medicamentosa. Because of the risk of this disorder, especially in patients with allergic rhinitis who may experience significant relief with prolonged use, it is not advised to use intranasal vasoconstrictors except during a period of infectious rhinitis. The rebound effect can be mitigated when intranasal decongestants are combined with INCS. Oral decongestants are not associated with rhinitis medicamentosa (Ricketti and Cleri 2009). It is also important to note that decongestants do not affect other symptoms such as rhinorrhea, pruritus, and sneezing (Gentile et al. 2015).

5.7.2.4 Intranasal Anticholinergics

Intranasal anticholinergic sprays such as ipratropium are used primarily for non-allergic rhinitis; they have a drying effect for improvement of copious nasal drainage. Parasympathetic stimulation leads to a watery secretion mediated by acetylcholine and a vasodilatory effect. Ipratropium's anticholinergic effect leads to a block of the parasympathetic stimulation. It does not penetrate the blood-brain barrier and is poorly absorbed by the nasal mucosa. It does not affect congestion or sneezing symptoms but does control the watery nasal discharge. It is helpful in the common cold, gustatory rhinitis, and rhinorrhea in elderly patients (Ricketti and Cleri 2009). However, adverse effects include overly dry nose leading to irritation and burning (Marcdante and Kliegman 2015). These effects are dose dependent in their severity. Less common side effects include dry mouth, headache, and nasal congestion. It is not used as a first-line agent for treatment of allergic rhinitis due to its lack of effect on

symptoms other than rhinorrhea. In patients with a primary symptom of rhinorrhea, ipratropium combined with an INCS or antihistamine is a consideration (Ricketti and Cleri 2009).

5.7.2.5 Intranasal Cromolyn Sodium

Intranasal cromolyn sodium is another product for use in patients with allergic rhinitis. It stabilizes mast cell membranes and prevents antigen-induced degranulation. Cromolyn is effective in both seasonal and perennial allergic rhinitis for treatment of symptoms of sneezing, rhinorrhea, and nasal pruritus. It has a significant prophylactic effect when used prior to a known allergen exposure, reducing immediate and late symptoms after the exposure. Adverse effects are rare and include an unpleasant taste as well as local irritation. Recommendations for seasonal rhinitis treatment are for use 2–4 weeks prior to the allergen season and continued use throughout the exposure period. Cromolyn has a delayed onset when used for chronic disease treatment, and therefore antihistamine therapy is frequently needed in addition to control symptoms. Regular use leads to maximal benefit. However, studies show that INCS, intranasal antihistamines, and oral antihistamines have a more significant effect than intranasal cromolyn (Ricketti and Cleri 2009).

5.7.2.6 Leukotriene Receptor Antagonists

Montelukast is approved for both seasonal and perennial allergic rhinitis, although it is commonly used in asthma treatment as well (Marcdante and Kliegman 2015). It is a leukotriene receptor antagonist that results in a variety of potential benefits, including reduced eosinophil recruitment and mucous production. However, montelukast does not have a dramatic effect on symptoms but is similar to that of oral antihistamine with the exception of not improving itch and sneeze. Symptom scores and quality of life improvement are statistically significantly improved with montelukast (Lang 2010). Montelukast does relieve nasal symptoms but not to the degree of an INCS. Montelukast is generally an adjunct for patients without adequate response to an antihistamine or nasal corticosteroid, but the reduction in symptoms is not clearly demonstrated with this additional therapy (Ricketti and Cleri 2009).

5.7.2.7 Nasal Lavage

A non-medication treatment option recommended for allergic rhinitis patients with congestion and rhinorrhea symptoms is nasal lavage or saline wash (Fischer 2007). Isotonic and hypertonic saline solutions reduce symptoms (Garcia-Lloret 2011). Mechanisms of action thought to be involved in this process include improvement in mucociliary clearance, washing out of allergens and inflammatory mediators, and a protective effect on nasal mucosa. Side effects are minor, and local burning and irritation are identified as the most common adverse effects. These side effects can be due to improper technique, with nausea occurring if the wash is swallowed. There are no established optimal volumes or dose frequencies for this non-pharmacologic therapy (Gentile et al. 2015).

5.7.3 Allergen Immunotherapy

Environmental control measures and medications are used first to treat allergic rhinitis. If symptoms remain uncontrolled and continue to affect quality of life, allergen immunotherapy should be considered.

Allergen immunotherapy, also known as AIT, is the repeated administration of specific allergens in incremental doses to patients with IgE-mediated conditions therefore preventing the allergic symptoms and inflammatory reactions (Ricketti and Cleri 2009). AIT is the only disease-modifying treatment for allergic rhinitis (Finkas and Katial 2016). Subcutaneous AIT is the traditional and common form of allergen immunotherapy, referred to as "SCIT" or "allergy shots." Recently sublingual immunotherapy, known as SLIT, has been approved for allergy to certain grasses, ragweed, and house dust mite. Although AIT is not recommended for infants and toddlers, it can be initiated in children under the age of 5 years if indicated by severity of disease, risk, and benefit and ability of physician

to correlate the clinical presentation with allergy testing. However, no FDA-approved products are approved for SLIT in children younger than 5 years. There are reports of efficacy of AIT in children as young as 3 years of age. There is also no upper age limit for initiating AIT in the elderly, since clinical benefits have been reported in the older age groups (Cox et al. 2011). Other considerations for starting SCIT should be the transportation available to the patient for regular clinic visits to administer the injections (Gentile et al. 2015).

The mechanism of action for AIT is complex but involves decreased production of specific IgE due to targeted therapy with the triggering allergens. There is also involvement of an immunoglobulin G (IgG)-blocking antibody and alteration of cytokine expression produced in response to allergens (Marcdante and Kliegman 2015). Allergen-specific IgG induced from AIT block degranulation of basophils and mast cells works as an anti-inflammatory process. There is a shift from allergen-specific Th2 cells to T-regulatory cell predominance during the process of immunotherapy, with IL-10 suppressing total and allergen-specific IgE. Tolerance is therefore induced due to this suppression of the IgE response. The pathophysiology of allergen and immune system response is detailed in Sect. 3.2.

Initially, there is an increase in specific IgE followed by a gradual decrease. Clinical improvement may occur before decrease in specific IgE, and some patients do not have a reduction in their IgE level. Efficacy is therefore not entirely dependent on reduction of specific IgE, but AIT does decrease the seasonal elevation in specific IgE level for seasonal allergens. Other benefits of AIT are suppression of late-phase inflammatory responses in the skin and respiratory tract (Ricketti and Cleri 2009). The advantage regarding AIT as opposed to pharmacologic treatment is that the immunotherapy effect is long lasting; studies show at least 2 years of consecutive treatment result in persistent tolerance for pollen allergy, although longer courses, up to 3 years, are needed for perennial allergens (Corren 2014).

SCIT vaccines are prepared based on the patient's specific allergy testing results. It should be administered at a physician's office/clinic with an observation period of 30 min afterward. Due to risk of anaphylaxis, the office/clinic needs to be prepared to treat and manage this risk. It may be advantageous that an epinephrine autoinjector or other form of injectable adrenaline is carried to and from every appointment to ameliorate this anaphylaxis risk, especially in patients with a history of prior reaction (Cox et al. 2011). Conventional recommendations for SCIT involve initial injections given once or twice a week then spaced out according to physician preference to maintenance dosing which is usually every 3–4 weeks. Occasionally, two or three injections may be needed at each visit since mixing compatibility depends on the allergen extracts involved.

Patients should be evaluated every 6–12 months while receiving AIT in order to assess efficacy, discuss any reactions, determine compliance with treatment and establish a timeline for discontinuation or adjustments in dose (Cox et al. 2011). Treatment with SCIT is recommended for a total of 3–5 years for maximal benefit (Ricketti and Cleri 2009). There are other forms of SCIT dosing known as rush or cluster therapy, which involve a quicker dose and concentration escalation to reach maintenance therapy. These may involve incremental injections over a shorter time period of days to weeks in order to reach the maintenance concentration within a period of 1–2 months. The risk of adverse reactions is higher with these protocols, and if a patient is needing quicker escalation than the conventional treatment, it is suggested to have this completed with very close supervision and medication pretreatment (Frew 2013).

A frequent reason for AIT discontinuation by the patient is the unrealistic pretreatment expectation. The magnitude of symptom reduction is variable in patients, although it is usually significant; however, there is no cure for allergic rhinitis. For SCIT, there is persistent improvement after discontinuation of therapy in those who complete the 3–5-year recommended course. The effectiveness of SCIT in allergic rhinitis has been confirmed in many trials specifically with pet allergens, grass, ragweed, and birch pollen (Frew 2013). The benefit of treatment is

significant, especially because it is a cost-effective therapy with long-term improvement and reduced medication costs (Ricketti and Cleri 2009).

Medical therapy will modulate the symptoms of the disease, but immunotherapy alters the natural course of the disease. There is a disease-modifying effect of AIT with reduction of new-onset asthma and the incidence of new sensitizations in children. The mechanisms underlying these processes are not yet fully understood, but these are another positive effect of AIT (Frew 2013).

A major risk of SCIT is systemic reaction and anaphylaxis. There are rare cases of death due to SCIT (Ricketti and Cleri 2009). Children are not at higher risk of reaction to conventional SCIT than adults (Cox et al. 2011). Some adverse events have been due to incorrect dosing, and others occur when patients receive increased concentrations of their dose. This awareness is important when switching vials or escalating dosing, as changes in concentrations or doses affect patients differently. Systemic reactions are also more likely if the patient has an illness or an asthma exacerbation; it is recommended to delay the injection if a patient is experiencing these issues. It is also important to obtain a thorough medication history and review this history at each visit, since use of beta-blocking medications can impact treatment of potential anaphylaxis with reduced responsiveness to epinephrine (Fischer 2007). Pregnancy is a relative contraindication to starting SCIT, but in an established patient on maintenance dosing, this treatment can be continued (Frew 2013). There are no controlled studies on risk or effect of SCIT in patients with immunodeficiency or autoimmune disorders, and concerns about increased risk of SCIT in this group are hypothetical. Therefore, it can be considered in these patient groups if risks and benefits are weighed on an individual basis (Cox et al. 2011).

SLIT, in comparison to SCIT, is an option for patients with a limited number of specific allergies. A ragweed tablet and house dust mite tablet are available, as well as two grass pollen allergy tablets (Greenhawt et al. 2017). Treatment involves a rapid build-up phase or no build-up followed by treatment with rapidly dissolving tablets containing allergens; of note, doses and regiments can vary, especially between Europe and the United States. Oral dosing at home after the first dose given in a medical setting provides the benefit of convenience. Information on these currently available SLIT options as well as their dosing and indications can be found in Table 5. There are statistically significant reductions in rhinitis symptoms and use of allergy medications with SLIT.

Systemic reactions are rare in SLIT, although local reactions such as oral and sublingual itching are common. However, it is an FDA recommendation to provide an epinephrine autoinjector or other form of injectable adrenaline to patients treated with SLIT. The epinephrine would be necessary for outside clinic use in case of a severe allergic reaction following SLIT dosing (Greenhawt et al. 2017). SLIT is safer than subcutaneous therapy, but there continues to be a discussion on its effectiveness when compared to SCIT. More recent studies show equal efficacy, at least with a limited number of allergens (Frew 2013).

5.7.4 Treatments Under Study

Other routes of immunotherapy administration, such as epicutaneous immunotherapy, are undergoing clinical trials to assess their benefit. New technologies for immunotherapy continue to develop. Omalizumab is a recombinant humanized monoclonal antibody which forms complexes with free IgE; it blocks interactions of IgE with mast cells and basophils, as well as lowers free IgE in the circulation (Bousquet et al. 2006). It is approved for treatment of severe allergic asthma and chronic spontaneous urticaria, although it has been studied in treatment of allergic rhinitis. Efficacy has been shown although the cost is prohibitive for routine treatment. In particular, the efficacy of this treatment compared to antihistamines and INCS has not yet been established. Agents that block interleukins are also under consideration, with IL-4 and IL-5 as specific targets. These targeted therapies have some effect in asthmatics and continue to be

Table 5 Commercially available SLIT in the United States

	FDA-approved	Indications	Dosing
House dust mite (Odactra™)	Yes	Patients 18–65 years of age with house dust mite allergy as indicated by positive specific IgE testing or skin prick testing	1 tablet sublingually daily, first dose to be given in office with 30-min observation period
Ragweed (Ragwitek™)	Yes	Patients 18–65 years of age with ragweed allergy as indicated by positive specific IgE testing or skin prick testing	1 tablet sublingually daily, first dose to be given in office with 30-min observation period Begin treatment 12 weeks before ragweed pollen season for best results
Northern grasses (Oralair™)	Yes	Patients 10–65 years of age with allergy to any of the following grasses as indicated by positive specific IgE testing or skin prick testing: sweet vernal, orchard, perennial rye, Timothy, Kentucky blue grass	10–17 yo: 1 tablet (100 IR) day 1, 2 tablet (200 IR) day 2, 1 tablet (300 IR) day 3 and following, once daily sublingually 18–65 yo: 1 tablet (300 IR) once daily sublingually Begin treatment 4 months before grass pollen season for best results First dose to be observed in office with 30-min observation period
Timothy grass (Grastek™)	Yes	Patients 5–65 years of age with Timothy grass or cross-reactive grass allergy as indicated by positive specific IgE testing or skin prick testing	1 tablet sublingually daily, first dose to be given in office with 30 min observation period Begin treatment 12 weeks before grass pollen season, recommend 3-year daily consecutive use for sustained effectiveness

studied for potential benefit in allergic rhinitis treatment. CpG bacterial DNA repeats as adjuvants with vaccines and in immunotherapy, with the goal of altering allergen processing or modifying the immune response, is another treatment under study (Henke 2009).

5.7.4.1 Special Populations

Pregnant women with rhinitis should utilize non-drug therapies initially. Nasal rinses with normal saline are first recommended in order to remove thick mucus, and physical nasal dilators are also available. However, in many women, medications will be needed. Intranasal cromolyn sodium has an excellent safety profile with a an FDA pregnancy category B rating and is appropriate for use in pregnant women. Budesonide is the preferred INCS in pregnancy due to its category B rating. Other INCS are category C in pregnancy. Gestational risk has not been confirmed, and the reported safety data of commercially available products are reassuring. Oral antihistamines can also be considered if this is the patient's preference, and primary symptoms are rhinorrhea, sneezing, and itching. Both diphenhydramine and chlorpheniramine, although older medications, have a long record of use during pregnancy. However, some patients will have significant central nervous system and anticholinergic effects that make these difficult to tolerate. In that case, loratadine and cetirizine are classified as pregnancy category B and can also be used. Olopatadine and azelastine, intranasal antihistamine sprays, are pregnancy category C and are infrequently used in pregnancy (Corren 2014). It would therefore be recommended to avoid them in favor of the abovementioned oral antihistamines, cromolyn nasal spray, or intranasal budesonide spray.

Oral decongestants should also be avoided during the first trimester; there is a questionable association with congenital malformations such as gastroschisis (Corren 2014). Intranasal decongestants can provide temporary relief, but the

recommendations for use of intranasal decongestants for no more than 5 days is to limit the risk of rhinitis medicamentosa (Ellegård 2006). SCIT can be continued during pregnancy if it has not caused systemic reactions and is helpful, but allergen vaccine doses should be maintained and not increased. If pregnancy occurs during a build-up phase and the dose is unlikely to be therapeutic, discontinuation of the immunotherapy should be considered. SCIT should also not be started during pregnancy (Cox et al. 2011). There is insufficient data regarding safety of initiating or continuing SLIT in pregnant or breast-feeding women, and no official recommendations can be made (Greenhawt et al. 2017). There is no evidence of increased risk in prescribing or continuing SCIT during breast-feeding (Cox et al. 2011). It should be noted that the FDA began implementing the Pregnancy Lactation Labeling Rule (PLLR) in 2015, removing categories from drug labeling and instead providing benefit and risk information as a summary. The older category classification is being used in this chapter due to historical familiarity and understanding.

The elderly population also requires special consideration due to the concern for dry nasal mucosal membranes and medication intolerance. Improving moisture content and removing dry secretions are primary concerns for this group. Nasal irrigation should be used by those with chronic rhinitis, especially if non-allergic etiology. An INCS can cause more bleeding than in younger patients due to fragile mucous membranes. First-generation oral antihistamines are not recommended due to the sedation potential and increased risk for anticholinergic side effects, especially in patients with history of glaucoma or benign prostatic hypertrophy. Oral decongestants can cause side effects of hypertension, cardiac arrhythmias, insomnia, agitation, and urinary tract obstruction effects; they are also not recommended in the elderly (Corren 2014).

Children are considered a special consideration in treatment, as there are age recommendations for certain medications. Instruction in proper use of medications, especially intranasal sprays, is essential in this group. A summary of the dosing of medications for allergic rhinitis in children and adults can be found in Table 6.

5.8 Complications of Allergic Rhinitis

The socioeconomic effects from allergic rhinitis are significant. The spectrum of disease ranges from mild to debilitating. Patients on the more severe end of the spectrum have difficulty with quality of life, specifically productivity at work or school and social functioning (Gentile et al. 2015). The indirect costs are remarkable, with impaired productivity or missed work in 52% of patients (Ricketti and Cleri 2009). Decreased productivity rates were approximately 2.3 h per workday with absences of 3–4 days due to the symptoms. Losses for workers total near $600 a year (Ricketti and Cleri 2009). For children, absenteeism from school can also affect a parents' work due to missed work to take care of the child. Children with allergic rhinitis experience significant quality of life disturbance with sleep issues, irritability, and limitation of both physical and social activity that can impact social development and academic performance (Marcdante and Kliegman 2015). In adults, sleep loss is identified as a primary factor for daytime fatigue leading to poor work performance (Corren 2014). A quality of life survey administered to patients with allergic rhinitis and asthma showed similar physical and mental impairment between the two diseases, with lower social functioning in patients with allergic rhinitis when compared to asthma (Ricketti and Cleri 2009).

Other complications of allergic rhinitis are related to comorbidities. Asthma is present in approximately 40% of patients with chronic rhinitis. 80–90% of those with asthma have persistent nasal symptoms of congestion, rhinorrhea, or a combination that can be related to allergic or non-allergic rhinitis (Corren 2014; Scadding et al. 2012). Rhinitis is a risk factor for development of asthma, as allergen exposure can affect the nose and lungs (Scadding et al. 2008). Therefore, patients with severe allergic rhinitis and asthma can experience worsening of their asthma when

Table 6 Common medications for allergic rhinitis

	Generic (common brands)	Over the counter	Adult dose	Pediatric dose	Dose strengths
Intranasal corticosteroids	Fluticasone (Flonase™, Veramyst™)	Flonase: yes Veramyst: no	Both: 1 SEN* qday** (>11 yo***) Can use 2 SEN qday for worsened symptoms for short period of time	Flonase: 4–11 yo 1 SEN qday Veramyst: 2–11 yo 1 SEN qday Both: can use 2 SEN qday for worsened symptoms for short period of time	Flonase 1 spray = 50 mcg Veramyst 1 spray = 27.5 mcg Max- 110 mcg/d Veramyst, 200 mcg/d Flonase
	Budesonide (Rhinocort™)	Yes	1–2 SEN qday (≥12 yo) Can use up to 4 SEN qday for worsened symptoms for short period of time	6–11 yo: 1 SEN qday, can use 2 SEN qday for worsened symptoms for short period of time	1 spray = 32 mcg Max- Peds: 128 mcg/d Adult: 256 mcg/d
	Triamcinolone (Nasacort™)	Yes	1 SEN qday (>12 yo) Can use 2 SEN qday for worsened symptoms for short period of time	2–6 yo: 1 SEN qday 6–12 yo: 1 SEN qday, can use 2 SEN qday for worsened symptoms for short periods of time	1 spray = 55 mcg Max- Peds: 110 mcg/d for 2–6 yo >6 yo and adult: 220 mcg/d
	Ciclesonide (Zetonna™, Omnaris™)	No	Zetonna (≥12 yo): 1 SEN qday Omnaris (≥6 yo): 2 SEN qday	Zetonna not approved for children less than 12 yo Omnaris not approved for children less than 6 yo	Zetonna: 1 spray = 37 mcg Max- 74 mcg/d Omnaris: 1 spray = 50 mcg Max- 200 mcg/d
	Beclomethasone (Qnasl™, Beconase AQ™)	No	Qnasl: 2 SEN qday (≥12 yo) Beconase AQ: 1–2 SEN BID****	Qnasl: 4–11 yo 1 SEN qday Beconase AQ: 6–11 yo 1 SEN BID, can increase to 2 SEN BID for worsened symptoms for short period of time	Qnasl (peds): 1 spray = 40 mcg Max- 80 mcg/d Qnasl (adult): 1 spray = 80 mcg Max- 320 mcg/d Beconase AQ: 1 spray = 42 mcg Max- 336 mcg/d
	Mometasone (Nasonex™)	No	2 SEN qday (≥12 yo)	2–11 yo: 1 SEN qday	1 spray = 50 mcg Max- Peds: 100 mcg/d Adult: 200 mcg/d

(*continued*)

Table 6 (continued)

	Generic (common brands)	Over the counter	Adult dose	Pediatric dose	Dose strengths
Combination intranasal corticosteroid and antihistamine	Azelastine/ fluticasone (Dymista™, Ticalast™)	No	1 SEN BID (≥6 yo)	Not approved for children <6 yo	1 spray = 137 mcg azelastine/50 mcg fluticasone Max- 548 mcg azelastine/ 200 mcg fluticasone
Intranasal antihistamine (second generation)	Azelastine (generic, Astepro™)	No	Generic (≥12 yo): 1–2 SEN BID Astepro 0.15% (≥12 yo): 2 SEN qday or BID	Generic: 5–11 yo 1 SEN BID Astepro 0.1%: 6 mo–5 yo 1 SEN BID Astepro 0.1% or 0.15%: 6–11 yo 1 SEN BID	Generic: 1 spray = 137 mcg Max- Peds: 548 mcg/d Adult: 1096 mcg/d Astepro 0.1%: 1 spray = 137 mcg Peds Max- 548 mcg/d Astepro 0.15%: 1 spray = 205.5 mcg Max- Peds: 822 mcg/d Adult: 1644 mcg/d
	Olopatadine (Patanase™)	No	2 SEN BID (≥12 yo)	6–11 yo: 1 SEN BID	1 spray = 665 mcg Max- Peds: 2660 mcg/d Adult: 5320 mcg/d
First-generation oral antihistamine	Diphenhydramine (Benadryl™)	Yes	50–100 mg q4–6 h (≥12 yo)	6–11 yo: 1 mg/kg q4–6 h or 12.5–25 mg q4–6 h	Max- Peds: 150 mg/d Adult: 300 mg/d
	Chlorpheniramine (Aller-Chlor™)	Yes	Immediate release (≥12 yo): 4 mg q4–6 h Extended release (≥12 yo): 12 mg q12 h	Immediate release: 6–11 yo 2 mg q4–6 h Extended release: not approved for children <12 yo	Max- Peds: 12 mg/d Adult: 24 mg/d
	Hydroxyzine (Vistaril™)	No	25 mg TID***** or QID****** (≥6 yo)	<6 yo: 50 mg/d in divided doses or 2 mg/kg/d in divided doses for patients ≤40 kg	Max- Peds: 50 mg/d Adult: 100 mg/d
Second- and third-generation oral antihistamine	Cetirizine (Zyrtec™)	Yes	10 mg once daily (≥6 yo)	6–<12 mo: 2.5 mg qday 12 mo–<2 yo: can increase to 2.5 mg BID 2–5 yo: can increase to 2.5 mg BID or 5 mg qday	Max- Peds: 5 mg/d Adult: 10 mg/d
	Loratadine (Claritin™)	Yes	10 mg once daily (≥6 yo)	2–5 yo: 5 mg qday	Max- Peds: 5 mg/d Adult: 10 mg/d

(*continued*)

Table 6 (continued)

	Generic (common brands)	Over the counter	Adult dose	Pediatric dose	Dose strengths
	Fexofenadine (Allegra™)	Yes	60 mg q12 or 180 mg qday (≥12 yo)	2–11 yo: 30 mg q12	Max- Peds: 60 mg/d Adult: 120 mg/d of 60 mg formulation, 180 mg/d of 180 mg formulation
	Desloratadine (Clarinex™)	No	5 mg qday (≥12 yo)	6–11 mo: 1 mg qday 12 mo–5 yo: 1.25 mg qday	Max- Peds: 1.25 mg/d Adult: 5 mg/d
	Levocetirizine (Xyxal™)	Yes	2.5–5 mg qday (≥12 yo)	6 mo–5 yo: 1.25 mg qday 6–11 yo: 2.5 mg qday	Max- Peds: 2.5 mg/d Adult: 5 mg/d
Intranasal decongestants	Phenylephrine (4-Way™)	Yes	0.25–1% solution: 2–3 SEN q4, max of 3–5 d (≥12 yo)	2–5 yo: 0.125% solution 2–3 SEN q4, max 3–5 d 6–11 yo: 0.25% solution, 2–3 SEN q4, max 3–5 d	Max dosing as listed for no more than 5 days
	Oxymetazoline (Afrin 0.05%™)	Yes	2–3 SEN BID, max 3–5 d (≥6 yo)	Not recommended in children under 6 yo	Max dosing as listed for no more than 5 days
Oral decongestants	Pseudoephedrine (Sudafed™)	State Dependent, restricted OTC sale	Immediate Release (≥12 yo): 60 mg q4–6 h Extended release (≥12 yo): 120 mg q12 or 240 mg qday	4–5 yo: Immediate Release 15 mg q4–6 h 6–12 yo: Immediate Release 30 mg q4–6 h Extended release not recommended for <12 yo	Max- Peds: 4–5 yo 60 mg/d 6–11 yo 120 mg/d Adult: 240 mg/d
	Phenylephrine (Sudafed PE™)	Yes	10 mg q4 h for max 7 d (≥12 yo)	4–5 yo: 2.5 mg q4 h for max 7 d 6–11 yo: 5 mg q4 h for max 7 d	Max- Peds: 4–5 yo 15 mg/d 6–11 yo 30 mg/d Adult: 60 mg/d
Leukotriene receptor antagonist	Montelukast (Singulair™)	No	10 mg qday (≥15 yo)	6 mo–5 yo: 4 mg qday 6–14 yo: 5 mg qday	Max- Peds: 6 mo–5 yo 4 mg/d 6–14 yo 5 mg/d Adult: 10 mg/d
Miscellaneous intranasals	Cromolyn (NasalCrom™)	Yes	1 SEN TID or QID, can increase up to 6 times daily (≥2 yo)	Not approved for children <2 yo	1 spray = 5.2 mg Max- 62.4 mg/d

(*continued*)

Table 6 (continued)

	Generic (common brands)	Over the counter	Adult dose	Pediatric dose	Dose strengths
	Ipratropium	No	0.03% solution: 2 SEN BID or TID (≥6 yo) 0.06% solution: 2 SEN QID for max 3 weeks (≥5 yo)	0.06% solution 2–4 yo: 1 SEN TID for max 14 days	0.03% solution: 1 spray = 21 mcg Max- 252 mcg/d 0.06% solution: 1 spray = 42 mcg Max- 672 mcg/d

*SEN: spray each nostril, **qday: once daily, ***yo: year old, ****BID: twice daily, *****TID: three times daily, ******QID: four times daily

rhinitis symptoms are at their peak (Corren 2014). Asthma and allergic rhinitis both involve airway inflammation, with asthma affecting the lower airways with bronchial inflammation and allergic rhinitis affecting upper airways with nasal inflammation (Scadding et al. 2008). Patients with allergic rhinitis but without known asthma often have bronchial hyperresponsiveness to inhalation challenges with histamine or methacholine, further indicating the need to assess patients with allergic rhinitis for asthma (Lang 2010). Children with asthma and allergic rhinitis have higher risk of hospitalization than those with asthma alone (Fischer 2007). Appropriate treatment and management of allergic rhinitis can lead to improved asthma in patients with both conditions.

Cross-reactivity between food and inhalant allergens occurs, resulting in pollen-food syndrome, formerly known as oral allergy syndrome. Pollen-food syndrome results in mild localized reactions to certain foods due to sensitization to specific pollens. For example, patients with allergy to birch pollen can develop oral allergy symptoms to raw apples with mouth or throat itching after ingestion of the fruit; patients with oral allergy syndrome do not react to cooked products. Anaphylaxis is extremely uncommon in oral allergy syndrome, as are other systemic symptoms (Ricketti and Cleri 2009; Scadding and Scadding 2016).

There are also side effects due to chronic inflammation leading to dysfunctional eustachian tubes, otitis media, sinusitis, chronic cough, and tonsillar and adenoid hypertrophy. Children with repeated episodes of otitis media have a 35–50% increased risk of having an allergy. The link between allergic rhinitis and nasal polyposis is controversial, but there are documented higher recurrence rates of nasal polyps in patients with allergic rhinitis (Ricketti and Cleri 2009). Rhinosinusitis develops more commonly in those with allergic rhinitis due to impaired sinus drainage.

Sleep issues related to allergic rhinitis occur due to unrelieved nasal obstruction and congestion, which leads to apnea, hypopnea, and frequent arousal from sleep (Corren 2014). These symptoms are most pronounced in the early hours in the morning and worsened when lying down (Scadding et al. 2012).

With treatment adherence to an appropriate regimen for allergic rhinitis, the prognosis is good, and complicating factors can be avoided. However, adherence is difficult as medication doses can be missed, and regular visits for SCIT can be problematic to maintain.

5.9 Conclusion

Allergic rhinitis is a chronic disorder that can cause significant impairment if not diagnosed and treated appropriately. Skin prick testing is a standard for diagnosis, but serum testing can also

be used. Empiric treatment in mild cases is reasonable. Avoidance of the inciting allergen is key when possible, but pharmacotherapy and immunotherapy may also be necessary. The development of advanced treatments and potential cures for allergic rhinitis is desirable; newer therapies in the United States include SLIT. The goal for treatment is to manage the condition and decrease the impact on quality of life, which may be more significant than in patients with asthma. Managing comorbid conditions is critical for preventing disease progression and improving control. It is also important to differentiate allergic rhinitis from non-allergic medical conditions since the symptoms are nonspecific and both conditions may occur simultaneously, but the treatments differ. With a thorough understanding of allergic rhinitis, the goal is to identify this condition early in the symptom progression in order to improve the patient's quality of life and prevent complications.

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Chronic Rhinosinusitis and Nasal Polyposis

6

Leslie C. Grammer

Contents

Abstract

Chronic rhinosinusitis (CRS) is a common disease, affecting up to 10% of the population at some time. Symptoms alone do not define the disease; objective evidence of inflammation by nasal endoscopy and/or sinus CT scan is also required. In the USA alone, the estimated annual direct and indirect costs exceed $30 billion. There are two subtypes, depending upon whether nasal polyps (NP) are present: CRSw(with)NP and CRSs (without)NP. A variety of risk factors and comorbidities have been described; in most cases, an aeroallergen evaluation should be performed, and, in recalcitrant cases, an immunodeficiency evaluation should be considered. The pathogenesis is unclear; a variety of factors have been implicated as contributory. They include impaired antimicrobial responses, ciliary abnormalities, epithelial dysfunction, microbial dysbiosis, autoantibodies, and *S. aureus* enterotoxins acting as allergens and/or superantigens. Maximal medical therapy, often including corticosteroids, antibiotics, and saline irrigations, is the initial treatment. Only those who fail are considered for surgical treatment.

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Chronic rhinosinusitis · Nasal polyps · Aspirin-exacerbated respiratory disease · Antibody deficiency

6.1 Introduction

Rhinosinusitis is a significant health issue that appears to be increasing in frequency. Rhinosinusitis is generally divided into acute or chronic based on whether the requisite signs and symptoms have been going on for more than 12 weeks. Chronic rhinosinusitis (CRS) is associated with poor quality of life, absenteeism, presenteeism, and a large financial burden in both direct and indirect medical expenditures. Recent estimates of the indirect costs of CRS in the USA, $12.8 billion, are thought to exceed direct costs (DeConde and Soler 2016). There are two forms of CRS, one with nasal polyps (CRSwNP) and one without (CRSsNP). While the focus of this review is on CRSwNP, for contrast, information on CRSsNP is included as well. In the past decade, there have been several documents published relative to CRS including practice parameters, position papers, and guidelines (Scadding et al. 2008, Fokkens et al. 2012, Kaplan 2013, Peters et al. 2014, Orlandi et al. 2014, Bachert et al. 2014, Hellings et al. 2017).

The inflammation of CRSsNP can be any combination of T helper type 1 (Th1), Th2, and/or Th17 (Tan et al. 2017). The inflammation of CRSwNP tends to be Th2, with eosinophilia. However, the NP of some ethic groups, for example, Asians, is less likely to be eosinophilic; in addition the NP of certain disease states, like cystic fibrosis (CF), is less likely to be eosinophilic (Zhang et al. 2017).

The inflammation of CRS can last for decades; glucocorticoids and antibiotics are the most common medical treatments. As they are unsatisfactory in some patients, approximately 300,000 surgeries are performed every year in the USA for CRS; the most common procedure is functional endoscopic sinus surgery (FESS), but other procedures such as balloon sinuplasty (BSP) are also performed. BSP catheters were approved by the FDA more than a decade ago. While there is literature that BSP can be a useful technique (Chandra et al. 2016), there are reports of failure rates as high as 66% (Tomazic et al. 2013).

The nasal and sinus microbiomes of CRS patients are different than normals. Whether that is causal or an epiphenomenon is unknown. There are a variety of other alterations in CRS, including decreased epithelial barrier integrity, altered levels of cytokines, decreased antimicrobial peptides produced in the sinonasal mucosa, changes of the epithelium toward mesenchymal transition, and mucociliary dysfunction. What role those and other described alterations play in the pathogenesis of CRS is unclear (Schleimer 2017).

6.2 Epidemiology and Risk Factors

CRS is estimated to affect 5–15% of the population in Europe and North America; however, doctor diagnosed CRS estimates are in the 2–4% range (Fokkens et al. 2012; Orlandi et al. 2014). A systematic review of 2014 costs associated with adult CRS in the USA estimated the direct costs to be $6.9–$9.9 billion and the indirect costs to be $13 billion (Smith et al. 2015). In that same study, annual medication costs prior to FESS ranged from $1547 to $2700 per patient; costs of medications were reduced after outpatient FESS which ranged in price from $8200 to $10,500. A study of insurance claims data also concluded that the costs of CRS were reduced after FESS (Bhattacharyya et al. 2011); in this study the reduction was approximately $885 in year 1 and $1331 in year 2. Another study of claims data also reported that costs of CRS were reduced after FESS (Purcell et al. 2015); the reported reduction averaged $600/year for each of the 3 years of follow-up. In addition, they found that disease-specific costs for conditions often associated with CRS such as depression, allergy, and asthma also decreased as did antibiotic use (28.2 days vs. 15.9 days per year). A retrospective database analysis of 35.5 million covered lives has reported that FESS within 1 year of diagnosis of CRS reduces both cost and healthcare utilization as

compared to FESS which occurred after >5 years of medical management (Benninger et al. 2015). There are no long-term follow-up studies to determine whether the cost of surgery is eventually paid for by reduction of postoperative costs of CRS.

CRSsNP is more prevalent than CRSwNP. Men are more likely to have CRSwNP than women. The most common age of onset is in the third or fourth decade of life. A number of diseases are associated with CRS. As those diseases often predate the CRS, it is generally accepted that they are predisposing or risk factors. Details can be found in a recent practice parameter publication (Peters et al. 2014).

Multiple studies of allergic rhinitis (AR) and CRS report association in both children and adults. In adults with CRS, 40–84% have AR (Van Lancker et al. 2005). One study reported that there is a correlation between extensive sinus disease on CT and AR (Ramadan et al. 1999). Surgical outcomes, corticosteroid use, and symptomatology, in those with CRSwNP, do not seem to be influenced by AR (Bonfils and Malinvaud 2008). There are also multiple studies of nasal lavage that implicate allergic responses in CRS; specifically, CRS patients have higher levels than normal individuals of allergic mediators such as leukotrienes, histamine, and Th2 cytokines (Peters et al. 2014).

Immunodeficiency can contribute to CRS and should especially be considered and evaluated in CRS patients that are resistant to medical and/or surgical treatments. Just as patients with recurrent acute sinusitis or recurrent pneumonia should be evaluated for immunodeficiency, so should recalcitrant CRS patients, in whom the prevalence of immunodeficiency has been reported to be about 15% (Carr et al. 2011). The American Red Cross and the Jeffery Modell Foundation both consider at least two serious sinus infections per year as a warning sign of primary immunodeficiency (PID) (Jeffery Modell Foundation 2012). While humoral PID is the most likely cause of recalcitrant CRS, other deficiencies including complement and cellular may play a role (Cunningham-Rundles and Bodian 1999). Prior to highly active antiretroviral therapy (HAART), the prevalence of CRS was significant in the HIV-infected population. However, the prevalence of CRS in that population receiving HAART is only 3–6%, similar to the general population (Campanini et al. 2005).

In a study of 446,480 electronic health records of individuals with and without CRS, several associations were reported. Compared to CRSsNP and control subjects, those with CRSwNP were more likely to be older and male. Prior to CRS diagnosis, those with CRS had a higher prevalence of a number of diseases including AR, asthma, gastroesophageal reflux, sleep apnea, anxiety, and headaches (Tan et al. 2013). Other risk factors reportedly associated with CRS include bronchiectasis (Bose et al. 2016), ciliary impairment, aspirin sensitivity, biofilms (layers of bacteria and their extruded polysaccharide matrix adherent to a biologic or non-biologic surface), and cigarette smoking (Fokkens et al. 2012; Bachert et al. 2014). Smoking cessation reduces corticosteroid use and improves CRS symptoms as well as quality of life scores (Phillips et al. 2017). A recent systematic review of the environmental and occupational literature related to CRS was unable to identify occupational or environmental exposures that play a role in CRS (Sundaresan et al. 2015). Table 1 enumerates factors associated with CRS as well as the references for those associations.

6.3 Pathogenesis

While the pathogenesis of CRS remains unclear, a variety of factors may be contributory; all described factors occur locally in the sinonasal tissue. Among them are epithelial dysfunction, epithelial to mesenchymal transition (EMT), mucociliary impairment, decreased innate antimicrobial responses, increased innate type 2 lymphoid cells (ILC2s), increased B cells and plasmablasts, increase in type 2 cytokines, alterations of the clotting pathway, autoantibodies, and staphylococcus enterotoxins acting as allergens or superantigens. Table 2 is a partial compilation of factors reported to be different in CRS compared to normal, healthy individuals without sinonasal disease.

Table 1 Clinical factors associated with CRS subtypes

Factor associated	CRS type	Reference
Aeroallergen sensitization	CRSsNP and CRSwNP	Van Lancker et al. 2005
Asthma	CRSsNP and CRSwNP	Tan et al. 2013
Primary immunodeficiency, especially humoral	CRSsNP and CRSwNP	Carr et al. 2011
Gastroesophageal reflux	CRSwNP and CRSsNP	Tan et al. 2013
Bronchiectasis	CRSsNP more than CRSwNP	Bose et al. 2016
HIV-related immunodeficiency	CRSsNP only if not on HAART	Campanini et al. 2005
Cystic fibrosis	CRSwNP	Marshak et al. 2011
Aspirin respiratory reactions	CRSwNP	Lee et al. 2010

CRS chronic rhinosinusitis, *CRSwNP* CRS with nasal polyps, *CRSsNP* CRS without nasal polyps, *HAART* highly active retroviral therapy

Table 2 Possible pathogenic molecules and processes contributing to CRS

Molecule or process	CRSsNP	CRSwNP	Reference
S100 proteins: Calprotectin, psoriasin,	Lower in tissue than normal controls	Lower in tissue than normal controls	Tieu et al. 2010
Autoantibodies	Similar to control	Elevated anti-dsDNA in polyp tissue but not in peripheral blood	Tan et al. 2011
SETs[a], IgE against SETs	Similar to normal control	Present in approximately half of CRSwNP	Gevaert et al. 2005
Vbeta skewing of T cell receptors associated with SETs acting as superantigens	Similar to normal control	Present in approximately 1/3 of CRSwNP	Seiberling et al. 2005
Group 2 innate lymphoid cells	Similar to control	Elevated compared to CRSsNP	Miljkovic et al. 2014
Fibrin, tissue plasminogen activator (tPA), fibrin split products (FSP)	Similar to control	Increased fibrin that is cross-linked, decreased tPA and FSP	Takabayashi et al. 2013
Epithelial to mesenchymal transition (EMT)	Increased in tissue compared to normal controls	Increased in tissue compared to normal controls	Zhang et al. 2016
Ciliary function	Decreased	Decreased	Chen et al. 2006

[a]*SET staphylococcus enterotoxins*

Potential contributing epithelial dysfunctions in CRS include acantholysis (loss of intercellular connections), acanthosis (diffuse epidermal hyperplasia), and EMT (Schleimer 2017). In addition, proteins such as periostin, laminin, and vimentin, known to be associated with EMT, are increased in the sinonasal tissue (Zhang et al. 2016). Mucociliary dysfunction in CRS has been reported for many years; the severity of CRS likely correlates with the amount of dysfunction (Chen et al. 2006). Some bacteria produce toxins that cause ciliary damage; among them are bacteria that are associated with CRS: *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Pseudomonas aeruginosa* (Brook 2016). Numerous studies have reported that microbial dysbiosis, particularly a decrease in diversity compared to normal subjects, occurs in CRS (Psaltis and Wormald 2017). However, whether microbial dysbiosis is a cause, an association or an epiphenomenon of CRS is not clear.

Another epithelial abnormality that commonly occurs in CRS is changes in local, sinonasal antimicrobial responses. For example, multiple proteins of the innate immune system that are important for pathogen recognition and destruction tend to be increased in CRS. However, some innate molecules are reduced in CRS. In some

cases, such as with toll-like receptors (TLRs), it is unclear which ligands and receptors are increased, decreased, or unchanged compared to controls (Hamilos 2014). A genetic polymorphism in the bitter taste receptors, e.g., T2R38, can contribute to CRSsNP (Lee and Cohen 2015). In normal people, when those receptors are engaged by molecules produced by bacteria, the epithelial cells respond by producing antimicrobial molecules to kill the bacteria. This response is abrogated in those with certain polymorphisms. A group of antimicrobial peptides, the S100 proteins, including psoriasin and calprotectin, may be reduced in CRS (Tieu et al. 2010). Enzymatic antimicrobial molecules such as lactoferrin and lysozyme also may be reduced in CRS (Psaltis et al. 2008). Complement deficiency, specifically, mannose-binding lectin deficiency, has been reported in some CRS patients. There are multiple studies that conclude that humoral immunodeficiency, both specific antibody deficiency (SAD) and common variable immunodeficiency (CVID), contributes to CRS in some patients (Chiarella and Grammer 2017).

Injured respiratory epithelium is likely to produce Th2-promoting cytokines such as thymic stromal lymphopoietin (TSLP). TSLP is elevated in CRSwNP (Miljkovic et al. 2014). That is likely contributing to the TH2 cytokines found in most European CRSwNP (Hulse et al. 2015). In addition, large numbers of B cells, plasma cells, and plasmablasts occur in mucosal tissue (Gevaert et al. 2005). There are also reports of autoantibodies, both against double-stranded DNA and the bullous pemphigoid 180 antigen, in the CRS tissue but not systemically in patients with CRSwNP (Tan et al. 2011). Enterotoxins such as staphylococcal enterotoxins A and B (SEA and SEB), from staphylococcus may drive inflammation of CRSwNP by acting as both allergens and superantigens (Seiberling et al. 2005; Bachert and Zhang 2012). Finally, macrophages and IL-13 are higher in CRSwNP than in CRSsNP or in controls. IL-13 suppresses tissue plasminogen activator (tPA) and macrophages produce factor XIIIA, resulting in cross-linked fibrin with very little fibrinolysis (Takabayashi et al. 2013).

In some diseases such as cystic fibrosis and in some populations such as CRSwNP in Asians, eosinophilic mucosal inflammation is less likely. The reasons for greater neutrophil predominance in certain diseases and populations are an area of active investigation (Zhang et al. 2017).

6.3.1 Genetics

There are several publications that suggest that CRS occurs more commonly in families (Fokkens et al. 2012; Rugina et al. 2002). However, when a search of the literature was performed in 2013, except for mutations in the cystic fibrosis transmembrane conductance regulator gene (CFTR), no other genetic polymorphisms were confirmed in reference populations (Hsu et al. 2013). Subsequently, a bitter taste receptor gene polymorphism (e.g., T2R38) has been associated with CRS in one US study (Lee and Cohen 2015). This finding was replicated in two Canadian populations (Mfuna Endam et al. 2014). However, the association was not replicated in an Italian population (Gallo et al. 2016). In a 2017 review of the literature, familial clustering was again confirmed. The authors concluded that there are reports of a number of discovery cohorts in which polymorphisms were associated with CRS (Cohen 2017). Information about selected genes studied in CRS can be found in Table 3. However, in attempted replication cohorts, except for CFTR and the bitter taste receptors, genetic polymorphisms associated with CRS are unconfirmed (Halderman and Lane 2017).

6.3.2 Diagnosis

The definition of CRS has evolved over the past several decades. In more recent publications, there is a consensus about the definition (Fokkens et al. 2012; Peters et al. 2014). Table 4 shows the diagnostic criteria for CRS. First, the duration of signs and symptoms should be at least 12 weeks. Second, nasal and sinus inflammation should be present resulting in at least two symptoms, one of which must be nasal obstruction/congestion or

Table 3 Selected genes reported to be associated with CRS

Gene function	Gene	Chromosome location	Replication
Chloride ion transport	CFTR	7q31	Yes
Human leukocyte antigens (HLA)	MHC class I, HLA-A, HLA-B HLA-C	6p21	No
	MHC class II HLA-DR, HLA-DQ	6p21	No
Innate immunity	CD14	5q31	No
	IRAK4	12q12	No
	Bitter taste receptor T2R38	7q36	Yes
	TLR2	4q32	No
TH2 inflammation	IL-4	5q31	No
	IL-13	5q31	No
Other inflammation	IL-1	2q14	No
	IL-6	7p21	No
	TNF	6q23	No
Arachidonic acid metabolism	LTC4	5q35	No
	PTGDR	14q22	No

CFTR cystic fibrosis transmembrane conductance regulator, *MHC* major histocompatibility complex, *IRAK4* IL-1 receptor-associated kinase 4, *TLR2* toll-like receptor 2, *IL* interleukin, *TNF* tumor necrosis factor, *LTC4* leukotriene C4, *PTGDR* prostanoid DP receptor

Table 4 Diagnostic criteria for CRS

1. Symptoms must be continuously present for at least 12 weeks
2. Inflammation of sinonasal tissues resulting in two or more symptoms, one of which should be nasal congestion/blockage/obstruction or nasal discharge which can be anterior, posterior, or both. Other symptoms are facial pain/pressure or reduction in olfaction; in children the latter can be replaced by cough
3. Endoscopic findings compatible with CRS: nasal polyps, mucopurulent discharge, edema mucosal obstruction and/or
4. Sinus CT findings of mucosal inflammation/thickening of sinuses and/or ostiomeatal complex

nasal discharge (posterior or anterior rhinorrhea). Other symptoms are facial pain/pressure and reduction or loss of olfaction. In children, loss of olfaction can be replaced by cough. In addition, the sinonasal inflammation must be supported by endoscopic findings of nasal polyps, mucopurulent discharge, or edema and/or CT (computed tomography) findings compatible with CRS. Figure 1 is a sinus CT showing normal anatomy. Figure 2 is a CT scan of CRSwNP.

The timing and cost-effectiveness of imaging, in particular, sinus CT scan without contrast, has been studied. There are not studies of the cost-effectiveness of anterior rhinoscopy or nasal endoscopy. In patients with compatible symptoms for at least 12 weeks, sinus CT scans are cost effective, mostly due to reduction in antibiotic use (Leung et al. 2014; Lobo et al. 2015). In these studies, more than half of sinus CT scans were normal even though the patients had symptoms compatible with CRS for more than 12 weeks. The most common diagnoses subsequent to a normal sinus CT scan were perennial allergic rhinitis, non-allergic rhinitis, headache syndromes, and facial pain syndromes. It has been recognized for more than a decade that most patients with self-diagnosed or physician-diagnosed sinus headaches actually have migraines (Tepper 2004). Rhinorrhea and nasal congestion, two of the cardinal CRS symptoms, occur in more than half of the subjects when they experience migraines.

6.3.3 Prognosis

The prognosis of CRS depends upon a variety of factors including severity, treatment, and comorbidities. The initial treatment for CRS is generally medical which is covered in the next section. Prior to consideration of surgery for CRS, most would give a course of maximal medical therapy (MMT) that includes corticosteroids and antibiotics (Patel et al. 2017). There are no

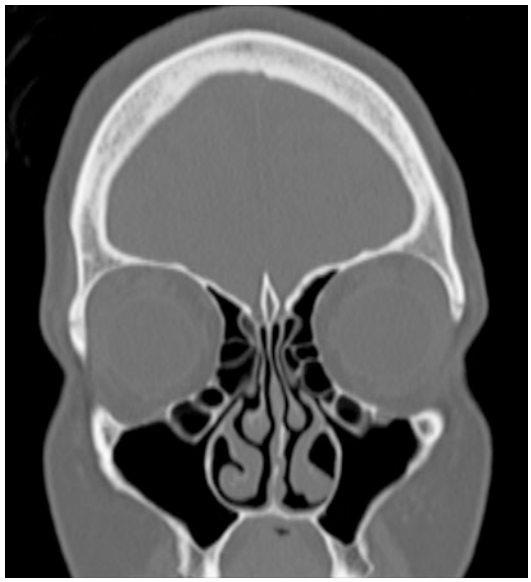

Fig. 1 Coronal CT scan view showing normal sinus anatomy. Normally sinuses should be black as they are air-filled; bone is white and soft tissue or fluid is gray

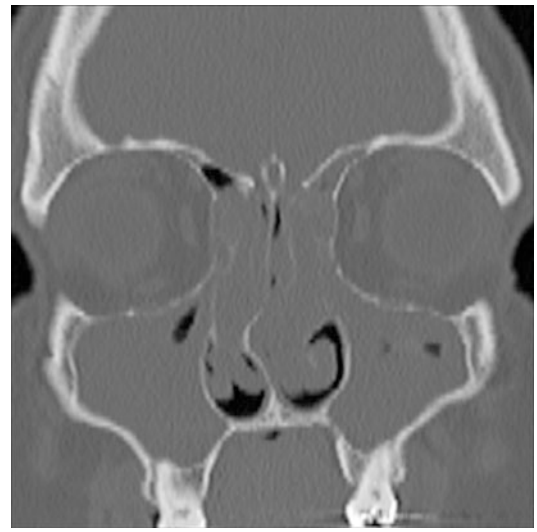

Fig. 2 Coronal CT scan view showing CRSwNP. Most of the sinuses are gray as they are filled with polypoid, eosinophilic inflammation

studies that describe the long-term outcomes of such MMT, i.e., the number and proportion of individuals who are able to maintain sufficient improvement that they do not seek a surgical option, which is generally FESS.

The surgical prognosis is influenced by several factors. It should be noted that most follow-up studies are 12–24 months, with the longest follow-up being 6 years. In CRSsNP, the T2R38 genotype that codes for a nonfunctional bitter taste receptor may have worse outcomes than other genotypes (Adappa et al. 2016). Recurrence of nasal polyps (NPs) after FESS is 35%, 38%, and 40% at 6, 12, and 18 months, respectively (DeConde et al. 2017). In a Portuguese study of CRSwNP, nonatopic asthma and exposure to occupational dust were associated with recurrence of NPs (Veloso-Teles and Cerejeira 2017). Osteitis (inflammation of the bone without invasion of bacteria or neutrophils) and biofilm formation are bad prognostic comorbidities that almost always require surgical treatment (Zhao and Wormald 2017). There are short-term (6-month follow-up) studies post FESS that report improvement of quality of life in children, even if they have CF as a comorbidity (Fetta et al. 2017).

The amount of improvement in the Sinonasal Outcome Test (SNOT-22) after FESS is variable. In a study from the UK, 66% achieved clinically relevant improvement, whereas in studies in the USA and Canada, the proportion tends to be above 80% (Hopkins et al. 2015). Outcomes such as olfaction, cognitive function, and sleep quality have also been evaluated after FESS. A meta-analysis reported that olfaction improved after FESS; this improvement was more pronounced in those with CRSwNP (Kohli et al. 2016). In another study of FESS, there was improvement in cognitive function as measured by the Cognitive Failures Questionnaire (CFQ) in CRSwNP patients; no significant improvement was found for those with CRSsNP (Alt et al. 2016). In a study in which patients chose medical or surgical treatment for CRS, those who opted for FESS had significant improvement in the Pittsburgh Sleep Quality Index (PSQI). Those who chose medical management did not improve and had PSQI scores that were worse than the control population (Alt et al. 2017).

While it is beyond the scope of this article to cover, it should be noted that there is a significant body of literature that suggests that CRS outcome has an impact on asthma; specifically, in patients

who have CRS and asthma, CRS exacerbations are likely to be significantly associated with worsening asthma (Lee et al. 2017). Therefore, the CRS prognosis also affects the asthma prognosis. With an emphasis on personalized medicine, there is investigation into the endotypes of CRS. The objective is to understand the various endotypes which should allow for individualized treatment, the subject of the next section (Kim and Cho 2017).

6.4 Management

Recent guideline and practice parameter publications include several management scheme diagrams that illustrate an algorithmic approach to patients with CRS (Fokkens et al. 2012; Peters et al. 2014). Once the diagnosis of CRS is established, consideration should be given to determining if aeroallergens might be contributing to the inflammation. This is especially important with aeroallergens such as dust mite and animal dander for which avoidance measures could be helpful. If patients are having frequent exacerbations of CRS requiring antibiotics or if the CRS is recalcitrant to therapy, consideration of an immunodeficiency evaluation is in order. Specifically, laboratory tests that could be useful include quantitative immunoglobulins and specific antibody responses to vaccines. In those patients with CVID, immunoglobulin replacement may be useful in reducing CRS inflammation (Walsh et al. 2017). In those patients who have normal immunoglobulins but low levels of antibody against *Streptococcus pneumoniae* serotypes, a 23 valent pneumococcal vaccine may result in the patient developing normal amounts of protective antibody and fewer exacerbations of CRS requiring antibiotics (Kashani et al. 2015; Keswani et al. 2017). In those patients who do not respond to vaccination with increased *S. pneumoniae* antibody, a diagnosis of specific antibody deficiency (SAD) would be appropriate. The mainstay of therapy for patients with SAD is prophylactic antibiotics; however, there are no standardized protocols and no controlled studies of efficacy (Perez et al. 2017). Published guidelines recommend immunoglobulin therapy for SAD patients, based on retrospective studies (Perez et al. 2017). In patients with CRS and antibody deficiency, either SAD or CVID, immunoglobulin replacement may reduce Lund-Mackay CT sinus scores and frequency of CRS exacerbations (Walsh et al. 2017).

Medical management is the initial approach for patients with CRS. Many references suggest that MMT should be tried prior to consideration of FESS. MMT protocols vary widely and include the following interventions for variable amounts of time: nasal corticosteroids (91% of MMT protocols include this intervention), oral antibiotics (89%), systemic corticosteroids (61%), saline rinse irrigation (39%), oral antihistamines (11%), oral/topical decongestants (10%), and oral mucolytics (10%) (Dautremont and Rudmik 2015). Intranasal corticosteroids (INCS) are generally used on a daily basis; a 2016 Cochrane review reported that INCS results in a moderate benefit for nasal blockage and a small benefit for rhinorrhea (Chong et al. 2016a). Patients with CRSwNP often require twice daily doses of INCS. Nasal saline irrigation is useful if patients adhere to the regimen (Chong et al. 2016b). The use of antibiotics should be culture directed if possible (Fokkens et al. 2012; Peters et al. 2014); amoxicillin-clavulanic acid is a reasonable empiric antibiotic, while clindamycin would be appropriate for the penicillin allergic individual. Antibiotics are more likely to be useful in CRSsNP (Head et al. 2016b). Short-course (3–7 days) oral corticosteroids may be useful for exacerbations, particularly of CRSwNP (Head et al. 2016a); however, the risk/benefit ratio of prescribing oral corticosteroids needs to be considered as side effects can occur. A range of systemic corticosteroid prescribing options for CRS has been reported (Scott et al. 2017). Oral prednisone is the most commonly prescribed preparation; the median starting dose was 50 mg (20–80 mg), and the average duration was 5 days (1–21 days). Biologics, including omalizumab, mepolizumab, benralizumab, and dupilumab, are increasingly reported to be useful in the

Table 5 Indications for urgent evaluation and treatment of complications of CRS

1. Neurologic signs, e.g., ophthalmoplegia
2. Unilateral symptoms
3. Periorbital edema and/or erythema
4. Displaced globe
5. Double or impaired vision

medical management of CRS (Bachert et al. 2015; Chiarella et al. 2017); at the time this article was written, no biologic has been approved by the FDA to treat CRS. If medical treatment is successful, the patient can use INCS and saline as maintenance therapy. Occasional use of antibiotics and/or short-course (3–7 days) oral corticosteroids may be needed for exacerbations.

However, if maintenance therapy with INCS and saline is not sufficient; if the patient requires frequent, more than twice a year, oral corticosteroids and/or antibiotics; or if the patients wants to explore a surgical option, surgery, specifically FESS in adults, should be considered. In children with CRS, there is evidence that the adenoids may serve as a reservoir for pathogenic bacteria; as a result, adenoidectomy is a surgical treatment that has been reported to be useful in the pediatric population (Mahdavinia and Grammer 2013). A prospective, non-randomized study comparing medical and surgical therapy for CRS in adults has been published (Smith et al. 2013). Patients who elected FESS had fewer course of antibiotics, fewer missed school/work days, and improved quality of life during the 2-year follow-up. In short, when aggressive medical management fails to control CRS, surgery may result in better outcomes. In a recent study of CRS patients, multivariate logistic regression was used to evaluate factors that increase the likelihood of the patient choosing FESS over continuing medical management (Chapurin et al. 2017). Those factors were CRSwNP as compared to CRSsNP odds ratio (OR) =4.28, cystic fibrosis OR = 2.42, and academic site (compared to a community site) OR = 1.86. As mentioned above, long-term follow-up studies after surgery for CRS have not been reported.

6.5 Special Issues

There are several aspects of CRS that require special consideration: complications, cystic fibrosis (CF), aspirin-exacerbated respiratory disease (AERD), and allergic fungal rhinosinusitis (AFRS).

The complications of CRS are primarily due to changes in the surrounding bone in response to chronic inflammation. Among those changes are osteitis, mucoceles, metaplastic bone, bone erosion, and expansion that can damage adjacent structures resulting, for example, in optic neuropathy (Fokkens et al. 2012). Another complication is the spread of infection from the sinuses to surrounding tissues causing cellulitis or osteomyelitis, invasion of the bone by bacteria, and neutrophils as opposed to osteitis which is bone inflammation without invasion. Imaging studies are necessary to define these complications which may require urgent intervention to prevent serious sequelae like blindness. Some indications for urgent evaluation and treatment are found in Table 5.

Nasal polyps in children should raise the possibility of CF (Marshak et al. 2011). CRS may be the initial problem in those CF patients with milder CFTR gene mutations. Almost all CF patients have CRS, with about one third having CRSwNP; those NPs tend to be neutrophilic, not eosinophilic. In CF patients, the pathogens in the upper and lower airway tend to be similar. FESS tends to be useful in CF patients with refractory CRS; there have been reports of improvement in lung function after such surgery (Kovell et al. 2011). However, long-term prospective studies of lung function after FESS are not available.

There is a subset of patients with CRSwNP and asthma who have respiratory reactions after ingesting aspirin or other nonsteroidal anti-inflammatory drugs (NSAIDs); those patients have aspirin-exacerbated respiratory disease (AERD). In general, it is recommended that such patients avoid NSAIDs. In these patients, FESS has been reported to improve asthma, but long-term prospective studies have not been reported; AERD patients are more likely to experience regrowth of NP than other patients with CRSwNP

(Fokkens et al. 2012). Desensitization followed by daily aspirin therapy may decrease the rate of NP recurrence (Lee et al. 2010; Kowalski et al. 2016). Other therapies that have been recommended for AERD include leukotriene-modifying drugs, saline irrigation, and nasal corticosteroids (Levy et al. 2016).

The role of fungi in the pathogenesis of CRS has been investigated in the past decade; it is generally agreed that fungi do not contribute to the pathogenesis of most CRS (Zhao et al. 2017). However, in some patients who have immediate-type hypersensitivity to fungi, eosinophilic mucin, and characteristic CT findings of high attenuation, it is thought that the fungi play a role in the CRSwNP that is termed allergic fungal rhinosinusitis (AFRS) (Fokkens et al. 2012; Peters et al. 2014). Patients with AFRS tend to require surgery as well as long-term oral and/or topical corticosteroids to maintain control. As adjunctive therapy, oral antifungals may play a role. While immunotherapy with fungal antigens initially was reported to be useful, more recent studies do not show benefit (Marple et al. 2002).

6.6 Conclusions

Chronic rhinosinusitis is a very common disease resulting in significant morbidity. The initial approach is medical management, but surgical intervention may be required in those whose response is suboptimal. A variety of comorbidities and subtypes are recognized that need somewhat different approaches to management: aeroallergen sensitization, immunodeficiency, bone complications, infectious complications, CF, AERD, and AFRS. There is a need for studies of long-term outcome data, especially postsurgery, to enhance clinical decision-making in CRS.

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Part III

Allergic Skin Diseases and Urticaria

Atopic Dermatitis

7

Neeti Bhardwaj

Contents

Abstract

Atopic dermatitis (AD) or eczema is a common chronic relapsing skin disease that is often associated with other atopic conditions like allergic rhinitis and asthma. It is a major problem in developing as well as developed

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countries, with a pronounced increase in prevalence in recent decades. It is often the first clinical manifestation of atopy and the start of atopic march (Spergel, Ann Allergy Asthma Immunol 105:99–106, 2010). The hallmark is epidermal barrier dysfunction leading to dry skin and IgE-mediated sensitization to food and environmental allergens. The pathogenesis of AD involves complex interrelationships among genetic, immunologic, environmental, and environmental factors. Recent insights into the genetic and immunologic mechanisms that drive cutaneous inflammation in AD have improved our understanding of its natural history with development of novel immunomodulatory and anti-inflammatory agents. Early and proactive management may improve the outcome and overall quality of life for these patients.

Keywords

Atopic dermatitis · Atopic march · Filaggrin · Topical corticosteroids · Topical calcineurin inhibitors

Abbreviations

AD	Atopic dermatitis
AMP	Antimicrobial peptides
CCL17	Chemokine ligand 17
CLA	Cutaneous lymphocyte associated
FLG	Filaggrin
GM-CSF	Granulocyte-macrophage colony-stimulating factor
HDM	House dust mite
IFN-g	Interferon gamma
IL-4	Interleukin-4
IL-5	Interleukin-5
IL-12	Interleukin-12
IL-13	Interleukin-13
LC	Langerhans cell
PDE4	Phosphodiesterase 4
SCORAD	Scoring atopic dermatitis
TARC	Thymus- and activation-regulated cytokine
TCI	Topical calcineurin inhibitor
TLR	Toll-like receptors
TSLP	Thymic stromal lymphopoietin

7.1 Introduction

Atopic dermatitis (AD) or eczema is a common chronic relapsing skin disease that is often associated with other atopic conditions like allergic rhinitis and asthma (Boguniewicz and Leung 2011). It is a major problem in developing as well as developed countries, with a pronounced increase in prevalence in recent decades (Kapoor et al. 2008). It is often the first clinical manifestation of atopy and the start of atopic march (Spergel 2010). The hallmark is epidermal barrier dysfunction leading to dry skin and IgE-mediated sensitization to food and environmental allergens. The pathogenesis of AD involves complex interrelationships among genetic, immunologic, environmental, and environmental factors (Boguniewicz and Leung 2011).

7.2 Epidemiology

The prevalence of atopic dermatitis has increased substantially in English-speaking, industrialized countries: 15–30% of children and 2–10% of adults are affected (Williams and Flohr 2006). The International Study of Asthma and Allergies in Childhood (ISAAC phase III) on 385,853 participants aged 6–7 years in 60 countries showed prevalence ranging from 0.9% in India to 22.5% in Ecuador (Williams et al. 2008; Pearce et al. 2007). Highest occurrence among 13–14-year-olds was noted in Africa and Latin America, emphasizing the importance of AD as a global health problem. A systematic review estimated the annual direct and indirect costs of atopic dermatitis in the United States at $364 million to $3.8 billion (Mancini et al. 2008). This disorder is often the first clinical manifestation of atopic march, characterized by progression of AD to asthma and allergic rhinitis. The defective skin barrier is believed to facilitate primary sensitization to food and environmental allergens (Spergel 2010). Atopic dermatitis frequently starts in early infancy. A cross-sectional study of a cohort of 2270 children with physician-confirmed AD showed that 66% had symptoms of asthma or atopic dermatitis and 80% had an additional allergic manifestation by the third year of life (Kapoor et al. 2008). About 45% of all

cases begin within the first 6 months of life. About 85% cases begin before the fifth birthday; up to 70% of these children have spontaneous remission before adolescence (Illi et al. 2004). Adult-onset disease typically does not have IgE-mediated sensitization (Novak and Bieber 2003).

7.3 Genetics

Atopic dermatitis has a complex pathogenesis. Several genes are involved in its development, but there's a strong influence of innate and adaptive immune responses and environmental factors. There is a 77% concordance rate among monozygotic twins, compared to 15% among dizygotic twins (Schultz Larsen and Holm 1985). Several atopic dermatitis-related loci have been identified using genome-wide scans. These include chromosomes 3q21, 1q21, 16q, 17q25, 20p, and 3p26 (Palmer and Cardon 2005). Chromosome 1q21 harbors a family of genes called epidermal differentiation complex (Cookson 2004). Genes on chromosome 5q31-33 encode cytokines interleukin-4, interleukin-5, interleukin-12, interleukin-13, and granulocyte-macrophage colony-stimulating factor (GM-CSF) (Morar et al. 2006; Hoffjan and Epplen 2005). These cytokines are involved in regulation of IgE synthesis. Interleukin-5 and interleukin-13 upregulate production of IgE. These cytokines, along with IL-4, are produced by type 2 helper T cells (Th2) (Bieber 2008). Interleukin-12 and interferon-ɣ, produced by type 1 helper T cells (Th1), suppress IgE production. Individuals with atopic dermatitis have a genetic predominance of Th2 cytokines, favoring production of IgE from B cells (Bieber 2008). Skin barrier abnormalities play a significant role in the causation of AD. Loss-of-function mutations of the gene encoding the epidermal barrier protein filaggrin have been shown to be a major predisposing factor for AD (Palmer et al. 2006; Weidinger et al. 2006; Marenholz et al. 2006). FLG gene mutations are associated with early-onset, severe, and persistent AD and increased risk for development of asthma, as well as food and inhalant allergies (Bieber 2008). FLG mutations are found in up to 40% of patients with severe AD. However, less than 20% of these patients with severe disease are homozygous for FLG mutations (Mohiuddin et al. 2013). Moreover, FLG mutations are identified in only 30% of European patients with atopic dermatitis (Vasilopoulos et al. 2004). Only a minority of Asian patients and none of the African American patients with AD have FLG mutations (Mcaleer and Irvine 2013; Irvine et al. 2011). Loss-of-function mutations in serine protease inhibitors (e.g., SPINK5) promote protease-activated pathways, leading to enhanced Th2 responses (Cork et al. 2009).

7.4 Causes of Epithelial Skin Barrier Dysfunction in AD

An intact epidermal compartment is critical for the physical and chemical barrier function of the skin. The innermost layer of the epidermis, the basal layer, is the site of cell proliferation. As the cells divide, they migrate upward to form the spinous cell layers. Here, cell junctions are tightened and keratin proteins are expressed. Dense cytoplasmic granules composed primarily of profilaggrin are seen in cells of the granular layer (Irvine et al. 2011). These are required for the formation of flattened, dead cells of the outermost stratum corneum that is primarily responsible for the barrier function of the skin. The stratified, cornified squamous epithelium of the skin prevents water loss and also blocks entry of foreign substances (allergens, antigens, irritants, pathogens) from the external environment (Irvine et al. 2011). According to the "bricks and mortar" model of the stratum corneum, the flattened cells (squames) act as brick sand and the cornified cell envelope acts as the mortar (Proksch et al. 2003). A schematic of barrier function of the skin is depicted in Fig. 1.

7.4.1 Filaggrin

Filament-aggregating protein (filaggrin) is a key epidermal protein involved in the formation of epidermal barrier. A robust association has been found between loss-of-function mutations in the gene encoding filaggrin (FLG) with the risk of AD.

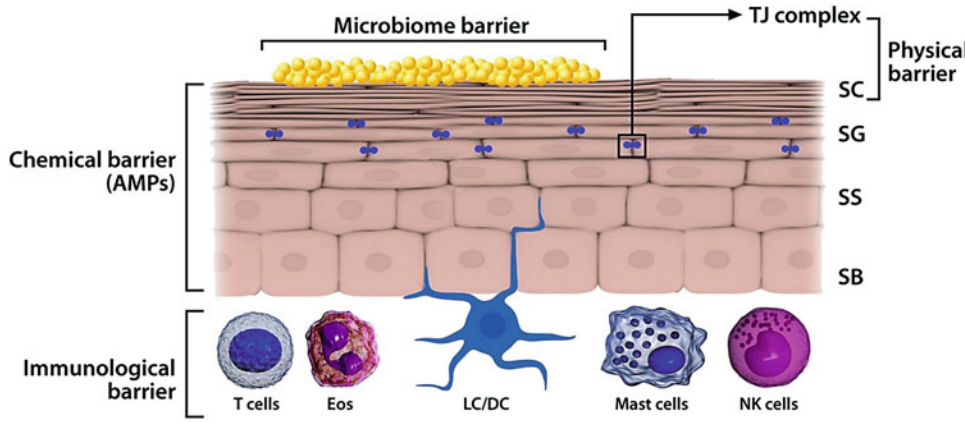

Fig. 1 The skin as a multitiered barrier. The stratum corneum (SC) is the first physical barrier protecting the skin from the environment. Gene mutations (e.g., filaggrin null mutations) or cytokines (e.g., IL-4, IL-13, IL-25, and IL-33) downregulating epidermal proteins, including filaggrin, leads to allergen or microbial penetration through this barrier. Tight junctions *(TJs)* found at the level of the stratum granulosum *(SG)* provide an additional barrier. Disruption of both physical barriers enables the uptake of allergens, irritants, and microbes by Langerhans cells (*LCs*)/DCs. Keratinocytes produce AMPs as a chemical barrier in response to pathogen colonization/infection. The skin surface is colonized by a diverse array of microorganisms (microbiome barrier) that dysregulate local immune responses and inhibit pathologic microbes. There is also infiltration of a number of cells into the AD skin lesion, including T cells, eosinophils (*Eos*), DCs, natural killer *(NK)* cells, and mast cells/basophils. Collectively, these cells constitute the cutaneous immunologic barrier. Pattern recognition receptors regulate the function of all of these barriers (physical, chemical, microbiome, and immunologic). *SB,* stratum basale, *SS*, stratum spinosum (Reproduced with permission from Journal of Allergy and Clinical Immunology 2014, 134, 769–779)

The gene FLG is located in the epidermal differentiation complex located on chromosome 1q21 (Palmer et al. 2006; Weidinger et al. 2006; Marenholz et al. 2006). Patients with these mutations tend to have early-onset disease which is persistent and often associated with asthma, food allergy, and microbial infection (Irvine et al. 2011). Profilaggrin is one of the most histidine-rich and glutamine-rich proteins in the human genome. These amino acids modulate the pH of the stratum corneum, help with intracytoplasmic retention of moisture, and possibly have antimicrobial effect on *Staphylococcus* (Irvine et al. 2011). It has been experimentally shown that the epidermis of filaggrin-deficient mice allows passive transfer of protein allergens (Mildner et al. 2010; Gruber et al. 2011). The knockdown of filaggrin expression by RNA interference in cultures of human keratinocytes causes increased uptake of fluorescein dyes. The overall odds ratio of atopic dermatitis in individuals with FLG mutations is 3.12–4.78 (Weidinger et al. 2006; Van Den Oord and Sheikh 2009). Filaggrin loss-of-function mutations have a complex association with asthma, conferring an overall risk ranging from 1.48 to 1.79; however, this effect is limited to subjects with AD or history of it (Henderson et al. 2008; Gao et al. 2009). Since filaggrin is not expressed in the respiratory epithelia, it is assumed that AD is a risk factor for asthma and systemic allergen sensitization (Ying et al. 2006). It is believed that allergen and pathogen penetration through a defective skin barrier stimulates production of thymic stromal lymphopoietin (TSLP) by keratinocytes (Ziegler and Artis 2010). This, in turn, exerts distal effects on the lungs. Moreover, FLG mutations confer an overall odds ratio of 5.3 for peanut allergy (Brown et al. 2011). The ratio when corrected for atopic dermatitis is 3.8. The impressive association of filaggrin mutations with atopic dermatitis supports the outside-inside hypothesis meaning that the primary defect is in the skin, leading to immunological dysfunction. There are various mechanisms that cause defective stratum corneum barrier in filaggrin deficiency, one of them being

impaired filament aggregation in the transitional zone of stratum corneum. This impairs the maturation and excretion of extracellular lamellar bodies (Gruber et al. 2011). Tight junctions that are critical in sealing epidermal cell-to-cell integrity are reduced in number in filaggrin-deficient individuals (De et al. 2011). Moreover, they have a decreased density of corneodesmosin, the major component of corneodesmosomes that are critical for stratum corneum cell-to-cell adhesion (Gruber et al. 2011). Filaggrin breakdown products have an acidifying effect (Krien and Kermici 2000). An elevation of pH of the stratum corneum facilitates adhesion and multiplication of *Staphylococcus aureus* (Irvine et al. 2011). Only about 42% of all FLG heterozygotes develop atopic dermatitis, indicating that genetic and environmental modifiers are important (Henderson et al. 2008). Figure 2 summarizes the role of filaggrin in pathogenesis of AD.

7.4.2 Skin Barrier Dysfunction: Beyond Filaggrin

Genes other than FLG encoding a cluster of the epidermal differentiation complex located on chromosome 1q21 have been associated with AD (Cookson 2004). These include filaggrin 2, hornerin, and SPRR3, a cornified envelope precursor (De Guzman Strong et al. 2010). However, the function of these epidermal differentiation complex gene variants in AD is not completely understood. Loss-of-function mutations in serine protease inhibitors (e.g., SPINK5) are known to augment protease-activated pathways that, in turn, enhance Th2 responses (Samuelov and Sprecher 2014). In the normal skin, a series of barriers work together to ensure retention of water and prevent penetration of the skin by allergens and microbes. Deficiency of structural proteins like filaggrin leads to breach of the stratum corneum. The light junction proteins such as claudins located on opposing membranes of stratum granulosum cells form a second physical barrier in the epidermis (Leung and Guttman-Yassky 2014; Kuo et al. 2013). Downregulation of claudin protein has been shown in the epidermis of patients with AD. When these two physical barriers (filaggrin and tight junctions) are compromised, Toll-like receptors expressed on keratinocytes and antigen-presenting cells in the skin must initiate a rapid innate immune response, leading to the release of AMPs and strengthening of tight junctions to limit penetration of allergens and microbes. Patients with AD have been found to have depressed TLR function (Kuo et al. 2013).

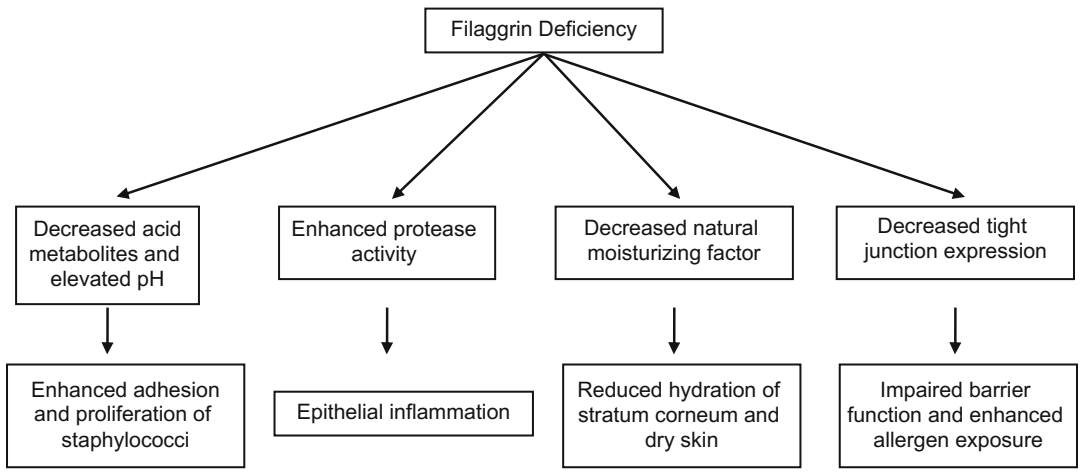

Fig. 2 Filaggrin deficiency and possible mechanisms of disease

7.4.3 Microbial Agents

The skin of more than 90% of patients with atopic dermatitis is colonized with *Staphylococcus aureus* (Verhagen et al. 2006). Overall suppression of the innate immune system of the skin in AD predisposes to the increased rate of colonization, which, in turn, contributes to allergic sensitization and inflammation. The ability of keratinocytes from the skin of patients with AD to produce AMPs needed to control *S. aureus* replication is depressed. *S. aureus* enterotoxins interact with major histocompatibility complex class 2 molecules and T-cell receptors inducing antigen-independent proliferation of T cells (Bieber 2008). Moreover, there is upregulation of expression of the skin-homing receptor cutaneous lymphocyte-associated (CLA) antigen on T cell. Furthermore, the enterotoxins induce the competing β-isoform of the glucocorticoid receptor in mononuclear cells, leading to resistance to local corticosteroid treatment (Bieber 2008). AD patients can be colonized by *S. aureus* bacteria that secrete more than one superantigen (Cardona et al. 2006). Superantigens have an additive effect with conventional allergens in inducing cutaneous inflammation. Therefore, *S. aureus* colonization of the skin of patients with AD contributes to decreased barrier function through multiple pathways.

7.4.4 Immunopathologic Mechanisms

Several immunopathologic abnormalities have been described in AD (Fig. 3). B cells from patients with AD synthesize high levels of IgE to multiple allergens, including foods, aeroallergens, microbes, and enterotoxins. IgE-mediated sensitization often precedes the lesions by several weeks or months, suggesting that the skin is the site of sensitization (Illi et al. 2004). The initial mechanisms inducing skin inflammation are unknown. Neuropeptide-, irritation-, or pruritus-induced scratching could cause release of inflammatory cytokines from keratinocytes (Bieber 2008). Or T-cell-mediated reactions to allergens present in the defective epidermal barrier or in food could be the inciting event. The epidermal barrier dysfunction leads to penetration of high-molecular-weight allergens in pollens, dust mite, microbes, and foods (Traidl-Hoffmann et al. 2005; Kupper and Fuhlbrigge 2004). These allergens skew T-cell polarization toward Th2 type. The skin is very rich in T cells, numbering 10^6 memory T cells per square centimeter of the body surface area (Kupper and Fuhlbrigge 2004; Clark et al. 2006). Moreover, keratinocytes in the atopic skin produce high levels of TSLP that favors Th2 polarization (Soumelis et al. 2002). Allergen-specific Th2 cells secreting IL-4, IL-5, and IL-13 are found at increased frequency in patients with AD, in the skin lesions, as well as in circulation (Boguniewicz and Leung 2011). Moreover, circulating skin-homing (CLA+) type 2 cytokine-producing cells are seen at increased frequency than CLA+ type 1 cytokine-producing cells in the blood of AD patients (Teraki et al. 2000). IL-4 not only upregulates production of IgE, but it also downregulates production of IFN-γ and differentiation of Th1 cells (Vercelli et al. 1990). Also, prostaglandin E2 and IL-10 which are produced in increased amounts by monocytes of patients with AD inhibit IFN-γ production (Chan et al. 1993). Other immunoregulatory abnormalities noted in AD include increased levels of T-cell-attracting chemokine (CTACK) and thymus- and -activation-regulated chemokine (TARC) (Hijnen et al. 2004). There is a decreased immunosuppressive activity of CD4+/CD25+ regulatory T (Treg) cells after superantigen stimulation.

The inflammation in atopic dermatitis is biphasic: an initial Th2 phase is followed by a chronic phase in which Th0 cells and Th1 cells predominate (Grewe et al. 1995). The dominating cytokines in the acute phase are IL-4, IL-5, and IL-13 which are produced by Th2 cells (Taha et al. 1998). There's an increase in interferon-γ, interleukin-12, and GM-CSF in chronic phase characterized by Th0 and Th1 predominance. Th0 cells share activities of both Th1 and Th2 cells. Their differentiation into Th1 or

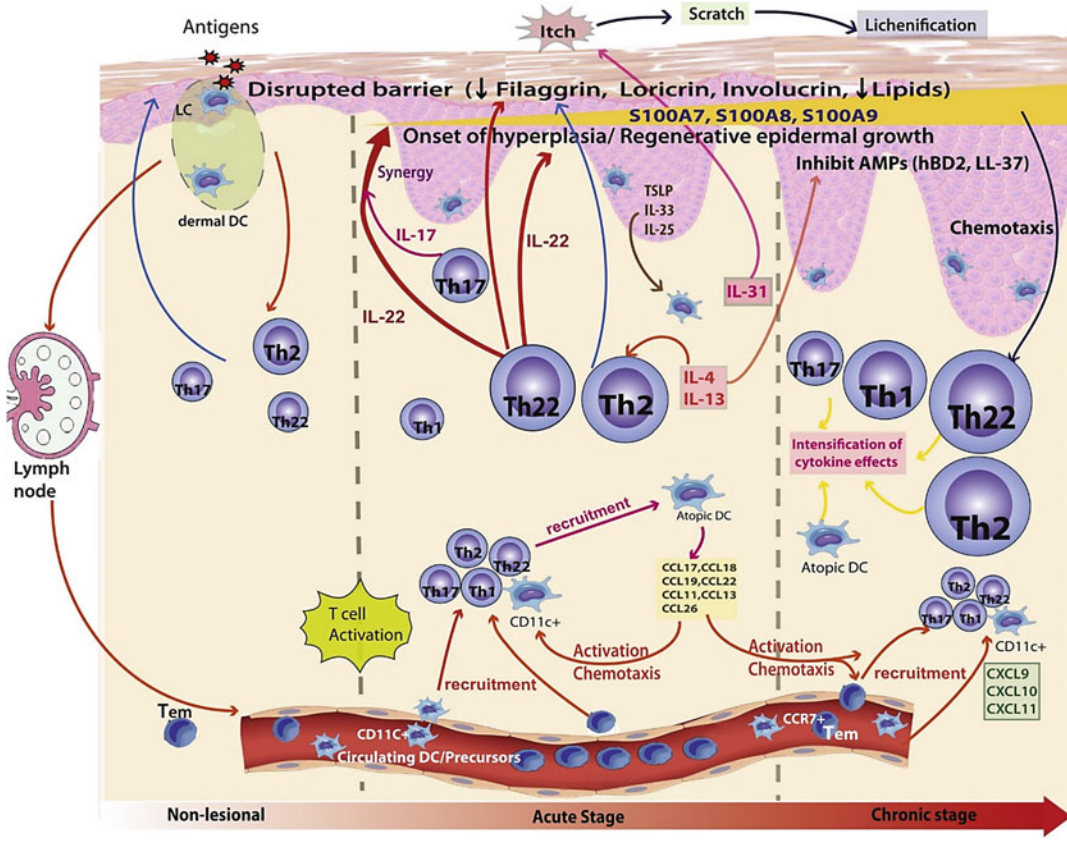

Fig. 3 Immunologic pathways involved in different phases of AD. Nonlesional AD skin lesions contain immune infiltrates that produce cytokines, such as IL-4 and IL-13, which contribute to a defective epidermal barrier. Barrier defects lead to penetration by epicutaneous allergens that encounter Langerhans cells in the epidermis and dermal DCs in the dermis to activate T_H2 and T_H22 cells involved in acute disease onset. Smaller increases in T_H1 and T_H17 immune axes are also found in acute lesions. A progressive activation of T_H2 and T_H22, as well as T_H1, pathways is a characteristic of patients with chronic AD. IL-22 induces epidermal hyperplasia and, synergistically with the T_H17 cytokine IL-17, drives an abrupt increase in a subset of terminal differentiation genes, specifically S100A7, S100A8, and S100A9 proteins. The increases in levels of these barrier proteins contrast with the uniformly disrupted epidermal differentiation gene products (e.g., filaggrin, loricrin, and corneodesmosin) throughout the nonlesional, acute, and chronic AD skin. The T_H2 and T_H22 cytokines contribute to inhibition of the terminal differentiation proteins. IL-31 is thought to contribute to the itch in patients with acute AD. TSLP thymic stromal lymphopoietin (Reproduced with permission from Journal of Allergy and Clinical Immunology 2014 134, 769–779)

Th2 cells depends upon the cytokine milieu. A complex network of homeostatic and inflammatory chemokines produced by the skin orchestrates the recruitment of T cells into the skin (Homey et al. 2006; Nomura et al. 2003a, b). Keratinocyte-derived TSLP induces dendritic cells to produce Th2 cell-attracting chemokine TARC/CCL17 (Gilliet et al. 2003).

7.5 Management of Atopic Dermatitis

Management of atopic dermatitis is based heavily on its pathophysiology which supports the concept that the role of allergens, irritants, microbes, physical environment, and emotional stressors needs to be assessed. An individualized

treatment plan needs to be devised for each patient considering the above factors. Moreover, patients and their families need to be aware that treatment is not curative. Instead, avoidance of exacerbating factors along with an effective skin care routine is crucial to the long-term control of this condition.

7.5.1 Irritants

The skin barrier being defective in patients with AD, the threshold for irritant responsiveness is lower. Therefore, irritants should be recognized and avoided for successful control. Irritants include detergents, soaps, chemicals, pollutants, and extremes of temperature and humidity (Schneider et al. 2013; Boguniewicz et al. 2003). Cleansers with minimum defatting activity and neutral pH are preferred to soaps. New clothing may have formaldehyde and other irritating chemicals and should, therefore, be laundered prior to first use. Using liquid rather than powder detergent and adding an extra rinse cycle are helpful in preventing residual detergent irritating the skin. Cotton clothing should be preferred to occlusive synthetic clothing. Since sweat is known to irritate the skin, the temperature in home and work environment should be maintained at a temperate level. Patients should shower and use a mild soap immediately after swimming to remove chlorine or bromine and other potentially irritating chemicals present in pool water. Prolonged sun exposure should be avoided due to risk of evaporative losses, overheating, and sweating. The use of nonsensitizing sunscreens is recommended to prevent sunburns.

7.5.2 Allergens

Atopic dermatitis results from a complex interaction between various susceptibility genes, defective skin barrier function, and dysregulated immunologic response and an interaction with microbial agents and the host environment. The role of allergens in AD has been extensively researched. An allergenic component is strongly implicated at cellular and molecular levels, especially in children. Epidermal barrier dysfunction in genetically predisposed individuals results not only in enhanced transepidermal water loss, but it also facilitates penetration of environmental allergens; these include aeroallergens as well as food allergens (Boguniewicz and Leung 2011). In a recent study, it was shown that application of skin preparations containing peanut oil on the inflamed skin of children who had never been exposed to peanut during prenatal period and with negative results for peanut-specific IgE in the cord blood led to peanut allergen sensitization (Lack et al. 2003). This result indicated that primary sensitization to food occurred through a route other than the oral route. Primary sensitization to food allergens occurs primarily via the gastrointestinal tract in nonatopic as well as atopic individuals. The immune response to an allergen in the skin of AD patients occurs via both IgE-mediated immediate immune responses and T-cell-mediated delayed immune responses (Prescott et al. 2006). Serum IgE titers for food, and inhalant allergens above the normal range have been detected in approximately 85% of patients with AD (Sampson 1997). Langerhans cells (LCs) with allergen-specific IgE antibodies on their surface are more abundant in AD lesions and may play a role in allergen presentation to T-helper 2 (Th2) cells in the skin (Taha et al. 1998). Moreover, FceRI is expressed at higher levels on the LCs in the inflammatory AD environment. The IgE-bearing LCs are very efficient at presenting the allergens to Th2 cells and activating their proliferation (Sampson 2003).

7.5.2.1 Food Allergens

Hen's egg, milk, peanut, nuts, soy, wheat, finned fish, and shellfish are responsible for more than 90% of food allergy in patients with AD (Sicherer and Sampson 1999). The incriminated foods vary according to the age of the patients, with cow's milk, egg, wheat, and soy being the most commonly implicated foods in infancy. Children aged 2–10 years have cow's milk, egg, peanut, tree nuts, fish, shellfish, and sesame as the more common allergens (Sampson 2004). Adolescents and adults show sensitivity to pollen-associated foods also (Sampson 2004). Food-induced allergic

reactions in AD may occur at various times after ingestion (Werfel et al. 2007). Immediate IgE-mediated reactions usually occur within 2 h of ingestion and typically consist of urticaria, angioedema, or other symptoms involving the respiratory or gastrointestinal tracts. Isolated eczematous delayed reactions presenting as flares of eczema 6–48 h after ingestion are non-IgE-mediated reactions. A combination of early IgE-mediated and delayed eczematous reactions has been described in more than 40% of children who reacted to oral food challenges (Werfel et al. 2007).

The diagnosis of food allergy in AD patients requires a stepwise approach. The diagnostic workup should start with a detailed history and physical examination of the patient. This may be followed by measurement of food-specific IgE antibodies, skin prick tests, atopy patch tests (APT), diagnostic elimination diet, and/or oral challenges (Caubet and Eigenmann 2010). Carefully taken history can identify a potential relationship between symptoms and a specific food, especially for immediate IgE-mediated hypersensitivity. However, in delayed eczematous reactions, the predictive value of positive case history is lower. Especially in patients with severe AD, the history is not particularly helpful as a large number of other factors (*Staphylococcus* infection, irritants, heat, humidity, etc.) can lead to flares (Breuer et al. 2004). In vivo (skin prick tests) and/or in vitro tests (measurement of food-specific IgE) should be performed if food allergy is suspected. The negative predictive value of skin prick tests is high (more than 95%) whereas the positive predictive value is low (about 40%) (Sampson 1983; Sampson and Mccaskill 1985). Therefore, a negative prick test can be helpful to rule out allergy, but a positive test cannot be considered diagnostic of clinical food allergy. Measurement of specific IgE antibodies in the blood is also useful for detection of sensitization to food allergens, with a negative test result excluding an IgE-mediated reaction to a specific food. A positive result has a lower specificity (Sampson 2003). While quantitative measurements of food-specific IgE appear to be useful in predicting clinical reactivity, an oral food challenge is needed to confirm food hypersensitivity. Due to the high number of clinically irrelevant positive results in routine diagnostic testing, the diagnosis of food allergy in patients with AD is difficult to establish. Positive tests must be confirmed by an elimination diet and a controlled oral food challenge (Caubet and Eigenmann 2010).

Unfortunately, a large number of AD patients undergo testing for food allergies and are placed on empiric elimination diets based on false-positive results, not supported by clinical history and exam findings (Caubet and Eigenmann 2010). While food allergens are important triggers for AD, unnecessary elimination diets lead to malnutrition and decreased quality of life. A diagnostic elimination diet over a period of 4–6 weeks for a specific food may be initiated based on history supported by diagnostic test results (Werfel et al. 2007). Multiple dietary restrictions are rarely necessary and should be avoided. If AD remains stable during a diagnostic elimination period of 4 weeks, the food is unlikely to be a trigger and should be reinstated. In patients who have been on a long-lasting elimination of an incriminated food, supervised oral challenge should be performed when reintroducing that food as immediate, potentially severe allergic symptoms may develop upon reintroduction (Sampson 2003). Such oral challenges should be performed only in patients with stable skin condition. The extent of the skin lesions should be scored, such as by SCORAD (SCORing Atopic Dermatitis), before and 24 h after the oral challenge. A difference of ten SCORAD points is considered a positive reaction (Werfel et al. 2007). When food elimination is recommended based on history and test results, the avoidance diet should be thorough and carefully defined. Approximately a third of children with AD outgrow their food hypersensitivity, depending on the food they are allergic to (Sampson 2004). Allergy to egg white, cow's milk, and wheat is generally short lasting, as compared to allergy to peanut, tree nuts, fish, and shellfish which tend to last longer (Sampson 2004). Children with food allergy in association with their eczema should be evaluated every 12–18 months, especially for cow's milk and egg

white, for persistence of allergy. Peanut and tree nut allergies may be evaluated less frequently as they last longer. Lower initial levels of IgE antibodies generally predict a more favorable outcome than higher levels (Caubet and Eigenmann 2010).

7.5.2.2 Aeroallergens

The prevalence of food allergy decreases after the age of 3 years, while sensitization to inhalant allergens becomes more common (Caubet and Eigenmann 2010). Patients with moderate-to-severe AD have been shown to have a higher incidence of positive IgE tests to house dust mites (HDM), molds, and fungi (e.g., *Alternaria*) and yeasts (*Malassezia*) than asthmatics and non-atopic controls (Scalabrin et al. 1999). In fact, a study demonstrated that intranasal application of aeroallergens could exacerbate AD and that environmental avoidance of HDM could cause improvement in skin symptoms (Tuft 1949; Tuft and Heck 1952). Moreover, Tupker et al. reported new-onset AD lesions and worsening of pre-existing skin lesions after bronchoprovocation with a standardized HDM extract (Tupker et al. 1996). Epicutaneous application by patch test on the nonlesional skin of patients with AD has been shown to elicit eczematous reactions, supporting a role for aeroallergen sensitization through direct skin contact (Ring et al. 1997; Seidenari et al. 1992). A recent study showed the presence of IgE to HDM in 95% of AD patients (Scalabrin et al. 1999). Moreover, the presence of HDM-specific T cells in the lesional skin and at the site of positive HDM patch test supports the concept of aeroallergen sensitization via the percutaneous route in these patients (Van Reijsen et al. 1992). Aeroallergens have been shown to exacerbate AD via direct contact with the skin as well as inhalation. The most commonly incriminated allergens are HDM, animal dander, and pollen. Identification of pollens or animal dander allergens as triggers depends on a thorough history coupled with skin prick tests or measurements of specific IgE antibodies. Atopy patch tests (APT) can also be used to assess a skin-specific response to various aeroallergens. According to the European Academy of Allergy and Clinical Immunology (EAACI), APT should be considered if there is a suspicion of aeroallergen-related symptoms in the absence of positive SPT and/or positive specific IgE and severe and/or persistent AD with unknown triggering factors or multiple IgE sensitizations without established clinical relevance (Turjanmaa et al. 2006). Most studies investigating the effect of aeroallergen avoidance on AD have focused on HDM allergy and have shown a positive effect of HDM avoidance (Darsow et al. 2010). In addition to avoidance, immunotherapy may be an effective intervention for aeroallergen-driven eczema. A multicenter trial with HDM immunotherapy involving 51 patients did support a potential role of this mode of treatment in environmental allergen-triggered AD (Werfel et al. 2006).

7.5.3 Patient Education

Patients and caregivers need to understand the chronic nature of this condition, along with exacerbating factors and treatment options (Nicol and Ersser 2010). The International Study of Life with Atopic Eczema (ISOLATE) found that initiation of treatment for AD flares is often delayed by patients and their caregivers, who often have concerns about the prescribed medications (Zuberbier et al. 2006). Detailed written skin care recommendations should be provided to the patients and their families and reviewed at each follow-up visit. The National Eczema Association, a not-for-profit organization, has educational materials suitable for use by patients and their families.

7.5.4 Hydration and Moisturization

Since patents with AD have increased transepidermal water loss, decreased water-binding capacity, and decreased ceramide levels in the skin, hydration by soaking in warm water for about 10 minutes followed by generous application of an occlusive agent to retain the absorbed water is a critical component of therapy (Boguniewicz et al. 2003; Schneider et al. 2013). A wet facecloth or towel may be used for the face

and neck. During flares of AD, baths may need to be taken several times a day. The occlusive preparation should be applied within a few minutes after hydrating the skin to prevent loss of water, which is damaging to the epidermis. Moisturizers are available as lotions, creams, and ointments. Lotions, being water based, have an evaporative effect and may be further associated with irritation due to added preservatives and perfumes. Therefore, creams and ointments are more effective. Since emollients need to be applied to large areas of the skin, and multiple times a day, they should be prescribed in 1-pound (454 g) jars, instead of tubes. The jar aids with scooping out a decent amount for application. Vegetable oil shortening (e.g., Crisco) and petroleum jelly are excellent inexpensive alternatives that are very effective at sealing water after bathing. Effective use of emollients when combined with hydration helps restore and preserve the stratum corneum barrier and may decrease the need for topical corticosteroids (Lucky et al. 1997). Bathing removes allergens and irritants and decreases colonization with *S. aureus* (Boguniewicz et al. 2003, 2008). Bleach baths with dilute sodium hypochlorite help reduce skin infections (1/4 to 1/2 cups of household bleach per tub full of water) (Huang et al. 2009). Bleach baths may be irritating to the skin, if not followed immediately by thorough rinsing of the skin. A recently published systematic review of all studies evaluating the efficacy of bleach baths for AD concluded that bleach baths were not more effective than water baths alone at decreasing severity of AD (Chopra et al. 2017).

7.5.5 Corticosteroids

Topical corticosteroids have been the mainstay of therapy for AD, since their introduction approximately 50 years ago (Boguniewicz et al. 2003). They are efficacious for acute as well as chronic disease. They reduce inflammation and pruritus and, moreover, have an effect on bacterial colonization, decreasing the density of *S. aureus* (Nilsson et al. 1992). They are available in different potencies ranging from extremely high (class 1) to low (class 7) preparation (Table 1, Boguniewicz et al. 2003). The choice of corticosteroid preparation to use depends on the severity of eczema and the areas of the skin involved. Patients and their families should be counseled about the potential side effects. An attempt should be made to select the preparation that has the least potency but the most benefit for the patient (Boguniewicz et al. 2003). However, the use of a preparation that is too mild to cause significant improvement of symptoms may lead to decreased adherence to the regimen. Prescribing high-potency topical corticosteroids for 7–14 days without a plan to step down to a lower-potency preparation can lead to rebound flares. Moreover, prescribing the medications in inadequate amounts can also lead to poorly controlled eczema, especially in patients with widespread disease. It takes approximately 30 g of medication to cover the entire body of an average adult (Boguniewicz et al. 2003). The fingertip unit (FTU) has been proposed as a measure for applying topical corticosteroids. It is the amount of the topical medication that extends from the tip to the first joint on the palmer aspect of the index finger. It takes 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 (Long et al. 1998). While these medications are not appropriate for maintenance therapy due to their side effects, long-term control can be achieved by twice-weekly therapy, as shown in several studies with fluticasone propionate in patient as young as 3 months of age (Friedlander et al. 2002; Van Der Meer et al. 1999; Hanifin et al. 2002). Some patients may not respond to topical corticosteroids if there is ongoing exposure to allergens and irritants. Other causes may be *S. aureus* superinfection, inadequate potency of the steroid preparation, or inadequate amount prescribed. The most common cause of failure to respond is nonadherence because of fear of adverse effects (Boguniewicz et al. 2003). Thinning of the skin with telangiectasias, bruising, hypopigmentation, acne, striae, and secondary infections are some of the adverse effects associated with these medications; however, they are infrequent with low- to medium-potency preparations (Boguniewicz et al. 2003). The face,

Table 1 Treatment modalities for atopic dermatitis

Treatment	Action
Avoidance of allergens and irritants	Prevents allergenic and irritant response
Moisturizers and occlusives	Restore and preserve stratum corneum barrier
Topical corticosteroids	Reduce inflammation and pruritus
Topical calcineurin inhibitors	Reduce inflammation and tacrolimus approved for proactive use in Europe
Tar preparations	Reduce inflammation, can be alternated with corticosteroids and shampoo useful in scalp dermatitis
Wet-wrap dressings	Improve penetration of topical corticosteroids, help repair epidermal barrier
Topical or systemic antibiotics	Treat bacterial, viral, and fungal infections
Antihistamines and anxiolytics	Tranquilizing and sedative effects prevent itching and skin excoriation
Immunomodulation agents	
Systemic corticosteroids	Decrease inflammation
Cyclosporin A	Suppresses transcriptional activation of cytokine genes in helper T cells
Mycophenolate	Inhibits purine biosynthesis
Azathioprine	Inhibits purine biosynthesis
Methotrexate	Inhibits purine and pyrimidine synthesis
Phototherapy	Decreases expression of Th2/Th22 cytokines and restores epidermal barrier, decreases colonization by *staphylococcus aureus*
Allergen immunotherapy	Induces immunoregulatory responses and immune deviation toward Th1

especially the eyelids, and intertriginous areas are particularly susceptible, so only low-potency preparations should be applied to these areas. Topical corticosteroids are available in a variety of vehicles, including ointments, creams, lotions, gels, and solutions. Ointments provide better delivery and are most occlusive and so prevent evaporative losses. Generally topical corticosteroids are discontinued after the inflammation resolves, while hydration and moisturization should be continued.

Since the normal appearing nonlesional skin in patients with AD shows inflammation and immunologic dysregulation, topical corticosteroids may be used as "proactive" or maintenance therapy (Schmitt et al. 2011). This approach results in fewer relapses. Systemic corticosteroids are sometimes prescribed for quick relief of symptoms, especially during flares. However, their use should be avoided. The dramatic improvement seen with their use is often associated with flaring of symptoms after discontinuation of the medication. Therefore, topical skin care should be intensified during the taper of the systemic drug to suppress rebound flaring (Boguniewicz et al. 2008).

7.5.6 Topical Calcineurin Inhibitors

The approval of the topical calcineurin inhibitors (TCIs) tacrolimus ointment 0.03% and 0.1% and pimecrolimus cream 1% marked a historic development in AD management (Boguniewicz et al. 2003). Both these medications work through inhibition of phosphorylase activity of the calcium-dependent serine/threonine phosphatase calcineurin and the dephosphorylation of the nuclear factor of activated T-cell protein (NF-ATp), a transcription factor necessary for expression of inflammatory cytokines (Tocci et al. 1989; Stuetz et al. 2001). Both drugs have proven effective with a good safety profile for treatment up to 4 years with tacrolimus ointment and up to 2 years with pimecrolimus cream (Hanifin et al. 2005). Currently, tacrolimus ointment 0.03% is approved for intermittent treatment of moderate-to-severe AD in children 2 years and older and tacrolimus 0.1% ointment for intermittent treatment of moderate-to-severe AD in adults (Schneider et al. 2013). Pimecrolimus cream 1% is approved for intermittent therapy of mild-to-moderate AD in patients 2 years and older. Because the use of TCIs is not associated with skin atrophy, they are useful in treatment of eczema involving the face, axillae, or groin. A common side effect with TCIs is a transient

burning sensation at site of application, although a minority of patients may experience prolonged burning or stinging.

The FDA has issued a boxed warning for tacrolimus ointment 0.03% and 0.1% (Protopic, Astellas) and pimecrolimus cream 1% (Elidel, Novartis) for association with rare malignancies; however, no causal link has been established. Long-term safety studies with TCIs are ongoing. A review of the available data by a joint task force of the American College of Allergy, Asthma and Immunology and the American Academy of Allergy Asthma and Immunology concluded that the risk/benefit ratios of tacrolimus ointment 0.03% and 0.1% and pimecrolimus cream 1% are similar to those of conventional therapies for AD (Fonacier et al. 2005). A case-control study of a large database ($n = 293{,}253$) did not find an increased risk of lymphoma in patients treated with TCIs (Arellano et al. 2007). Studies have suggested that earlier use of TCIs can lead to better long-term outcomes and fewer flares (Schmitt et al. 2011). In fact, proactive use of tacrolimus is approved in Europe for up to 12 months in patients 2 years or older.

7.5.7 Crisaborole

Crisaborole 2% ointment was approved in the Unites States in 2016 for topical treatment of mild-to-moderate atopic dermatitis in patients 2 years of age and above. The most common adverse reaction occurring in $\geq$1% in subjects is application site pain. Phosphodiesterase 4 (PDE4) is a key regulator of inflammation in AD. Its activity is increased in circulating inflammatory cells of patients with AD. In vitro studies have shown that inhibition of PDE4 activity in monocytes is associated with reduction in release of proinflammatory cytokines (Dastidar et al. 2007; Freund et al. 2012). The efficacy and safety of crisaborole ointment were assessed in two identically designed, vehicle-controlled, double-blind studies in patients ages 2 years and above, with mild-or-moderate AD, showing a favorable safety profile and improvement in overall disease severity, pruritus, and other signs of AD (Paller et al. 2016). Crisaborole has low systemic absorption and is quickly metabolized to its inactive metabolites, reducing the risk of systemic side effects. It is, therefore, a promising therapeutic alternative to topical corticosteroids and topical calcineurin inhibitors, which are both associated with adverse side effects restricting their long-term use.

7.5.8 Wet-Wrap Therapy

Wet-wrap therapy helps in multiple ways. It improves penetration by topical corticosteroids and acts as a barrier to trauma by preventing scratching of the skin (Boguniewicz et al. 2008). It, moreover, aids in epidermal barrier recovery that persists even after the wet-wrap therapy is discontinued (Lee et al. 2007). In fact, significant clinical improvement has been reported by combining this modality even with low-potency corticosteroids (Wolkerstorfer et al. 2000). Overuse of wet-wrap dressings may lead to maceration of the skin and secondary infections, although infrequently. Since this modality is quite labor intensive, its use should be limited to acute exacerbations or areas of recalcitrant disease. TCIs should not be used under an occlusive dressing.

7.5.9 Anti-infective Therapy

Patients with AD are typically colonized with *S. aureus* and often secondarily infected. Hydration, moisturization, and topical anti-inflammatory agents such as topical corticosteroids and TCIs can reduce the bacterial burden (Boguniewicz and Leung 2013). Systemic antibiotics may be needed to treat overt infections. Choice of agent should be directed by culture and sensitivity results. Treatment with semisynthetic penicillins or first- or second-generation cephalosporins for 7–10 days is generally effective (Boguniewicz et al. 2008). Topical anti-staphylococcal antibiotic mupirocin applied three times daily to the affected areas for 7–10 days is effective for localized infection (Huang et al. 2009). Nasal carriage of *S. aureus*

may be reduced by twice-a-day use of a nasal preparation of mupirocin for 5 days. Bleach baths with dilute sodium hypochlorite (1/4–1/2 cup of household bleach per full tub of water) can be considered for patients with recurrent skin infections especially with methicillin-resistant *S. aureus* (Birnie et al. 2008; Krakowski et al. 2008; Boguniewicz and Leung 2010). Bleach baths may cause skin irritation, and further worsening of eczema is not followed by generous rinsing off of the chemical. Disseminated eczema herpeticum should be promptly treated with systemic antiviral agents such as acyclovir. Daily prophylactic acyclovir is useful for recurrent cutaneous herpetic infections (Boguniewicz and Leung 2010).

7.5.10 Antipruritic Agents

The dominant symptom in atopic dermatitis is persistent pruritus, which compromises the patient's quality of life. The fact that antihistamines are not effective speaks against the role of histamines in causing this symptom (Diepgen and Group 2002). Interleukin-31 is strongly pruritogenic. It stimulates the production of cytokines by epithelial cells (Sonkoly et al. 2006; Neis et al. 2006). A number of mediators, including neuropeptides and cytokines, are involved in the pathogenesis of pruritus (Metze et al. 1999). Both IL-31 and its receptor are overexpressed in the lesional skin. Moreover, exposure to staphylococcal enterotoxins upregulates its expression in vitro (Bieber 2008). Patients with AD have CLA+ T cells that produce higher levels of IL-31. Calcineurin inhibitors that target T cells are effective at reducing pruritus in AD patients.

It is prudent to address the itch-scratch cycle for successful management of AD since pruritus is the least tolerated symptom of this condition. Even partial reduction of pruritus may improve the quality of life. First-generation antihistamines and anxiolytics are useful, especially at bedtime, due to their sedating and tranquilizing effects (Schneider et al. 2013). The use of topical antihistamines and topical anesthetics should be avoided due to potential sensitization (Shelley et al. 1996; Boguniewicz and Leung 2013). Behavioral modification and biofeedback therapy are also useful as adjunctive therapy.

7.5.11 Systemic Immunomodulatory Agents

A broad set of systemic immunomodulatory agents have been used for severe AD refractory to topical modalities. There is extensive clinical experience with cyclosporine A. It is a potent immunosuppressive that works by inhibiting calcineurin. Its efficacy in treatment of severe eczema in children and adults has been established in multiple studies (Berth-Jones et al. 1996; Zonneveld et al. 1996). Short-term oral cyclosporine A therapy can result in increased serum urea, creatinine, and bilirubin concentrations, but these numbers normalize after discontinuation of treatment. Extended treatment may cause progressive or irreversible nephrotoxicity (Sowden et al. 1991; Van Joost et al. 1994). Discontinuation of treatment generally results in relapse of skin disease (Salek et al. 1993). Antimetabolites including mycophenolate mofetil, methotrexate, and azathioprine have also been used for recalcitrant AD but are all associated with significant risks of systemic toxicities (Grundmann-Kollmann et al. 2001; Heller et al. 2007; Kuanprasert et al. 2002; Schram et al. 2011).

Dupilumab is a human monoclonal antibody against interleukin-4 receptor alpha that inhibits signaling of interleukin-4 and interleukin-13 (Beck et al. 2014; Hamilton et al. 2014). These are type 2 cytokines which are pivotal to the atopic process, including atopic dermatitis. In two phase III randomized, placebo-controlled trials of identical design involving patients with moderate-to-severe AD whose disease was inadequately controlled with topical medications, dupilumab improved the signs and symptoms of atopic dermatitis, including pruritus, symptoms of anxiety and depression, and quality of life as compared to placebo (Simpson et al. 2016). It was approved in 2017 for use in adults with moderate-to-severe atopic dermatitis not

adequately controlled with topical prescription medications or when those therapies are not advisable. It is available for subcutaneous injection (300 mg/2 mL solution in a prefilled syringe) under the brand name DUPIXENT®. The recommended dose is an initial dose of 600 mg followed by 300 mg given every other week. Most common adverse reactions (incidence ≥1%) are injection site reactions, conjunctivitis, blepharitis, oral herpes, keratitis, eye pruritus, other herpes simplex virus infection, and dry eye.

7.5.12 Phototherapy

Ultraviolet light therapy can be useful for treatment of recalcitrant AD but should be done only under the supervision of an experienced dermatologist. Broadband UVB, broadband UVA, narrowband UVB (311 nm), UVA-1 (340–400 nm), psoralen ultraviolet A-range (PUVA), and combined UVA-UVB phototherapy may be used (Krutmann et al. 1998; abeck et al. 2000; Tintle et al. 2011). Phototherapy is associated with improvement of symptoms as well as decrease in use of topical corticosteroids. Narrowband UVB phototherapy was shown to suppress Th2, Th22, and Th1 immune pathways in an open trial in patients with moderate-to-severe eczema (Tintle et al. 2011). The expression of epidermal barrier proteins normalized. A prospective analysis of narrowband UVB phototherapy in children found that it is effective as well as well tolerated (Tan et al. 2010). A systemic review of phototherapy in AD found that UVA1 is effective for control of acute flares, while UVB modalities, especially narrowband, should be used for management of chronic AD (Meduri et al. 2007). UVB phototherapy has been shown to significantly reduce colonization with toxin-producing *S. aureus* on the skin of children with AD (Silva et al. 2006). Short-term adverse effects of phototherapy include erythema, burns, pruritus, and pigmentation. Long-term adverse effects include premature aging and cutaneous malignancies.

7.5.13 Allergen Immunotherapy

Allergen immunotherapy practice parameters state that there are some data indicating the efficacy of immunotherapy for AD when it is associated with aeroallergen sensitivity (Cox et al. 2011). A randomized, double-blind study of adults with AD did demonstrate a dose-response effect of dust mite immunotherapy on severity of the disease (Werfel et al. 2006). In a systematic review of four comparable placebo-controlled studies on immunotherapy for AD, statistically significant improvement in symptoms was seen in patients receiving subcutaneous immunotherapy (Glover and Atherton 1992). An open-label study of patients with dust mite hypersensitivity and AD treated with subcutaneous dust mite immunotherapy demonstrates serologic and immunologic evidence of development of tolerance as well as objective improvement in clinical severity scores (Bussmann et al. 2007). A summary of treatment modalities for AD is provided in Table 2.

7.5.14 Investigative Approaches

7.5.14.1 Intravenous Immunoglobulin

High-dose intravenous immunoglobulin has been shown to have immunomodulatory effect in the management of AD (Schneider et al. 2013). It may have direct effect on toxin-producing microbes that have been implicated in the pathogenesis of AD (Takei et al. 1993). In vitro activation of T cells by staphylococcal toxins has been shown to be inhibited by high concentrations of staphylococcal antitoxins present in intravenous immunoglobulin (Takei et al. 1993). However, the results with this modality have been conflicting. Children appear to have a better response, but the efficacy of this treatment needs to be established definitively in large controlled studies. In a randomized, placebo-controlled trial involving 48 children with moderate-to-severe AD, three injections of 2 g/kg intravenous immunoglobulin and placebo were given at 1-month intervals over a 12-week period. The disease severity index significantly decreased 3 months after completing the

Table 2 Select topical corticosteroid preparations

Group	Preparations
1	Clobetasol propionate (Temovate) 0.05% ointment/cream
	Betamethasone dipropionate (Diprolene) 0.05% ointment/cream
2	Mometasone furoate (Elocon) 0.1% ointment
	Halcinonide (Halog) 0.1% cream
	Fluocinonide (Lidex) 0.05% ointment/cream
	Desoximetasone (Topicort) 0.25% ointment/cream
3	Fluticasone propionate (Cutivate) 0.005% ointment
	Halcinonide (Halog) 0.1% ointment
	Betamethasone valerate (Valisone) 0.1% ointment
4	Mometasone furoate (Elocon) 0.1% cream
	Triamcinolone acetonide (Kenalog) 0.1% ointment/cream
	Fluocinolone acetonide (Synalar) 0.025% ointment
5	Fluocinolone acetonide (Synalar) 0.025% cream
	Hydrocortisone valerate (Westcort) 0.2% ointment
6	Desonide (DesOwen) 0.05% ointment/cream/lotion/gel
	Alclometasone dipropionate (Aclovate) 0.05% ointment/cream
7	Hydrocortisone (Hytone) 2.5% and 1% ointment/cream

Representative corticosteroids are listed from superpotent (group 1) to least potent (group 7) (Reproduced with permission from Middleton's Allergy: Principles and Practice, Eighth Edition 34, 540-564)

treatments as compared to baseline values ($p < 0.05$). However, improvements waned off after 6 months (Jee et al. 2011).

7.5.14.2 Omalizumab

Both clinical benefit and lack of improvement have been reported in case reports and small case series involving patient with AD treated with omalizumab (Krathen and Hsu 2005; Lane et al. 2006; Park et al. 2010; Amrol 2010). A prospective analysis evaluated the efficacy of omalizumab in 21 patients with moderate-to-severe persistent allergic asthma and AD, 14–64 years of age. AD severity was assessed by means of investigator global assessment scale at 0, 1, 3, 6, and 9 months. All 21 patients showed statistically significant improvement in their AD (Sheinkopf et al. 2008). However, a placebo-controlled trial of omalizumab in 20 patients with AD for 16 weeks did not show any improvement (Heil et al. 2010).

7.5.14.3 Rituximab

Rituximab is a chimeric anti-CD20 mAb which was originally developed to treat B-cell malignancies. Its use in patients with AD has been investigated in an open trial (Simon et al. 2008). Six patients with severe AD received two intravenous infusions of 1000 mg of rituximab 2 weeks apart. All patients showed improvement in their disease within 4–8 weeks, and their eczema area and severity index decreased significantly ($p < 0.001$). Histology of skin biopsy specimen showed decrease in spongiosis and acanthosis. Lesional B-cell counts decreased by 50%. Expression of IL-5 and IL-13 was also reduced after therapy (Simon et al. 2008). In contrast, administration of 500 mg rituximab intravenously twice at a 2-week interval in two patients with severe AD resulted in transient improvement only (Sedivá et al. 2008).

7.5.14.4 Probiotics

Probiotics are not currently FDA regulated, and clinical trials of their use in AD have yielded varying results (Kalliomäki et al. 2003; Rosenfeldt et al. 2003; Weston et al. 2005; Michail et al. 2008). One meta-analysis suggested a modest role of probiotics in children with moderately severe disease (Michail et al. 2008). Another study found more convincing evidence for prevention rather than treatment of pediatric AD (Lee et al. 2008). Another study found that supplementation with *Lactobacillus* GG during pregnancy and early infancy neither reduced the incidence not altered the severity of AD in the affected children. It was, moreover, associated with increased incidence of wheezing bronchitis (Kopp et al. 2008). A Cochrane review concluded that probiotics are not effective in treatment of childhood AD (Salfeld and Kopp 2009). A recent meta-analysis of RCTs through 2011 found a reduction of approximately 20% in the incidence

of IgE-associated AD in infants and children with probiotic use (Pelucchi et al. 2012). At this time, the role of probiotics in management of AD remains investigational.

7.5.15 Summary

Atopic dermatitis is a chronic relapsing inflammatory skin disease that often heralds the beginning of atopic march. Higher prevalence rates of AD have been observed in developing as well as developed nations. Recent insights into the genetic and immunologic mechanisms that drive cutaneous inflammation in AD have improved our understanding of its natural history. This has direct implications on its management. Studies identifying new mutations in stratum corneum proteins, Th2 cells with skin-homing capability, role of Th22 cells, dendritic cells and Langerhans cells, as well as the multifactorial role for IgE in skin inflammation have all provided the rationale for development of novel immunomodulatory and anti-inflammatory agents in the treatment of chronic AD. Early and proactive management may improve the outcome and overall quality of life for these patients.

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Acute and Chronic Urticaria

8

William J. Lavery and Jonathan A. Bernstein

Contents

Abstract

Urticaria is a heterogeneous skin disease involving episodic wheals and/or angioedema, which occurs in 10–20% of people at some point in life. Although there are a wide array of etiologies, including infections, medications, allergic reactions, or physical stimuli, most cases remain idiopathic. Many systemic disorders are associated with urticaria, such as various forms of vasculitis, mastocytosis, or rheumatologic illnesses. Diagnosis is largely made by history and exam, at times involving a provocation test to reproduce the lesions if the history suggests inducible (aka physical) urticaria. Treatment with long-acting nonsedating H1-antihistamines is effective in over 50% of cases, but when not, other therapies such as biologics, immunosuppressive agents, or other anti-inflammatory agents may be necessary to control the hives.

Keywords

Hives · Urticaria · Angioedema · Acute · Chronic

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8.1 Introduction and Definition

Urticaria is a heterogeneous skin condition characterized by episodic appearance of wheals and/or angioedema. Wheals are cutaneous swellings of variable size, typically with reflex erythema which is usually very pruritic but could manifest as a burning sensation in some cases. Wheals manifest as a result of extravasation of fluid into epidermal spaces, with return of normal skin appearance in about 1–24 h. Angioedema, in contrast, is defined as rapid and marked extravasation of fluid into deeper dermis tissue spaces. This results in swelling which may be characterized by pain due to stretching nerve fibers, rather than pruritus, with significantly slower resolution, on the order of 1–3 days (Zuberbier et al. 2018; Godse et al. 2018; Kaplan 2002; Bernstein et al. 2014).

Acute urticaria involves episodic hives which last less than 6 weeks, whereas chronic urticaria involves symptoms on most days of the week for more than 6 weeks. The prevalence of urticaria is estimated to affect up to 20% of the general population at some point in life, but the etiology is rarely elucidated (Greaves 1995).

8.2 Epidemiology and Natural History

Acute urticaria is thought to affect approximately 10–20% of people at some point in life, with development of chronic spontaneous urticaria in approximately 1% of the population (Greaves 1995). Although more common in adults, it can also afflict children, but epidemiologic data on this population is lacking. Women seem to be affected about twice as frequently as men, typically starting in the third to fifth decades of life. Urticaria affects up to 1% of the general population in the United States at any particular point in time with similar prevalence described in other countries (Zuberbier et al. 2010; Gaig et al. 2004; Cooper 1991; Champion et al. 1969; Ferrer 2009; Juhlin 1981). Chronic urticaria is often a self-limited disorder, with average disease duration of 2–5 years (Greaves 2000). In patients with no clear etiology or identified underlying cause of urticaria, 30–50% will have spontaneous remission at 1 year. However, it is not uncommon for symptoms to persist for many years (Kulp-Shorten and Callen 1996; Kozel et al. 2001; Kulthanan et al. 2007; Gaig et al. 2004). A study in Spain indicated a prevalence of urticaria of 0.8% in the past year and prevalence of chronic urticaria of 0.6%. In this study, mean age of urticaria was 40 years, with disease duration of 1–5 years in 8.7% of study subjects and more than 5 years in 11.3% of study subjects (Gaig et al. 2004). Angioedema with concomitant hives is present in 40–50% of patients with chronic spontaneous urticaria. About 10% of patients experience angioedema alone without hives, while about 40% of patients exhibit hives alone (Greaves 2000; Kaplan 2002; Grattan 2004; Zuberbier et al. 2018).

8.3 Etiologies, Classification, and Pathophysiology

Diagnosis and classification of urticaria and angioedema are made largely by history (Charlesworth 1996; Beltrani 1996, 2004). Urticaria can be classified into various types and subtypes based on different eliciting stimuli. Most forms of urticaria follow into one of three broad categories: spontaneous urticaria, physical urticaria, or special/uncommon causes of urticaria (Sanchez-Borges et al. 2012; Lang et al. 2013; Zuberbier et al. 2018). Spontaneous urticaria includes acute spontaneous urticaria (episodic spontaneous hives and/or angioedema of less than 6 weeks duration) and chronic spontaneous urticaria (episodic hives and/or angioedema lasting more than 6 weeks duration).

The signs and symptoms of urticaria are mediated by cutaneous mast cells and basophils in the superficial dermis. Upon activation of mast cells and basophils, a variety of mediators are released, including histamine that causes the characteristic pruritus and vasodilation resulting in localized swelling in the epidermis in the case of hives and angioedema when the swelling extends to the deeper dermis/subcutaneous tissue (see Fig. 1) (Ying et al. 2002; Beck et al. 2017).

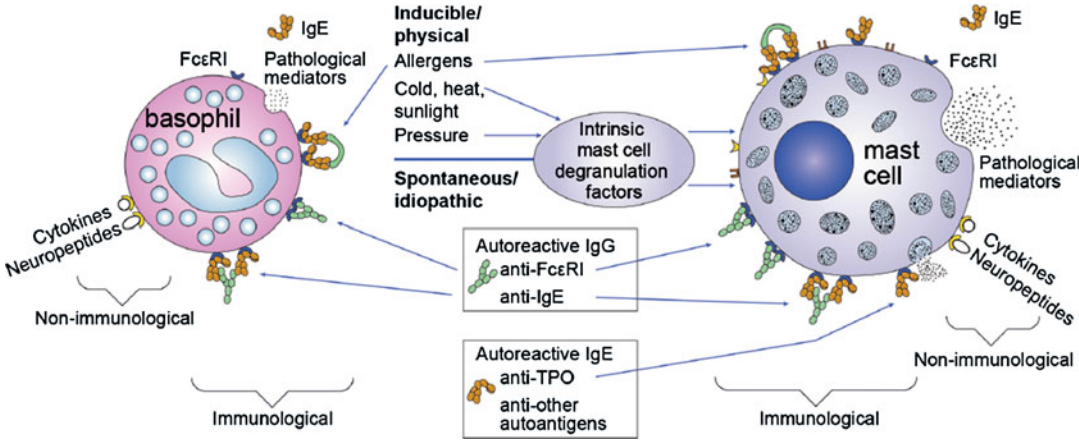

Fig. 1 Pathogenesis of chronic urticaria (CU). CU signs and symptoms develop when skin mast cells or basophils degranulate and release histamine and other pro-inflammatory mediators. In chronic spontaneous urticaria, the degranulation of these cells in some patients is thought to be due to the effects of autoantibodies directed against a subunit of the high-affinity IgE receptor, FcƐRIa, or to IgE itself. Other mechanisms of mast cell or basophil activation that are potentially relevant to chronic spontaneous urticaria involve autoantigens and IgE directed against these autoantigens, as well as complement components, cytokines, and neuropeptides. *TPO* thyroperoxidase (Beck et al. 2017)

There are myriad of potential etiologies for urticaria. There is a greater likelihood of identifying a specific trigger for acute urticaria compared to chronic urticaria. Causes include foods; medications (Fernandez et al. 2017; Kuyucu et al. 2014; Martin-Serrano et al. 2016); envenomation due to insect stings (Matysiak et al. 2013); latex exposure through recreational, occupational, or surgical/dental application (Sussman and Beezhold 1995); and a number of contactants from plant, animal, or occupational exposures (Bourrain 2006).

Infections represent another common cause of urticaria. Viral or bacterial infections, especially in children, are a particularly common cause of urticaria, with reports of as high as 80% of acute urticaria in children being attributed to viral or bacterial infections (Sackesen et al. 2004; Mortureux et al. 1998; Minciullo et al. 2014; Imbalzano et al. 2016; Plumb et al. 2001). In studies where children were evaluated in emergency departments with urticaria in a setting of sick symptoms, viral and bacterial illness were the leading identifiable trigger for urticaria (Mortureux et al. 1998). In one study in which children with sick symptoms, also on beta-lactams, were tested for both viral illness and re-exposed to beta-lactam, roughly 66% were positive for viral illness, while only 4% had recurrence of urticaria with re-exposure to the antibiotic (Mortureux et al. 1998; Caubet et al. 2011). *Mycoplasma pneumoniae* infection in children has been documented to cause acute urticaria that is refractory to antihistamines but responsive to azithromycin (Wu et al. 2009; Shah et al. 2007). Parasitic infections have been well-characterized as a cause of acute, self-limited urticaria in association with peripheral eosinophilia. Examples include *Strongyloides*, *Filaria*, *Echinococcus*, *Trichinella*, and *Toxocara* species (Di Campli et al. 1998).

Nonsteroidal anti-inflammatory drugs (NSAIDs) are an important trigger of urticaria and angioedema. This can occur either by an immediate-type hypersensitivity or by a pharmacologic or pseudoallergic reaction, in which an agent such as ibuprofen or aspirin inhibits cyclooxygenase-1 enzyme resulting in urticaria, presumably due to that individual having an underlying anomaly in arachidonic acid metabolism (Moore-Robinson and Warin 1967; Warin 1960; Champion et al. 1969).

Another trigger of acute urticaria includes the direct activation of mast cells through specific

non-IgE receptors. For example, vancomycin infusion causing "red man syndrome" is a common inpatient cause of urticaria in both children and adults. Human and animal studies of red man syndrome indicate that histamine and other vasoactive mediators are released by direct mast cell activation, with some studies indicating that degree of serum histamine release relating directly to clinical severity of disease (Healy et al. 1990). The mechanism is thought to involve non-immunologic mast cell activation of phospholipase C and phospholipase A2 pathways and may partially occur in an extracellular calcium-dependent manner (Horinouchi et al. 1993; Veien et al. 2000). Often related to the rate of infusion, the phenomenon can be ameliorated by either slowing down the infusion and/or pre-treating with antihistamines (Healy et al. 1990; Renz et al. 1998; Newfield and Roizen 1979; Veien et al. 2000; Wallace et al. 1991). Other triggers of direct mast cell activation include opiates and their derivative products, radiocontrast media, foods high in lectins and/or histamine such as strawberries and tomatoes, or the stinging nettle plant *Urtica dioica*, from which the disorder "urticaria" derives its name (Robledo et al. 2004; Cochran 2005; Plumb et al. 2001; Anderson et al. 2003; Cummings and Olsen 2011; Uslu et al. 2011).

Although rare, there have been several case reports of urticaria triggered by progesterone-containing oral contraceptives or progesterone-containing hormone replacement therapies (Poole and Rosenwasser 2004; Shank et al. 2009; Bernstein et al. 2011).

Several systemic syndromes where urticaria may be a prominent or presenting symptom include urticarial vasculitis, cutaneous small-vessel vasculitis, systemic mastocytosis, systemic lupus erythematosus, rheumatoid arthritis, or other autoimmune disorders (Confino-Cohen et al. 2012).

8.4 Chronic Urticaria

Chronic urticaria (CU) is defined as episodic hives occurring most days of the week for 6 or more weeks. Approximately 40% of patients with CU also experience angioedema (Greaves 2000). In the United States, CU has a prevalence of about 1% in the general population, with similar prevalence reported in other countries (Gaig et al. 2004; Greaves 2000; Lapi et al. 2016). CU affects both children and adults, although it is more common in adults. Women are twice as likely as men to be affected. CU can occur at any time but typically begins in the third to fifth decades of life (Confino-Cohen et al. 2012).

The diagnosis of CU is made clinically based on history and exam (see Table 1). Initial extensive laboratory work-up for CU, unless there are specific clues in the history, is not recommended as studies have demonstrated that empiric blood testing does not impact the management of disease in most cases (Tarbox et al. 2011). However, both the US and international guidelines agree that a routine complete blood count with differential, C-reactive protein and/or erythrocyte sedimentation rate should be obtained at diagnosis. A thyroid-stimulating hormone may also be appropriate in many cases (Jacobson et al. 1980; Jirapongsananuruk et al. 2010). As many as 80–90% of adults and children with CU have no specifically identified trigger and are thus diagnosed with chronic idiopathic urticaria (CIU). Skin biopsy is not routinely recommended for CU, but is indicated to exclude potentially concerning disease processes in the presence of other signs/symptoms, such as urticarial vasculitis. CU is typically a self-limited disease process. Spontaneous remission occurs in 30–50% of patients within 1 year, with an average disease duration of 2–5 years, and only 20% of patients having persistent symptoms beyond 5 years (Kulthanan et al. 2007; Harris et al. 1983). However, patients with a physical/inducible component tend to have a more protracted course (Kozel et al. 2001).

8.5 Antibody-Associated or Autoimmune Urticaria

Autoantibody-associated urticaria involves the presence of autoantibodies such as thyroid autoantibodies or IgE receptor autoantibodies with

Table 1 Guidelines for diagnostic work-up of patients with chronic urticaria (Najib and Sheikh 2009)

History and physical examination
Onset (e.g., timing of symptoms with any change in medication or other exposures)
Frequency, duration, severity, and localization of wheals and itching
Dependence of symptoms on the time of day, day of the week, season, menstrual cycle, or other pattern
Known precipitating factors of urticaria (e.g., physical stimuli, exertion, stress, food, or medications)
Relation of urticaria to occupation and leisure activities
Associated angioedema or systemic manifestations (e.g., headache, joint pain, or gastrointestinal symptoms)
Known allergies, intolerances, infections, systemic illnesses, or other possible causes
Family history of urticaria and atopy
Degree of impairment of quality of life
Response to prior treatment
Physical examination
Laboratory evaluation
Routine evaluation: Testing should be selective. There is an honest difference of opinion concerning the appropriate tests that should routinely be performed for patients with CU in the absence of etiologic considerations raised by a detailed history and careful physical examination.
A majority of members of the Practice Parameters Task Force expressed a consensus for the following routine tests in managing a patient with CU without atypical features
CBC with differential
Erythrocyte sedimentation rate, C-reactive protein level, or both
Liver enzymes
TSH
The utility of performing the above tests routinely for patients with CU has not been established.
Additional evaluation might he warranted based on patients' circumstances and might include but not be limited to the diagnostic tests listed below. A thorough history and meticulous physical examination are essential for determining whether these additional tests are appropriate:
Skin biopsy
Physical challenge tests
Complement system (e.g., C3, C4, and CH_{50})
Stool analysis for ova and parasites
Urinalysis
Hepatitis B and C serologies
Chest radiography, other imaging studies, or both
Antinuclear antibody
Rheumatoid factor, anticitrullinated protein
Cryoglobulin levels
Serologic and/or skin testing for immediate hypersensitivity
Thyroid autoantibodies
Serum protein electrophoresis

More detailed laboratory tests, skin biopsies, or both merit consideration if urticaria is not responding to therapy as anticipated. Additional laboratory testing might be required before initiation of certain medications, such as G6PD screening before prescribing dapsone

concomitant urticaria and is considered a subset of chronic idiopathic urticaria. A large study of nearly 13,000 patients with CU compared to over 10,000 control patients indicated increased prevalence of numerous autoimmune disorders, including thyroid disorders, celiac disease, Sjögren syndrome, systemic lupus erythematosus, dermatomyositis, polymyositis, rheumatoid arthritis, and type 1 diabetes mellitus in CU patients. In particular, in patients with CU, hypothyroidism was diagnosed in 9.8% of subjects (compared to 0.6% of controls) and hyperthyroidism in 2.6% of subjects (compared to 0.5%

of controls) (Confino-Cohen et al. 2012). A study in Korea indicated that individuals with Hashimoto's thyroiditis and Graves' disease had higher rates of CU compared to control subjects (hazard ratio 1.5, 95% confidence interval 1.3–1.7) (Kim et al. 2017).

Thyroid autoantibodies, including thyroid peroxidase antibodies and antimicrosomal antibodies, as well as antinuclear antibodies, are more prevalent in patients with CU compared to the general population (Leznoff et al. 1983). However, the presence of autoantibodies does not necessarily correlate with autoimmune disease. For example, detection of serum thyroid autoantibodies does not necessarily correlate with thyroid dysfunction, and the majority of patients with CU and detectable thyroid autoantibodies have normal thyroid function. Furthermore, treatment with thyroid supplement in these patients has not been demonstrated to control urticaria. Thus, serology to diagnose underlying autoimmune disease in initial evaluation of CU is not warranted in the absence of additional attributes suggestive of concomitant autoimmune disease. The role of autoantibodies in CU is unclear, as it may simply reflect an underlying tendency toward the production of autoantibodies. Interestingly, patients with detectable thyroid autoantibodies who are euthyroid are often poorer responders to standard therapy for CU. The role of IgE antibodies to high-affinity IgE receptors (FcER1 alpha subunit) on mast cells and basophils is also unclear. Autologous serum skin testing and the serologic chronic urticaria index (CUI) assay are not predictive of response to therapy, and therefore, their clinical relevance is still poorly elucidated. Of note, a recent study suggests that patients with FcER1 alpha subunit antibodies refractory to high-dose H1-antihistamines may be slower to respond to omalizumab (Leznoff et al. 1983; Kaplan and Greaves 2009; Kikuchi et al. 2003; Najib et al. 2009; Greiwe and Bernstein 2017).

8.6 Physical or Inducible Urticarias

Physical urticaria, now referred to as inducible urticaria, is a subgroup of chronic urticaria characterized by hives that are reproducibly triggered by physical stimuli, such as scratching of the skin (dermatographism), exposure to cold, physical pressure, exercise, sunlight, heat, and rarely water or vibration (see Table 2). These same physical triggers can also provoke angioedema (Lang et al. 2013; Sanchez-Borges et al. 2012). The term inducible has replaced physical as there are cholinergic and less commonly adrenergic urticaria conditions that are induced by stimuli which provoke the autonomic nervous system such as stress and emotions.

Dermatographism is urticaria that occurs in response to stroking the skin with a firm object, such as a tongue blade or an instrument with a firm edge. Simple dermatographism is present in about 2–5% of the population, while only a minority of people have symptoms to a degree that prompts medical attention (Orfan and Kolski 1993; Kirby et al. 1971). Initially, a white line develops on the skin as a consequence of reflex vasoconstriction. This is followed by development of a linear raised swelling at the challenge site. The response typically occurs within 1–3 min and resolves in about 30 min (Orfan and Kolski 1993; Bernstein et al. 2014; Sanchez-Borges et al. 2012).

Cold urticaria involves hives elicited by cold fluids, air, wind, or contact with cold objects. Provocative cold testing, such as an ice cube challenge, can confirm diagnosis of cold urticaria. A common method is to place an ice cube (0 °C to 4 °C) contained in a plastic bag on the forearm for 5 min, followed by observing the challenge site as skin rewarms to room temperature. Development of a wheal or flare response during skin rewarming is a positive test (Wanderer et al. 1986). If, after 5 min, there is no observed reaction, the test may be repeated incrementally up to 10 min. The optimal duration of challenge testing to exclude cold urticaria has not been determined (Wanderer and Hoffman 2004). Notably, a cold stimulus should not be reapplied at a site previously challenged, as this could result in a "false-negative" result due to local desensitization of skin. Variants of acquired cold urticaria have been described in which provocative cold testing is negative. The variants include systemic atypical acquired cold urticaria, cold-dependent dermatographism, cold-induced cholinergic

Table 2 Characteristics of physical or inducible urticarias, including clinical features and diagnostic tests (Lang et al. 2013)

Type	Clinical features	Familial	Angioedema	Diagnostic test	Transfer factor[a]
Aquagenic	More common in women than in men	Yes	No	Application of room-temperature wet compress to upper body for 30 min at 35 °C	No
Cholinergic	Itchy, small 3- to 5-mm monomorphic pale center with surrounding erythema	Yes	Yes	Methacholine intradermal injection, exercise, or hot water immersion	Yes
Cold (primary vs secondary)	Itchy, pale lesions (5% with cyrogiobulins)	Yes	Yes	5- to 10-min ice-cube test	Yes
Delayed pressure	Large painful or itchy lesions	No	Yes	Dermographometer: application of weight or force to a skin area, e.g., 15-lb weight for 15 min	No
Dermatographism	Linear lesions	Yes	No	Light stroking of skin	Yes
Exercise-induced urticaria and anaphylaxis	Hives distinguishable from cholinergic lesions	Yes	Yes	Treadmill exercise challenge; can be performed without or after ingestion of inciting food or other agent	No
Solar	Itchy pale or red swelling	Yes	Yes	Irradiation by solar simulator	Yes
Vibratory	Erythema and edema sharply demarcated from normal skin	Yes	Yes	Vortex mixer for 1–5 min	No

[a]Transfer factor refers to the ability to passively transfer a physical urticaria by intracutaneous injection of serum from a patient with a specific physical urticaria to a naive patient

urticaria, acquired delayed cold urticaria, and localized cold reflex urticaria (Wanderer and Hoffman 2004).

Delayed pressure urticaria and angioedema (DPUA) involves the development of swelling in response to exposure to a pressure stimulus about 30 min to 12 h (peak of 4–6.5 h) after exposure to the stimulus (Ryan et al. 1968; Czarnetzki et al. 1984; Sussman et al. 1982; Dover et al. 1988; Warin 1989). Biopsy of angioedema lesions brought about by a pressure stimulus exhibits an intense inflammatory infiltrate characterized histologically by an infiltrate rich in both eosinophils and neutrophils in the deeper dermis and subcutaneous tissue (Winkelmann et al. 1986; Mekori et al. 1988). Diagnosis of DPUA can be confirmed by application of a pressure stimulus, such as a weight or force, to a specific area of skin, with subsequent development of angioedema at the challenge site after 4–6 h. Various published protocols indicate different pressure stimuli to be used and the challenge duration. Positive and negative values for this challenge procedure have not been determined (Estes and Yung 1981). One example of a recommended challenge involves suspension of a 15 pound weight across the patient's shoulder for 10–15 min (Ryan et al. 1968; Sussman et al. 1982). A painful reaction at the challenge site 2–12 h later (peak swelling at 4–6.5 h) is a positive response. Other approaches include the use of calibrated dermographometer or use of weighted metal rods. The challenge procedure should only be performed if concomitant chronic idiopathic urticaria and angioedema (which may also be present in patients with DPUA) are reasonably well controlled (Estes and Yung 1981; Lawlor et al. 1989; Illig and Kunick 1969).

Exercise-induced urticaria and angioedema are forms of physical urticaria that can be confirmed by an exercise challenge in a controlled setting (Sheffer et al. 1983, 1985). As exercise increases one's risk for anaphylaxis, this challenge should only be performed in a setting with appropriately trained personnel, supplies, and equipment to handle management and treatment of such a possibility. In patients with a specific food (i.e., celery) linked to exercise-induced urticaria and angioedema, the relevance of the specific food suspected by history can be assessed with immediate hypersensitivity skin testing if patients aren't dermatographic or on prophylactic H1-antihistamines or by in vitro serum-specific IgE antibody. If food-associated exercise-induced urticaria and angioedema are still suspected, then a challenge procedure in a supervised setting can be performed with and without food consumption. It is important for the clinician to be mindful that urticaria may also occur during an exercise challenge in patients with cholinergic urticaria as exercise increases body temperature. In this case, the diagnosis of cholinergic urticaria can be confirmed by passive heating and/or intracutaneous injection of methacholine. Furthermore, the morphology of lesions can be used to distinguish these two conditions (Sheffer et al. 1983; Kaplan et al. 1981; Casale et al. 1986)

Solar urticaria is provoked by ultraviolet and/or visible light. The diagnosis is confirmed with photo-testing, to stimulate provocation of urticarial lesions with sunlight. Reactions are more often observed with ultraviolet (UVA) or visible wavelengths and less commonly with UVB or infrared wavelengths (Farr 2000). One common provocation test involves using a xenon arc lamp with monochromator to ascertain the minimal urticarial dose at different wavelengths of light. A non-sun-exposed portion of the skin, such as mid and lower back, is ideal for phototesting. Other light sources, such as slide projector light bulb for physical light, fluorescent black light or fluorescent sunlamp for UVA and UVB wavelengths, or infrared lamp for infrared wavelengths can also be used if a xenon lamp with monochromator is unavailable (Roelandts 2003; Alora and Taylor 1998; Uetsu et al. 2000). For each light source or wavelength used, a positive challenge results if a pruritic erythematous wheal develops during or shortly after irradiation and fades within a few minutes after removal of the light stimulus (Roelandts 2003). It is important to distinguish solar urticaria from a polymorphous light eruption. Lesions of polymorphous light eruptions tend to last more than 24 h, in contrast to the short-lived lesions of solar urticaria. Erythropoietic protoporphyria involves lesions that are painful, rather than pruritic, and typically are associated with a positive family history and elevated protoporphyrin levels (Murphy 2003; Fesq et al. 2003).

Cholinergic urticaria is a phenomenon in which an increase in body temperature, either passively or actively, results in sweat release and subsequent provocation of urticaria. The diagnosis can be confirmed by intracutaneous injection of 0.01 mg of methacholine in 0.1 mL of saline with subsequent formation of at least one hive. Unfortunately, this technique has poor sensitivity since as little as 33% of patients with cholinergic urticaria will have a positive methacholine test response and responses that are positive are not always consistently reproducible. Therefore, this test has a poor negative predictive value, and although this test may confirm a diagnosis if positive, it cannot definitively rule out diagnosis if negative (Commens and Greaves 1978). Challenges that increase body temperature, such as hot water immersion or exercise, may have higher sensitivity. For example, partial immersion of a patient in a 42 °C bath, leading to a 0.7 °C body temperature increase, resulting in hives may have a higher sensitivity (Orfan and Kolski 1993). Finally, some patients with cholinergic urticaria may exhibit a wheal and flare response to autologous diluted sweat, suggesting that the sweat of these patients contain factors that lead to histamine release (Fukunaga et al. 2005). It has been reported in such patients that rapid desensitization to autologous sweat has been shown to be as efficacious as therapeutic intervention. However, sweat may be a different entity and not reflective of cholinergic hives (Kozaru et al. 2011).

Vibratory angioedema involves the development of angioedema after exposure to an intense

vibratory stimulus. The diagnosis can be confirmed by an exaggerated reaction to the stimulation of the skin with a vortex mixer. There are currently no standardized recommendations regarding the optimal vibratory stimulus to use, duration of exposure to vibration, or grading of a positive reaction. One generally accepted challenge procedure entails supporting a patient's forearm under the wrist and elbow, so the skin of the forearm, hand, or finger rests in the rubber cup of a vortex mixer. The mixer is vibrated at constant speed for 1–5 min. Subsequent development of erythema and edema that is sharply demarcated from normal skin within 4 min of simulation and persistent for 1 h defines a positive response. If desired, the response can be quantified by measuring the change in the forearm circumference or finger volume (Patterson et al. 1972; Metzger et al. 1976). Delayed onset of erythema and pruritus after vibratory provocation has been reported with peak symptoms occurring 4–6 h after the vibratory stimulus (Keahey et al. 1987).

Aquagenic urticaria is a water-induced etiology with diagnosis confirmed by hives following direct water exposure. One way to confirm the diagnosis is application of a water compress at 35 °C to the upper body skin for 30 min (Baptist and Baldwin 2005). The appearance of punctate 1–3 mm hives at site of application is considered a positive response. This diagnosis should be distinguished from other disorders including aquagenic pruritus, in which water exposure provokes itching but without wheal formation (Greaves et al. 1981); cold urticaria, which is induced by cold rather than water; and cholinergic urticaria, in which punctate lesions manifest in response to heat, rather than water. Notably, cases of concurrent aquagenic urticaria with cold or cholinergic urticaria have been reported (Davis et al. 1981; Mathelier-Fusade et al. 1997).

8.7 Treatment of Acute and Chronic Urticaria

The treatment of acute and chronic urticaria begins with the use of H1 non-sedating antihistamines which can be dosed 1–4 times the Food and Drug Administration (FDA)-approved recommended dose. Treatment begins at a step appropriate for the patient's level of severity and previous treatment history. At each level of the stepwise algorithm, medication(s) should be assessed for patient adherence, tolerance, and efficacy. Once consistent control of urticaria/angioedema is achieved (usually 3–6 months after complete control of hives), a "step-down" approach to treatment can begin (Bernstein et al. 2014; Fine and Bernstein 2016). The US and international guideline treatment algorithms are illustrated and compared regarding similarities and differences in Fig. 2. For the US guidelines, Step 1 involves starting monotherapy with a second-generation non-sedating H1-antihistamine, such as cetirizine, in addition to strict avoidance of suspected or known triggers (such as NSAIDs) and any relevant physical factors if a form of inducible urticaria/angioedema syndrome is present. Step 2 comprises one or more of the following: increasing the dose of the second-generation antihistamine started in Step 1 to 2–4 times the original dose (maximum dose 4× the approved treatment dose), adding another second-generation antihistamine, adding an H2-receptor antagonist medication, adding a leukotriene receptor antagonist, and/or adding a first-generation antihistamine to be taken at bedtime. Recent international guidelines object to using a combination of second-generation antihistamines or a first-generation antihistamine due to the lack of scientific evidence. Concerns about first-generation antihistamines are related to their sedating effects which can affect cognition and motor coordination. Step 3 therapy includes dose advancement to a more potent combination antihistamine (such as doxepin or hydroxyzine) as tolerated. Again, this step is not recommended by the international guidelines due to sedation affecting cognition and mental performance. Finally, Step 4 therapy in the US guidelines, which is Step 3 in the international guidelines, recommends adding an alternative agent, such as cyclosporine, omalizumab, or other anti-inflammatory therapies such as hydroxychloroquine, sulfasalazine, dapsone, or

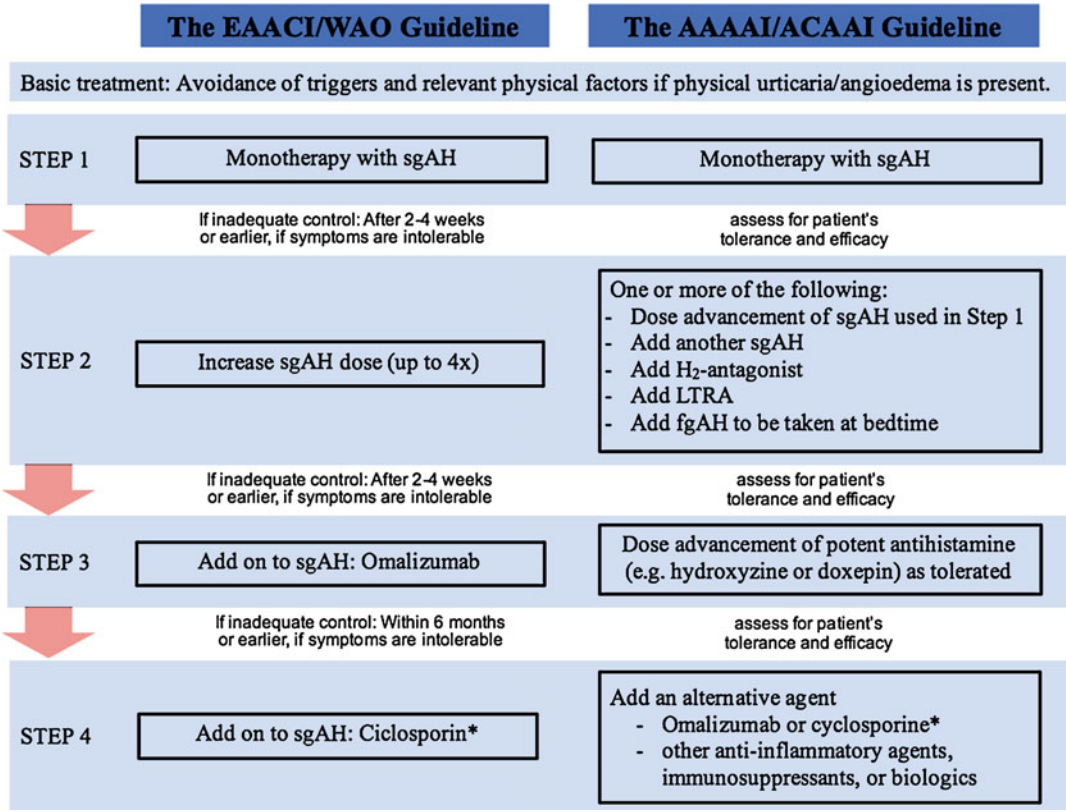

Fig. 2 Comparison of the international and US urticaria guideline treatment algorithms (Zuberbier and Bernstein 2018). *EAACI*, European Academy of Allergy and Clinical Immunology; *fgAH*, first-generation antihistamine; *LTRA*, leukotriene receptor antagonist; *sgAH*, second-generation antihistamine; *WAO*, World Allergy Organization. *Different spellings as used in respective guideline. Additional comments: EAACI/WAO: A short course of corticosteroids may be considered in case of severe exacerbation. AAAAI/ACAAI: Begin treatment at step appropriate for patient's level of severity and treatment history; "step-down" treatment is appropriate at any step, once consistent control of urticaria/angioedema is achieved. Used with permission from Zuberbier and Bernstein "*A Comparison of the United States and International Perspective on Chronic Urticaria Guidelines*", *Journal of Allergy and Clinical Immunology in Practice*, 2018 May 18

colchicine. The international guidelines only recommend omalizumab as Step 3 therapy due to the strength of medical evidence supporting this treatment for hives. For the international guidelines, Step 4 involves starting cyclosporine. This treatment is recommended after omalizumab due to a less robust strength of evidence and its toxicity. Oral corticosteroids may be used short term (1–3 weeks maximum) for exacerbations of urticaria or angioedema but are not recommended on a frequent or continuous basis due to short-term and long-term side effects (Zuberbier et al. 2014). A number of therapies recommended by the US guidelines such as montelukast and H2-antihistamines for Step 1 therapy, sedating combination and/or first-generation antihistamines for Step 3 therapy, or anti-inflammatory agents for Step 4 therapy are not recommended by the international guidelines; rather they are relegated to an "alternative treatment" box because of low level of scientific evidence supporting their use (Table 3) (Zuberbier and Bernstein 2018). However, clinicians can use these agents in the proper context for the treatment of their patients unresponsive or incompletely responsive to antihistamines.

Table 3 Alternative treatment options, suggested by the international guideline, that can be considered if treatment according to the recommended algorithm fails or is not possible

Intervention	Substance (class)	Indication
Widely used		
Antidepressant	Doxepin[a]	CSU
Diet	Pseudoallergen-free diet[b]	CSU
H_2-antihistamine	Ranitidine	CSU
Immunosuppressive	Methotrexate Mycophenolate mofetil	CSU ± DPU[c] Antibody associated/autoimmune CSU[d]
Leukotriene receptor antagonist	Montelukast	CSU, DPU
Sulfones	Dapsone Sulfasalazine	CSU ± DPU CSU ± DPU
Infrequently used		
Anabolic steroid	Danazol	Cholinergic urticaria
Anticoagulant	Warfarin	CSU
Antifibrinolytic	Tranexamic acid	CSU with angioedema
Immunomodulator	Intravenous immunoglobulin Plasmapheresis	Antibody associated/autoimmune CSU[d] Antibody associated/autoimmune CSU[d]
Miscellaneous	Autologous blood/serum Hydroxychloroquine[e]	CSU CSU
Phototherapy	Narrow band UVB	Symptomatic dermographism
Psychotherapy	Holistic medicine	CSU
Rarely used		
Anticoagulant	Heparin	CSU
Immunosuppressive	Cyclophosphamide Rituximab	Antibody associated/autoimmune CSU[d] Antibody associated/autoimmune CSU[d]
Miscellaneous	Anakinra Anti-TNF-alpha Camostat mesilate[f] Colchicine Miltefosine Mirtazepine PUVA	DPU CSU ± DPU CSU CSU CSU CSU CSU
Very rarely used		
Immunosuppressive	Tacrolimus	CSU
Miscellaneous	Vitamin D Interferon alpha	CSU CSU

Annotations by authors of the original figure (Zuberbier and Bernstein 2018)

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DPU, delayed pressure urticaria; *PUVA*, psoralen and ultraviolet A; *UVB*, ultraviolet B

[a]Has also H_1- and H_2-antihistaminergic properties

[b]Includes a low histamine diet as the pseudoallergen-free diet is also low in histamine; not widely accepted in the United States

[c]Treatment can be considered especially if chronic spontaneous urticaria and DPU are coexistent in a patient

[d]The international guideline states "autoimmune chronic spontaneous urticaria" only, whereas the US guideline differentiates autoimmune from the presence of antibodies (e.g., FcεR1alpha) that are associated but not cause and effect

[e]More widely used in the United States

[f]Not available in the United States

8.8 Conclusions

Acute and chronic urticaria can be challenging conditions to evaluate and treat. However, if guidelines are followed in an algorithmic manner, the majority of these cases can be treated very successfully which should result in improvement in patient quality of life, decreased morbidity, and reduced health care costs. The clinician should be knowledgeable about the US urticaria guidelines as well as the recent international guidelines and how they agree and differ.

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Hereditary Angioedema

9

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Contents

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Abstract

Hereditary angioedema (HAE) is a rare disease affecting approximately 1 in 50,000 people and presents with recurrent cutaneous and mucosal membrane swelling. The result is recurrent angioedema, intermittent abdominal obstruction and pain, and airway swelling. Though death is rare in patients diagnosed and on therapy, upper airway swelling can be fatal. Disability and absenteeism secondary to the frequent attacks lasting up to 3 days can limit quality of life and education and occupational stability. Multiple therapies have been approved in the last decade and have made drastic improvements in this orphan disease. This chapter will discuss epidemiology, signs and symptoms, differential diagnosis, diagnosis, treatment, and management of the HAE patient.

Keywords

Hereditary angioedema (HAE) · Angioedema · Bradykinin · C1 inhibitor (C1-INH) · C1-esterase inhibitor

9.1 Introduction

Hereditary angioedema (HAE) is a relatively rare, life-threatening disorder characterized by recurrent intermittent attacks of subcutaneous or submucosal edema. Skin and mucosal tissue of the upper respiratory and gastrointestinal tracts are the most commonly affected sites. While HAE has been recognized for over 100 years, the last several decades have seen rapid advances in management and therapeutic options.

There are four major subtypes of HAE. Type I is due to a deficiency of C1-INH (quantitative loss), while type II involves C1-INH dysfunction (qualitative loss). Newer nomenclature suggests replacing type I and type II with HAE with deficient C1-INH and HAE with dysfunctional C1-INH, respectively; however, for simplicity we will use type I and II in this chapter. Type I accounts for 85% of all HAE cases, with type II comprising approximately 15%. An uncommon third form of HAE has normal quantity and function of C1-INH with a positive family history along with a mutation in Factor XII (FXII-HAE), and a fourth subtype is of unknown etiology (U-HAE). These latter two types are often grouped under type III HAE or HAE with normal C1-INH.

Acute attacks of HAE can certainly be life-threatening; approximately 50% of patients will have at least one attack with involvement of the upper airway, where edema can lead to asphyxiation and death. However, the majority of acute attacks have cutaneous or gastrointestinal involvement and resolve within 2–5 days even without therapy. The primary focus for patients, caregivers, and medical providers should be to improve quality of life, productivity, absenteeism, and anxiety by early treatment of attacks or preventing attacks.

In this chapter, we review the major subtypes and pathology of angioedema, followed by guidelines on the best clinical approach to managing an HAE patient.

9.2 Epidemiology of HAE

The estimated prevalence of HAE is 1 in 50,000 individuals, with some studies estimating a range from 1 in 10,000 to 1 in 150,000 (Bowen et al. 2010). Males and females of all ages appear to be affected in equal measures, and no differences have

been noted among ethnic groups (Roche et al. 2005; Zanichelli et al. 2015). Most guidelines have been established based on studies of adults in Western Europe and North America. Since demographics do not appear to alter risk or prognosis, the differences in guidelines around the world are largely in the available treatments. In Sect. 8, we review the most common treatment options.

The age of onset of HAE attacks ranges from 4.4 to 18 years, with the mean age of first attack at 10 years. Approximately 40% of individuals will experience an attack by the age of 4 and 75% by the age of 15 (Bork et al. 2006; Agostoni and Cicardi 1992). Early symptom onset is a poor prognostic factor and suggests a more severe course of disease. Attacks typically increase in severity at puberty, particularly in females, and may also be precipitated by the introduction of estrogen-containing medications. Attacks also tend to decrease in frequency with advancing age.

The mutations associated with HAE types I and II have varied penetrance, such that multiple affected members of a single family can have drastically different clinical presentation, frequency, and severity of disease. The exact contribution of factors that determine these outcomes is still unknown.

9.3 Subtypes of Angioedema

Angioedema is a pathophysiological process that occurs due to leakage of plasma from post-capillary venules. This process is mediated by (1) unregulated generation of bradykinin or (2) by excessive activation of mast cells.

9.3.1 Bradykinin-Mediated Angioedema

One pathway to developing angioedema is the excess production of the peptide bradykinin, a potent mediator of vasodilation. Bradykinin mediates this process by inducing the release of prostacyclin, nitric oxide, and endothelium-derived hyperpolarizing factor. These inflammatory mediators reduce vascular integrity to allow for fluid to move out of the vessels and into the surrounding tissues, resulting in the edema that characterizes HAE. A crucial distinction between the angioedema of HAE and the edema associated with cardiovascular, renal, and liver disease is that angioedema is not dependent on gravity. For example, edema most commonly presents in cardiovascular disease as pooling of fluids in the lower extremities, whereas angioedema occurs in gravity-independent tissues such as the face and the bowels. Other bradykinin-mediated diseases are acquired angioedema with low C1-inhibitor (AA) and ACE-I-induced angioedema (ACE-I-A). AA, unlike HAE, usually occurs in older populations, most commonly above the age of 40 years. It is usually associated with monoclonal gammopathy or lymphoma and is often distinguished from HAE by a low C1q and more frequent upper airway and facial involvement. ACE-I-A is secondary to inadequate catabolism of bradykinin and is more often seen in older individuals since this is the population that frequently is treated with ACE-inhibitors. Because of genetic factors, African American females are more likely to develop ACE-I-A. Similarly to AA, ACE-I-A more likely involves the face and upper airway. Since it is decreased catabolism and not overproduction, the tests used for diagnosis of AA and HAE will all be normal. A distinction from histamine-mediated angioedema is that most angioedema secondary to histamine is associated with urticaria, resolves rapidly, and responds to antihistamines. In bradykinin-mediated disease, urticaria is not a component of the presentation, swelling is refractory to antihistamines, and the angioedema persists for days.

9.3.2 Mast Cell-Mediated Angioedema

While bradykinin-mediated angioedema is the underlying pathophysiology of HAE, most angioedema is secondary to mast cells, which release inflammatory mediators that cause vasodilation and increase permeability of vessels. As noted above, a key difference between bradykinin- and mast cell-mediated angioedema is that mast cells will also typically give rise to urticaria

Table 1 Hereditary angioedema subtypes

	Type I	Type II	FXII-HAE	U-HAE
C1-INH levels	Low	Normal/elevated	Normal	Normal
C1-INH function	Low	Low	Normal	Normal
Complement C4	Low	Low	Normal	Normal
Factor XII	Normal	Normal	Mutated	Normal

and pruritis. Mast cells can be trigged by a variety of factors including opiates, muscle relaxants, radiocontrast agents, fragments of the complement system to include C3a and C5a, and NSAIDs. A variety of environmental factors, such as certain foods, insect stings, medications, and latex can also trigger a response, usually through IgE. Once activated, mast cells release a variety of inflammatory mediators (i.e., histamine, heparin, leukotriene C4, prostaglandin D2) that lead to venous dilation and increased permeability, allowing fluid to seep into the surrounding tissues. In most cases angioedema secondary to histamine will respond to antihistamines, corticosteroids, and epinephrine.

9.3.3 Hereditary Angioedema Classifications

There are four subtypes of HAE: HAE with deficient C1-INH (type I), HAE with dysfunctional C1-INH (type II), HAE with normal C1-INH and a gain of function mutation in coagulation factor XII (FXII-HAE), and HAE with normal C1-inhibitor and unknown etiology (U-HAE), as summarized in Table 1. Types I and II together make up the C1INH-HAE subclass. C1INH-HAE has an autosomal dominant pattern of inheritance, and the majority of patients will have a positive family history of the disorder. However, up to 25% of cases arise from de novo mutations (Tosi 1998; Pappalardo et al. 2000), and thus a negative family history should not be used to rule out a diagnosis of HAE. HAE with normal C1-INH is classified into two subtypes, one with a mutation in coagulation factor XII (FXII-HAE) (Bork et al. 2007b; Dewald and Bork 2006) and one with no discernable defect, HAE of unknown origin (U-HAE) (Cicardi et al. 2014a).

Type I HAE accounts for 85% of C1INH-HAE and is defined by a quantitative decrease in secretion of functional C1-INH. In this scenario, both the levels of protein and function will be low. Type II HAE accounts for approximately 15% of C1INH-HAE and is due to the presence of dysfunctional C1-INH. Here, the protein is found at normal and sometimes even elevated levels. Elevation of C1-INH is thought to be due to the defective protein failing to complex with proteases, thus remaining in circulation longer and demonstrating an increased plasma half-life (Prada et al. 1998). These patients will also exhibit a decrease in complement C4 due to the increased presence and activity of C1, which is responsible for cleaving C4.

FXII-HAE patients have normal C1-INH levels and function and thus also have normal C4 levels. Four FXII mutations associated with HAE have been identified to date. U-HAE is the classification given to patients with no discernable genetic or biochemical defect.

9.4 Pathology

The production of bradykinin is a direct result of the kinin-kallikrein system, which is comprised of high-molecular-weight kininogen (HMWK), low-molecular-weight kininogen (LMWK), bradykinin, kallidin, and a group of enzymes which regulate the dynamics of these molecules. These enzymes are known as kininases and include angiotensin-converting enzyme, aminopeptidase P, carboxypeptidase N, and kallikreins. C1-INH is a serine protease inhibitor and serves to inhibit the kinin-kallikrein system as well as multiple other pathways, such as the complement, fibrinolytic, and coagulation pathways. A deficiency in functional C1-INH, which defines HAE types 1 and 2, allows plasma kallikrein to stay active,

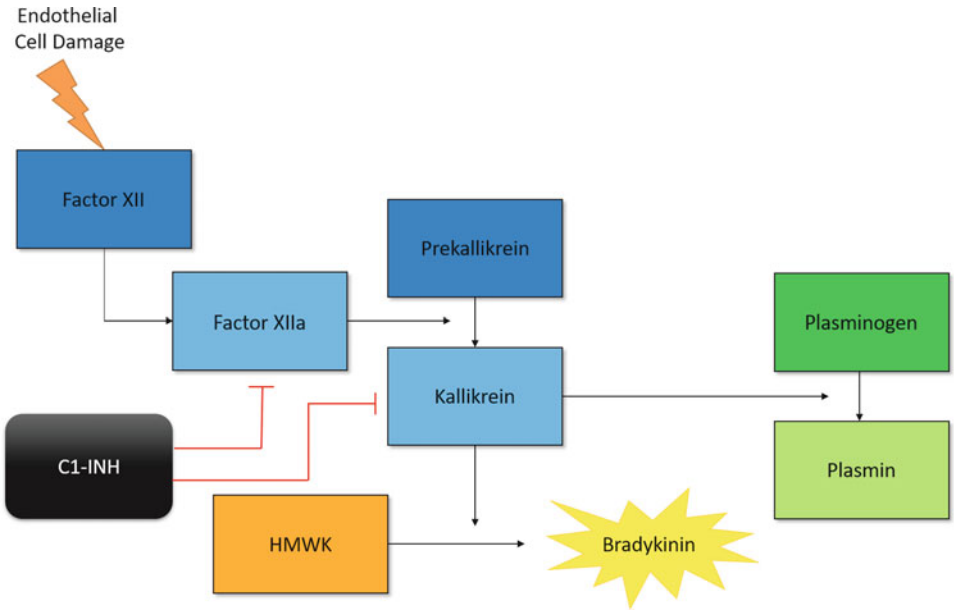

Fig. 1 Release of bradykinin by the kinin-kallikrein pathway

thus increasing the production of bradykinin. In fact, it has been shown that during acute attacks, HAE patients can have up to a sevenfold increase from baseline bradykinin levels (Bork et al. 2007a).

The initiating event of the molecular pathway leading to an acute attack of bradykinin-mediated angioedema is unclear. It is thought that local activation of Factor XII and plasma prekallikrein on the surface of endothelial cells is required for the process to begin. In particular, it is believed that phospholipids released from damaged endothelial cells triggers the activation of Factor XII to Factor XIIa which then mediates the conversion of prekallikrein to kallikrein. Kallikrein facilitates the cleavage of HMWK, releasing bradykinin in the process (Fig. 1). C1-INH maintains the level of bradykinin in the plasma by inhibiting Factor XIIa and kallikrein; thus, deficiencies of C1-INH increase the potential for acute attacks of angioedema (Kaplan and Joseph 2010; Cugno et al. 2009).

The most common location of edema is the skin, present in 91% of patients, followed by abdominal involvement (73%) and the upper airway (48%). Involvement of the gastrointestinal mucosa often presents with debilitating pain. Roughly one quarter of patients will present with abdominal pain as their first symptom of an acute HAE attack. Laryngeal involvement, a potentially life-threatening event, is rare per acute attack (0.9%) but occurs at least once in 51.7% of patients. Additional sites of involvement are the lips, kidneys, bladder, urethra, and genial mucosa (Fig. 2). Approximately one-third of patients will develop erythema marginatum, an erythematous non-pruritic rash (Gompels et al. 2005; Bork et al. 2006; Kusuma et al. 2012). It is important to note that HAE attacks are without urticaria and pruritis and that most attacks of angioedema are self-limited and resolve in 3–7 days (Bork et al. 2003b).

9.5 The Clinical Encounter

9.5.1 History

Most patients with HAE are otherwise healthy, although a few disease associations are known. These include depression, anxiety, pancreatitis, and autoimmune disorders. Severe, uncontrolled HAE can significantly impact quality of life and lead to depression and anxiety (Lumry et al. 2010). The association with pancreatitis is not

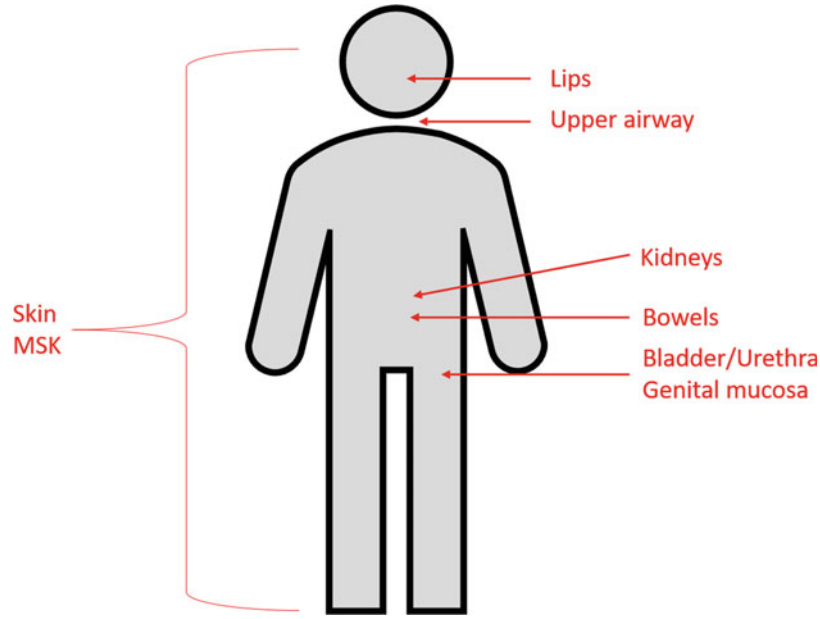

Fig. 2 Involved locations of angioedema

clearly understood but has been widely reported (Cancian et al. 2011; Matesic et al. 2006). Many autoimmune conditions, such as thyroiditis, systemic lupus erythematosus, Sjogren's syndrome, and inflammatory bowel disease, have also been shown to be associated with HAE. It is unclear whether the presence of one of these autoimmune disorders predisposes one to present with HAE or whether the pathophysiological abnormalities of HAE lend to the development of the autoimmune disorders (Brickman et al. 1986; Koide et al. 2002; Palazzi et al. 2005). There are some who believe that the dysfunction of the complement cascade secondary to the lack of C1-INH predisposes people to autoimmune diseases since there is less removal of immune complexes.

Thus, a careful and thorough history must be taken in patients presenting with presumed angioedema. HAE should be suspected in patients who report recurrent episodes of angioedema lasting 2–5 days. Importantly, these episodes should not be associated with urticaria or pruritis. Another presentation which should raise suspicion for HAE is if the patient describes recurrent attacks of colicky abdominal pain that self-resolves within 3–4 days with no clear etiology. Any episode of laryngeal edema with no clear medical explanation is a red flag for HAE, as is a positive family history. If cutaneous angioedema is reported in the absence of a clear trigger of an allergic reaction, especially if without hives and is refractory to antihistamines, suspicion for HAE should be high.

9.5.2 Physical

The three most common sites of edema are the skin, the GI tract, and the upper airway. Most attacks will typically only have involvement in one of these areas, but it is not infrequent to progress from one site to another. The edema can range in severity but will be nonpitting. Below we describe the most common clinical presentations of patients with angioedema.

9.5.2.1 Cutaneous Edema

Patients will typically present with involvement of the skin or GI tract. Edema of the distal extremities and lower face is depicted in Fig. 3. These attacks range in severity, ranging from mild cutaneous edema to laryngeal edema, which is a potentially life-threatening medical emergency.

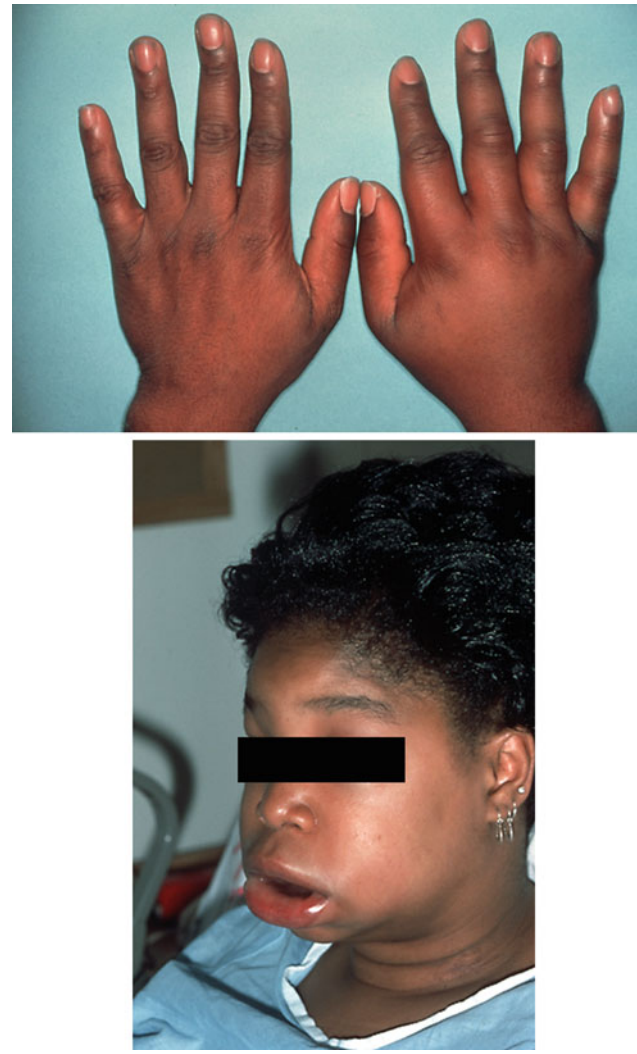

Fig. 3 Examples of cutaneous edema. Top, angioedema of the distal upper extremities. Bottom, swelling of the lower face, including the lips

Frequency of attacks ranges from none to one episode every week or more. Patients will describe experiencing prodromal symptoms hours to minutes prior to the onset of an acute attack, including fatigue, nausea, GI discomfort, myalgias, and flu-like symptoms. They may also report cutaneous changes that are said to resemble "chicken-wire," called erythema marginatum, which are often associated with pain and dysfunction (Reshef et al. 2013).

Episodes of cutaneous involvement often begin with tingling in the affected areas followed by a feeling of fullness as the edema increases within 2–3 h. Most acute attacks peak at 24 h and gradually subside over the following 48–72 h (Bork et al. 2003b).

9.5.2.2 Laryngeal Edema

Laryngeal edema (Fig. 4), on the other hand, is a rare occurrence. Although these attacks have the potential to be life-threatening, they are also typically self-limited in the same manner as other acute attacks and resolve before the entire airway is obstructed. In fact, one study demonstrated that less than 2% of laryngeal edema attacks required intubations or cricothyrotomies. Furthermore,

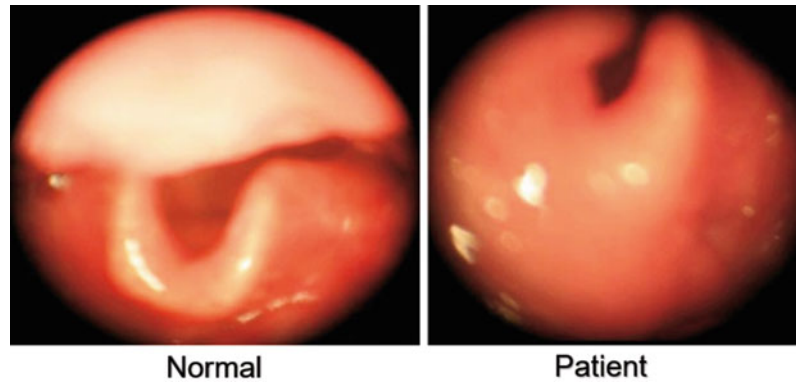

Fig. 4 Laryngeal edema. Left, visualization of normal vocal cords. Right, edematous vocal cords

Table 2 Stages of laryngeal edema

	Predyspnea	Dyspnea	Loss of consciousness
Symptoms	Lump in throat Throat tightness Difficulty breathing	Frank dyspnea	Loss of consciousness
Duration	3.7 h (0–11 h)	41 min (2 min to 4 h)	9 min (2–20 min)

while up to 50% of patients will experience one episode of laryngeal edema in their lives, recurrent attacks involving the upper airway are rare. In fact, multiple retrospective studies have shown that laryngeal attacks only comprise 1% of total HAE attacks. Manipulation of the oral cavity, such as with tooth extractions or oral surgery, is a common trigger (Bork et al. 2003b, 2006).

The mean time to onset of laryngeal swelling is 7 h. It is important to note that the first acute presentation of HAE in children can be in the form of upper airway edema; several case reports describe fulminant attacks that lead to death within a half hour from onset. However, in adults, death from airway swelling is unlikely in those that are diagnosed and have on demand therapy to treat an attack. In fact, most deaths associated with airway swelling occur in patients who have not yet been diagnosed.

It has been proposed that there are three distinct stages of the fatal laryngeal attack, as summarized in Table 2. The attack begins with the predyspnea phase, which typically begins with a lump in the throat, feeling of tightness, or difficulty breathing. On average, this lasts 3.7 h until true dyspnea develops. The second phase, dyspnea, lasts until loss of consciousness. This dyspneic phase lasts 41 min on average. The loss of consciousness phase lasts an average of 9 min and ends in death. With each progressing phase, the window of opportunity for intervention fades (Bork et al. 2012).

9.5.2.3 Gastrointestinal Edema

Edema of the GI tract can present clinically as nausea, vomiting, gastrointestinal colic, or diarrhea, all of which are a direct consequence of swelling of the bowel wall (Fig. 5). GI involvement is common during acute attacks and for many patients can be the primary clinical presentation of their edema. The nonspecific nature of these symptoms can cloud and delay appropriate diagnosis of HAE, which increases the possibility of acute attack and thus raises morbidity. Furthermore, severe bowel edema can mimic the presentation of acute surgical emergencies of the GI tract. Thus, proper history taking is imperative to avoid unnecessary surgical procedures. Notably, most attacks of bowel edema will not be associated with fever or peritoneal signs; however, elevation in white blood cells may occur due to pain and stress. Potential findings do include elevated neutrophils, hypovolemia, and hemoconcentration, the latter findings

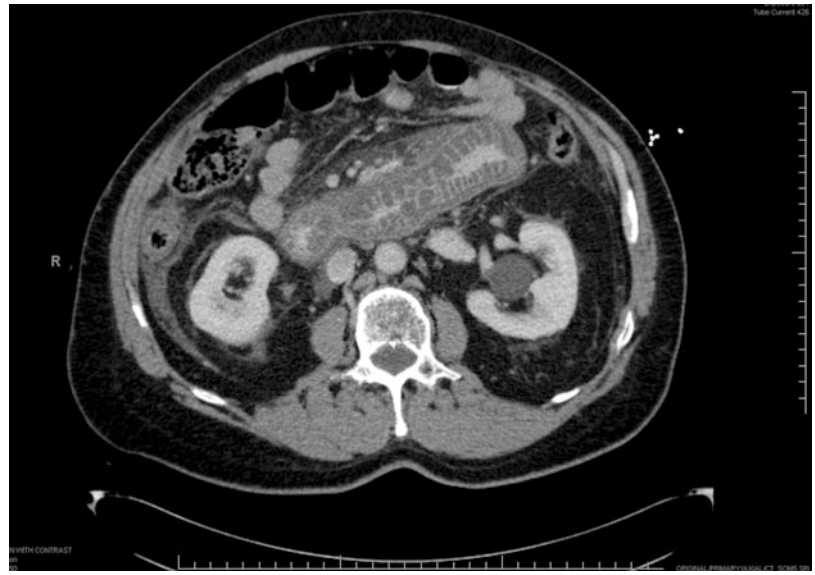

Fig. 5 Acute angioedema of the bowels

Table 3 Sites of edema

Cutaneous
Laryngeal
Gastrointestinal
Bladder/urethra
Kidneys
Musculoskeletal system

due to extravasation of fluid from the vasculature (Nzeako and Longhurst 2012; Gompels et al. 2005; Ohsawa et al. 2013).

9.5.2.4 Other Sites of Edema

While the skin, GI tract, and upper airway are the most common and consequential sites of angioedema, nearly all tissues can be involved (Table 3). In particular, there have been reports of bladder, urethra, and kidney involvement. The joints can also swell and present with intense pain, as can the pleural and pericardial space (Bork et al. 2006; Bonnaud et al. 2012).

9.5.3 Diagnosis

While a positive family history supports the diagnosis of type I and type II HAE, it is not required. Although the majority of C1INH-HAE is transmitted in an autosomal dominant pattern of inheritance, approximately 25% of patients have de novo mutations (Tosi 1998; Pappalardo et al. 2000). Genetic testing is not required or recommended for confirmation of C1INH-HAE since the biologic tests are adequate for the diagnosis except for in the very young.

Complement C4 levels is an easy screening test for a patient suspected to have HAE. In the classical complement pathway, the C1 complex acts to cleave C4. Thus, in the setting of C1-INH deficiency in either type I or type II HAE, the increased activity of C1 will lower levels of C4. Although not directly related to the pathophysiology of HAE, C4 complement serves as a sensitive, but not specific, screening test for C1INH-HAE. The diagnosis requires two sets of tests performed at least 1 month apart and should correlate with low levels or function of C1-INH. Greater than 90% of C1INH-HAE patients will have persistently low C4; however, in a small percentage of patients, C4 may be within normal limits while they are asymptomatic (Zanichelli et al. 2015; Zuraw et al. 1986; Tarzi et al. 2007). Thus, a normal C4 test cannot rule out C1-INH HAE; however, during an attack it would be very unusual to have a normal C4. C4 levels will be normal in FXII-HAE and U-HAE.

A trial therapy of high-dose antihistamines should be undertaken for both therapeutic and

Table 4 Differential diagnosis of angioedema

Allergic reactions
Anaphylaxis
Drug-induced angioedema
NSAIDs
ACE-inhibitors (ACE-I-A)
Contact dermatitis
Autoimmune disorders
Systemic lupus erythematous
Polymyositis
Dermatomyositis
Sjogren's syndrome
Scleroderma
Systemic sclerosis
Hyperthyroidism
Hypothyroidism
Superior vena cava syndrome
Head and neck tumors
Lymphomas
Trichinosis
Low C4
Systemic lupus erythematous
Mixed cryoglobulinemia
Membranoproliferative glomerulonephritis
Acquired angioedema (AA)
Idiopathic angioedema

diagnostic purposes in patients with angioedema, no urticaria and normal tests. HAE, which is bradykinin induced, will not respond to either antihistamines or glucocorticoids. For example, a 1-month course of cetirizine 20 mg bid should be tried before using the diagnosis of HAE type 3, FXII-HAE, and U-HAE (Zuraw et al. 2012).

9.6 Differential Diagnosis

Many disorders present with the clinical features and laboratory abnormalities of HAE and are summarized in Table 4.

Cutaneous and laryngeal swelling can be part of various disease processes that are not mediated by bradykinin, including allergic reactions and anaphylaxis, both which are histamine driven. However, compared to the acute attacks of HAE, allergic reactions have a more rapid onset and resolution and usually involve multiple organ symptoms. Thus, simultaneous presentation of urticaria, wheezing, nausea, vomiting, or diarrhea may be present. While HAE with gastrointestinal involvement may mimic some of these, urticaria and wheezing are not associated with HAE attacks. In the setting of laryngeal edema, anaphylaxis must be ruled out immediately, because timely administration of epinephrine is crucial for a positive outcome.

NSAIDs and ACE-inhibitors are associated with angioedema, with the oral mucosa and upper airway most commonly affected. Taking a thorough history is imperative for ruling out drug-induced angioedema. In this setting, complement and C1-INH levels will be normal.

Many autoimmune conditions are associated with edema, particularly in the face and periorbital regions. Systemic lupus erythematosus, polymyositis, dermatomyositis, and Sjogren's syndrome can all present with such episodes of edema, as can early stages of scleroderma and systemic sclerosis. However, whereas HAE attacks are typically self-limited, the swelling associated with autoimmune conditions persists longer and often requires intervention for resolution.

Both elevation and deficiency of thyroid hormone leads to cutaneous swelling that may initially be confused with angioedema. This swelling is usually slow-progressing and persistent, in contrast to the relatively rapid and limited appearance of angioedema. TSH, T3, and T4 studies will be abnormal in these settings, whereas C1-INH and C4 will be normal.

Superior vena cava syndrome, obstruction of the superior vena cava most commonly due to physical compression of the vessel from a tumor or aneurysm, can present with rapid swelling of the face, neck, and upper extremities. Lymphomas and tumors of the head and neck are also associated with swelling. However, these are associated with chronic swelling that is not self-resolving. C1-INH and C4 levels should be normal in these disorders.

Trichinella spiralis infections cause trichinosis, which in addition to a variety of gastrointestinal symptoms can present with periorbital edema. With this infection, eosinophils will be elevated, whereas C1-INH and C4 will be normal.

Low C4 levels are found in systemic lupus erythematous, acquired C1-INH deficiency, mixed

cryoglobulinemia, and membranoproliferative glomerulonephritis. These are potentially severe diseases that require a full assessment to exclude. Hereditary and acquired angioedema are clinically identical, with certain key differences. Patients present with HAE almost always in the first two decades of life, while those with acquired disease present after their 40s (Gelfand et al. 1979; Frémeaux-Bacchi et al. 2002). Additionally, acquired angioedema typically arises in setting of an underlying lymphoproliferative disorder and often with a monoclonal gammopathy.

Idiopathic angioedema is a diagnosis of exclusion in the setting of angioedema described above and must be on the differential until an underlying etiology can be identified.

9.7 Disease Management

The guiding principles of HAE management are to reduce morbidity and mortality while maximizing quality of life. The 2010 International Consensus Algorithm for the Diagnosis, Therapy, and Management of HAE established the following parameters to ensure that HAE patients receive optimal care. All patients should:

- Be provided with an action plan for acute exacerbations.
- If on C1-INH, undergo hemovigilance for hepatitis B, hepatitis C, hepatitis G, HIV, HTLV, and parvovirus at baseline, followed by annual screenings.
- Be vaccinated against hepatitis A and hepatitis B since blood products are frequently received.
- Avoid estrogens and ACE-inhibitors.
- If on androgens, have baseline laboratory testing for adverse events to androgens, including CBC, BUN/creatinine, LDH, creatine kinase (CK), urine analysis, liver function tests, and a lipid panel.
- If on androgens, have annual ultrasounds of the liver and spleen.

The prognosis for patients with HAE is highly variable. The disease rarely wanes after the first attack, but with proper management and education, the frequency and severity of future attacks can be minimized. Before the advent of the multiple modalities of HAE treatment that are available today up to one-third of patients died of an upper airway attack that resulted in asphyxiation.

9.7.1 Emergency Action Plan

An action plan is recommended for all patients in the event of an acute exacerbation. This includes readily available personal and insurance data to provide a complete medical picture. Edema of the upper airway is involved in many acute exacerbations and may require intubation, leaving the patient unable to provide a thorough medical history. Thus, an appropriate action plan would include information about the patient, their medical providers, a medication list, and personalized information regarding their diagnosis and appropriate medical intervention.

9.7.2 Hemovigilance and Vaccinations

Infusions of C1-INH and fresh frozen plasma (FFP) as part of the HAE treatment regimen raise the risk of transmission of blood-borne pathogens. Thus, all patients should be screened annually as a preventative measure and additionally vaccinated against hepatitis A and B. Although tightly regulated procedures have minimized the risk of transmitting blood-borne diseases through blood products, both human and machine errors have been reported. Thus, preventive measures against viral transmission remain a mainstay of HAE management.

9.7.3 Avoidance of Exacerbating Substances

There are several known triggers and exacerbating factors of HAE; careful questioning and history taking should aim to identify potential triggers and educate the patient on avoiding them to prevent future attacks. Mental or physical stress, along with trauma and surgical/dental procedures, are the primary triggers of acute attacks.

Potent physical triggers are things that involve manipulation of the oral cavity, such as dental procedures or oral surgery. Prophylaxis is strongly recommended for such events (see Sect. 8.2). Sexual intercourse can initiate genital swelling in women, as can bike or horse riding (Caballero et al. 2012).

Several medications have been reported to increase the frequency and severity of attacks. These include estrogen-containing medications, tamoxifen, and ACE-inhibitors. Increases in estrogen, which occurs naturally with the onset of puberty and during pregnancy, worsen disease in HAE patients, as do estrogen-containing contraceptive pills and hormone replacement therapies (Bork et al. 2003a; Bouillet et al. 2008; Chinniah and Katelaris 2009; Martinez-Saguer et al. 2010). Tamoxifen is a selective estrogen-receptor modulator used in the treatment of breast cancer. The mechanism of action of ACE-inhibitors, which are used to treat high blood pressure and heart failure, is to lower blood pressure by inhibiting angiotensin; however, this inhibition decreases the catabolism of, and thus increases the concentration of, bradykinin.

9.7.4 Screening Laboratory Tests

For patients taking androgens for prophylaxis, liver enzymes, lipid profile, CBC, and urinalysis should be checked every 6 months. For patients on high doses of danazol, more than 200 mg daily, an ultrasound of the liver should be performed every 6 months; for doses lower than 200 mg per day, annual ultrasounds are recommended. TA therapy should be additionally screened for CK and renal function every 6 months with an annual ophthalmologic evaluation.

9.7.5 Family Members

Parents, siblings, and children of an HAE patient should undergo testing to determine whether they are also at risk for acute attacks of angioedema. Recommended testing includes C4 levels, C1-INH levels, and C1-INH function. For children of affected parents, testing should be performed after at least 1 year of age, as C1INH levels are physiologically lower in infants. If urgent, genetic testing may be performed on infants and even prenatally. It should be noted, however, that 25% of type I and type II HAE arise from de novo mutations, and thus early diagnosis cannot always be made on the basis of family history.

9.8 Treatment

Treatment of HAE is divided into three categories: on demand therapy for acute attacks, short-term prophylaxis preceding procedures, and long-term prophylaxis. Choosing the correct treatment regimen requires a conversation between the medical provider and the patient to account for all potential variables, including disease severity and frequency, age, gender, comorbidities, and access to medical care. Proper education should be provided for the patients and their family members, with the goal of ensuring compliance and maximizing quality of life. The recommendations below are compiled from the Canadian Hereditary Angioedema Guideline (CHAEN), the World Allergy Organization (WAO), the Hereditary Angioedema International Work Group (HAWK), Hungary/Western Europe, and more (Craig et al. 2012; Bowen et al. 2008, 2010; Longhurst et al. 2015; Cicardi et al. 2012, 2014a, b; Betschel et al. 2014; Zuraw et al. 2012, 2013).

9.8.1 Acute Treatment

Early recognition of acute events is crucial; involvement of the upper airway must be identified quickly and be treated as a medical emergency. First-line agents for treatment of acute attacks include C1-INH, ecallantide, and icatibant. If unavailable, the second option is to treat with solvent detergent-treated plasma (SDP) or FFP.

9.8.1.1 C1-INH

C1-INH replacement is recommended for acute attacks of all severities, occurring in any anatomic location. Currently, there are two available

C1-INH formulations, Berinert and Cinryze. Both medications have comparable efficacy and limited side effects; both can be used in pregnant women and children. The recommended dosage is 20 units/kg. The adverse reactions include anaphylaxis, thrombosis, and the possible transmission of blood-borne pathogens. Both Berinert and Cinryze are administered intravenously, which restricts use in certain subsets of patients. Recently a high concentration of Berinert has been approved and can be used IV but is marketed as HAEGARDA for subcutaneous use for prophylaxis.

A recombinant C1-INH, Ruconest, is approved for use in adults and is also available only as an intravenous formulation. Ruconest is produced using rabbit serum and thus is not recommended for patients with known rabbit allergies in case of residual rabbit antigen in the final product. If suspected, patients can be tested for serum IgE specific for rabbit antigen prior to initiating the therapy. It is dosed as 50 units/kg.

9.8.1.2 Ecallantide

Ecallantide, a kallikrein inhibitor, is approved for use in patients older than 12 years. This medication is associated with a risk of anaphylaxis in 3% of patients. Unlike the C1-INH replacement medications, ecallantide can be administered subcutaneously; however, this formulation cannot be self-administered due to the risk of anaphylaxis. Instead specialty pharmacies have nurses trained in anaphylaxis to go to the home and administer the ecallantide.

9.8.1.3 Icatibant

Icatibant is a bradykinin receptor antagonist approved for adults with HAE. This medication, dosed at a maximum of 30 mg daily, is tolerated very well, with a favorable side effect profile primarily featuring transient local injection site reactions, such as erythema, wheals, pruritis, and burning sensation. Additionally, icatibant can be self-administered as a subcutaneous injection and is room temperature stable, making this a practical option for a wider subset of patients. The only disadvantage is the short half-life that often necessitates a second or third dose in the following days.

9.8.1.4 Solvent Detergent-Treated Plasma and Fresh Frozen Plasma

The C1-INH formulations, ecallantide, and icatibant are all very expensive medications. When these first-line agents are not available for use in HAE patients, guidelines are to switch to FFP and SDP as alternate treatments. Although not common, studies have shown that there is a small risk of worsening an acute attack when administering FFP (ref). As with all blood products, FFP carries a risk of allosensitization, anaphylaxis, and blood-borne pathogen transmission.

9.8.2 Short-Term Prophylaxis

Short-term prophylaxis is indicated for HAE patients undergoing procedures such as aggressive dental work or surgery. Particular care should be taken when procedures involve mechanical manipulation of the laryngeal areas, for example, intubation, bronchoscopy, and endoscopy. For these procedures to prevent acute exacerbations, prophylaxis is indicated. Prophylaxis can also be considered in times of extreme stress, such as that experienced during important events. The recommendation for C1-INH is 10–20 U/kg or a fixed dose of 1000 units IV 1–6 h prior to the procedure.

For low-risk procedures, short-term prophylaxis can be avoided if on demand options for acute exacerbations are readily available. In these situations, it is important to have two doses of C1-INH, ecallantide, or icatibant on hand for immediate administration in the event that symptoms develop.

Alternately, androgens such as danazol or stanozolol can be administered emergently following a low-risk procedure if the first-line treatments are unavailable. Androgens are typically taken orally, are easy to use and inexpensive, and can safely be given to children. During pregnancy, however, androgens are contraindicated. Androgens should be started 5–7 days before the procedure and be continued for 2 days after. Danazol should be used as a dose of 200 mg TID, and stanozolol is recommended at 2 mg TID.

Tranexamic acid (TA) is another option for short-term prophylaxis, although its efficacy for

this indication has not been fully established. If used, dosing should be 25 mg/kg 2–3 times daily, with a maximum dose of 3–6 grams daily.

9.8.3 Long-Term Prophylaxis

Long-term prophylaxis is indicated for patients with severely symptomatic HAE types 1 and 2 and also in those that despite less severe HAE have a poor quality of life. Disease severity, frequency of attacks, available resources, and failure to appropriately manage disease with on demand therapies are all factors that should be considered. The primary indication for initiation of long-term prophylaxis is failure to achieve an adequate quality of life with on demand therapies.

Long-term prophylaxis primarily consists of C1-INH concentrate or androgens, which should be picked based on contraindications, adverse events, risk factors, tolerance, response to medication, route of therapy, cost, and dose required for appropriate control. It is important to note that neither C1-INH nor androgens are approved at high enough doses for definitive prevention of HAE attacks.

Both Berinert and Cinryze may be used as long-term prophylaxis and should be titrated to ensure optimum control. In addition to C1-INH, patients should have access to on demand therapy with rC1-INH (Ruconest), ecallantide, icatibant, or additional C1-INH doses in the event of a breakthrough attack. Recently data was published that also demonstrated that Ruconest is effective as a prophylactic agent given twice a week IV.

Androgens should be used cautiously for long-term prophylaxis due to their adverse effect profile. If androgens must be used, it is important to begin therapy at a low dose, 200 mg/day or less, to minimize adverse effects. Androgens can cause virilization in women, as well as menstrual disorders, amenorrhea, diminished libido, acne, and worsening depression and aggression. Androgen use is contraindicated during pregnancy and in prepubertal children. Additionally, androgens can induce hepatitis in a dose-dependent manner and have been shown to alter serum lipids, necessitating annual lipid and LFT screening.

TA can also be used for long-term prophylaxis and should be dosed at the same frequency as for short-term prophylaxis, at 20–50 mg/kg/day. Although not approved for long-term HAE prophylaxis, antifibrinolytic agents are commonly used in children and in the developing world when C1-INH or androgen therapies are not available or are contraindicated. Antifibrinolytics are readily available and inexpensive, making them an attractive alternative, even though there is a dearth of data to support its efficacy. Adverse effects of these agents include gastrointestinal symptoms, myalgia, creatine kinase elevation, and possible risk of thrombosis. These medications are thus contraindicated in patients with thrombophilia or those with increased thrombotic risk. Dosing is recommended at 30–50 mg/kg b.i.d. or t.i.d., with a maximum of 6 g daily.

Recently, a concentrated form of Berinert was approved. It is dosed 60 units/kg subcutaneous twice a week. The trade name is HAEGARDA. Adverse effect profiles appear to be similar to placebo. The efficacy is approximately 95%.

9.9 Unique Cohorts

9.9.1 Elderly Population

The elderly population has a higher incidence of chronic conditions, which complicate medical management of HAE. Additionally, IV access may be difficult to obtain and medications may not be appropriately self-administered. Coordination of care with the patient, their caregiver, or nursing providers is essential for optimizing therapy and improving quality of life.

Short-term prophylaxis is imperative in the elderly due to the increased risk of morbidity and mortality from surgical complications. C1-INH replacement 1–6 h prior to surgery is recommended. Alternatively, if C1-INH is unavailable or the procedure is low-risk, androgens should be administered for 5 days prior to surgery and continued for 2 days post-op. FFP can also be used as prophylaxis during low-risk procedures.

Medications used for management of chronic conditions common in the elderly population,

such as hypertension, have the potential to precipitate HAE attacks. Additionally, estrogen-containing hormone replacement therapy and tamoxifen, which are used for management of menopause and breast cancer, also can give rise to adverse events in HAE patients. Avoidance of these medications can reduce the frequency and severity of HAE attacks. If required, they should be prescribed with caution.

9.9.2 Pregnancy and Prenatal Testing

Contraceptive options should be discussed with female patients of childbearing age. Estrogen-based birth control should be avoided due to the risk of precipitating an acute event. However, progesterone-only pills and intrauterine devices have demonstrated equivalent efficacy and are well-tolerated by HAE patients.

Proper counseling should be provided for patients of childbearing age when discussing fertility. TA should be discontinued several days prior to conception, and androgens should be discontinued at least 2 months before attempting to conceive.

High estrogen levels during the first trimester of pregnancy may predispose patients to higher frequency of attacks. There is no evidence that labor and delivery precipitates attacks, and thus prophylaxis is only recommended in the event of a C-section. However, attacks can occur immediately following or within 48 h of delivery, and therefore patients should be monitored for 72 h following delivery.

C1-INH concentrate is the recommended first-line therapy for HAE attacks during pregnancy and has been demonstrated to be safe for both the mother and the fetus. Although presumed safe and effective, there is a lack of controlled studies using icatibant, ecallantide, and rcC1-INH, and thus these should be used as second-line agents when C1-INH is unavailable. FFP can also be used as an alternative therapy.

It is rare for the first HAE attack to occur during pregnancy; however, if a work up must be performed on a pregnant woman, it should be noted that C1-INH levels may be slightly decreased due to the dilutional effect of pregnancy (Caballero et al. 2012).

If prenatal diagnosis is requested, it can be performed by sampling the chorion villus after the 10th week of gestation or from the amniotic fluid after the 15th week. Serum C1-INH in the fetus and infants up to 1 year of life may also be lower than normal; thus, proper diagnosis of HAE in this population should include genetic testing. This testing should include comparison of the fetus/infant's genes with the affected parent.

9.9.3 Pediatrics

The first occurrence of upper airway swelling in children can be fatal. It is thus imperative that children of adults with HAE be tested so that they may be adequately prepared in an emergent acute attack. C1-INH is the treatment of choice in children and is approved for all ages of the pediatric population. In the United States, ecallantide is approved for use in children 12 years and older; icatibant has not been thoroughly validated for use in children, but most consider it safe. Ruconest can also be used off-label for children. Second-line agents for attacks are SDP and FFP.

In much of the developing world, first-line treatments for acute HAE events may not be readily available. TA is frequently utilized in developing countries as first-line therapy. Although well-tolerated, there are no robust studies demonstrating efficacy in children and thus are not officially recommended for pediatric dosing by any guidelines. Androgens are also increasingly used in countries where C1-INH is unavailable. If androgen therapy must be initiated, best outcomes are achieved when they are initiated after puberty or when full height has been achieved; one potential adverse effect of androgen use in children is early closure of the epiphyseal plate.

Human-derived C1-INH is the first-line recommendation for short-term prophylaxis in the pediatric population. Androgens may be an effective and much less expensive option and are safe for use in children when given as a brief course. 200 mg of danazol can be given three times daily for 5–7 days before and 2 days after the procedure.

C1-INH replacement therapy is the long-term prophylaxis of choice. Androgens are not

recommended for long-term use in children or adolescents (Wahn et al. 2012).

9.10 Conclusion

HAE is a life-threatening disease that can significantly inhibit quality of life and productivity. The average person with HAE has 6–20 attacks per year with each lasting 2–5 days. Obviously because of this amount of sick time, patients may miss work and school frequent enough to inhibit their education or promotion, and even maintaining employment may be a challenge. For this reason, "on demand therapy" for attacks is important. Self-therapy as early as possible during an attack will decrease the possibility of death and also limit morbidity and absenteeism. In those who have a compromised quality of life despite on demand therapy, prophylaxis should be considered. Androgens are inexpensive and cheap but have an adverse event profile that limit their use. For this reason, C1-INH use is considered the treatment of first choice for all ages. This is especially true now that a subcutaneous form of treatment is available. C1-INH is also the drug preferred for short-term prophylaxis, but for this indication IV C1-INH should be used. With present therapies most patients with HAE should be very well controlled and should feel free to vacation, travel on airplanes, and live a relatively normal life.

9.11 Research Needs

There are many aspects of the pathophysiology, presentation, and management of HAE that remain unknown. Below are several descriptions of future research endeavors that will elucidate better the underlying mechanisms of HAE pathophysiology and hopefully will lead to new, safer treatments and potentially even cures.

1. Multiple affected members of a single family can have drastically different clinical presentation, frequency, and severity of disease, despite carrying the same mutation. The exact contribution of factors that determine these outcomes are still unknown.
2. The role of the bradykinin receptor 1 has not been well described. How it affects HAE severity, spreads, and if it initiates the process still needs to be investigated further.
3. Only 40% of attacks occur secondary to a trigger. Determining what initiates the HAE attack when there is no obvious trigger may lead to other therapies for HAE.
4. Most swelling resolves in 2–3 days even without therapy. How and why the contact system self-regulates itself is unknown.
5. Attacks of HAE as noted above are limited using to a small area. We do not know why the angioedema is limited and does not spread systemically.
6. A phase 3 trial of a monoclonal antibody against kallikrein was shown to be effective with minimal adverse effects and 80% efficacy. If it is FDA approved, how will it affect how we manage HAE?
7. An oral kallikrein inhibitor just finished phase 1 studies and looks safe and effective for prophylaxis. Further research is needed to better define tolerance and efficacy.
8. Can gene therapy be implemented to reverse the specific deficiency in HAE patients? Thus far hepatic inflammation has limited this method.
9. U-HAE is by definition a subtype of HAE in which we do not understand the mechanism driving angioedema. Several mutations have been documented in association with C1INH-HAE and FXII-HAE, but none have yet been found in U-HAE patients. With the advent of more accessible and thorough deep genome sequencing methods, perhaps further insight into the pathophysiology of this little-understood HAE subtype will emerge and allow for the development of targeted therapies to improve morbidity and mortality among these patients.

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Allergic Contact Dermatitis

10

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Abstract

Contact dermatitis, generally defined as an inflammation of the skin, results from exposure to an external agent and is most often classified as irritant contact dermatitis (ICD) or allergic contact dermatitis (ACD) (Tan et al. Clin Dermatol 32(1):116–124, 2014). Considerable overlap exists between the two conditions in clinical, histological, and molecular presentation, while the two may also coexist (Taylor and Amado. Contact dermatitis and related conditions. http://www.clevelandclinicmeded.com/medicalpubs/diseasemanagement/dermatology/contact-dermatitis-and-related-conditions/. Accessed 25 Oct 2017, 2010; Lachapelle and Maibach 2012).

A thorough history and physical exam may lead to diagnosis in select cases such as nickel or poison ivy allergy; however, distinction between ACD and ICD is best accomplished through patch testing. Patch testing is an attempt to reproduce the eczematous reaction of ACD on a smaller scale by applying a collection of allergens under occlusion at non-irritating concentrations on intact skin of the affected patient (Mowad et al. J Am Acad Dermatol 74(6):1029–1054, 2016). The clinician must be mindful of the varying patch testing materials and methods, procedural details, patch test reading and scoring, and various patch testing side effects. In treating ACD, the primary focus is avoidance of the allergen with several strategies and supplementary treatment options discussed in the following chapter.

Keywords

Allergen · Allergic contact dermatitis · Irritant · Irritant contact dermatitis · Patch testing

10.1 Introduction

Contact dermatitis, generally defined as an inflammation of the skin, results from exposure to an external agent (Tan et al. 2014). The third most common presenting condition in a dermatologist's office, contact dermatitis consists of both irritant contact dermatitis (ICD) and allergic contact dermatitis (ACD). While the most severe irritants often result in characteristic skin necrosis with acute burning and stinging, the majority of irritants in the environment produce delayed, eczematous-like reactions that very closely resemble those of ACD (Marks and DeLeo 2016). In addition to the

similar clinical presentation, considerable overlap exists between the two conditions in histological and molecular presentation (Taylor and Amado 2010; Lachapelle and Maibach 2012). However, distinction between the two conditions is critical, as allergens should be generally avoided, while irritants can often be tolerated in small amounts. For this reason, this chapter will also include a discussion of closely related ICD.

10.1.1 Irritant Contact Dermatitis

In irritant contact dermatitis (ICD), the lesion results from a combination of exogenous and endogenous factors: the physiochemical property of the agent and activation of the innate immune system (Tan et al. 2014). Response to an irritant may occur to any individual with some variance; however, it is not to the degree of variation among individuals to allergens in ACD (Marks and deLeo 2016). Toxins most often exert their physical irritant properties on the lipid membranes of keratinocytes, which comprise 95% of epidermal cells; keratinocytes are also responsible for initiating the inflammation in ICD through the release of various cytokines (Marks and deLeo 2016; deJongh et al. 2007). While the profile of cytokine release depends on a number of variables, ICD is most often associated with IL-1α, IL-1β, IL-6, IL-8, TNF- α, GM-CSF, and IL-10 (anti-inflammatory cytokine) (Bonneville et al. 2004). In particular, IL-1α and TNF-α seem to be crucial in their ability to induce numerous secondary mediators required to recruit leukocytes to the damaged skin site (Lachapelle and Maibach 2012). Infiltration by nonresident skin cells, such as neutrophils and lymphocytes, produces much of the damage in ICD resulting from activation of the innate immune system (Marks and deLeo 2016).

In cases of the mild irritant that result in ICD following several applications, it is believed the toxin gradually damages the stratum corneum, resulting in delipidization and transepidermal water loss (Marks and deLeo 2016). This allows for exposure of viable keratinocytes to the mild irritant and activation of the innate immune system (Marks and deLeo 2016). In pure irritant contact dermatitis, prior sensitization is neither required nor induced.

10.1.2 Allergic Contact Dermatitis

Conversely, allergic contact dermatitis (ACD), a type IV hypersensitivity reaction, requires prior sensitization and can be separated into an initial *sensitization phase* and an *elicitation phase* with reexposure to the allergen (Mowad et al. 2016). An ACD response requires a genetic susceptibility to be sensitized to that allergen; however, 90% of the population can be sensitized to dinitrochlorobenzene, and 60% of Caucasians adults are allergic to Rhus oleoresin, the causative allergen in poison ivy dermatitis (Marks and DeLeo 2016).

In the sensitization phase, the unprocessed chemical allergen, known as a hapten, penetrates the lower levels of the epidermis, where it is engulfed by the Langerhans cell (Marks and deLeo 2016). The Langerhans cell chemically alters the hapten to form the allergen, which is presented on the surface of the cell (Marks and deLeo 2016).

In order for proper T-cell stimulation, Langerhans cells presenting the allergen must be fully activated via keratinocyte release of cytokines (Mowad et al. 2016). In particular, IL-1α, IL-1β, IL-8, IL-18, TNF- α, and granulocyte-macrophage colony-stimulating factor are critical (Mowad et al. 2016). Langerhans cells are then able to present the complex to naïve T cells in the regional lymph nodes and lymphatic system (Marks and deLeo 2016). The unique interaction of the antigen-presenting cells and T cells allows for clonal expansion of T cells capable of responding to the antigen. The T cells reenter circulation, and the exposed individual is now sensitized and capable of producing a substantial T-cell response when re exposed to the allergen (Marks and deLeo).

The elicitation phase begins with reexposure to the allergen; Langerhans cells uptake the hapten, chemically alter it, and present the antigen on its surface in a similar manner to the previous exposure (Marks and deLeo 2016). Dermal antigen-presenting cells activate sensitized CD4 T cells,

leading to an additional cascade of events promoting inflammation and recruitment of additional immune cells (Marks and deLeo 2016). While reactions are typically much more complex and depend on the particular allergen, CD8+ TC1 cells are most often responsible for direct damage to keratinocytes; CD4+ T cells help to promote activation of CD8 T cells in the skin and also further expansion of CD8 T cells in the lymphatic system (Lachapelle and Maibach 2012).

10.2 History/Clinical Assessment

Similar to diagnosis of most conditions, the history component of the patient encounter is critical; it is estimated history alone can lead to the correct diagnosis around 50% of the time when common allergens are involved (Ale and Maibach 2002). However, in cases of rare allergens, the experienced clinician will correctly diagnose the patient around 10% of the time (Fischer et al. 1989).

Clinicians should take a complete dermatological history and narrow the focus of the interview when ACD is suspected. It is important to obtain the history of present illness, past medical history with emphasis on dermatological diseases, a list of commonly encountered materials and chemicals, and an occupational history if warranted (Marks and deLeo 2016). A summary of helpful clinical information to obtain in the patient interview is listed in Table 1. Some of the easiest diagnoses occur when patients suspect a clear allergen (i.e., an overt allergen); however, much of the time patients are uneducated regarding the presenting symptoms in allergic contact dermatitis. This may be due to the many misconceptions of ACD. Contrary to popular belief, ACD lesions do not occur immediately, can appear over areas outside of allergen contact, are not less frequent with more expensive products, and can occur with products of different brand names but similar composition (Marks and deLeo 2016). The primary presenting complaint of ACD patients most often includes pruritus, while burning, stinging, pain, and/or disfigurement are also common associated symptoms (Tan et al. 2014).

Table 1 Clinical data for the assessment of ACD

History of exposure to the sensitizer (present or past)
Occupational exposure Complete job description and materials Personal protective measures at work (gloves, masks, barrier creams) Other materials present in working environment
Nonoccupational exposure Homework, hobbies Skin care products, nail and hair products, fragrances Pharmaceutical products (by prescription and over the counter) Personal protective measures. Use of gloves, detergents, etc. Jewelry and clothing
Indirect contact (skin care and other products of partner, fomites, etc.)
Seasonal related contact (plants and other environmental agents)
Photoexposure
Type of exposure: dose, frequency, site
Environmental conditions: humidity, temperature, occlusion, vapors, powders, mechanical, trauma, friction, etc.
Clinical characteristics of the present dermatitis Time of onset and characteristics of the initial lesions Dermatitis area corresponding to the exposure site Some morphologies suggest specific allergens Clinical course (caused or aggravated by the exposure) Time relationship to work. Effect of holidays and time-off work
History of previous dermatitis and other clinical events Past exogenous dermatitis with similar or different characteristics Previous patch testing Other endogenous skin diseases (psoriasis, atopic dermatitis, stasis, etc.)
Personal and family atopy and history of other family skin diseases

Adapted from Ale (2004)

The time course of the dermatitis is not always a reliable diagnostic tool, as the sensitization phase of ACD can take 10–14 days or up to years (Tan et al. 2014). In addition, with each subsequent exposure, the dermatitis may be more severe and rapid in onset. The exposure period for ICD is also variable, as it can present acutely after exposure to strong acids or bases or chronically after repeated exposure to one or multiple irritants (cumulative irritant dermatitis). ICD is characterized by the "decrescendo phenomenon," in which the reaction reaches its peak early

and then starts to heal (Lachapelle and Maibach 2012). In contrast, ACD is often characterized by the "crescendo phenomenon," in which the reaction peaks later and resolution occurs more slowly (Lachapelle and Maibach 2012).

Factors that lead to decreased barrier function of the skin increase susceptibility to ACD, such as "decreased environmental humidity, sweating, friction, heat, and exposure to skin irritants" (Mowad et al. 2016). Other factors to consider include a history of seasonal contact dermatitis; this is often suggestive of a photoallergic contact dermatitis, which is frequently reported to exacerbate following sun exposure in summer months (Tan et al. 2014). Critical aspects of the clinical history are discussed in further detail in the subsequent subsections.

Table 2 Sources of information on exposure and drawbacks of different sources

Product labeling
Labeling depends on regulatory policies that can vary in different countries
Substances used in the manufacturing process are usually not included
Substances added to raw materials may not be declared
Information from manufacturers or suppliers
Time consuming
Many times specialized information is not available
Depends on the manufacturer's cooperation
Product databases
Sometimes inadequate or information is not updated
Information from textbooks
Sometimes not updated
Chemical analysis of the products
Time consuming
Difficult to perform in complex products
Methodology is still not available or not validated for certain substances

Adapted from Ale (2004)

10.2.1 Overt Versus Covert

Based on the history of the patient, contact dermatitis can be considered overt or covert, with overt contact dermatitis resulting from exposure to a clear irritant/allergen (e.g., poison ivy or poison oak exposure in a patient presenting with a streaking, erythematous rash, and a history of recent hiking). Unfortunately, most cases of contact dermatitis presenting in health-care settings tend to be covert and require further investigation (Eiermann et al. 1982). Exposure to fragrances and preservatives, which are frequently implicated in ACD, can be encountered in numerous cosmetics, household products, and consumer goods and hence are difficult for the patient to identify as the causative irritant or allergen. Often the sources of exposure remain unknown, requiring further investigation of household and industrial products. Table 2 outlines sources of information on exposure and their drawbacks.

10.2.2 Medical History

Clinicians should obtain a complete dermatologic medical history and specifically inquire about atopic conditions present in the patient or family. ACD is associated with increased medical and family history of atopic diseases (Mortz et al. 2001). Individuals with a history of atopy, specifically atopic dermatitis, have higher rates of positive patch tests to allergens and are also believed to be more susceptible to ACD and ICD (Tan et al. 2014). Those with poorly controlled atopic dermatitis and chronic dermatitis are susceptible to weaker allergens (Mowad et al. 2016). In addition, a history of atopic conditions has an impact on the progression of disease, as ACD coupled with inhalant allergy has been associated with a poor prognosis in studies (Rystedt 1985).

10.2.3 Occupation/Hobbies

Contact dermatitis is estimated to comprise 95% of all occupational skin diseases (Taylor and Amado 2010) and represents the second most common occupationally related condition behind only musculoskeletal work-related injury (Cashman et al. 2012). The workplace is a frequent site of exposure, so a thorough occupational history is imperative. An occupational history should include a detailed job description and investigation of personal protective equipment, comparable reactions among coworkers, and resolution of symptoms

when away from work. Clinicians should also plan to contact the employer for a list of chemical exposures and the Material Safety Data Sheets (MSDS). According to recent studies on the incidence of airborne allergic contact dermatitis, almost all reported cases were occupational; the most common implicated occupational agents in order of prevalence include drugs; plants, natural resins, and wood allergens; plastics, rubber, and glue components; preservatives and other chemicals; and metals (Swinnen and Goossens 2013). Healthcare workers, cosmetologists, gardeners, florists, food industry workers, and other high-risk professions with a typical ACD clinical picture should raise high suspicion for occupational exposure.

In addition to occupational exposure, patient hobbies are also a considerable source of contact dermatitis. Clinicians should obtain a complete list of patient hobbies, especially those commonly implicated such as gardening and woodworking. In a similar manner to occupational history, clinicians should also question about any protective measures used by patients, progression of dermatitis, and resolution of symptoms away from a particular hobby.

10.3 Clinical Presentation and Differential Diagnosis

10.3.1 Presentation and Physical Exam

The physical should include an examination of the entire skin surface, as the location may often reveal the source of the potential allergen (Marks and deLeo 2016). Most acute ACD presents with erythema and papules, coalescent vesicles, bullae, and, in severe cases, oozing (Lachapelle and Maibach 2012). This early acute presentation is due to early inflammatory changes in the dermis with spongiosis resulting from rupture of the intercellular attachments (Ale and Maibach 2004). Contact allergy can even present with urticarial and dermal reactions in addition to the typical eczematous appearance (Marks and deLeo 2016). Although ICD occasionally presents with vesicles, their presence in the acute stage is more characteristic of ACD (Ale and Maibach 2004).

Several factors may result in the development of chronic ACD, including persistence of an allergen within the skin, continuous exposure to the causative allergen, mechanical trauma, and exposure to additional irritants or allergens (Ale and Maibach 2004). Chronic ACD most frequently presents as xerosis, scaling, lichenification with occasional fissuring, and possible vesiculation (Ale and Maibach 2004; Belsito 2003; Frosch and John 2011). Chronic ACD presentation is reflective of histological changes such as acanthosis, hyper- and parakeratosis, and cellular infiltration into the dermis (Ale and Maibach 2004). Subacute ACD most often presents with a combination of findings seen in acute and chronic ACD.

The pattern of distribution is the most important clinical clue in a patient presenting with ACD (Ale and Maibach 2004). Locations highly suggestive of ACD include unilateral distribution as well as lesions of the hands, feet, face, and eyelids (Mowad et al. 2016). The distribution of the ACD represents the areas of maximum contact with the allergen; however, it should be noted that severe dermatitis occasionally occurs at sites distant from the primary lesion due to transfer of the antigen by the hands of the individual (Ale and Maibach 2004). The location of a lesion can also affect the acute presentation; lesions of the eyelids, mouth and lips, vulva, penis, and scrotum are most often characterized by erythema and edema rather than vesiculation (Lachapelle and Maibach 2012).

Additional alternative presentations of contact allergy are described in Sect. 5.1

10.3.2 Differential Diagnosis

Differential diagnosis for contact dermatitis is broad and can include any eczematous eruption with some of the more common conditions listed in Table 3 (Lachapelle and Maibach 2012). Much of the difficulty exists in differentiation between ICD and ACD. Table 4 lists some common clinical characteristics of ICD and ACD; however, both conditions share similar clinical signs and symptoms and may also coexist. For example, allergens are more likely to present with pruritus,

Table 3 Differential diagnosis for contact dermatitis

Other types of eczema or dermatitis	Other dermatoses	Infections
Asteatotic eczema (dry skin)	Psoriasis	Cellulitis
Atopic dermatitis	Lupus erythematous	Impetigo
Dyshidrotic eczema	Parapsoriasis	Herpes simplex
Factitious dermatitis	Cutaneous T-cell lymphoma	Varicella zoster
Nummular eczema	Contact urticaria	Superficial fungal infections
Photoallergic contact dermatitis		
Phototoxicity		
Seborrheic dermatitis		
Stasis dermatitis with autoeczematization		
Sunburn		

Adapted from Taylor and Amado (2010)

whereas irritants may more likely present with burning and stinging (Marks and DeLeo 2016). ACD more frequently presents with an ill-defined lesion with extension beyond the site of allergen exposure, whereas ICD is often sharply demarcated and restricted to the site of the irritant (Lachapelle and Maibach 2012). In addition, intense vesiculation should raise suspicion for ACD, although it is often not present in chronic ACD (Lachapelle and Maibach 2012). Once the dermatitis becomes chronic, it becomes even more difficult to distinguish between the two, as both present with hyperkeratosis, lichenification, and fissuring (Marks and DeLeo 2016). While the histopathological processes differ in the acute disease, the chronic stages of the two diseases are similar, which might explain the greater resemblance of ACD and ICD in the later periods of disease.

Theoretically, ICD lesions should show histological evidence of an innate immunity reaction: polymorphic inflammatory infiltrate, apoptosis/necrosis of epidermal cells with resulting proliferation of keratinocytes, and no evidence of T-cell involvement, while an ACD lesion should demonstrate the clear presence of T-cell-induced inflammation (Lachapelle and Maibach 2012). However, histopathological examination has been an unreliable method to distinguish between the two conditions. While history, physical exam, and histopathological examination have proven inaccurate in differentiating eczematous conditions, patch testing often aids in diagnosis when performed by an experienced physician. However, clinicians must recognize that the dermatitis is occasionally mixed in the case of a positive patch test.

10.4 Common Irritants

Of the 85,000 plus chemicals present in our environment, many are potential irritants at sufficient concentrations (Taylor and Amado 2010). Some common irritants grouped by category are listed in Table 5. Some factors thought to affect an individual's susceptibility to irritants include age, sex, body site, atopy, and environmental factors (Tan et al. 2014). Reactivity to irritants tends to decrease with older age and increase in individuals with atopic dermatitis and in those living in colder climates with low ambient humidity (Tan et al. 2014). Atopic dermatitis predisposes patients to ICD due to an intrinsically lower threshold to inflammation, decreased barrier protection, and increased skin healing times (Chew and Maibach 2003). Women are more commonly diagnosed with ICD, but this is most likely due to increased exposure (Tan et al. 2014). However, the most important factors contributing to ICD remain the physiochemical properties of the irritant and degree of exposure experienced by the individual; strong acids and alkalis require very little exposure time, while weaker irritants require longer exposure times to induce clinically relevant dermatitis (Taylor and Amado 2010).

10.5 Common Allergens

In order for a chemical to be an allergen, it must be capable of eliciting a type IV hypersensitivity reaction. Frequently, allergens also possess irritant properties capable of producing

Table 4 Clinical differences between ICD and ACD

	ICD	ACD
Clinical course	Acute ICD may appear after first exposure with strong irritants	Sensitizing exposure required
	Lesions typically appear minutes to hours after first exposure, while delayed reactions are also seen	Clinical lesions appear after subsequent challenges with representation of the antigen to already-primed (memory) T cells Lesions usually appear 24–72 h after the last exposure to the causative agent, but they may develop as early as 5 h or as late as 7 days after exposure
	Characterized by "decrescendo phenomenon," in which lesions reach peak quickly and then start to heal	Characterized by the "crescendo phenomenon," in which the kinetics of resolution are slower
Morphology	Acute ICD includes erythema and edema and sometimes vesicles or bullae, oozing, and pustules necrosis and ulceration may also be seen with corrosive materials	Pustules, necrosis, or ulceration are rarely seen
	Subacute or chronic ICD is characterized by hyperkeratosis, fissuring, glazed, or scalded appearance of the skin	Intense vesiculation increases the suspicion of ACD, but it may not be present in chronic ACD
	Lesions are characteristically sharply circumscribed to the contact area. Usually there is absence of distant lesions, but sometimes dermatitis may be generalized depending on the nature of the exposure	Clinical lesions are stronger in the contact area, but their limits are usually ill defined. Dissemination of the dermatitis with distant lesions may occur
Symptoms	Symptoms of acute ICD are burning, stinging, pain, and soreness of the skin pruritus may be present in chronic ICD	Pruritus is the main symptom of ACD

Table adapted from Lachapelle and Maibach (2012)

ICD (Lachapelle and Maibach 2012). There is an estimated greater than 4350 chemicals that act as allergens with the most frequently positive patch tested allergens listed in Table 6. Table 7 organizes allergens into adhesives, corticosteroids, disinfectants, fragrances, medications, metals, personal care products, plants, rubber, systemic allergens, sunscreens, and textiles (Mowad et al. 2016).

Nickel comprises many of the ACD cases of the metal allergens and is the most common allergen worldwide (Lachapelle and Maibach 2012). It is present in various alloys including "electroplated metal, earrings, watches, buttons, zippers, rings, utensils, tools, instruments, batteries, machinery parts, working solutions of metal cutting fluids, and nickel plating for alloys, coins, pigments, orthopedic plates, keys, scissors, razors, spectacle frames, kitchenware, etc" (Lachapelle and Maibach 2012). In addition, cobalt is believed to be a major contributor to metal ACD and is used in a vast array of products; it is often used with nickel in metal plating and added to alloys in order to make more durable products such as dental implants, artificial joints, and other consumer metal products. In addition, cobalt is used in paints for glass and porcelain while also commonly found in makeup and hair dyes (Marks and DeLeo 2016). Concomitant sensitization, otherwise known as cosensitization, may occur with nickel and chromates; spot testing, discussed later in "Other Diagnostic Tests and Spot Tests," can help determine the significance of both nickel and cobalt to the patient's ACD.

Fragrances constitute a large portion of ACD cases and are present in a wide variety of cosmetics, household items, medicaments, and occupational items. Fragrances are frequently covert allergens due to the wide range of use in everyday products. *Myroxylon pereirae* resin, otherwise known as balsam of Peru, is frequently used as a fragrance in various cosmetics, household

Table 5 Common irritants by category

Category	Examples
Water and its additives	Salts and oxides of calcium, magnesium, and iron
Skin cleansers and industrial cleaning agents	Soaps, detergents, "waterless cleansers," and additives (sand, silica), sulfonated oils, wetting agents, emulsifiers, enzymes
Alkalis	Soap, soda, ammonia, potassium and sodium hydroxides, cement, lime, sodium silicate, trisodium phosphate, and various amines
Acids	Severe irritancy (caustic): sulfuric, hydrochloric, nitric, chromic, and hydrofluoric acids Moderate irritancy: acetic, oxalic, and salicylic acids
Oils	Cutting oils with various additives (water, emulsifiers, antioxidants, anticorrosive agents, preservatives, dyes, and perfumes) Lubricating and spindle oil
Organic solvents	White spirit, benzene, toluene, trichloroethylene, perchloroethylene, methylene chloride, chlorobenzene Methanol, ethanol, isopropanol, propylene glycol Ethyl acetate, acetone, methyl ethyl ketone, ethylene glycol monomethyl ether, nitroethane, turpentine, carbon disulfide Thinners (mixtures of alcohols, ketones, and toluene)
Oxidizing agents	Hydrogen peroxide, benzoyl peroxide, cyclohexanone peroxide, sodium hypochlorite
Reducing agents	Phenols, hydrazines, aldehydes, thioglycolates
Plants	Citrus peel and juice, flower bulbs, garlic, onion, pineapple, pelargonium, iris, cucumbers, buttercups, asparagus, mustard, barley, chicory, corn Various plants of the spurge family (Euphorbiaceae), Brassicaceae family (Cruciferae), and Ranunculaceae family
Animal products	Pancreatic enzymes, bodily secretions
Miscellaneous irritants	Alkyl tin compounds and penta-, tetra-, and trichlorophenols (wood preservatives) Bromine (in gasoline, agricultural chemicals, paper industry, flame retardant) Methylchloroisothiazolinone and methylisothiazolinone (irritant at high concentrations during production or misuse) Components of plastic processing (formaldehyde, phenol, cresol, styrene, di-isocyanates, acrylic monomers, diallyl phthalate, aliphatic and aromatic amines, epichlorohydrin) Metal polishes Fertilizers Propionic acid (preservative in animal feed) Rust-preventive products Paint removers (alkyl bromide) Acrolein, crotonaldehyde, ethylene oxide, mercuric salts, zinc chloride, chlorine

Adapted from Brasch et al. (2006)

items, and medications as well as flavor in "tobacco, drinks, pastries, cakes, wines, liquors, and spices" and is a common cause of ACD (Lachapelle and Maibach 2012).

Preservatives are also used in a wide variety of products, often making it difficult to determine the source of the allergen. Some of the common implicated preservative allergens include methylisothiazolinone(MI),formaldehyde, methylchloroisothiazolinone/methylisothiazolinone (MCI/MI), iodopropynyl butylcarbamate, and paraben mix (Mowad et al. 2016).

Medications are also a major contributor to ACD, with common implicated medications including neomycin and bacitracin. Neomycin is a broad-spectrum antibiotic that is frequently used in "topical creams, powders, ointments, and eye drops" (Lachapelle and Maibach 2012). Bacitracin is an antibiotic frequently used in wound care preparations in many topical creams, powders,

Table 6 Top 10 allergens based on positive patch test results from 2013 to 2014

Substance	n (# patients patch tested)	Positive reactions
Nickel sulfate hexahydrate, 2.5% pet	4850	975
Fragrance mix I, 8.0% pet	4858	576
MI, 0.2% aq	4857	527
Neomycin sulfate, 20.0% pet	4857	409
Cobalt (ii) chloride hexahydrate, 1.0% pet	4859	361
Bacitracin, 20.0% pet	4858	360
Myroxylon pereirae resin (balsam of Peru), 25.0% pet	4859	348
4-Phenylenediamine base, 1.0% pet	4853	342
Formaldehyde, 1.0% aq	4858	339
MCI/MI, 0.01% aq	4856	309

Adapted from DeKovan et al. (2017)

and ointments. Bacitracin most commonly results in ACD in patients with continued use on chronic wounds (Marks and DeLeo 2016). Patients with positive patch test reactions to bacitracin are often found to have positive reactions to neomycin sulfate as well. As both antibiotics are not chemically related, simultaneous sensitization to the two allergens is another example of concomitant sensitization (cosensitization) (Marks and DeLeo 2016). Other medication categories include corticosteroid allergens like tixocortol pivalate and budesonide (Mowad et al. 2016).

4-Phenylenediamine base (PPD) is used as a primary intermediate in hair dyes and textile dyes (Lachapelle and Maibach 2012). In addition, it is also used in "photographic developers, lithography, photocopying, oils, greases, gasoline, and as antioxidant/accelerator in the rubber and plastic industries" (Lachapelle and Maibach 2012). In addition, PPD may be present in low levels in pigments such as henna tattoos (Brancaccio et al. 2002).

Other common sources of allergens include rubber allergens such as carba, thiuram, and black rubber mixes and clothing allergens such as disperse blue 106 and melamine formaldehyde (Mowad et al. 2016).

10.5.1 Allergic Contact Dermatitis Syndrome

ACD is perhaps best understood when considered in three stages as "allergic contact dermatitis syndrome (ACDS)" (Lachapelle and Maibach 2012). The three steps are summarized below:

1. Stage 1: inflammation limited to the site of allergen application
2. Stage 2: area of inflammation extends beyond the area of application via lymphatic vessels
3. Stage 3: hematogenous spread of ACD or systemic reactivation of ACD

In stage 1 of ACDS, inflammation and its resulting signs/symptoms are limited to the site of allergen application. There are several morphological variants (purpuric ACD, lichenoid ACD, pigmented ACD, and lymphomatoid ACD) and topographical variants (ectopic ACD and airborne ACD), which may present in stage 1 of ACDS (Lachapelle and Maibach 2012). The purpuric variant presentation is most often seen on the lower legs and may be associated with an eczematous lesion, while the lichenoid variant is rare and will appear similar to oral lichen planus. Pigmented ACD is most common among the Mongoloids and appears a hyperpigmented area in the weeks following an acute episode of irritant or allergic contact dermatitis. Lymphomatoid ACD can only be distinguished from the other variants histopathologically (Lachapelle and Maibach 2012).

In addition to previously mentioned morphological variants, there are additional topographical variants that may convolute diagnosis (Lachapelle and Maibach 2012). "Ectopic" ACD and airborne ACD constitute the two most commonly seen topographical variants (Lachapelle and Maibach 2012). "Ectopic" ACD can occur via one of the two mechanisms: autotransfer or heterotransfer (Lachapelle and Maibach 2012). In autotransfer, the patient transfers the allergen from one part of his/her body to another, often via his/her hands. A common example is nail lacquer ACD, in which the individual transfers the nail lacquer via fingers to the eyelids or lateral neck. Heterotransfer, also referred to as connubial ACD, consort ACD, or

Table 7 American Contact Dermatitis Society (ACDS) core allergens grouped into main categories

Allergen	Allergen type
Core allergen panel I	
Nickel sulfate	M, S
Myroxylon pereirae	f, P, S
Fragrance mix I	f, P, S
Quaternium 15	P
Neomycin	m
Budesonide	m, c
Formaldehyde	P, S, T
Cobalt chloride	M, S
p-tert-Butylphenol formaldehyde resin	A
p-Phenylenediamine	P
Core allergen panel II	
Potassium dichromate	M, P, S
Carba mix	R, T
Thiuram mix	R, T
Diazolidinyl urea	P
Paraben mix	P, S
Black rubber mix	R, T
Imidazolidinyl urea	P
Mercapto mix	R, T
Methylchloroisothiazolinone/ methylisothiazolinone	P, R
Tixocortol-21-pivalate	m, c
Core allergen panel III	
Mercaptobenzothiazole	R, T
Colophony	A, P
Epoxy resin	A
Ethylenediamine	R, S, T
Wool alcohol	P
Benzocaine	m
Bacitracin	m
Mixed dialkyl thioureas	A, R, T
Fragrance mix II	f, P, S
Benzophenone-3	P, Su
Core allergen panel IV	
Disperse blue 106	T
Disperse blue 124	T
Gold sodium thiosulfate	M
Ethyl acrylate	A, P
Compositae mix	d, S
Sesquiterpene lactone mix	f, S
DMDM hydantoin	P
Tosylamide formaldehyde resin	P, S
Methyl methacrylate	A, P
Cinnamic aldehyde	f, P, S
Core allergen panel V	
Propylene glycol	P, S
Cetyl stearyl alcohol	P
2-Bromo-2-nitropropane-1,3-diol	P
Sorbitan sesquioleate	P, S
Cocamidopropyl betaine	P
Glyceryl thioglycolate	P
Ethyleneurea melamine formaldehyde	T
Iodopropynyl butylcarbamate	P
Chloroxylenol (PCMX)	P
Glutaraldehyde	d, P
Core allergen panel VI	
Ethyl cyanoacrylate	A, P
Benzyl alcohol	f, P, S
Benzalkonium chloride	d, P
Methyldibromoglutaronitrile	P
Propolis	P
n,n-Diphenylguanidine	R, T
Lanolin alcohol (Amerchol 101)	P
Triethanolamine	P
Amidoamine	P
Desoximethasone	m, c
Core allergen panel VII	
Triamcinolone	m, c
Clobetasol-17- propionate	m, c
Hydrocortisone-17-butyrate	m, c
4-Chloro-3-cresol (PCMC)	P
Benzophenone-4	P, su
Chlorhexidine digluconate	d, P
Ylang ylang	f, P
Phenoxyethanol	P
Sorbic acid	P, S
2, 6-Ditert-butyl-4-cresol (BHT)	P, S
Core allergen panel VIII	
Disperse orange 3	T
3-(Dimethylamino)propylamine (DMAPA)	P
Oleamidopropyl dimethylamine	P
Dl alpha tocopherol	P, S
Cocamide DEA	P
Lidocaine	m
Dibucaine	m

(*continued*)

Table 7 (continued)

Allergen	Allergen type
Jasmine absolute	f, P
Tea tree oil	f, P
Triclosan	P

Adapted from Mowad et al. (2016)
A adhesive, *c* corticosteroid, *d* disinfectant, *f* fragrance, *m* medication, *M* metal, *P* personal care product, *pl* plant, *R* rubber, *S* systemic (ingested) allergen, *su* sunscreen, *T* textile. This table is not meant to be an exhaustive grouping of allergens into various categories but rather to give examples of some ways to consider allergen function for patient education

ACD per procurationem, occurs when a partner transfers the allergen to the patient. Airborne ACD occurs when allergens are transferred via air as dust particles, vapors, or gases. In the majority of cases, airborne ACD presents with ill-defined lesions most severe over the face and neck; however, there is typically no spared area (Lachapelle and Maibach 2012).

In stage 2 of ACDS, dissemination of the allergen extends beyond the primary site via lymphatic vessels (Lachapelle and Maibach 2012). Lesions at this stage commonly appear as erythematous or erythematovesicular plaques with ill-defined margins. The dermatitis at the primary site is typically most pronounced, with eventual progressive fading of the lesion from the primary lesion outward. However, the extending dermatitis is occasionally more pronounced than the primary lesion, especially with nonsteroidal anti-inflammatory drugs and antibiotics. In addition, there are clinical variants in regional dissemination such as "True erythema multiforme lesions," "Erythema multiforme-like lesions," and "urticarial papular and plaque eruption," which was first described by Gooon and Goh (2011). In the "True erythema multiforme lesions" variant, the individual exhibits both clinical and histopathological signs of erythema multiforme with the most common implicated agents including "woods and plants (*Dalbergia nigra*, pao ferro, *Primula obconica*, etc.), metals (nickel and cobalt), paraphenylenediamine, and epoxy resin" (Lachapelle and Maibach 2012). Conversely, individuals with the "Erythema multiforme-like lesions" variant display clinical signs of erythema multiforme but histopathologic evidence of eczematous dermatitis (Goon and Goh 2011).

Stage 3 of ACDS can be divided into two distinct parts: "a generalized dissemination of skin lesions via blood vessels" and "systemic reactivation of allergic contact dermatitis" (Lachapelle and Maibach 2012).

In stage 3A, the allergen is able to disseminate to more distant skin sites, where it provokes secondary or "ide" reactions (Lachapelle and Maibach 2012). The reactions most often appear symmetrically erythematous, occasionally slightly elevated plaques, and rarely vesicular or squamous. While lymphatic and hematogenous dissemination of allergens are discussed separately, both stages 2 and 3A of ACDS may present simultaneously. Lastly, allergens that have been most closely tied to stage 3A include "paraphenylenediamine, cobalt, nickel, mercury, mercuric chloride, corticosteroids, and nonsteroidal anti-inflammatory agents" (Lachapelle and Maibach 2012).

Stage 3B occurs in a series of events that leads to systemic reactivation of ACD. A first event of ACD to a well-defined allergen occurs weeks to months before second contact with the allergen (Lachapelle and Maibach 2012). Often, clinical symptoms have resolved when contact with allergen ceases, and the patient may not recall the event. In a second episode, the allergen is often introduced systemically via ingestion, inhalation, or injection resulting in a generalized rash in a symmetrical pattern comparable to stage 3A of ACDS. In the second episode, it is possible that the responsible allergen is different from that in the first episode of ACD: the allergen can be chemically related to the initial allergen, or both allergens may be chemically different and undergo transformation into a common molecule. While stage 3A and 3B present similarly, stage 3B is distinct in that no contact with the skin allergen occurs in the second episode (Lachapelle and Maibach 2012).

10.5.2 Systemic Contact Dermatitis

When a patient is exposed to a previously sensitized topical allergen via a non-skin surface route (ingestion, parenteral, suppository, implanted, inhaled), it

is possible to develop systemic contact dermatitis (SCD) (Veien 2011). Systemic contact dermatitis presentation varies among patients with some presenting with oral, anogenital, and flexural dermatitis, while others present with a generalized widespread dermatitis, vasculitic lesions, or vesicular hand dermatitis. In addition, individuals may have a reactivation of a previously positive patch test site or previous dermatitis (Veien 2011). Patients may have additional systemic symptoms like fever, chest pain, urticaria, and other sepsis-like symptoms. Commonly implicated allergens include medications (e.g., antibiotics, corticosteroids, antiepileptics, antifungals), implants with metal parts (e.g., mercury, gold, nickel, chrome, cobalt, and titanium), plants (e.g., chamomile, chrysanthemum, as well as other members of the Compositae family), and produce (e.g., mango, garlic, shiitake mushrooms) (Veien 2011).

SCD is important to consider in patients that are not improving with cutaneous avoidance of allergens (Mowad et al. 2016). In patients with true SCD, dietary avoidance of the allergen may be beneficial found patients with SCD to react to nickel in dose-dependent manner, and it has been suggested that SCD patients allergic to nickel, cobalt, or chromium adhere to a point-based diet due to the common presence of the allergens in food.

10.6 Patch Testing

10.6.1 General Principles

Patch testing is an attempt to reproduce the eczematous reaction of ACD on a smaller scale by applying a collection of allergens under occlusion on intact skin of the affected patient (Mowad et al. 2016). Possible allergens are applied at non-irritating concentrations in order to help distinguish between true allergic reactions and irritant reactions. Some general indications for patch testing include a clinical picture suggestive of ACD (distribution, suggestive history, high-risk occupation), dermatitis with unclear etiology, worsening of a previously controlled dermatitis, and dermatitis unresponsive to treatment (Mowad et al. 2016). Others advocate for patch testing in all patients with chronic or nonresponsive eczematous dermatitis, especially those with hand and foot dermatitis (irritant, dyshidrotic, hyperkeratotic, and psoriasis and pustulosis palmaris et plantaris), stasis dermatitis, atopic dermatitis, and nummular eczema (Giordano-Labadie et al. 1999; Yiannias et al. 1998). In addition, patch testing may also be performed in individuals with unclassified eczema, eczematous psoriasis, essential pruritus, otitis externa, and suspected drug eruptions (Devos et al. 2004; Maibach and Epstein 1983; Roenigk et al. 1998; Barbaud et al. 1998). As previously mentioned, clinical history may lead the experienced clinician to the correct diagnosis for common allergens such as nickel. It should be noted that patch testing should not be performed in patients with history suggestive of poison ivy or poison oak-induced ACD, as sensitivity to the particular allergens is nearly universal, and patch testing may actually induce sensitization (Marks and deLeo 2016). However, patch testing should be performed in any patient with suspected contact dermatitis to uncover any allergens, which are not immediately evident from the patient history.

Before patch testing, patients should refrain from exposure to suspected allergens and discontinue use of personal care products in the areas of dermatitis (Marks and deLeo 2016). For example, patients with hand dermatitis should stop using hand lotion or any topical medication used to alleviate the dermatitis. Patients with suspected occupationally related dermatitis may need to momentarily avoid the workplace, while patients with suspected photoallergic contact dermatitis should attempt to minimize sun exposure (Marks and deLeo 2016).

10.6.2 Materials

Patch testing can be performed using antigens in several forms: antigens supplied in vehicles to eventually be placed in chamber or non-chamber units or antigens already contained in a polymer base, known as the Thin-Layer Rapid Use Epicutaneous (TRUE) Test (Marks and DeLeo 2016). Non-chamber units are an older means of patch testing and have largely been replaced by

the TRUE Test and chamber units. Some of the popular existing patch test chambers on the market include Finn Chambers, TROLAB® Patch Test Devices, plastic square chambers, IQ Square Chambers Chemotechnique, van der Bend New Square Chamber, Haye's Test (New Generation) Square chamber, and allergEAZE Chambers Brial (Lachapelle and Maibach 2012). In addition, reinforcement tape may be applied to these chambers, which is particularly helpful in hot climates.

Standardized allergens used in patch tests are manufactured by several companies and can be considered chemically defined and relatively pure (Lachapelle and Maibach 2012). The majority of allergens are dispersed into a white petroleum vehicle, while those that are unstable in petroleum must be dispersed in aqueous solutions. In deciding upon allergen concentration, the standard of practice is to use the highest concentration that does not cause irritant reactions in groups of patients enrolled in prospective studies. Allergens should be stored in dark, cool environment, while nonmarketed allergens should be prepared freshly (Lachapelle and Maibach 2012).

Due to variability among allergens and desire for a more standardized system for testing allergens, the TRUE Test was developed with emphasis on homogenous concentration of allergens and optimal delivery of the allergen to the skin (Andersen 2002). Allergens are incorporated into hydrophilic gels with the excipients (hydroxypropyl, cellulose, and polyvinylpyrrolidone) adapted to each allergen (Lachapelle and Maibach 2012). The gel is coated on a polyester sheet, and the strips are present in airtight aluminum pouches (Lachapelle and Maibach 2012). Perspiration and transepidermal water loss help promote rehydration of the dried gel layer and release of allergens into the skin (Andersen 2002). The TRUE Test includes 35 allergens contained in 3 different panels listed in Table 8 (Lachapelle and Maibach 2012). The main advantages of the TRUE Test include little preparation time, minimization of user preparation error, greater allergen consistency, and more accurate and reproducible results (Lachapelle and Maibach 2012). However, the TRUE Test is limited in the number of allergens and associated with a higher cost as compared to conventional patch testing (Lachapelle and Maibach 2012).

As previously mentioned, the TRUE Test only contains 35 allergens and 1 control and is estimated to miss 27% of potential allergens (Fransway et al. 2013; Warshaw et al. 2013). In order to expand the coverage of allergens, several series ordered from different manufacturing companies may be added including, but not limited to "bakery series, corticosteroid series, cosmetic series, epoxy resin series, hairdressing series, isocyanate series, metal series, (meth)acrylate series, plastics and glue series, rubber additives series, and textile dyes and finish series" (Lachapelle and Maibach 2012). See Table 9 for an example of a patch test order sheet.

Table 8 Standard TRUE Test series

Panel 1.3	Panel 2.3	Panel 3.3
Nickel sulfate	*p-tert*-Butylphenol formaldehyde resin	Diazolidinyl urea
Wool alcohols	Epoxy resin	Quinoline mix
Neomycin sulfate	Carba mix	Tixocortol-21-pivalate
Potassium sulfate	Black rubber mix	Gold sodium thiosulfate
Caine mix	Cl + Me-isothiazolinone (MCI/MI)	Imidazolidinyl urea
Fragrance mix	Quaternium-15	Budesonide
Colophony	Mercaptobenzothiazole	Hydrocortisone-17-butyrate
Paraben mix	*p*-Phenylenediamine	Mercaptobenzothiazole
Negative control	Formaldehyde (*N*-hydroxymethyl succinimide)	Bacitracin
Balsam of Peru	Mercapto mix	Parthenolide
Ethylenediamine dihydrochloride	Thimerosal (thiomersal)	Disperse blue 106
Cobalt dichloride	Thiuram mix	Bronopol

Adapted from Lachapelle (2012)

Table 9 Example of patch test order form

Patch test order sheet
☐ (70) North American Standard Series
☐ ( ) Topical Medication
☐ ( ) Skin Care/Cosmetics
☐ (16) Antibiotic/Antimycotics
☐ (19) Baking
☐ (09) Corticosteroids
☐ (24) Cosmetics
☐ (15) Dental Adhesive/Acrylates
☐ (31) Dental screen
☐ (06) Disinfectants
☐ (29) Drugs
☐ (15) Epoxy
☐ (48) Fragrances/Flavors
☐ (23) Food Additives
☐ (15) Hairdressing
☐ (06) Isocyanates
☐ (14) Medicaments
☐ (54) Metals, plus
☐ (11) Metals, Simple
☐ (32) Metal Implants
☐ (13) Nail Acrylates
☐ (35) Oil and Cooling Fluids
☐ (20) Ophthalmics
☐ (16) Photography Chemicals
☐ (17) Plants
☐ (25) Plastic and Glues
☐ (25) Preservatives
☐ (24) Printing Acrylates
☐ (26) Rubber
☐ (23) Shoe
☐ (33) Textiles, Colors, and Finishes
☐ (31/62) Photo Allergens (w/uva) *or* (w/o uva)
☐ (21/42) Sunscreen (w/uva) *or* (w/o uva)
☐ Light Testing
☐ Immediate Testing

10.6.3 Procedure

It is suggested to provide patients with written material regarding the testing procedure basics; however video is often the most effective tool in patient education when the content is procedural, as in patch testing education (Mowad et al. 2016). Perhaps the best approach in patch testing is to start with a standardized allergen panel and expand tested allergens as indicated by history. As previously mentioned, clinicians may use testing material in which the allergen is already integrated, like the TRUE Test, or use chamber units in which the clinician applies each allergen to a separate chamber unit (Lachapelle and Maibach 2012). Patch test units should be reinforced with hypoallergenic tape and remain occluded until the first reading at 48 h; clinicians should instruct patients to refrain from tampering with patch tests and educate on common side effects such as general discomfort and pruritus. Common and rare side effects are discussed more extensively in Subsection 6.7.

There should be an additional delayed reading from 72 to 168 h after application of the allergens as an additional measure to account for any delayed reactions and further distinguish between allergic and irritant contact dermatitis; transient ICD reactions sometimes occur, while ACD reactions are more likely to persist to the delayed reading (Uter et al. 1996; Mowad et al. 2016). The preferred site for patch testing is the upper back, while the outer aspect of the upper arm is considered acceptable when retesting (Lachapelle and Maibach 2012). Other sites including the lower back and volar forearm have been associated with increased incidence of false negatives. Different scoring systems for patch test reactions exist; however, perhaps the clearest system is that suggested by Wilkinson et al. (1970). The authors developed a scoring system with seven different categories, which includes a negative reaction (−), irritant reaction (IR), non-tested area (NT), and four possible positive reaction categories based on the severity [doubtful (?+), weak (+), strong (++), extreme (+++)] (Wilkinson et al. 1970). Positive reactions are scored on the appearance of the reaction: erythematous, edematous or vesicular, and bullous or ulcerative (Wilkinson et al. 1970). Further details regarding the previously mentioned scoring system are included in Table 10.

10.6.4 Reading and Scoring Patch Tests

The size of the reaction is most often limited to the size of the patch chamber; however, there are circumstances in which the allergen may extend beyond the patch test unit (Lachapelle and Maibach 2012). When non-chamber test units are used, the reaction more often extends into neighboring areas, making patch test interpretation more difficult (Lachapelle and Maibach 2012).

Table 10 Scoring of patch reactions according to Wilkinson et al.

Score	Interpretation
–	Negative reaction
?+	Doubtful reaction[a]; faint erythema only
+	Weak (nonvesicular) reaction[b]; erythema, slight infiltration
++	Strong (edematous or vesicular) reaction; erythema, infiltration, vesicles
+++	Extreme (bullous or ulcerative)[c]
IR	Irritant reactions of different types
NT	Not tested

Reading and scoring have to be repeated at each individual visit to check the progression or regression of the reaction (day 2, day 4, day 6, or day 7)
Adapted from Lachapelle (2012)
[a]?+ is a questionable faint or macular (nonpalpable) erythema and is not interpreted as a proven allergic reaction
[b]+ is a palpable erythema, suggestive of a slight edematous reaction
[c]From coalescing vesicles

Often, allergic reactions may appear ring or square shaped, conforming to the edges of the patch chamber unit; Lachapelle and Maibach (2012) uses the term "edge effect" to describe this phenomenon. It is likely that the allergens accumulate at the edges of the patch test chamber unit, while the pressure of the unit itself might also explain the appearance of the reaction (Lachapelle and Maibach 2012; Fyad et al. 1987). In addition, the "edge effect" has also been reported when using the TRUE Test (Lachapelle and Maibach 2012). Corticosteroids often produce a special type of "edge effect," in which the center of the reaction is whiter in color. This is possibly due to the vasoconstrictive effect of the corticosteroid in the center where penetration of the allergen is the greatest (Lachapelle and Maibach 2012).

When testing with allergens of the standard or additional series, a doubtful reaction (?+) can be attributed to the true allergenic nature of the reaction (Lachapelle and Maibach 2012). However, when testing less common, a doubtful reaction is more difficult to interpret. In order to obtain a more concrete answer, Lachapelle and Maibach (2012) recommends employing the following strategy:

(a) Check the patch test reproducibility by repeating the test with/without serial dilutions of the suspected allergen (dose/concentration relationship).
(b) Repeat test in control subjects.
(c) Conduct additional testing including possible open tests, semi-open tests, and ROATs.
(d) Consider serial dilution testing; allergic responses often reproduce marginal irritant reaction at lower concentrations (especially in chromates, parabens, fragrance mix, and formaldehyde do so frequently).

It is important to note that when reproducing the same patch test in a different area, most discrepancies occur when the initial reading is doubtful (?+) or weak (+) (Lachapelle and Maibach 1989).

With the advent of more standardized patch testing techniques, irritant patch test reactions have become more rare (Lachapelle and Maibach 2012). As in normal ICD reactions, the appearance of irritant patch test reactions varies with the concentration and type of irritant (Foussereau et al. 1982). Classic irritant patch test reactions are described below.

In irritant reactions in which erythema is predominant, the edges of the reaction will usually be sharply demarcated and will closely resemble the shape of the patch test unit (Lachapelle and Maibach 2012). Erythematous irritant reactions are rarely edematous but may occasionally be discretely scaly. Allergens from the standard series that are commonly implicated in marginal irritant reactions include fragrance mix, thiuram mix, and paraben mix (Lachapelle and Maibach 2012).

Purpuric irritant reactions are common with cobalt chloride and may also be observed with paraphenylenediamine, IPPD, and some drugs (Lachapelle and Maibach 2012).

Blistering or bullous irritant reactions may occur after testing with nondiluted caustic products such as "gasoline, kerosene, and turpentine," while patch tests with quaternary ammonium salts may blister even when low concentrations of the allergen are used (Lachapelle and Maibach 2012).

The most severe irritant reactions have a characteristic necrotic or escharotic appearance (Lachapelle and Maibach 2012). Caustic soda,

acetone, and kerosene have been reported to result in such reactions (Lachapelle and Maibach 2012).

Pustular irritant reactions are sometimes observed following bullous reactions (Lachapelle and Maibach 2012). However, less common is a bacterial superinfection, most often with *Staphylococcus aureus*, in which case there will be a large pustule at the site of application. Occasionally, metallic salts like chromate, cobalt, nickel, copper, and mercury may produce uniformly distributed small pustules over an erythematous background in atopic patients. This reaction can be exclusively irritant in nature or irritant superimposed on an ACD reaction (Lachapelle and Maibach 2012).

"Soap or shampoo effect" reactions occur, as the name indicates, in response to many soaps and detergents (Lachapelle and Maibach 2012). The skin appears erythematous and often shiny and wrinkled while also usually lacking vesicles or any reported pruritus. Proper dilution techniques have helped reduce "soap and shampoo effect" reactions (Lachapelle and Maibach 2012).

10.6.5 Additional Considerations

It is important to perform patch tests on intact, clean skin; performing patch testing on a patient with recent history of extensive sun exposure can result in increased rates of false-negative reactions, while patch testing on a patient with severe atopic dermatitis is associated with increased rates of false-positive reactions (Tan et al. 2014). Before applying test strips, it is recommended that excess hair and sebum be removed. Patients should avoid wetting the test site, including refraining from showers over the patch test area, excessive exercise, and irradiation during the 48-h testing period (Tan et al. 2014). Several medications can possibly interfere with patch testing, including corticosteroids, antihistamines, and immunomodulators (Lachapelle and Maibach 2012). In addition, patients should be informed about typical itch and discomfort experienced with patch testing. Although there is no evidence that small amounts of allergen can cause deleterious effects on the fetus, physicians should refrain from patch testing on pregnant patients for medicolegal reasons. Most physicians agree that patch testing children is safe and should be performed with the same allergen concentration in adult patch tests (Lachapelle and Maibach 2012).

10.6.6 Clinical Relevance

In order to diagnose allergic contact dermatitis, a patient must both demonstrate clinically relevant allergens and also display sensitivity to one or several allergens through positive patch testing (Lachapelle and Maibach 2012). Diagnosis is frequently difficult as patch testing interpretation is subjective and without a universal scale used by dermatologists. However, evaluating the clinical relevance of a positive patch test may be the most challenging part in diagnosis. Patch testing is conducted according to relevant clinical history; however, the process in evaluating ACD is bidirectional, with positive patch test results directing the clinician toward further questioning (Ale and Maibach 2004).

In assessing clinical relevance, it is helpful to assess both the "current" and "past" relevance of the allergen. A patient exhibits current and/or past relevance when a positive patch tests explains current and/or past clinical disease, respectively. However, it is often difficult to discriminate between past and current relevance because recurrent but discontinuous contact with an allergen frequently occurs (Lachapelle 1997). Lachapelle (1997) developed a scoring system in order to ascertain the allergen relevance score, ranging from 0 to 3, in which 0 = not traced, 1 = doubtful, 2 = possible, and 3 = likely. It should be noted, however, that clinical relevance is often unattainable and frequently complicated with multiple possible allergens and overlying irritants.

Relevance scores are improved when a comprehensive view of the patient's environment is obtained. This should include reassessment of a patient's clinical history, a possible workplace visit, assessment of intrinsic sensitization potential of the substance (data from predictive tests, data from epidemiological studies, structure/activity analysis), additional physiochemical properties of the substance (solvent properties,

hygroscopicity, substantively, wash and rub, resistance to removal), assessment of exposure parameters (route of exposure, specific site of contact and surface area, dose, duration, frequency of exposure, and simultaneous exposure factors: humidity, occlusion, temperature, mechanical trauma), cross-reacting and concomitant allergens, information from lists of allergens, databases, product's manufacturer, and chemical analysis of suspected products (Lachapelle and Maibach 2012). While history of exposure to the sensitizing allergen is essential for diagnosis, it is not sufficient to establish complete chemical relevance. Clinicians should also establish the "existence of a temporal relationship between the exposure and clinical course of the dermatitis" and a "correspondence between the exposure and clinical pattern (anatomic distribution) of the dermatitis" (Lachapelle and Maibach 2012).

10.6.7 Patch Test Side Effects

Side effects in patch testing are rare with the benefit of testing greatly outweighing the risk of adverse effects in suspected patients. Patch test side effects can be generally divided into common, expected side effects such as pruritus and tape irritation and more rare, serious side effects such as sensitization, scarring, infections, and anaphylaxis (summarized in Table 11) (Mowad et al. 2016). The following section details a number of side effects. Patch test sensitization and excited skin syndrome are described in Subsections 6.13 and 6.14, respectively.

Pruritus is a normal reaction to a positive patch test and should not be considered a side effect (Mowad et al. 2016). Pruritus is most often self-limited but can be treated with a short course of topical corticosteroid in more severe cases (Mowad et al. 2016).

The most common side effect is an irritant reaction to the occlusion tape, often presenting with itching and discomfort (Mowad et al. 2016). While the reaction is almost always self-limited, occasionally the reaction continues to worsen following removal of tape. In this case, clinicians should consider a possible ACD reaction to a component of the tape (Mowad et al. 2016).

Table 11 Potential patch testing side effects

Common side effects	Rare
Itching at site of patch testing	Anaphylaxis
Pruritus	Excited skin syndrome (angry back syndrome)
Tape irritation	Infection
	Koebnerization
	Persistent patch test reaction
	Scarring
	Sensitization

Adapted from Mowad et al. (2016)

Infrequently, an "ectopic" flare of dermatitis occurs, in which a positive patch test results in specific flare at a location of an existing or pre-existing dermatitis. Clinicians can reduce the incidence of this adverse effect by refraining from testing patients with current active dermatitis (Lachapelle and Maibach 2012).

Pressure effect occurs due to physical pressure from solid materials, presenting as a red, depressed mark (Lachapelle and Maibach 2012). The imprinted skin may result from either the rings of the patch test chamber or allergens in the solid form. It should be noted that pressure effect is distinct from a chemically induced "edge effect" of the allergen (Lachapelle and Maibach 2012).

Koebner phenomenon most often occurs in patients with active psoriasis or lichen planus when there is reproduction of these dermatoses at the patch site in weeks following a positive patch test reaction (Weiss et al. 2002). The use of topical corticosteroids usually results in quick resolution of the lesion (Lachapelle and Maibach 2012). Rarely, Koebner phenomenon may present in patients with lupus erythematous and lymphocytic infiltration of the skin (Deleuran et al. 2000; Bahillo-Monné et al. 2007). Avoiding testing in patients with active dermatitis can also help reduce this adverse effect.

Hyperpigmentation, although rare, most frequently occurs in darker pigmented individuals and usually fades with topical corticosteroid use (Lachapelle and Maibach 2012). Hyperpigmentation may also occur following exposure of

patch test sites, especially those with fragrance allergens, to UV light. In addition, hypopigmentation may occur at positive patch test sites; however, it is most often a more transient side effect (Lachapelle and Maibach 2012).

Necrosis, scarring, and keloids may occur with irresponsible clinician testing with strong irritants such as acids, alkalis, or chemicals of unknown composition (Lachapelle and Maibach 2012). Scarring is most likely to occur when there are severe bullous reactions to allergens (Mowad et al. 2016). With good practice, such side effects are extremely rare (Lachapelle and Maibach 2012).

Anaphylactoid reactions are extremely rare, often occurring within 30 min of application of patch test allergens (Lachapelle and Maibach 2012). The most commonly implicated agent is the hair bleach, ammonium persulfate, while neomycin and bacitracin have also been reported (Hoekstra et al. 2012; Lachapelle 2012).

Infections are also a rare side effect of patch testing and most often present with an overlying impetigo from *Staphylococcus aureus* or other bacterial agents (Mowad et al. 2016). In addition, there have been reported cases of herpes simplex virus reactivation within patch test sites (Mowad et al. 2016).

A persistent positive patch test reaction, another rare side effect, should be suspected when a reaction begins within the first week of allergen application and persists, sometimes greater than 30 days after testing (Mowad et al. 2016). While the mechanism is not known, it is hypothesized that dermal antigen-presenting cells sequester the agent within the skin, resulting in persistent inflammation (Sperber et al. 2003). Gold in the form of gold chloride or sodium gold thiosulfate is the most commonly reported allergen responsible for persistent positive patch test reactions (Sperber et al. 2003; Aro et al. 1993; Andersen and Jensen 2007).

10.6.8 Sensitivity, Specificity, and Predictive Value

Clinicians frequently overlook statistical principles inherent in diagnostic testing. The sensitivity is the proportion of individuals with a positive test result of all of those with disease, while the specificity measures the proportion with a negative test result of all of those without disease. Positive predictive value indicates what percentage of all positive test results includes those with true disease. The proportion of individuals with a true negative test out of all negative tests is known as the negative predictive value.

There have been few studies in which patch testing is performed in healthy patients, making data on previously mentioned statistical variables rare. Nethercott and Holness (1989) tested 1032 patients with two different standard patch test series, the ICDRG and the NACDG, using Finn Chambers or Al-Test patches. The authors considered false-positive test results to be those in which the patients tested positive for allergens but had no clinical evidence of disease, while those with negative results who subsequently tested positive to allergens were considered false-negative results. The authors found sensitivity, specificity, positive predictive value, and negative predictive value numbers for the ICDRG and NACDG to be 0.68, 0.77, 0.66, and 0.79 and 0.77, 0.71, 0.66, and 0.79, respectively. While patch testing remains the gold standard for ACD, the subjectivity and the technical component of testing remains a common source of error.

10.6.9 False Positives

False-positive reactions to patch testing occur in the absence of a true contact allergy and are mainly due to technical error in the patch test. Some common errors include elevated test substance concentration; impure or contaminated test substance; adverse reaction to the vehicle (solvents more common than petroleum), adhesive tape, solid test material, or patch itself; and current or recent dermatitis at the test site (excited skin syndrome) (Lachapelle and Maibach 2012). In order to minimize false-positive test reactions, clinicians should use manufactured allergens as opposed to allergens prepared at the test site to avoid unevenly distributed test substance or crystals in the vehicle (Lachapelle and Maibach 2012).

Excited skin syndrome is discussed in further detail below.

10.6.10 False Negatives

False-negative reactions are negative reactions when there is a true presence of contact allergy. Like false-positive reactions, many false-negative reactions often occur due to technical error including insufficient penetration of the allergen, a prematurely read patch test reading, a test site previously exposed to UV light or treated with topical corticosteroids, patient systemic corticosteroid or immunomodulator treatment, allergen degraded or in non-active form, and compound allergy (Lachapelle and Maibach 2012). Insufficient penetration of the allergen may be due to "too low a test concentration for a defined allergen, the test substance is not released from the vehicle or retained by the filter paper, insufficient amount of test preparation applied, insufficient occlusion, duration of contact too brief (the test strip has fallen off or slipped), or the test was not applied to the recommended site (the upper back)" (Lachapelle and Maibach 2012). Clinicians should follow recommended testing duration and reading times in order to avoid missing delayed reactions, which are more common with certain allergens such as neomycin and corticosteroids. It is also important to ensure sufficient oxidation for certain allergens such as oil of turpentine, rosin compounds, and d-limonene (Lachapelle and Maibach 2012). Compound allergy is discussed in further detail below.

10.6.11 Compound Allergy

Technically not a true false positive or false negative, compound allergy should be suspected when a patient tests positive to cosmetic compounds or formulated products but tests negative to each individual ingredient in the compound. While compound allergy can occasionally be explained by the intrinsic irritancy of the product, a more likely explanation is a reaction of ingredients to form a novel allergenic compound; this can either occur metabolically in the skin or within the product itself (Lachapelle and Maibach 2012; Bashir and Maibach 1997). In addition, it is possible that allergens are tested at usage concentrations, which may be too low to elicit a positive reaction. However, in the majority of cases, technical errors in patch testing are responsible for negative patch testing (Lachapelle and Maibach 2012).

For example, cinnamic aldehyde occasionally induces sensitization when patch tested by itself but induces no sensitization when mixed with other fragrance compounds like eugenol or d-limonene (Lachapelle and Maibach 2012). Referred to as the "quenching phenomenon," patients sensitized to cinnamic aldehyde are often able to tolerate perfumes containing the allergen due to chemical changes that are thought to occur during the aging process of a perfume (Marks et al. 1982; Ale and Maibach 2008).

10.6.12 Cross-Sensitization, Concomitant Sensitization (Cosensitization), and Polysensitization

Cross-sensitization occurs when allergic contact dermatitis can be induced or worsened by chemicals related or structurally similar to the primary allergen (Lachapelle and Maibach 2012). For example, patients occasionally have a positive patch test reaction to p-phenylenediamine dye and chemicals that have an amino group in the para position like azo compounds, some local anesthetics, and sulfonamides (Fregert 1985).

Concomitant sensitization, otherwise known as cosensitization, occurs when sensitization occurs simultaneously to two allergens often found together in a product (Lachapelle and Maibach 2012). For example, sensitization may occur to nickel and cobalt in nickel products in which cobalt is present as an impurity (Lachapelle and Maibach 2012). Other examples include chromates and cobalt with cement contact, proparacaine and tetracaine in ophthalmic formulations, and bacitracin and neomycin (Lachapelle and Maibach 2012; Marks and DeLeo 2016).

Polysensitization refers to individuals who are sensitized to multiple, unrelated groups of allergens

(Lachapelle and Maibach 2012). Underlying contribution from genetic and environmental factors remains unclear, while others believe polysensitization represents a clear phenotype with increased susceptibility to sensitization (Carlsen et al. 2008; Schnuch et al. 2008; Gosnell et al. 2015).

10.6.13 Patch Test Sensitization (Active Sensitization)

Patch test sensitization occurs when patch testing is the cause of sensitization to a particular allergen; a flare occurs 10–20 days after an initial negative reaction (Lachapelle and Maibach 2012). On repeat testing around 3 days following the flare, if the patient has a positive test reaction to the same allergen, the sensitization can be attributed to the patch testing procedure itself. The most common implicated allergen is *p*-phenylenediamine (PPD), while thiuram mix, epoxy resin, sesquiterpene lactone mix, primula extracts, isothiazolinones, and acrylates have also been reported (Lachapelle and Maibach 2012; Björkner et al. 1986; Kanerva et al. 1988). It should be noted that clinicians should suspect a persistent patch test reaction rather than patch test sensitization when gold salts are the cause of a late reaction (Mowad et al. 2016). While likely underreported due to lack of patient recognition of a late reaction, the risk of patch test sensitization is thought to be low with a clear benefit to patch testing patients with suspected allergic contact dermatitis (Lachapelle and Maibach 2012). It should be noted that Lachapelle and Maibach (2012) advises against "prophetic" patch testing of nondermatitic patients.

10.6.14 Excited Skin Syndrome (Angry Back Syndrome)

Excited skin syndrome (ESS), also known as angry back syndrome (ABS), occurs when there is a strong positive regional reaction induced by a particular tested allergen, resulting in additional positive reactions to other allergens, which are negative on subsequent testing (Lachapelle and Maibach 2012). This condition occurs most often with marginal irritants like formaldehyde, potassium dichromate, and nickel sulfate. When in doubt over the possibility of ESS, it is suggested to conduct *sequential testing* with each possible allergen on different test sites (Lachapelle and Maibach 2012).

ESS has become less frequent, possibly due to only patch testing patients that are dermatitis-free and the use of smaller amounts of allergen in patch test chambers (Lachapelle and Maibach 2012).

It should be noted that ESS is clinically distinct from "status eczematicus," which occurs when there is a nonspecific reaction at many patch test sites due to skin hypersensitivity (Lachapelle and Maibach 2012). It is best avoided by refraining from patch testing on patients with an active dermatitis like atopic dermatitis (Lachapelle and Maibach 2012).

10.6.15 Patch Test Readings in Ethnic Populations

Currently, most literature describes patch testing methodology and reading in Caucasian groups. While there is no current evidence of differences in irritant reactions between Caucasian and oriental or Caucasian and black groups (Schnuch et al. 2008; Modjahedi and Maibach 2006), there exist special considerations when patch testing. In darker-skinned black, oriental, Malaysian, and Indian populations, test sites may be difficult to mark and occasionally requires the use of a marking ink (Lachapelle and Maibach 2012). In these same populations, erythema is difficult to discern, often necessitating the use of palpation to aid in detecting allergic reactions. In black populations, vesicles of eczematous reactions often appear yellow and may be confused with pustules (Lachapelle and Maibach 2012).

10.6.16 Patch Testing in Different Climates

In temperate climates, patch testing in warmer months leads to more positive reactions overall,

possibly due to increased temperature and humidity, resulting in more patient sweating (Lachapelle and Maibach 2012). However, patch testing in winter months may lead to increased false positives to certain allergens such as formaldehyde, mercurials, and propylene glycol due to chapping of the skin (Lachapelle and Maibach 2012).

In tropical climates, the higher humidity and temperature are likely to further aggravate ACD reactions (Lachapelle and Maibach 2012). Clinicians should also consider additional occlusive support over the patch test chambers to prevent patch test slippage due to patient perspiration (Lachapelle and Maibach 2012).

10.7 Photopatch Testing

10.7.1 Introduction

Photoallergic contact dermatitis (PACD) occurs after skin contact with an allergen that often requires the addition of ultraviolet light (generally UVA) in order to fully activate the hapten (Lachapelle and Maibach 2012). PACD should be suspected when face, neck, dorsal arms, and forearms are involved with general sparing of areas not exposed to the sun. Common photoallergens include sunscreen agents such as *p*-aminobenzoic acid (PABA) and NSAIDs such as ketoprofen, while there have also been numerous fragrances that have since been withdrawn from the market (Lachapelle and Maibach 2012).

In photopatch testing (PPT), allergens are tested in a similar manner to patch testing except with the addition of UV irradiation in order to detect the responsible photoallergen (Lachapelle and Maibach 2012). PPT is intended to detect photoallergens in photoallergic contact dermatitis and photoallergic drug eruptions; however, PPT cannot differentiate between other conditions that are also worsened by UV irradiation, such as chronic actinic dermatitis and polymorphic light eruption. In addition, it is possible for photoallergic contact dermatitis to be superimposed on other photodermatitis conditions such as polymorphic light eruption (Lachapelle and Maibach 2012).

It is often difficult to distinguish between PACD and airborne allergic contact dermatitis due to their similar distribution; however, there exist several key features that may aid in differentiation (Lachapelle and Maibach 2012). PACD often spares the "shadow areas" such as the eyelids and retroauricular folds, while airborne allergic contact dermatitis often presents with edema over these areas. In addition, PACD usually presents with a negative conventional patch test and a positive photopatch test; airborne allergic contact dermatitis most often features positive conventional patch tests with negative PPT.

10.7.2 Procedure

A common protocol for PPT involves applying possible photoallergens in duplicates (Lachapelle and Maibach 2012). In one set, the chamber units are removed after 24–48 h and irradiated with ultraviolet A, while the other set serves as a standard patch test and is not irradiated. Photopatch test readings should be recorded preirradiation, immediately postirradiation, and 48 h postirradiation. Allergens can often result in contact allergy as well as photocontact allergy, but in order to be considered a true photoallergen, it must display increased reaction following irradiation. A summary of PPT interpretations is included in Table 12. In addition, clinicians must be aware of false-positive phototoxic responses, which appear as slight erythema that fades over 24–48 h. In selection of tested photoallergens, the Task Force

Table 12 Summary of photopatch testing interpretation

Irradiated side	Nonirradiated side	ACD	PACD
–	–	No	No
–	+	Yes	No
+	–	No	Yes
++	+	Yes	Yes[a]

Adapted from Mowad et al. (2016)

ACD allergic contact dermatitis, *PACD* photoallergic contact dermatitis

[a]ACD and possibly PACD. This is controversial, and PACD should be interpreted with caution in this setting. Clinical correlation is necessary, and retesting may be required

recommends including sunscreen agents, some NSAIDs, and additional allergens based on the patient's history (Lachapelle and Maibach 2012).

10.8 Other Testing Procedures and Spot Tests

In select circumstances, there are additional modifications to the conventional patch test that may aid in diagnosis or provide more convenient testing conditions.

In the strip patch test, patch test sites are stripped of the stratum corneum prior to application of the allergen. Strip patch tests are helpful for allergens with poor penetration such as neomycin or eosin; however, clinicians should be aware of minor irritant reactions from the stripping itself (Lachapelle and Maibach 2012).

Another modification of the conventional patch test is the open test, which is often used when testing unknown or new products (Lachapelle and Maibach 2012). In an open test, the patient or clinician applies a small amount of the product to the volar aspect of the forearm without any occlusion. An open test is a useful initial test for new products due to its convenience and minimal risk; however, a negative test does not indicate absence of an allergy. A negative open test may also allow a clinician to proceed with conventional patch testing (Lachapelle and Maibach 2012).

The semi-open test can be viewed as a combination of an open test and conventional patch testing, as it uses adhesive tape over the allergens without individual patch test chambers. It provides more occlusion when compared to an open test while providing fewer irritant reactions when compared to conventional patch testing. This limits the number of false negatives due to inadequate allergen penetration, common in open application tests and limits false positives due to irritant reactions from conventional patch testing.

The repeated open application test (ROAT) is a variant of the open test; the substance is repeatedly applied twice daily for 7 days to the volar aspect of the forearm, antecubital fossa, or scapular area (Lachapelle and Maibach 2012). The patient should be instructed to stop application when he/she notices a reaction (Hannuksela and Salo 1986). Erythema and follicular elevations are commonly observed, while edematous and/or vesicular reactions may rarely occur (Lachapelle and Maibach 2012). A ROAT is particularly helpful when there is a strong clinical suspicion for a causative product despite negative patch testing to the allergenic component. In addition, it also helpful for comparative studies such as comparing a scented cosmetic applied to one side of the body versus the unscented cosmetic on the other side of the body (Lachapelle and Maibach 2012). However, it is important that "wash off" products be tested as such instead of left on the skin to avoid false positives to products that are not normally allergenic under instructed use (Mowad et al. 2016).

Clinicians should use caution when testing suspected products or materials brought in by the patient (Lachapelle and Maibach 2012). Physicians should request product safety information from the manufacturer including ingredient list and concentrations in order to isolate potential allergens. In addition, clinicians should ensure the product tested is between the pH of 1 and 9. In cases of an entirely new substance with no data on toxicity, it is advisable to start with an open test or a semi-open test, proceeding with occlusive patch testing if negative. For cosmetic products, open tests, semi-open tests, and ROAT tests are recommended, as they provide the most information on the pathogenesis of the dermatitis. When unsure of the composition of cosmetics, it is often helpful to perform in vitro spot tests to identify specific allergens. Examples of spot tests include dimethylglyoxime test for nickel, diphenylcarbazide test for hexavalent chromium, chromotropic acid test for formaldehyde, and disodium 1-nitroso-2-naphthol-3,6-disulfonate test for cobalt (Lachapelle and Maibach 2012).

While patch testing has been successful in identifying potential allergens, its many inconveniences, such as bathing restrictions and multiple dermatologist visits, have fueled attempts to search for alternatives. Thus far, experts have experimented with using peripheral blood lymphocytes in the presence of suspected antigens with thymidine and assessing the level of proliferation as a measure in the degree of T-cell allergen sensitization (Mowad et al. 2016).

However, efforts to use lymphocyte transformation tests in assessment of contact allergy have had limited success due to its low sensitivity, limited availability, and narrow spectrum of allergens able to be used (Popple et al. 2016; Mowad et al. 2016). At present, patch testing remains the gold standard for contact allergy testing.

10.9 Therapy

10.9.1 Prevention and Counseling

Contact dermatitis is best treated by avoidance of the eliciting chemical. In order for the patient's dermatitis to improve, clinicians should plan to extensively educate patients. Clinicians should provide both written and oral material regarding the causative allergens and their synonyms, allergen avoidance, and label reading. It is often most helpful to group allergens based on their function so that they can better understand how to avoid them. For example, allergens are often found in personal care products in the form of preservatives and fragrances; items worn on the skin such as metals in jewelry, belt buckles, and zippers; rubber additives in gloves, shoes, and elastics; textiles containing dyes and formaldehyde resins; and topical drugs containing allergens in either active or inactive components of the medication (Mowad et al. 2016). Also, many allergens have more than one function such as ethylenediamine (stabilizer in cosmetics and used in latex emulsion), colophony (used in adhesives, cooling fluids, hair removal wax), and formaldehyde (used as a preservative, in synthetic rubber production, textiles, leather tanning, and dental plastics) (Marks et al. 1982; Fowler et al. 1992). Clinicians should educate patients with formaldehyde allergies regarding formaldehyde-releasing products (FRPs) commonly found in many personal care products, as FRPs may be the causative allergen (Mowad et al. 2016).

It is helpful to ask patients to demonstrate understanding of ingredient label reading; however, there are many different means for manufacturers to disguise the presence of an allergen, whether intentional or not. For example, allergens are often listed in ingredient lists under different names, while products may be listed as fragrance-free if the fragrance has another function in the product, such as an emollient (Mowad et al. 2016). In short, clinicians should not rely on the patient's ability to detect allergens within products and should instruct patients to perform repeat open application tests (ROAT) in addition to ingredient scanning whenever trying new products (Tan et al. 2014). In the USA, products often list fragrances generically as "fragrance," making avoidance of a particular fragrance allergy difficult (Mowad et al. 2016). In this case, patients should avoid all fragrances until clearing of the dermatitis and add fragrance products once every 2 weeks (Mowad et al. 2016).

When giving patient written material, it is important to consider literacy level and distribute material that is simply written, concise, and with lists and pictures when possible (Wilson and Wolf 2009). Some organizations and manufacturers provide allergen information on their websites including Chemotechnique (www.chemotechnique.se), T.R.U.E. Test (www.truetest.com), Smart Practice (www.allergeaze.com), the American Contact Dermatitis Society (ACDS) (www.contactderm.org), and Preventice (www.allergyfreeskin.com). In addition, CAMP and CARD are two databases that provide lists of allergen-free products for patients. While CAMP is a member benefit of ACDS, CARD requires an annual subscription; both allow physicians to print lists for patients with ACD (Mowad et al. 2016). Should patients fail to improve in 4–6 weeks following identification of the likely causative allergen, it is often practical to review patient allergy information and resources (Mowad et al. 2016).

Maintaining appropriate hydration of the skin may help minimize susceptibility to certain irritants. Moisturizers are believed to aid in prevention of ICD via minimizing transepidermal water loss (Chew and Maibach 2003). However, it is important to consider the possibility of preservatives or other irritants in moisturizers as the cause of a possible ICD.

10.9.2 Topical Therapy

When the eliciting substance is avoided, topical corticosteroids have been successful in the treatment of ACD; however, the effectiveness of topical steroids in ICD remains in question (Taylor and Amado 2010). In mild to moderate cases of ACD, twice daily application of topical corticosteroids for 2 weeks has proven an effective treatment; patients should use milder corticosteroids applied over the face and intertriginous areas and higher potency steroids over the torso and extremities (Taylor and Amado 2010). Clinicians should select corticosteroids with few preservatives, especially in those that have patch tested positive to one or more preservatives (Marks and deLeo 2016). Topical tacrolimus and pimecrolimus may aid in the management of facial dermatitis and can be used as an alternative to lower potency steroids (Ashcroft et al. 2005).

10.9.3 Systemic Therapy

Systemic corticosteroids are occasionally used in the acute phase of severe or widespread contact dermatitis; however, they should be generally avoided due to accompanying adverse side effects. In cases of severe contact dermatitis that are unresponsive to systemic corticosteroids, immunomodulators and biologics may be considered for treatment (Tan et al. 2014). In cases of secondary infections, clinicians should select antibiotics effective against *Staphylococcus aureus* and *Streptococcus pyogenes* (Taylor and Amado 2010). Lastly, in cases of severe pruritus, sedating histamines can be prescribed before bedtime for relief of itching (Taylor and Amado 2010).

10.10 Prognosis

Prognosis of ACD depends on a number of factors, namely, the length of time the patient has been exposed to the particular allergen and whether or not the patient has developed chronic dermatitis. It is believed the greatest predictor of future dermatitis is a history of chronic dermatitis, while recent studies have found patients who did not improve clinically to have a longer average exposure period to the allergen (Hogan et al. 1990; Agrup 1969; O'Quinn et al. 1972; Gallant 1986; Adisesh et al. 2002).

In addition, the ability of the patient to avoid the allergen plays a large role in prognosis; this depends on factors such as proper patient education, patient compliance, and prevalence of the allergen in patient home and workplace. For example, nickel ACD is typically associated with a worse prognosis due to the widespread nature of the allergen, while ACD due to uncured epoxy resin is associated with a better prognosis (Fregert 1975; Menné and Bachmann 1980). Other factors like exposure to additional irritants and mechanical trauma also play a large role in prognosis.

10.11 Conclusion

Despite greater awareness and efforts to reduce the presence of contact allergens in our environment, ACD remains a common condition in the dermatologist's office and a frequent cause for occupational absence. With the abundance of products that enter the market, it is likely that new allergens

Table 13 Supplementary reading

Author	Title
Lachapelle JM, Maibach HI	*Patch Testing and Prick Testing: A Practical Guide Official Publication of the ICDRG*
Alikhan A, Lachapelle JM, Maibach HI	*Textbook of Hand Eczema*
Wahlberg JE, Boman A, Estlander T, Maibach HI	*Protective Gloves for Occupational Use, Second Edition*
Chew A-L, Maibach HI	*Irritant Dermatitis*
Rustemeyer T, Elsner P, John SM, Maibach HI	*Kanerva's Occupational Dermatology, Second Edition*
Rietschel RL, Fowler JF	*Fisher's Contact Dermatitis, 6e* (Rietschel, Fisher's Contact Dermatitis)
Johansen JD, Frosch PJ, Lepoittevin J-P	*Contact Dermatitis, Fifth Edition*

will emerge, and ACD will continue to require significant support from health-care providers. While efforts are underway to develop new means of testing for the presence of contact allergy, the patch test remains the gold standard and is continually undergoing changes to improve its accuracy. Detecting the causative allergen is frequently a challenge but only the beginning of the process in the patient's clinical improvement. Proper patient education and patient compliance are critical components to allergen avoidance and, hence, resolution of the ACD.

For supplementary reading, please see the following recommended texts listed in Table 13.

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Part IV

Asthma

Asthma Phenotypes and Biomarkers

11

Farnaz Tabatabaian

Contents

Abstract

For many years asthma has been described as a single disease. However, asthma is a heterogeneous syndrome with complex pathophysiology contributing to numerous clinical phenotypes. Despite various treatments a large proportion of patients remain uncontrolled or poorly controlled. Understanding the underlying inflammatory process in asthma is key for stratification of patients toward personalized therapy. Recently described inflammatory pathways include T2-high and T2-low or non-T2 inflammation. Clinically, T2-high inflammation is associated with atopic/allergic disease with increased evidence of eosinophils in the airway and the peripheral blood, whereas T2-low inflammation is correlated with neutrophilic or paucigranulocytic cells in the airways. Several biomarkers have been identified for T2-high inflammation; however, their utility is limited. Linking the clinical phenotypes to the underlying molecular biology will enhance the successful development of personalized therapies for asthma in the future.

Keywords

Asthma phenotype · T2-high asthma · T2-low asthma · Asthma endotype · Asthma biomarkers · Asthma biologics

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11.1 Introduction

Asthma is a chronic disease that affects 5–10% of children and adults in many developed countries. In the United States, 21.8 million people live with asthma, and 46.9% of those report having one or more asthma attack annually. In 2013, 1.6 million emergency room visits displayed asthma as the primary diagnosis. The average length of hospitalization for patients with asthma is 3.6 days. An estimated US$19.7 billion dollars annually makes asthma one of the top ten conditions impacting healthcare costs. Despite therapeutic advancement it is unclear why patients remain uncontrolled or poorly controlled (Centers for Disease Control and Prevention 2015). Although lack of adherence to the prescribed medications is a significant factor, asthma is a heterogeneous disease with variability in clinical presentation. Various attempts have been made to define phenotypes and evolution of asthma. Traditional classification of asthma has been associated with common triggers such as allergens, aspirin, obesity, exposure to cigarette smoke, viruses, and exercise. Several studies have taken an unbiased approach in analyzing variables in asthma that provide insight into the complexity of persistent asthma; however, it is difficult to ascertain the clinical value. Linking the observable characteristics to underlying molecular inflammation in the lungs, often referred to as the endotype, is a shift in asthma management toward individualized therapy. In this chapter, we will discuss the clinical asthma phenotypes and different mechanisms of inflammation intrinsic to the current endotypes of asthma defined (Fig. 1). Furthermore, we will address the utility of point-of-care biomarkers available for optimization of targeted therapy.

11.2 Asthma Phenotypes: Cluster Analysis and Clinical Subgroups

Phenotype is defined as "observable characteristics of an organism that are produced by the interactions of the genotype and the environment" (Phenotype). Several groups have taken a less biased approach using cluster analysis in grouping important variables to identify asthma phenotypes (Table 1) (Haldar et al. 2008; Moore et al. 2007). Taking into account steroid bursts, emergency room visits, hospitalization, measurement of airway obstruction via forced expiratory volume in 1 s (FEV1), sputum eosinophils, and bronchodilator responsiveness, several similarities were identified in patients (Wenzel 2012). In the National Institutes of Health-sponsored Severe Asthma Research Program (SARP) data, early-onset asthma was associated with atopy and allergic disease (Moore et al. 2007, 2010). Interestingly, the severity of disease did not correlate to the degree of allergen skin test reactivity, higher IgE, or higher exhaled nitric oxide (FeNO) which are markers of atopic disease. Rather severity was closely linked to duration of disease, medication use, and lung function (Fitzpatrick et al. 2011). The children in the study had normal weights with increased prevalence in boys before pubescence. The correlation of early-onset asthma to other atopic disease including allergic rhinitis and atopic dermatitis has been confirmed by multiple other cluster analyses. In fact, 40% of patients with early-onset asthma have a history of atopic dermatitis compared to only 4% of people with adult-onset asthma (Miranda et al. 2004).

A second phenotype described is the late-onset persistent eosinophilic asthma, characterized by a higher degree of eosinophils in the sputum and peripheral blood. Some individuals did have a mixture of eosinophils and neutrophils in the sputum (Hastie et al. 2010). This phenotype lacks clinical allergy with a much less degree of family history of asthma as observed in early-onset disease (Wenzel 2012). Adults show greater airflow obstruction with a decrease in bronchodilator response. This cluster of patients displays difficult-to-control disease and more frequent asthma exacerbation (Teague et al. 2018). A subtype of this phenotype is aspirin-exacerbated respiratory disease (AERD) with severe eosinophilic asthma, concurrent sinusitis, and nasal polyposis with severe non-IgE-mediated reaction to aspirin and other cyclooxygenase-1 inhibitors (Rodriguez-Jimenez et al. 2018).

Obesity plays a role in asthma with regard to control and severity of disease. Several studies support the increased expression of pro-inflammatory cytokines like TNF-α, interleukin-6 (IL-6),

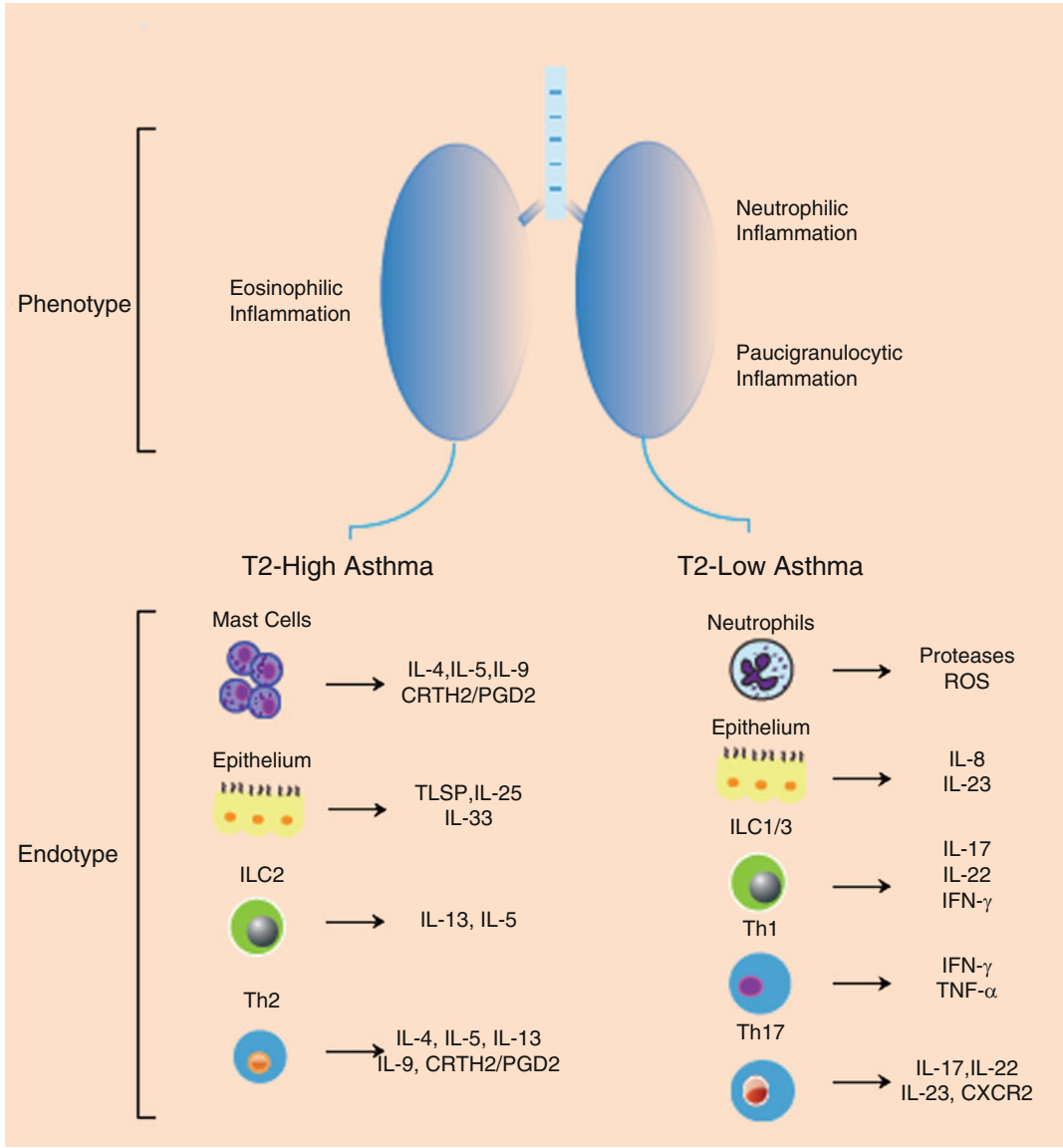

Fig. 1 Various inflammatory patterns in the airway contribute to different underlying molecular mechanism among various cells. In T2-low pattern, a predominant neutrophilic and paucigranulocytic inflammation is consistent with patients who are less responsive to corticosteroid therapy. An increase in TNF-α, IL-17, IL-23, and IL-8 is seen at the molecular level. Innate lymphoid cells groups 1 and 3 are more predominate in T2-low disease. Eosinophilic inflammation correlates with phenotype of patients who are more likely to respond to corticosteroids and the various biologics currently available on the market that are FDA approved for persistent asthma. In T2-high asthma, type 2 cytokines including IL-4, IL-5, and IL-13 play a central role in the underlying inflammation. IgE produced by B cells and innate cytokines TSLP, IL-25, and IL-33 produced by the epithelial cells are present in T2-high inflammation. PGD_2, prostaglandin D_2; *IFN-γ*, interferon gamma; *TNF-α*, tumor necrosis factor-alpha; *ROS*, reactive oxygen species; *ILC1*, *type 1* innate lymphoid cells; *ILC2*, group 2 innate lymphoid cells; *ILC3*, group 3 innate lymphoid cells; *NKT*, natural killer cells; *IgE*, immunoglobulin E; *TSLP*, thymic stromal lymphopoietin. (Adapted from Sonnenberg et al. *Nature Immunology* and Muroro et al. *Journal of Allergy and Immunology*)

Table 1 Asthma phenotypes and clinical characteristics

	Natural history and clinical characteristics
Early-onset disease	Childhood onset with mild-to-severe symptoms Allergic symptoms associated with atopy
Late-onset disease	Adult onset with more severe disease Increased eosinophils in sputum, less allergic AERD is a subgroup
Obesity related	Adults Females with increased oral corticosteroid use. Nonatopic and absence of eosinophilic inflammation
Neutrophilic asthma	Low FEV1 with significant air trapping. Frequent oral corticosteroid use
Exercise-induced	Intermittent associated with exercise

Adapted from (Wenzel 2012)

and leptins in obesity (Leiria et al. 2015). Obesity-related phenotype has an increased prevalence in women with later-onset disease and minimal allergic/atopic burden (Miranda et al. 2004; Teague et al. 2018). Patients also have fewer eosinophils in the sputum with diminished response to corticosteroid and higher burden of symptoms overall (Wenzel 2012). A separate adult-onset phenotype in the SARP cluster included individuals with neutrophilic asthma. Affected individuals had increased air trapping, lower lung function, and thicker airway as measured by computed tomography scans. Generally, the degree of obstruction was not reversible. Many of the patients were on systemic steroids with a high-intensity usage of healthcare and economic burden (Moore et al. 2007, 2010; Teague et al. 2018).

Exercise-induced asthma (EIA) is a phenotype that has been described for many years, typically associated with reactive bronchoconstriction after sustained exercise despite baseline mild asthma. Symptoms are exacerbated by cold or dry air. This phenotype is more common among atopic athletes; however, no distinct genetic factors or biomarkers have been identified. Histamine, prostaglandins, and cysteinyl leukotrienes secreted by mast cells are key players in EIA (Hastie et al. 2010; Caggiano et al. 2017).

While the various phenotypes have provided insight into patient population with asthma, the prognostic value in therapeutic decision is not clear. In linking the clinical characteristics to the underlying molecular pathway, several immunomodulatory biologic therapies have emerged. Better understanding the underlying pathophysiologic mechanisms of the different phenotypes, known as the endotype, will further advance and guide therapeutic decisions in treating asthma.

11.3 Asthma Endotypes: The Inflammatory Pathways in Asthma

Two main endotypes have been described in the asthma literature including T2 low (Th2-low) and T2 high (Th2-high) (Wenzel 2012; Fahy 2015). In T2 high there is an increase in eosinophils in the sputum. On the other hand, T2-low asthma is associated with neutrophilic or paucigranulocytic inflammation in the sputum and airways.

11.3.1 T2-Low Asthma or Non-T2 Asthma

Neutrophilic inflammation has long been associated with refractory asthma (Alam et al. 2017). Clinically these patients have adult-onset disease that is less responsive to corticosteroids (Wenzel 2012). In this type of inflammation, the expression of type 2 cytokines is absent (Liu et al. 2017; Lambrecht and Hammad 2015). Instead, a predominance of Th1 and Th17 cells is noted with an increased production of interleukin-8 (IL-8), a potent neutrophil chemoattractant. Several studies illustrate the role of IL-17 in inducing the production of IL-8 and airway remodeling (Lambrecht and Hammad 2015; Bellini et al. 2012). However, clinically the inhibition of IL-17 receptor A antagonist is of little benefit in patients with mild-to-moderate asthma (Busse et al. 2013a). In a small preliminary study of 12 patients on CXCR2 antagonist blocking IL-8, the sputum neutrophils decreased; however, there was no statistical improvement of FEV1 or

symptom scores (Barnes 2015). Hence, direct targeting of IL-8 through its chemokine receptor CXCR2 is of insignificant clinical value. In recent studies, immunophenotyping patients with Th2-/Th17-predominant asthma and Th2-/Th17-low asthma illustrated increased expression of pro-inflammatory cytokines including IL-1, IL-6, and C3 (Alam et al. 2017; Liu et al. 2017). Furthermore, the presence of subclinical infection led to a pronounced infection cytokine profile. Targeted therapy with antimicrobial agents and IL-1 receptor antagonist are potential therapeutic interventions (Alam et al. 2017; Liu et al. 2017). Further studies are needed to demonstrate clinical efficacy.

Paucigranulocytic inflammation is another subtype of T2-low endotype. In this inflammatory process, a normal number of eosinophils and neutrophils are found in the sputum with no evidence of IL-8 or type 2 cytokines (Alam et al. 2017). Clinically, patients are resistant to corticosteroid therapy presumably due to decreased levels of airway inflammation. The use of long-acting muscarinic receptor antagonist and long-acting beta-receptor agonists is of some benefit. Many patients in this subgroup ultimately may be candidates for bronchial thermoplasty to reduce airflow obstruction (Wilhelm and Chipps 2016). Unfortunately, a significant challenge in both neutrophilic and paucigranulocytic inflammation is the lack of reliable biomarkers. To date many of the targeted therapies have not proven effective.

11.3.2 T2-High Asthma

T2-high inflammation is central to allergic disease. As described earlier, childhood- or early-onset asthma is associated with atopic disease with increased eosinophils in the sputum and airway. Clinically this phenotype of patients is corticosteroid responsive. However, the degree of response may be variable (Woodruff et al. 2007, 2009). Haldar and colleagues used the epithelial brushings of asthma patients who were corticosteroid naïve to illustrate an increased level of IL-5 and IL-13 messenger RNA in subjects with increased atopy suggestive of T2-high asthma compared to those with T2-low asthma (Haldar et al. 2008). T2-high inflammation is a complex pathway between innate and adaptive immune response. This inflammatory process begins with the differentiation of uncommitted naive T cells toward Th2 cells under the stimulation of local cytokines and co-stimulatory molecules on dendritic cells (Fig. 2). The initial activation of Th2 cells and innate lymphoid cell type 2 (ILC2) is via innate cytokines IL-33, IL-25, and thymic stromal lymphopoietin (TLSP) that are secreted by the airway epithelial cells induced by external stimuli. The master regulator of T2 inflammation is the transcription factor GATA-3 which is required for the development and function of Th2 and ILC2. Th2 cells contribute to the production of type 2 cytokines which include IL-4, IL-5, and IL-13. ILC2s are an alternative source of IL-5 and IL-13. ILC2s do not express any phenotypic markers of dendritic or conventional lymphocytes. The continuous accumulation of type 2 cytokines is key for stimulation of eosinophils, mast cells, and basophils. Type 2 cytokines also cause mucous cell hyperplasia and fibrosis leading to airway remodeling. IL-4 and IL-13 are both involved in class switching of naïve B cells toward synthesis of immunoglobulin E (IgE). IL-5 is important for the survival of eosinophils and chemotaxis from blood vessels into the airway (Fahy 2015; Tabatabaian et al. 2017).

Several targets have been examined for down-regulation of T2-high inflammation. These mediators and cytokines include IgE, IL-5, IL-4, IL-13, IL-4 receptor alpha, TSLP, and chemoattractant receptor-homologous molecules on T2 cells (CRTH2) (Tabatabaian et al. 2017). Antagonists targeting IgE, IL-5, and IL-5 receptors are FDA approved for use in severe persistent asthma (Table 2). The challenge remains in identifying the right patient for these therapeutic interventions. Hanania et al. in a retrospective study used biomarkers to identify possible responders to an anti-IgE monoclonal antibody (Hanania et al. 2013). This was one of the first studies that separated patients to T2-high versus T2-low inflammation. Identification of biomarkers in T2-high inflammation can help guide the choice of therapy and assess responsiveness.

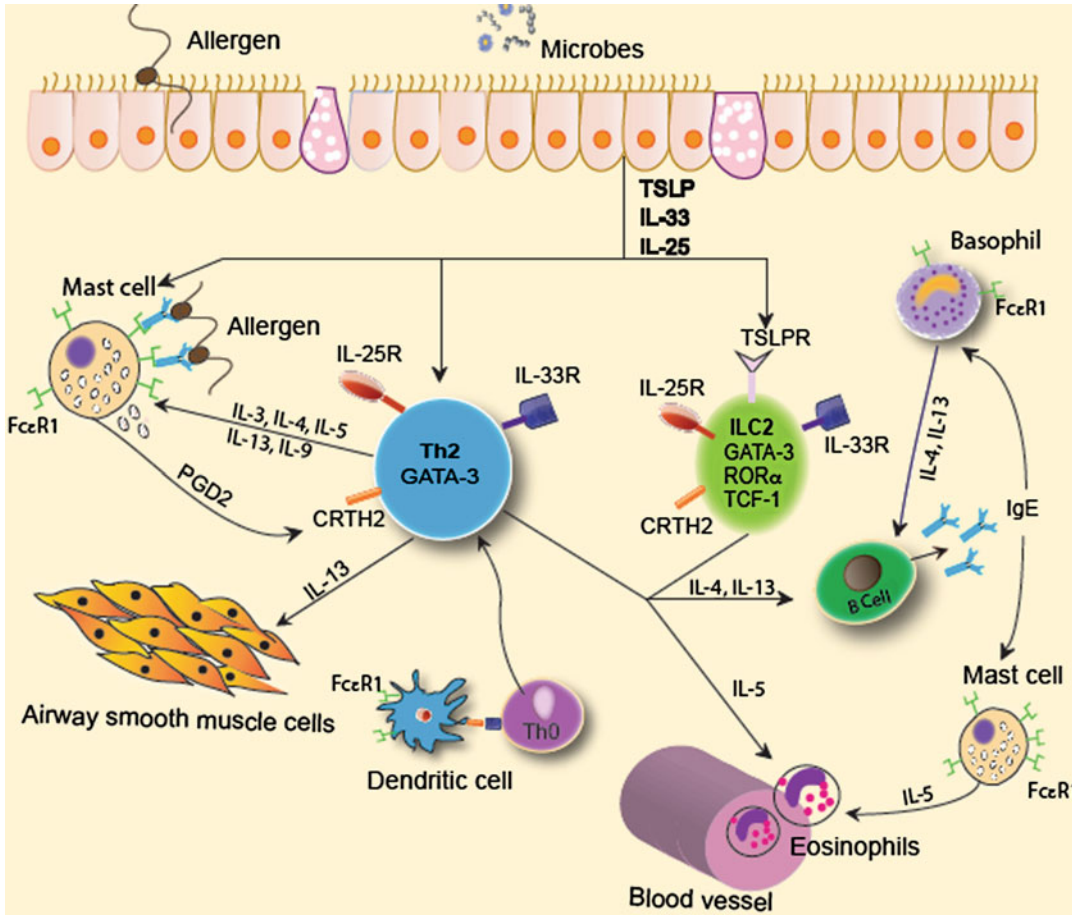

Fig. 2 A very complex interplay of various cytokines and inflammatory cells is central in T2-high inflammation. Airway epithelial cells activated by environmental stimuli produce innate cytokines TSLP, IL-25, and IL-33. These innate cytokines contribute to the expression of GATA-3, a master regulator and transcription factor, in both Th2 and ICL2, subsequently enhancing the production of type 2 cytokines. Secretion of IL-5 stimulates the production of eosinophils in the bone marrow and elicits the migration of eosinophils to the area of inflammation. IL-5 and IL-13 contribute to smooth muscle changes and remodeling changes. IL-4 contributes to IgE class switching in B cells. *TSLP*, thymic stromal lymphopoietin; *PGD2*, prostaglandin D_2; *CRTH2*, chemoattractant receptor-homologous molecule expressed on T_H2 cells; *GATA-3*, transcription factor

11.3.3 Biomarkers in T2-High Inflammation

Biomarkers have long been used as a surrogate for diagnosis and to assess disease progression as well as responsiveness to therapy. Examples of biomarkers include hemoglobin A1C (HgA1C) which is used to diagnose diabetes. In T2-low asthma, the development of biomarkers is much needed and is currently underway. A recent publication evaluated the role of sputum-to-serum hydrogen sulfide ratio in neutrophilic airway inflammation and association with asthma exacerbations (Suzuki et al. 2018). On the other hand, in T2-high asthma, a few biomarkers have been identified to help facilitate selection of patients that would likely respond therapeutically to FDA-approved biologics for severe persistent asthma (Busse et al. 2013b). These include blood and sputum eosinophils, periostin, IgE, and fractional exhaled nitric oxide (FeNO). Unfortunately, these biomarkers are not adequate for identification of early-onset asthma, nor are they all available at bedside for clinical use. Nevertheless, they

Table 2 Summary of biologics targeting T2-high asthma

Current therapies	Mechanism of action	Potential biomarkers	Effect	FDA approved	Route	References
Omalizumab	Blocks IgE interaction with FcεRI	Elevated IgE. Patients with higher FeNO and blood eosinophils >300 cells/μl better response	Decrease asthma exacerbations	Yes; ages 6 and older	150–375 mg sub-q q2–q4 weeks, frequency based on IgE and body weight Black box warning for anaphylaxis	(Hanania et al. 2013; Busse et al. 2013b; Humbert et al. 2014)
Mepolizumab	IL-5 antagonist	Peripheral eosinophil count of >150 cells/μl or 300 cells/μl	Decrease in asthma exacerbations and improvement in pre-post bronchodilator FEV1	Yes; ages 12 and older	30 mg sub-q q4 weeks; consider shingles vaccine prior to administration	(Pavord et al. 2012; Haldar et al. 2009; Flood-Page et al. 2007; Ortega et al. 2014)
Reslizumab	IL-5 antagonist	Peripheral eosinophil count of >400 cells/μl	Decrease in asthma exacerbations and improvement in FEV1	Yes; 18 and older	3 mg/kg IV q4 weeks Black box warning for anaphylaxis	(Castro et al. 2015; Corren et al. 2016)
Benralizumab	IL-5 receptor α-antagonists targeting both eosinophils and basophils	Elevated peripheral blood eosinophil count	Decreased asthma exacerbations. In a small study used in ER visit, setting administration contributed to a 50% drop in exacerbation over 12 weeks	Yes; 12 and older	100 mg sub-q every 4 weeks for the first three doses and subsequently every 8 weeks	(Laviolette et al. 2013; Castro et al. 2014; Nowak et al. 2015)
In clinical trials						
Dupilumab	Inhibits IL-13 and IL-4 by targeting IL-4-α, a common receptor domain for both cytokines	Peripheral eosinophil count of >300 cells/μl or sputum >3% with better response, but improvements in all patients	Decrease in asthma exacerbations and improvement in FEV1	Phase 3 trials	200 mg sub-q q2 weeks or 300 mg sub-q q4 weeks; administered at home	(Wenzel et al. 2013, 2016; Castro et al. 2018; Busse et al. 2018)

do provide some insight to the type of inflammation that might be involved.

11.3.3.1 Eosinophils

Several studies have illustrated that persistent or poorly controlled asthma with increased exacerbation is associated with increased blood or sputum eosinophils (Pavord et al. 2012; Berry and Busse 2016). Clinically it is difficult to measure eosinophils in the sputum; however, obtaining peripheral blood eosinophils is relatively easy. While peripheral blood eosinophilia is not an optimal surrogate for airway eosinophils, it is suggestive of T2-high inflammation. In a large UK cohort, patients with peripheral blood eosinophil counts of 400 cell/μl or greater had poor asthma control and experienced worse asthma exacerbation compared to those patients with blood eosinophil counts less than 400 cells/μl (Price et al. 2015). Current research is underway for other markers of eosinophils that might be useful. Eosinophil peroxidase (EPX), an eosinophil granule protein in the sputum, seems to correlate with respiratory disease activity. Measurement of nasal and pharyngeal EPX using a bioactive paper strip is a promising tool to use at bedside to measure the burden of eosinophils in the lungs (Tabatabaian et al. 2017; Rank et al. 2016).

11.3.3.2 Fractional Exhaled of Nitric Oxide (FeNO)

In the lung,the oxidation of amino acid L-arginine via nitric oxide synthase produces nitric oxide (NO). A variety of cells including epithelial cells, macrophages, mast cells, neutrophils, and endothelial cells produce various forms of nitric oxide synthase. In particular, the epithelial cells lining the airway and alveoli express a high quantity of inducible nitric oxide synthase (iNOS). Both IL-4 and IL-13, prominent in T2-high inflammation, contribute to increased expression of iNOS leading to production of NO. Hence, the measurement of FeNO is a noninvasive biomarker reflective of T2-high asthma that is easily obtainable (Hanania et al. 2013; Tabatabaian and Ledford 2018). Current available analyzers for the measurement of NO concentration in the lungs include NIOX MINO, NIOX VERO (Aerocrine, Stockholm, Sweden), and NO Breath (Bedfront Scientific LtD, Kent, UK).

For clinical use, guidelines by the American Thoracic Society propose FeNO <25 ppb in adults and <20 ppb in children as normal (Dweik et al. 2011). In adults, a FeNO >50 ppb is more responsive to inhaled corticosteroids (ICS). A decrease in FeNO is observed within 1 week of therapy (Mehta et al. 2009). Non-compliance or decreased corticosteroid responsiveness should be considered if FeNO remains >50 ppb in adults (>35 ppb in children) despite ICS use (Dweik et al. 2011). In children, a FeNO >49 ppb within 4 weeks of ICS discontinuation is associated with an increase in asthma exacerbations (Pijnenburg et al. 2005). In a Cochrane review of adjustment of asthma medication based on FeNO levels in both adult and children, a reduction in FeNO was not associated with improvement of daily symptoms but rather a reduction in asthma exacerbations (Petsky et al. 2016). Several studies have demonstrated that patients with severe persistent asthma with higher FeNO had greater reduction in asthma exacerbation with treatment of anti-IgE monoclonal antibody (omalizumab) compared to those with lower FeNO levels (Hanania et al. 2013; Mansur et al. 2017). In a recent study observing a biologic inhibiting IL-4 and IL-13, suppression of FeNO was observed in the treated group compared to placebo by week 2 of therapy (Rabe et al. 2018). Interestingly, the anti-IL-5 biologics have not demonstrated much effect on FeNO (Haldar et al. 2009). A host of environmental factors impact the level of FeNO measured. Spirometry and exercise prior to measuring FeNO contribute to transiently lower levels. Use of ICS, systemic steroids, leukotriene receptor antagonist, smoking, and obesity are associated with lower FeNO. High-nitrate foods falsely increase FeNO. In adults, males have higher FeNO compared to females. In children, FeNO increases at a rate of 5% per year attributed to height increase (Berry and Busse 2016). Despite the various factors that affect the measurement of FeNO, it serves as a clinical biomarker in T2-high inflammation and potentially predicts response to targeted T2-high asthma biologics.

11.3.3.3 Periostin

Periostin is another marker of T2-high inflammation secreted by airway epithelial cells and fibroblast in response to IL-13. Periostin gene expression is increased in the airway of those with asthma (Corren et al. 2011). Hanania et al. demonstrated a 30% reduction in asthma exacerbation in the high-periostin group (>50 ng/ml at baseline) compared to 3% reduction in low-periostin group (<50 ng/ml at baseline) of those treated with anti-IgE monoclonal antibody (Hanania et al. 2013). Treatment with IL-13 antagonist showed greater improvement in FEV1 in subjects with higher baseline periostin compared to those with lower periostin (Corren et al. 2011). Serum periostin is a good biomarker of T2 inflammation; however, the assay to measure it at bedside is not commercially available.

11.3.3.4 Serum IgE

Sensitization to aeroallergens and increased serum total IgE is a risk factor for allergic asthma. In pediatric cohorts, children with severe asthma had higher serum IgE and increased aeroallergen sensitization (Fitzpatrick et al. 2011). The processing of antigens by dendritic cells and presentation to naïve T cells shift the inflammatory pathway toward T2-high inflammation (Fig. 2). Th2 shift contributes to class switching of B cells and production of specific IgE. IgE bound FcεRI, the high-affinity IgE receptor, and cross-links the receptors initiating a signaling cascade of mast cell degranulation releasing histamine, leukotrienes, and other inflammatory factors. IgE also activates eosinophils, basophils, macrophages, and airway smooth muscles via FcεRI receptor to produce pro-inflammatory cytokines involved in tissue remodeling (Pelaia et al. 2017). Anti-IgE monoclonal antibodies decrease blood eosinophils and asthma exacerbations.

11.3.4 Biologics Targeting T2-High Inflammation

Early-onset asthma is a phenotype linked to atopy and allergic sensitization. In fact, 70% of patients with asthma have an allergic phenotype. IgE is an integral part of allergic asthma. The first biologic approved for asthma in the United states was omalizumab (Xolair; Genentech USA, Inc. and Novartis Pharmaceuticals Corporation). Omalizumab is a humanized monoclonal antibody with specificity for the IgE molecule. This drug also downregulates the high-affinity IgE receptor (FCεRI) on eosinophils, basophils, circulating dendritic cells, and mast cells (Fig. 3) (Humbert et al. 2014). Treatment with omalizumab reduces asthma exacerbation, use of ICS, and overall symptoms (Table 2). In clinical trials, improvement of lung function is less evident with the use of omalizumab (Humbert et al. 2014). Subjects with elevated T2-high biomarkers, including blood eosinophils and FeNO, seem to benefit most from this therapy (Hanania et al. 2013). In one study, peripheral eosinophil count of 300 cells/μl or more predicts a favorable response to omalizumab with a 60% drop in asthma exacerbations (Busse et al. 2013b). In the United States, omalizumab is approved as add-on therapy for moderate-to-severe persistent allergic asthma in children 6 years and older (XOLAIR).

As described above, patients with elevated peripheral and sputum eosinophils have increased asthma exacerbations and overall poorly controlled asthma. A key cytokine in T2-high inflammation is IL-5. Eosinophils require the presence of IL-5 for growth, differentiation, and migration into the airways. To date, three monoclonal antibodies have been FDA approved that effect IL-5 which include mepolizumab, reslizumab, and benralizumab (Table 2). Mepolizumab is a humanized monoclonal antibody that binds to IL-5. Flood-Page and colleagues, in an initial double-blind, placebo-controlled study, evaluated patients with uncontrolled moderate-to-severe asthma despite an inhaled corticosteroid treatment (Flood-Page et al. 2007). Those treated with mepolizumab showed significant improvement in rate of exacerbations, lung function, and overall quality of life. The authors also found a drop in the number of blood and sputum eosinophils in the mepolizumab group. Ortega and colleagues, in a randomized double-blind study, compared mepolizumab 75 mg IV or 100 mg sub-q to placebo administered every 4 weeks for a total of

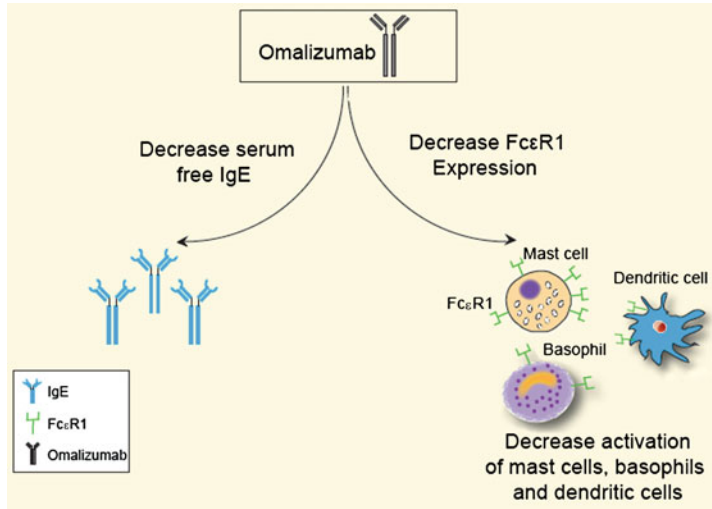

Fig. 3 Omalizumab is humanized monoclonal antibody that binds to IgE and decreases serum level of IgE. Omalizumab also downregulates the IgE high-affinity receptor (FcεR1) on mast cells, basophils, and dendritic cells. (Adapted from Tabatabaian and Ledford 2018)

32 weeks in subjects with recurrent asthma exacerbations and eosinophilic inflammation. Initial entry did require subjects to have peripheral eosinophil count of 150 cells/μl or greater than 300 cells/μl in the previous year. Compared to placebo both active groups had an overall 50% reduction in asthma exacerbation, 100 ml improvement in FEV1, better asthma quality of life scores, and a decrease in both peripheral blood and sputum eosinophils (Ortega et al. 2014). Mepolizumab is approved in the United States as an add-on therapy for severe persistent asthma given as a 100 mg sub-q injection every 4 weeks in patients 12 years and older. Individuals with higher levels of peripheral blood eosinophils have the greatest benefit. Most recently mepolizumab was approved for eosinophilic granulomatosis with polyangiitis at a higher dose of 300 mg sub-q every 4 weeks (Raffray and Guillevin 2018; NUCALA). Reslizumab is also a humanized anti-IL-5 monoclonal antibody that was FDA approved in 2016 as add-on therapy for severe eosinophilic asthma. Castro and colleagues, in two double-blind multicenter studies with patients between the ages of 12 and 75 and eosinophil count of 400 cells/μl or greater, illustrated a decrease in asthma exacerbations and significant improvement in FEV1 in those treated with IV reslizumab 3 mg/kg compared to placebo. All of the patients enrolled were on ICS plus another controller therapy and had reversibility on spirometry with use of short-acting beta-agonist (Castro et al. 2015). Several other studies confirmed the clinical benefit of reslizumab in a similar patient population (Bjermer et al. 2016; Corren et al. 2016). Compared to the other IL-5 blocking agents, reslizumab may elicit the greatest improvement in FEV1 (Castro et al. 2015; Bjermer et al. 2016; Corren et al. 2016). Reslizumab is administered IV at 3.0 mg/kg over a 20- to 50-min infusion. It does have a black box warning for a small risk of anaphylaxis (CINQAIR). The latest biologic approved that targets IL-5 is benralizumab. This drug binds to the alpha (α) chain of IL-5 receptor, enhancing the antibody-dependent cell-mediated cytotoxicity leading to apoptosis of eosinophils, basophils, and eosinophil progenitors in the bone marrow (Laviolette et al. 2013). Eosinophils can enter tissue independent of IL-5, making the direct effect of benralizumab more attractive. In a phase 2b trial, Castro et al. evaluated the impact of variable doses of benralizumab compared to placebo in subjects with uncontrolled eosinophilic asthma. Benralizumab was administered every 4 weeks for the first three doses and subsequently every 8 weeks. A decrease in exacerbation occurred in treated group compared to placebo, and those subjects with eosinophil count greater than 300 cells/μl had the greatest improvement in FEV1 (Castro et al. 2014). A subsequent small study illustrated a decrease of 50% in asthma exacerbation with one dose of benralizumab administered during an acute ER visit over the next 12 weeks (Nowak et al. 2015). This opens the door for a novel use of biologics in the ER to prevent

readmission rates and subsequent associated cost. Benralizumab is approved as an add-on therapy for severe persistent asthma eosinophilic phenotype in 12 years and older. It is a sub-q injection of 30 mg every 4 weeks for the first three injections and subsequently every 8 weeks (Fasenra). Although direct comparisons of the biologics targeting IL-5 do not exist, no clear superiority was elicited among the three therapies in an indirect meta-analysis (Cabon et al. 2017). All three biologics reduce asthma exacerbations and improve quality of life scores. To date, the ability to clearly identify the best therapeutic choice among the three available IL-5 inhibitors is lacking.

An attractive target for T2-high asthma is an IL-4 and IL-13 inhibitor. IL-4 is important for class switching of B cells and production of IgE. IL-13 enhances mucus production in the airway, induces airway hyperresponsiveness, stimulates proliferation of bronchial fibroblast, and recruits eosinophils and basophils. Biologics targeting IL-13 initially showed some promise. IL-13 stimulates epithelial cells to produce dipeptidyl peptidase-4 (DPP-4) and periostin. Both periostin and DPP-4 serve as good biomarkers to predict response to the IL-13 antagonist (Corren et al. 2011). Unfortunately, phase 2b and 3 trials of the two drugs targeting IL-13 did not prove to be effective in reducing asthma exacerbation or improving asthma control (Hanania et al. 2015). Dupilumab, a fully humanized monoclonal antibody directed toward the α-subunit of IL-4 receptor, blocks both IL-4 and IL-13 (Wenzel et al. 2013, 2016). This drug is FDA approved in the United States for moderate-to-severe atopic dermatitis (DUPIXENT). It is efficacious in nasal polyposis. In phase 2b trials, subjects with moderate-to-severe persistent asthma on high-dose ICS plus a long-acting beta-agonist had a significant decrease in asthma exacerbation. Individuals with peripheral eosinophil counts of 300 cells/μl or greater showed the most benefit (Wenzel et al. 2016). Castro et al. in a phase 3 trial showed dupilumab as an add-on therapy in severe uncontrolled asthma contributes to a 65% reduction in asthma exacerbation in patients 12 years of age or older given as sub-q injection at home bi-weekly (Castro et al. 2018). In another study, Wenzel and colleagues show improvement of asthma exacerbation and pulmonary function regardless of pretreatment eosinophil count. However, individuals with higher peripheral eosinophils have the greatest benefit (Wenzel et al. 2016). Several other targets in T2-high inflammation are under investigational review. The therapeutic efficacies of these drugs still need to be established.

11.4 Conclusion

Asthma is a common medical condition seen routinely in the outpatient setting by physicians and healthcare providers. Current guidelines recommend a stepwise approach in management of asthma. Clearly, educating patients on the appropriate use of inhalers and ensuring compliance are key for optimal control. Many patients still utilize urgent care systems, the ER and hospitals for acute asthma symptoms, suggesting lack of control in this population. By obtaining a complete history and physical exam, providers are able to identify the phenotype of asthma and further define prognosis of disease. Furthermore, addressing comorbid conditions, smoking, obesity, GERD, and OSA all contribute to asthma control. Most importantly our advancement in understanding of the molecular inflammation or endotypes in asthma has paved a path toward personalized medicine. Two main endotypes T2 high and T2 low have been defined to date. T2-low asthma is phenotypically associated with neutrophils in the sputum, adult-onset disease, and less corticosteroid responsiveness. Patients with neutrophilic inflammation seem to benefit from macrolide therapy. Those with underlying paucigranulocytic inflammation show therapeutic relief with the use of a long-acting antimuscarinic antagonist. Biomarkers reflecting T2-low asthma are not available for use at the bedside. Despite early attempts, targeting cytokines in T2-low asthma therapeutic interventions remains limited and further investigation is needed.

On the other hand, eosinophils in the sputum, early-onset asthma, and prior history of atopic

disease are the phenotype that correlates with T2-high asthma. Clinically accessible biomarkers reflecting T2-high inflammation include total serum IgE, FeNO, and peripheral blood eosinophils. In the United States and Europe, omalizumab, reslizumab, mepolizumab, and benralizumab are commercially available for use in uncontrolled asthma patients with T2-high inflammation. Unfortunately, the ability to predict better response to a specific T2-high targeted therapy is lacking. Current biomarkers are suggestive of T2 inflammation with clinical value, but they are limited in precision. Many uncertainties exist with the growing repertoire of biologics. None of them modify disease or induce remission. Furthermore, the optimal treatment duration or approach to discontinuation is not clearly defined. Nevertheless, emerging knowledge of asthma phenotypes, endotypes, and associated biomarkers is the first step toward new therapeutic intervention offering patients precision medicine.

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Adult Asthma

12

Robert Ledford

Contents

Abstract

Asthma is a global disease of varying presentations and complex pathophysiology which contributes to chronic symptom burden, loss of function and productivity, increased healthcare costs from emergency department visits and hospitalization, and severe medical complications including death. An estimated 25 million Americans and 300 million persons worldwide are affected and epidemiologic studies indicate that the prevalence of asthma is increasing. Understanding asthma requires knowledge of: lung function, immunology and hypersensitivity, disease presentation, pulmonary function testing, treatment mechanisms, and comorbid conditions. Management of

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patients with asthma demands longitudinal monitoring of symptoms, medication use and compliance, and frequent reassessment of response to therapy. Due to the complexity of the disease and multitude of treatment considerations, referral to specialists and advanced centers of excellence is required to achieve acceptable disease control in some instances. However, physicians in the primary care setting, emergency department, and hospital frequently encounter, diagnose, and manage asthma. As such, understanding the core principles of definition, mechanism, diagnosis, symptom burden, associated and mimicking diseases, and treatment options is necessary for all healthcare professionals. This chapter outlines the fundamental approach to asthma definition, diagnosis, pathogenesis, presentation, comorbid conditions, and treatment modalities.

Keywords
Asthma · Hypersensitivity · Eosinophilia · Inhaled corticosteroids · Immunotherapy

12.1 Introduction

Asthma is a worldwide health problem with increasing prevalence, increasing costs due to healthcare utilization and loss of work productivity, and complex interactions with environmental and genetic risk factors. Asthma currently has the greatest estimated prevalence and societal impact since it was first described in ancient Greece (Akinbami et al. 2012). Further complicating the understanding of asthma, a wide array of treatment options exists and numerous conditions can affect or mimic asthma. Therapies include medications which reduce inflammation as well as immunotherapy meant to alter the body's response to environmental factors. Comorbid conditions such as vocal cord dysfunction and rhinosinusitis can obscure the diagnosis or affect patients' response to therapy. Asthma is a disease with nuance that frequently requires subspecialty, advanced knowledge but presents to general medical practitioners with regularity. Patients who have more than mild, intermittent symptoms, note that asthma has a significant impact on their quality of life and daily functioning. As such, greater efforts are being undertaken to improve education for patients and physicians alike about recognizing asthma, initializing appropriate therapy, monitoring response to treatment, considering contributing conditions, and understanding need for appropriate referral.

12.2 Asthma Definition and Impact

Asthma is a chronic inflammatory disease of the lungs characterized by intermittent airway obstruction and hyperreactivity (EPR3 2007). Pulmonary symptoms include but are not limited to: chest tightness, wheezing, shortness of breath with activity, and cough. People with asthma demonstrate a greater susceptibility to airway infections which results in symptom worsening during and after the infection. The infections which typically exacerbate asthma are viral infections, particularly certain strains of rhinovirus, adenovirus, influenza, parainfluenza, respiratory syncytial virus, and metapneumovirus. Asthmatics may also note pulmonary symptoms with or after exercise, when exposed to inhalant allergens or irritants, or when the air temperature and humidity change. The airflow obstruction often manifests as chest tightness and shortness of breath and is assessed by spirometry, which measures the air movement during expiration and evaluates a response to medications which dilate the airways.

One of the challenging issues surrounding asthma is the variability. Symptoms are typically episodic and patients may lack demonstrable lung dysfunction between incidences. But, there is also significant variability in the natural history and associated triggers for patients. Patients can present in infancy or early childhood with a history of wheezing with and after respiratory infections. Others have a strong allergic burden manifested by sensitivity to many potential aeroallergens. Affected individuals, both those with and without allergy, also are susceptible to worsening of symptoms following inhaled irritants. And yet, some people don't develop asthma until they are later in

adulthood and have no history of allergies, eczema, or family asthma. As a result, physicians can struggle to recognize asthma or individualize treatment appropriately when patients do not present with a stereotypical history and symptom profile.

The cost of chronic diseases is significant. Asthma, as it affects the young and the old, is particularly so. Whether considering direct economic costs from emergency department visits and prolonged hospital stays or indirect costs from lost work productivity, the impact on resource allocation and utilization is enormous. A study recently analyzed data in the USA from 2008 to 2013 and estimated a financial loss of 81.9 billion USD related to asthma over that time period (Nurmagambetov et al. 2018). In addition to economic losses, there are the incalculable costs in terms of human suffering for the people living with chronic symptoms that limit quality of life, and emotional and physical encumbrances placed upon caregivers.

12.3 Pathogenesis

Historically, asthma has been considered a homogenous disease involving eosinophil and mast cell inflammation, airway hyperresponsiveness, and improvement subsequent to treatment with corticosteroids (Fahy 2010). However, it is now more clearly elucidated that a multitude of inflammatory cells and signaling molecules play variable roles in disease activity with numerous pathways to airway obstruction resulting in respiratory symptoms. The unifying principle is the presence of components of the inflammatory cascade leading to lung dysfunction intermittently, often as a result of an interaction between environmental factors, the airway and resident cells in the airway.

Mast cells, basophils, eosinophils, neutrophils, Th1 lymphocytes, Th2 lymphocytes, other lymphocyte subsets, macrophages immunoglobulins, histamine, leukotrienes, chemokines, and interleukin glycoproteins (IL) are all implicated in the airway pathology of asthma. These cells and proteins modify or contribute to the inflammatory response and determine interactions between the environment and lung tissue (epithelial, vascular, and neurologic cells) that ultimately cause airway constriction in asthmatic patients (Holgate 2008). In the traditional understanding of asthma pathogenesis, there is a propensity for a Th2 predominant immune response. T-helper cells are stimulated by antigen-presenting dendritic cells, macrophages, and B cells. After activation of the T-cell receptor via the presented antigen, the T-helper cell undergoes maturation predominantly along the Th1 or Th2 pathway. The determining factors for selection of one developmental route over others are multifactorial. The microenvironment of local cytokines along with genetically-driven propensities factor heavily in the differentiation (Blumenthal and Fine 2014). Once the T-helper cell differentiates, a cascade of ensuing inflammatory mediators propagates a specific immunologic response. Subsequent to maturation into a Th2 cell, the cell releases IL-4, IL-5, IL-10, and IL-13. This results in: increased Th2 differentiation in additional T-helper cells, immunoglobulin class switching to immunoglobulin E (IgE) in antibody production, eosinophil migration, mast cell recruitment, and mucous production (Lloyd and Hessel 2010). Thus, Th2-driven immunologic response triggers greater proportions of Th2 in the cellular matrix and the process is cyclically reinforced. This immunologic phenotype is the best understood mechanism for pathophysiology of asthma.

Our understanding of asthma now encompasses a greater awareness of alternative phenotypes and how alternative mechanisms, such as IL-17-induced neutrophil recruitment, can affect patient presentations and response to therapy. A disproportionate amount of severe asthma is characterized by neutrophil dominance in the cellular profile (Pelaia et al. 2015). These patients are more likely to be poorly responsive to corticosteroids, the most fundamental treatment of eosinophilic, and classically atopic, asthma. Understanding the complex pathophysiology more completely will allow for greater decision making capabilities for treatment of refractory cases.

Whatever the means of inflammatory pathogenesis, the resultant or associated airway hyperresponsiveness and bronchial smooth muscle

constriction causes reduction in airway caliber. This narrowing over time can be associated with fibrosis beneath the mucosa, hyperplasia or hypertrophy of the bronchial smooth muscle, increase in mucous producing cells, and changes in vascular supply and endothelial function (Avdalovic 2015). The process is generally referred to as airway remodeling. Based upon the critical role of inflammation and the prominent pathology of bronchospasm, treatments have traditionally and overwhelmingly focused on anti-inflammatory medications and smooth muscle dilators that act locally in the airway. Emerging understanding of the various drivers of inflammation as well as the ability to more easily measure the degree of inflammation has created new areas of study for therapeutic targets and preventative strategies.

12.4 Diagnosis

Diagnosis of asthma is based on clinical factors combined with measurement of lung function demonstrating obstruction, variability, and, typically, reversibility (GINA 2018). No single, isolated element defines the diagnosis. Spirometry is used to assess the volume of air that can be exhaled under maximal effort in an individual. The forced expiratory volume in 1 s (FEV_1) as well as during the entire respiratory cycle (FVC) is assessed with spirometry. By comparing these two values, physicians can determine the presence of airflow obstruction in the lung. The FEV_1/FVC ratio is predictable based on the patient's age, gender, ethnicity, and height. A FEV_1/FVC ratio less than 0.70–0.75 is generally indicative of airway obstruction; older patients may have a lower baseline without clinical obstruction and younger patients may exhibit airflow obstruction at higher ratios based on epidemiologic studies (Stanojevic et al. 2008). The airflow obstruction resultant from bronchial constriction and inflammation in the airways results in prolonging the time it takes for chest wall and alveolar recoil to propel air from the lungs thereby decreasing the FEV_1 (Figs. 1 and 2).

In addition to demonstrating the airflow obstruction in patients with suspected asthma, the physician assesses the presence of reversibility of this obstruction (Fig. 3). Reversibility is generally considered a hallmark of asthma and a key distinguishing characteristic from chronic obstructive pulmonary disease (COPD). However, evolving understanding of how obstruction in asthma can become irreversible over time, due to remodeling of the airway, and in the nuanced understanding of patient-specific phenotypes and genotypes has led to greater appreciation that reversibility is not universally present. The accepted definition of reversibility is an increase in FEV_1 of 200 mL and greater than 12% from baseline in response to inhalation of a bronchodilator (GINA 2018). FVC and FEV1/FVC ratio may also increase, but the FEV1 is generally the most reliable parameter for assessing reversibility. Reversibility may also be evaluated over a period of days to weeks following initiation of anti-inflammatory therapy, such as inhaled or oral corticosteroids (Table 1).

12.4.1 Biomarkers in Asthma

Supporting diagnostic features of asthma include elevated sputum eosinophil counts, elevated peripheral blood eosinophil counts, elevated serum IgE levels, increased concentration of exhaled nitric oxide (FeNO), and elevated serum periostin levels (Berry and Busse 2016). Sputum eosinophilia is the most well-described marker in asthma and has been part of the traditional understanding of allergic-asthma associated with atopy. However, as emerging understanding of various subsets of asthma has grown so too have the possible biomarkers which can be used to define the disease, treatment, or response. Furthermore, sputum eosinophils are not easily obtained and therefore have more limited clinical utility outside of clinical trials and basic science research.

Periostin has emerged as an increasingly relevant matrix protein implicated in multiple types inflammatory processes and diseases. It plays a role in fibroblast recruitment that contributes to organ fibrosis. Periostin is elevated in several types of inflammatory diseases including but not limited to: otitis media, bone marrow fibrosis,

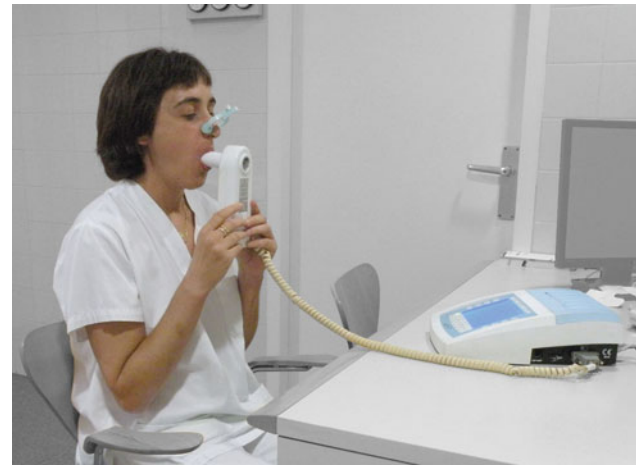

Fig. 1 Spirometry being performed

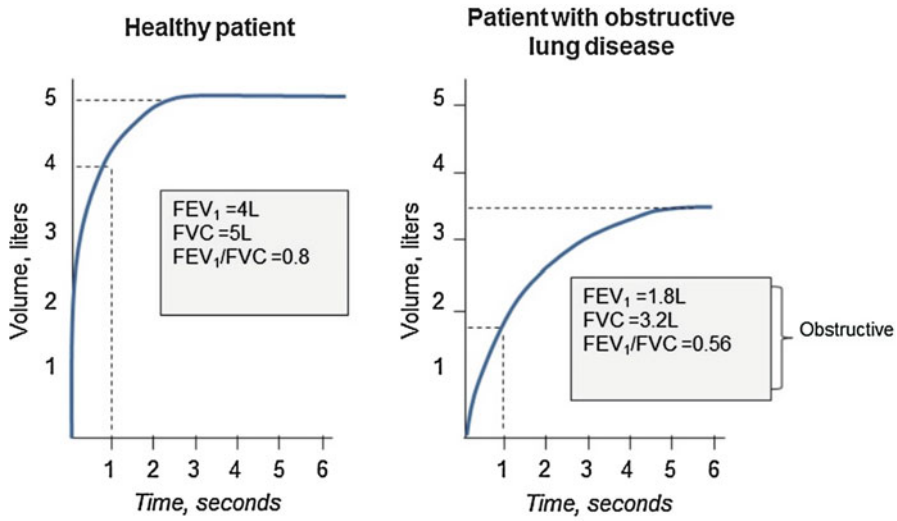

Fig. 2 Volume-time plot for spirometry comparing normal and obstructive disease

proliferative diabetic retinopathy, IgG-4 sclerosing disease, and scleroderma (Li et al. 2015). Atopic diseases, and particularly diseases associated with eosinophilia and/or increased IL-13 secretion, are strongly associated with periostin elevation. Atopic dermatitis, asthma, allergic rhinitis, and eosinophilic esophagitis are all positively correlated with increased blood periostin (Dellon et al. 2016). Asthma patients with elevated periostin are more likely to have late, adult onset asthma, concomitant nasal polyps and hyperplastic rhinitis, lower lung function, and aspirin sensitivity (Matsusaka et al. 2015).

Exhaled nitric oxide shows a relationship with airway inflammation and its elevation may predict responsiveness to inhaled corticosteroids in patients with asthma. However, titration of corticosteroid dose to lower exhaled nitric oxide is not associated with reduction of asthma exacerbation risk as consistently as the suppression of sputum eosinophilia (Jia et al. 2012).

Elevated IgE levels have long been linked with risk of asthma and risk of exacerbations (Platts-Mills 2001). This is most predominant in patients with allergic trigger-induced asthma. These patients frequently demonstrate allergen-specific

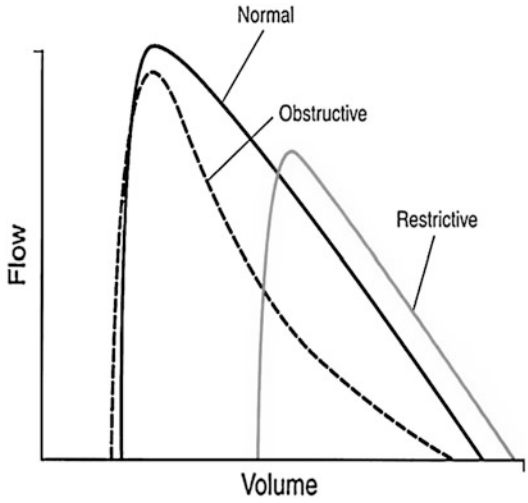

Fig. 3 Flow-volume loop from spirometry demonstrating normal, obstructive, and restrictive patterns

IgE increases and a hypersensitivity on prick testing to specific allergens.

Blood eosinophilia is a reasonably accurate surrogate marker of sputum eosinophilia, which is more difficult to obtain and to standardize (Wagener et al. 2014).

The use of these biomarkers does not supplant the role of a thorough clinical history, understanding of the nuance of the presentation of asthma, skilled physical diagnostics, and use of spirometry for lung function assessment. However, their identification and description of biomarkers has helped in the evolution of better understanding of the heterogeneity of asthma and, in particular, the assessment of patients with difficult to control disease or asthma unresponsive to corticosteroids.

12.5 Presentation and Phenotypes

Numerous symptoms are related to asthma. There are contributing signs from comorbid conditions, which may or may not be present, and many patients have only intermittent or transient complaints. As such, recognizing asthma can be difficult and categorizing asthma has been challenging. A phenotype is the set of observable characteristics of a person relating to the interaction of their genetic profile with the environment. Experts have described as many as nine phenotypes with overlap in the same patient (Lockey 2009) and considerable variation exists between asthma patients in the measurements used to categorize the disease (Busse et al. 2014). Such measurements include symptoms questionnaires, peripheral blood eosinophil count, IgE levels, degree of responsiveness to inhaled corticosteroids, and exhaled nitric oxide quantity.

Table 1 Diagnosis of asthma

Symptoms consistent with asthma
Variability of lung function and symptoms (except in severe disease where symptoms may be constant)
Response to bronchodilator therapy (>12% and 200 mL increase in FEV_1)

FEV_1 forced expiratory volume in 1 s

Patients may describe a history of cough and wheeze associated with viral infections in childhood and adolescence. There is often an atopic family or personal history including allergic rhinosinusitis, conjunctivitis, and eczema. Some patients do not present until later in life with chest tightness related to physical activity or nondescript breathlessness. The heterogeneity of asthma's presentation to the physician mirrors the array of inflammatory pathways and mediators that have been described in its pathogenesis. Describing asthma by phenotype is a useful classification tool to help clinicians consider the diagnosis and understand the disease. It should be noted that an individual patient may demonstrate overlap in their phenotype and they are therefore not exclusionary.

12.5.1 Allergic Asthma

Allergic asthma is the most prototypical and also the most common phenotype of asthma. This form of asthma is characterized by allergic sensitization to an allergen and a clinical history consistent with respiratory symptoms as a result of exposure to the antigen. Allergic asthma is more common in childhood asthma and is associated with a younger age of onset than other phenotypes. However, allergic asthma is still relevant in the adult population with asthma where the prevalence is described

as 60–75% of those with asthma (Lockey 2009). Sensitization is verified by either a positive reaction to skin prick testing or by detection of antigen-specific IgE in the patient's serum. Common antigens are fungal species, such as Aspergillus and Alternaria, dog, cat, grass, pollen, dust mite, and cockroach. Patients often describe perennial symptoms when they have sensitivity to nonseasonal allergens or with classic seasonal symptoms during pollen seasons. Family history of allergies and associated rhinosinusitis are frequently present. Patients classically have elevated eosinophil counts in sputum and serum, elevated IgE, and elevated periostin.

12.5.2 Nonallergic/Intrinsic Asthma

Nonallergic, or intrinsic, asthma has been difficult to define clinically and has been given various nomenclature over time. Predominantly, this form of asthma has been described more in how it differs from prototypical allergic asthma than in a cogent, unified phenotype in itself. Nonallergic asthma typically presents later in life is not associated with seasonal variation driven by aeroallergens and lacks the association with other atopic diseases. Literature often refers to intrinsic asthma as being synonymous with neutrophilic asthma. Patients with intrinsic asthma are more likely to have severe asthma and asthma that is poorly responsive to inhaled corticosteroids as compared to allergic asthma. There is an absence of skin prick test positivity or antigen-specific IgE and the total IgE in the serum is not elevated. Interestingly, IgE has been demonstrated in the airways of patients who lack atopic history or antigen-specific serum IgE and therefore are not characterized as allergic. Specific IgE directed against bacterial superantigens derived from staphylococcal species have been identified. Presence of superantigens may contribute to the poor responsiveness to inhaled corticosteroids that intrinsic asthma patients can display (Barnes 2009). However, the presence of eosinophilotactic cytokines and IgE in these patients shares homology with allergic asthma. Therefore, the inflammatory cascade in intrinsic and allergic asthma may have greater similarity than previously believed (Tak et al. 2015).

12.5.3 Aspirin Exacerbated Respiratory Disease

Aspirin-exacerbated respiratory disease has been known by various names as well. Sampter's Triad, Aspirin Triad, Aspirin Sensitive Asthma, and Aspirin or Nonsteroidal Anti-inflammatory Drug Exacerbated Asthma (AERD or NERD) have all been descriptive terms for the phenomenon. Epidemiologic studies suggest this form of asthma may be more common than commonly recognized. Some studies indicate the prevalence may be as high of 21% of adult asthmatics when tested by oral provocative challenge with aspirin (Lockey 2009). The age of onset is typically in early to mid-adulthood, though this may represent a diagnostic lag from lack of recognition. There is a slight female predominance in population analysis (Lockey 2009). AERD is classically associated with nasal polyposis, chronic rhinosinusitis, and peripheral eosinophilia. Frequently, the nasal symptoms of congestion, rhinorrhea, and anosmia precede the diagnosis or recognition of asthma, often by several years. Rhinosinusitis symptoms may be refractory to typical treatments and patients have a higher recurrence of polyposis after sinus surgery and more frequent need for repeat sinus surgery (Stevens and Schleimer 2016). The phenotype is defined by a documented asthmatic response after ingestion of aspirin or other nonsteroidal anti-inflammatory.

12.5.4 Infection-Induced Asthma

In patients with infection-induced asthma, the respiratory tract infection influences the asthma in several ways. Some patients are diagnosed with asthma after they have persistent wheezing, cough, and shortness of breath during and after a respiratory infection. In others, preceding asthma is exacerbated by the inflammatory response to infection. Respiratory infection can be the only trigger for asthma in patients or can be one of a

multitude of triggers in patients with other coexisting phenotypes, such as allergic asthma or AERD. Chronic rhinosinusitis exacerbated by acute infections can contribute to the airway symptoms in these patients. Infection is recognized as an impetus for severe asthma exacerbations in patients with all types of asthma. Respiratory syncytial virus (RSV), parainfluenza virus, human metapneumovirus, rhinovirus, and influenza virus have all been identified in patients with asthma exacerbations. In particular, the role of RSV in relationship to severe asthma exacerbations, as well as risk of asthma later in life in children, has been well described (Sigurs et al. 2005). However, more recent studies also postulate a role for mycoplasma and chlamydial infections in the pathogenesis of asthma development (Johnston and Martin 2005).

12.5.5 Exercise-Induced Bronchospasm

Exercise-induced bronchospasm (EIB), formerly referred to as exercise-induced asthma, is a complex phenomenon that creates confusion among patients and physicians. EIB manifests with chest tightness, cough, and wheeze that occurs after exercise. Symptoms typically peak approximately 10–15 min after cessation of vigorous activity. EIB is present in a substantial percentage of world-class athletes; estimates are as high as 25% of Olympic athletes and even 55% of endurance, cold-weather athletes (Molis and Molis 2010). A significant portion of patients with EIB do not have concomitant asthma when evaluated with provocation testing. Therefore, the diagnosis or suspicion of EIB should not lead to the assumption of underlying asthma. That being said, the majority of asthmatic patients will experience EIB when they exert themselves to a sufficiently high degree. Due to the inherent episodic and variable nature of asthma, occasionally, patients with mild intermittent asthma are labeled as having EIB. EIB is believed to be due to evaporative water and/or heat loss in the airway during exercise. Rapid breathing through the mouth during endurance exercise bypasses the humidifying and warming properties of the nasal passage resulting in cold, dry air interacting with the lower airway. Inflammatory mediators are augmented by this process resulting in bronchospastic response and symptoms. Interestingly, patients may experience a refractory period, wherein subsequent exercise does not trigger symptoms, for up to 4 h after the initial onset (Lockey 2009). EIB can be treated by pretreatment with inhaled short-acting beta-agonist therapy or oral montelukast.

12.5.6 Asthma COPD Overlap Syndrome

Asthma COPD overlap syndrome (ACOS) has emerged as an increasingly recognized, though controversial, phenotype of obstructive lung disease. Patients with this condition have features that are typical of chronic obstructive lung disease (COPD), such as chronic respiratory symptoms and poor reversibility on spirometry. However, they also display characteristics of intermittent worsening of symptoms and qualities of asthma phenotypes listed above: history of aeroallergen sensitization, personal and family history of atopy, and wheezing after respiratory infections. Often these individuals have a history of exposure to inhaled particles (e.g., environmental and occupational air pollutants, tobacco smoke) that are recognized to cause permanent lung damage. COPD and asthma share a common final pathway of airway remodeling, mucous production and resultant lung dysfunction, although the characteristics of the remodeling differ between asthma and COPD. Epidemiologic studies have demonstrated that poorly controlled asthma in childhood confers a greater risk for the development of fixed airway obstruction earlier in life (McGeachie et al. 2016). Cohorts of patients with chronic respiratory symptoms and poor reversibility, which suggest COPD, but also report a history of asthma, have increased frequency of exacerbations, increased healthcare utilization, and a more rapid decline in lung function (Hardin et al. 2014). Patients with ACOS have a reduced FEV_1/FVC ratio that typically remains less than 0.7 after

bronchodilator. However, they may exhibit a pronounced response to bronchodilator therapy with increase >12% of baseline FEV_1 or of >400 mL.

12.6 Comorbid Conditions

Numerous comorbid conditions can affect response to therapy or obscure the diagnosis of asthma. Prominent comorbid conditions that worsen asthma include: chronic rhinosinusitis, gastroesophageal reflux disease (GERD), obesity, obstructive sleep apnea, and depression (GINA 2018). Assessment for and management of these conditions is recommended for patients who have atypical asthma features or demonstrate poor responsiveness to therapy after formal diagnosis of asthma. The prevalence of vocal cord dysfunction is unknown but may affect up to 20% of subjects with asthma (Yelken et al. 2009). Vocal cord dysfunction may be aggravated by inhaled therapy for asthma resulting in the misperception of treatment resistant asthma. Less common conditions to consider in selected asthma cases include: hypersensitivity pneumonitis, eosinophilic bronchitis, atopic cough, bronchiectasis with or without associated immunodeficiency, bronchiolitis with or without connective tissue disease, interstitial fibrosis, cardiac failure with wheeze, and pulmonary hypertension. Patients with these conditions often complain of shortness of breath, cough, or wheeze and therefore can be mislabeled as having asthma due to the common nature of asthma in the general population. However, these conditions are not associated with bronchial hyperreactivity with provocation testing, such as methacholine, or variability in lung function (Morjaria and Kastelik 2011). The most difficult situations arise when patients have the presence of asthma alongside one of these mimicking conditions; symptoms are inevitably worse and escalation of asthma therapy does not improve the control of the comorbid condition.

Asthma plus syndromes include conditions where asthma is a defining feature of the disease with additional pathology that manifests as the phenotypic disease process. These include eosinophilic granulomatosis with polyangiitis (EGPA formerly designated Churg Strauss vasculitis) and allergic bronchopulmonary aspergillosis (ABPA). EGPA is defined by the vasculitis that coexists with asthma and requires systemic immunosuppression therapy to control disease. Pauci-immune glomerulonephritis and eosinophilia are hallmarks of the disease. ABPA describes patients with asthma that is exacerbated by sensitization to *Aspergillus* species or other select fungal genera. There is no universally accepted standards for diagnosis but suggested criteria include: presence of asthma, skin prick test positivity or specific IgE to *Aspergillus* species, elevated total IgE (typically >1000 IU/mL), precipitating serum antibodies to *Aspergillus fumigatus* or other species, radiographic abnormalities consistent with ABPA (bronchiectasis, mucous plugging, mosaic pattern air trapping), and eosinophilia (>500 cells/μL) (Agarwal et al. 2013) (Table 2).

Table 2 Conditions which can worsen asthma or asthma symptoms

Allergic rhinosinusitis
Aspirin sensitivity (aspirin-exacerbated respiratory disesae [AERD])
Allergic bronchopulmonary aspergillosis (ABPA)
Food allergy (increased risk of more severe asthma)
Ongoing exposure to sensitized aeroallergens (occupational, home, irritant)
GERD
Tobacco use
Obstructive sleep apnea
Obesity
Bronchiectasis
Vocal cord dysfunction
Immunodeficiency

Source: Adapted from Global Initiative for Asthma (GINA) 2018

12.7 Treatment

Treatment of asthma requires an understanding of core principles but also a recognition of the availability of alternate therapies and indications for referral to specialists. The focus of this chapter is the approach to core principles of treatment. Further details regarding biologic therapy and immunotherapy for desensitization is included elsewhere in this

work. It is important to recognize that close follow-up with patients to assess treatment response is a critical component of the care of the asthmatic patient. When symptoms are not improving, physicians should broaden their scope to think of comorbid or mimicking conditions as discussed above.

Education of the patient, on inhaler technique and awareness of symptoms, is fundamental to asthma treatment. This step at face value appears rudimentary but its importance cannot be overstated. Patient awareness of asthma activity and early intervention options improves outcomes (GINA 2018).

Therapy for asthma focuses on controller and rescue medications and is driven by patient symptoms and categorization of asthma by severity. There are many tables and references which outline the assessment of asthma severity and the appropriate controller medications to be considered based upon this assessment. Symptom severity is dependent on use of rescue medications, nighttime awakenings due to asthma symptoms, and limitation of activities. Asthma assessment requires measurement of lung function, usually with a peak expiratory flow rate or FEV_1 measurement. A stepwise approach is recommended by experts. This includes increasing the intensity of current therapy and adding additional agents when patients are not controlled and carefully reducing the intensity of therapy when patients demonstrate a sustained response and disease control (Tables 3 and 4).

Table 3 Asthma symptom control assessment

In the past 4 weeks has the patient experienced:
Daytime symptoms more than twice/week
Need to use rescue inhaler more than twice/week
Any limitation of activities due to asthma
Any nocturnal waking due to asthma
If none of these are present, then the patient is well controlled
If 1–2 of these are present, then the patient is partly controlled
If 3–4 of these are present, then the patient is uncontrolled/poorly controlled

Source: Adapted from Global Initiative for Asthma (GINA) 2018

The cornerstone of asthma control is the use of inhaled corticosteroid (ICS) therapy. This the most important pharmacologic component of asthma care. It does not provide immediate relief of symptoms but suppresses the inflammatory response in the airway that drives the underlying pathophysiology. Control of the inflammatory process is critical for long-term preservation of lung function, reduction in exacerbations, control of healthcare costs, and improvement in quality of life. ICS are organized in tiers of potency based on the concentration of the corticosteroid (Tables 5 and 6).

Inhaled corticosteroid therapy is safe and well tolerated. Dysphonia, oral candidiasis (thrush), and cough are the typical local side effects patients report. These effects are dose-dependent and a majority of patients report experiencing at least one of them (Williamson et al. 1995). The use of a spacer device and rinsing the mouth after ICS inhaler use reduces the likelihood of thrush. However, the dysphonia and cough result from laryngeal deposition and thus do not improve with these measures. Systemic effects are rare and typically only seen in patients using high dose ICS for prolonged duration. There is a measurable effect on suppression of the hypothalamic-pituitary-adrenal axis but the effect resolves when ICS therapy decreases and clinically significant adverse events are exceptionally rare (Kelly and Nelson 2003). There is also a marginal increased risk of osteoporosis with high-dose ICS taken for extended time periods (Kelly and Nelson 2003), and physicians can consider this when prescribing therapy in patients at a baseline higher risk of fracture. Reduction in growth velocity occurs in children receiving ICS therapy (CAMP 1999). This reduction in velocity of growth is typically transient after the first year of therapy but monitoring children to ensure return to normal growth patterns is a reasonable consideration. ICS use is additionally a risk factor for the development of glaucoma (Mitchell et al. 1999) and cataracts (Garbe et al. 1998). Highest risk for both of these conditions was in patients using high dose ICS for prolonged periods. Many of the reported side effects of ICS are confounded by intermittent

Table 4 Classification of asthma by symptom/severity

Parameter	Intermittent	Mild persistent	Moderate persistent	Severe persistent
Daily symptoms (cough, limitation of activity, breathlessness)	≤2 days/week	>2 days/week but not daily	Daily	Multiple times/day
Nocturnal awakening	≤2 nights/month [a]None	3–4 times/month [a]1–2 times/month	>1 time/week but not nightly [a]3–4 times/month	Nightly or more [a] > 1 time/week
Short-acting beta agonist use (rescue inhaler)	≤2 days/week	>2 days/week but not daily and not >1 time/day	Daily but not multiple times/day	Multiple times/day
Lung function	Normal FEV_1	Mild reduction possible in FEV_1 but >80% predicted	FEV_1 between 80% and 60% predicted	FEV_1 < 60% predicted

FEV_1 forced expiratory volume in 1 s
[a]Criteria for children <5 years of age
Source: Adapted from National Institutes of Health 2007

Table 5 Inhaled corticosteroid tiers for patients ≥12 years of age

Low-dose inhaled corticosteroids	Medium-dose inhaled corticosteroids	High-dose inhaled corticosteroids
Beclomethasone dipropionate (HFA) 100–200 mcg Budesonide (DPI) 200–400 mcg Ciclesonide (HFA) 80–160 mcg Fluticasone furoate (DPI) 100 mcg Fluticasone propionate (DPI or HFA) 100–250 mcg Mometasone furoate 110–220 mcg Triamcinolone acetonide 400–1000 mcg	Beclomethasone dipropionate (HFA) >200–400 mcg Budesonide (DPI) >400–800 mcg Ciclesonide (HFA) >160–320 mcg Fluticasone propionate (DPI or HFA) >250–500 mcg Mometasone furoate >220–440 mcg Triamcinolone acetonide >1000–2000 mcg	Beclomethasone dipropionate (HFA) >400 mcg Budesonide (DPI) >800 mcg Ciclesonide (HFA) >320 mcg Fluticasone furoate (DPI) 200 mcg Fluticasone propionate (DPI or HFA) >500 mcg Mometasone furoate >440 mcg Triamcinolone acetonide >2000 mcg

HFA hydrofluoroalkane propellant, *DPI* dry powder inhaler
Source: Adapted from Global Initiative for Asthma (GINA) 2018

Table 6 Inhaled corticosteroid tiers for patients 6–11 years of age

Low-dose inhaled corticosteroids	Medium-dose inhaled corticosteroids	High-dose inhaled corticosteroids
Beclomethasone dipropionate (HFA) 50–100 mcg Budesonide (DPI) 100–200 mcg Budesonide nebules 250–500 mcg Ciclesonide (HFA) 80 mcg Fluticasone furoate (DPI) 50 mcg Fluticasone propionate (DPI) 100–200 mcg Fluticasone propionate (HFA) 100–200 mcg Mometasone furoate 110 mcg Triamcinolone acetonide 400–800 mcg	Beclomethasone dipropionate (HFA) >100–200 mcg Budesonide (DPI) >200–400 mcg Budesonide nebules >500–1000 mcg Ciclesonide (HFA) >80–160 mcg Fluticasone propionate (DPI) >200–400 mcg Fluticasone propionate (HFA) >200–500 mcg Mometasone furoate ≥220–440 mcg Triamcinolone acetonide >800–1200 mcg	Beclomethasone dipropionate (HFA) >200 mcg Budesonide (DPI) >400 mcg Budesonide nebules >1000 mcg Ciclesonide (HFA) >160 mcg Fluticasone propionate (DPI) >400 mcg Fluticasone propionate (HFA) >500 mcg Mometasone furoate >440 mcg Triamcinolone acetonide >1200 mcg

HFA hydrofluoroalkane propellant, *DPI* dry powder inhaler
Source: Adapted from Global Initiative for Asthma (GINA) 2018

Table 7 Management based on severity

Therapy level	Step 1	Step 2	Step 3	Step 4	Step 5
Presentation	No risk factors for exacerbation and symptoms are well controlled (intermittent asthma classification)	Risk factor(s) for exacerbation present or symptoms only partly controlled (mild persistent asthma classification)	Uncontrolled symptoms (moderate persistent asthma classification)	Uncontrolled symptoms and poor response to prior step therapy (severe persistent asthma classification)	Severe symptoms and/or poor response to prior step therapy (severe persistent asthma classification)
Preferred controller	None	Low-dose ICS	If age > 11: Low-dose ICS/LABA If age < 11: Medium-dose ICS	If age > 11: Low-dose ICS/formoterol as controller and rescue[d] Or medium/high-dose ICS/LABA If age < 11: Referral to specialist	Referral to specialist for further assessment and adjunct treatment
Alternatives for control	Consider low-dose ICS if FEV1 < 80% of predicted	LTRA[a] If age > 11: Consider theophylline	Medium/high-dose ICS[b] Low-dose ICS + LTRA If age > 11: Low-dose ICS + theophylline	If age > 18: Add tiotroprium to regimen High-dose ICS + LTRA If age > 11: High-dose ICS + theophylline	If age > 18: Add tiotroprium to regimen Add oral corticosteroids to regimen Consider biologic therapy (anti-IL-5 or anti-IgE)
Rescue/reliever	PRN SABA	PRN SABA	If controller is low-dose ICS/formoterol, then use as PRN rescue as well[c] If not, then PRN SABA	If controller is low-dose ICS/formoterol, then use as PRN rescue as well If not, then PRN SABA	If controller is low-dose ICS/formoterol, then use as PRN rescue as well If not, then PRN SABA

ICS inhaled corticosteroid, *SABA* short-acting beta-agonist, *LABA* long-acting beta-agonist, *LTRA* leukotriene receptor antagonist

[a]LTRA are less effective than ICS for asthma control but maybe considered for patients unable to use

[b]Med/high-dose ICS is less effective than addition of LABA in patients >11 years of age

[c]Use of low-dose ICS/formoterol combination as both controller and rescue has shown to significantly reduce exacerbations and yield equally effective symptom control. It should be noted that this therapy is not FDA approved at this juncture but is being used in Europe. Source for footnote: Sobieraj et al. (2018)

[d]If patient is already on combination low-dose ICS/formoterol from step 3, then dose can be increased for maintenance therapy

Source: Adapted from Global Initiative for Asthma (GINA) 2018

or prior use of systemic corticosteroid therapy (Tables 7 and 8).

When ICS therapy alone is not sufficient for long-term symptom control, the addition of long-acting bronchodilators is the most typical next step in treatment. Long-acting beta-agonists (LABA) as well as long-acting anti-muscarinic agents (LAMA) are used in this capacity. There are numerous combination preparations of long-acting bronchodilators and ICS and choice of

Table 8 Tiered approach to asthma management

Current step	Current medication	Step down recommended
Step 5[a]	High-dose ICS/LABA + oral corticosteroid	Reduce dose of oral corticosteroid or replace with additional high dose ICS
Step 4	Medium- to high-dose ICS/LABA	Reduce ICS component of ICS/LABA combination by 50%
	Medium-dose ICS/formoterol as controller and rescue	Reduce to low-dose ICS/formoterol as controller and rescue
	High-dose ICS + alternative agent	Reduce ICS by 50% and continue alternative agent
Step 3	Low-dose ICS/LABA	Change to once daily use of low-dose ICS/LABA
	Low-dose ICS/formoterol as controller and rescue	Change to once daily use of low-dose ICS/formoterol as controller and continue PRN use as rescue
	Medium-dose ICS	Reduce ICS by 50%
Step 2	Low-dose ICS	Change to once daily use of low-dose ICS
	LTRA	Consider stopping controller if no symptoms for 6 months and no risk factors for worsening lung function present

LABA long-acting beta-agonist, *ICS* inhaled corticosteroid, *LTRA* leukotriene receptor antagonist
When using a combination ICS/LABA and stepping down therapy, focus on reduction of ICS dose but avoid elimination of LABA component as this has been shown to worsen asthma symptoms
Patients receiving ICS should not be taken off them completely as a general rule
[a]Strongly consider referral to asthma specialist for any Step 5 patients for step down management
Source: Adapted from Global Initiative for Asthma (GINA) 2018

agents should be based on cost to patient with consideration of insurance coverage and potency of ICS. Long-acting bronchodilator agents are not recommended as monotherapy in asthma as there is an increased risk of mortality in asthmatic patients treated this way. The US package label of ICS combination products with LABAs previously contained a warning statement of increased asthma death with LABAs. This statement was removed from ICS/LABA combination products in 2017 after several safety studies failed to confirm a risk of severe exacerbations or death with ICS plus LABA therapy. LAMA therapy has not been associated with increased asthma risk but is not recommended as monotherapy.

Additional medications to be considered when standard therapy is not effective or clinical conditions dictate include: leukotriene modifying agents, biologic therapies, immunotherapy, and theophylline. With the exception of leukotriene modifying agents, which are well tolerated and effective in the treatment of allergic asthma, use of these therapies should generally be done under the guidance of an asthma specialist. Further discussion about the details regarding biologic therapy (anti-interleukin (IL)-5, anti-IgE) is covered elsewhere and beyond the scope of this chapter.

Select patients with limited and sporadic symptoms, those with mild intermittent asthma or EIB for example, can use short-acting rescue therapy as their only pharmacologic management.

All asthmatic patients should be given access to and education on the use of rescue medications. Short-acting bronchodilators, typically short-acting beta-agonists but also short-acting anti-muscarinic medications, are central to rescue from symptoms of wheeze, chest tightness, and shortness of breath. These medications are important in symptom control and rapid relief, but their use should be monitored by patients and physicians alike and increased use is a clear sign of poor overall control. The use of short-acting agents is accepted as a marker of increased risk for worsening lung function and active asthma inflammation (GINA 2018). There is some newer research that indicates that as needed use of combination ICS/LABA with variable dosing, that is as a rescue medication in addition to being utilized as a controller medication, is as or more effective

than ICS/LABA fixed dose therapy as a controller with short-acting beta-agonist as rescue (Sobieraj et al. 2018).

Systemic corticosteroids are the mainstay treatment of significant exacerbations and rapid symptom improvement. Their side effects are well known and include hyperglycemia, hypertension, psychomotor activation, osteoporosis, diaphoresis, and others. Use of systemic corticosteroids is sometimes necessary chronically in a subset of severe asthma patients; these patients should be under the care of an asthma specialist who may consider use of advanced therapies based on biomarkers and phenotype. In some patients, often refractory to traditional therapy and disproportionately affected by exacerbations, the response to corticosteroids is blunted or lacking. Genetic alterations related to corticosteroid receptor function and responsiveness to corticosteroid administration have been identified in subpopulations (Sousa et al. 2000). Furthermore, increased numbers of neutrophils in the inflammatory substrate of some asthmatic patients and demonstration that these neutrophils do not respond as vigorously to corticosteroid-induced signaling has led to greater understanding of corticosteroid-resistant patients (Wang et al. 2016).

12.8 Conclusion

Asthma is a heterogeneous syndrome characterized by recognizable symptoms that are a manifestation of inflammation and maintained by a multitude of factors. Physicians need to understand the diagnosis of the disease based on measurable obstruction and variability as well as the conditions that accompany and mimic asthma. Therapy involves several medication types and potencies and guidelines are widely available to help guide clinical decision-making. Therapy should be directed at controlling inflammation and close follow-up with patients to ensure symptom control is critical to success and preservation of lung function. Whenever patients have poor response to fundamental treatments, physicians should consider referral to advanced specialists to guide care (Table 9).

Table 9 Asthma management key points

ICS is the mainstay of therapy
ICS should be added when patients have poorly controlled symptoms or have higher risk of exacerbations
LABA should not be monotherapy
Deescalating therapy should only be done when patient has been stable for prolonged period and should occur stepwise
If patient is using ICS/LABA therapy, deescalate by reducing ICS dose first
Refer to asthma specialist if patient is not responding appropriately to therapy

LABA long-acting beta-agonist, *ICS* inhaled corticosteroid
Source: Adapted from Ledford et al. (2018)

12.9 Cross-References

- Allergic Bronchopulmonary Aspergillosis
- Aspirin or Nonsteroidal Drug-Exacerbated Respiratory Disease (AERD or NERD)
- Asthma Phenotypes and Biomarkers
- Bronchodilator Therapy for Asthma
- Differential Diagnosis of Asthma
- Inhaled Corticosteroid Therapy for Asthma
- Occupational Asthma
- Pulmonary Function, Biomarkers, and Bronchoprovocation Testing

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Childhood Asthma

13

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Abstract

Asthma is the most common chronic respiratory disease in childhood. Although much progress has been made in the last decades in understanding the pathophysiology and management of asthma, the diagnosis and treatment of early childhood asthma remain great challenges. Due to the heterogeneity of asthma symptoms in childhood, it has been difficult to establish a clear and coherent definition of asthma in this population. Currently, in older children, the diagnosis of asthma is made similarly to that in adults and is based on chronic inflammation associated with airway hyperresponsiveness and reversible airflow limitation. However, the use of exhaled nitric oxide, bronchial challenge testing, and spirometry are often not feasible or reliable in younger children. In young children, the diagnosis of asthma is mostly based on symptom history, risk of allergic disease, and physical findings in the absence of respiratory tract infections. In all age groups, current asthma management guidelines focus on a stepwise approach to symptom and risk control while addressing comorbidities and other modifiable risk factors such as inhaler technique, treatment adherence, and environmental exposures. Asthma remains the leading cause of childhood morbidity from chronic disease as measured by rates of emergency department visits, length of hospitalization, and unscheduled school absences. Therefore, ongoing advances in the understanding of childhood asthma, the factors contributing to its development (both genetic and environmental), preventative strategies addressing these risks, and novel treatment options will continue to be crucial clinical considerations in the years to come.

Keywords

Asthma · Childhood asthma · Risk factors · Asthma treatment

13.1 Introduction

Asthma is the most common chronic respiratory disease in childhood and remains the leading cause of childhood morbidity from chronic disease as measured by rates of emergency department visits, length of hospitalization, and unscheduled school

absences. Although much progress has been made in the last decades in understanding the pathophysiology and management of asthma, the diagnosis and treatment of childhood asthma remain great challenges for pediatric physicians.

Due to the heterogeneity of asthma symptoms in childhood, especially in preschool children, it has been difficult to establish a clear and coherent definition of asthma in this population. Currently, the diagnosis of asthma in young children is mostly based on symptom history, risk of allergic disease, and physical findings in the absence of respiratory tract infections. In older children, the diagnosis of asthma is made similarly to that in adults and is based on chronic inflammation associated with airway hyper-responsiveness and reversible airflow limitation. While pulmonary assessments such as exhaled nitric oxide (F_ENO), bronchial challenge testing, and spirometry are useful in diagnosing asthma, these measures are difficult to obtain reliably in younger children.

It is well-accepted that asthma phenotypes result from a complex interplay of molecular mechanisms, epigenetic factors, and environmental exposures. However, there is a lack of consensus regarding asthma phenotypes in childhood, especially during infancy. While most childhood asthma is characterized by a T-helper type 2 (Th2) pathway, there is a growing body of evidence suggesting alternative mechanisms remain important in asthma development. Better understanding of childhood asthma phenotypes is needed and will be imperative for initiating asthma treatment, monitoring biomarkers, and targeting treatment strategies, especially as new therapies become available.

In addition, modifiable factors such as inhaler technique, treatment adherence, and harmful environmental exposures (e.g., tobacco smoke and pollution) persist as real challenges in disease control in children. These factors as well as the identification and treatment of comorbidities, such as atopic disease, sleep apnea, obesity, and gastroesophageal reflux, are critical in the evaluation of childhood asthma and in its treatment. Moreover, additional barriers to asthma care such as socioeconomic status, language proficiency, and literacy should be considered as part of a comprehensive asthma management program.

Finally, while the assessment and treatment of asthma are paramount for the pediatric physician, asthma prevention strategies must not be forgotten and should remain at the forefront of childhood asthma research.

13.2 Epidemiology

13.2.1 Prevalence of Childhood Asthma

Measure of asthma prevalence worldwide is challenging due to lack of consistent disease definition, difficulty with respiratory testing in some age groups, heterogeneous disease phenotypes, and socioeconomic impacts such as income, education, occupation, and area of residence. To date, the largest collaborative global cross-sectional survey of asthma prevalence in childhood has been the International Study of Asthma and Allergies in Childhood (ISAAC) (Asher et al. 1995). Phase I (1992–1996) included 721,601 pediatric participants from 156 centers in 56 countries. It used questionnaires to identify asthma-like symptoms in children (aged 6–7 years) and adolescents (aged 13–14 years). These results revealed a wide range of childhood wheezing prevalence worldwide, ranging from 4.1% to 32.1% in children (257,800 participants) and 2.1–32.2% in adolescents (463,801 participants). The highest prevalences of childhood wheeze were found in developed English-speaking countries (the United Kingdom, New Zealand, Australia, Canada, the United States) and some non-English-speaking Latin American countries (Asher and Weiland 1998); the lowest prevalences were found mostly in Asian countries (India, Taiwan, China, and Indonesia) (Asher et al. 1995).

ISAAC Phase III (2000–2003) was a repeat of the Phase I survey (with the inclusion of a new environmental questionnaire) occurring at least 5 years later with the intent to evaluate asthma trends. Phase III contained 193,404 children from 66 centers in 37 countries and 304,679 adolescents from 106 centers in 56 countries (Pearce et al. 2007). Results from Phase III revealed that asthma symptom prevalence mostly increased in

centers where it had previously been low and either stayed the same or decreased in centers where asthma symptom prevalence had previously been high (Pearce et al. 2007). However, almost all countries reported increases in lifetime asthma from Phase I to III irrespective of symptom prevalence (Pearce et al. 2007). These findings are consistent with other reports (Braun-Fahrländer et al. 2004; Kalyoncu et al. 1999; Mommers et al. 2005; Nowak et al. 2004; Ronchetti et al. 2001; Senthilselvan et al. 2003; Toelle et al. 2004).

13.2.2 Morbidity and Mortality

It is estimated that nearly 334 million individuals have asthma globally, and 14% of the world's children likely had asthma symptoms in the past year (Global Asthma Report 2014). Asthma morbidity is a major burden for children, their families, and healthcare systems. Asthma that is not well-controlled results in lifestyle disruption, reduced physical ability, school absences, and socioeconomic impacts resulting from lost work days, medication expenses, and healthcare costs associated with asthma care. In the United States alone, the total economic impact of asthma totals roughly $56 billion a year for the 25 million individuals with asthma (CDC 2011); more than half (53%) of individuals with asthma have an asthma attack per year, and, of those having an asthma attack, 59% of children and 33% of adults miss school or work, respectively (CDC 2011).

Overall, mortality from asthma is rare and comprises less than 1% of all deaths in most countries (Global Asthma Report 2014), likely due to better understanding of the underlying mechanisms of asthma and the availability of more effective treatments. In European countries, asthma mortality is highest among infants and preschool children, lower during school age, and increases again in adulthood (Wennergren and Strannegård 2002). In the United States, children with asthma have higher rates of primary care and emergency department visits but a lower death rate than adults (Akinbami et al. 2012); in 2007, in the United States, 185 children and 3262 adults died from asthma (CDC 2011).

13.3 Natural History of Asthma

Population studies assessing asthma remission or persistence/recurrence have differed in their results. Reported rates of childhood asthma remission range from 20% to 52% (Martin et al. 1980; Roorda et al. 1993; Vonk et al. 2004). Remission is associated with higher forced expiratory volume (FEV_1) in childhood and a higher increase in percent predicted FEV_1 through adulthood (Vonk et al. 2004), as well as earlier age of cessation of wheeze (Martin et al. 1980). Alternatively, analyses of population-based, childhood cohorts (starting age 7–9 years and followed through early adulthood) show asthma persistence rates ranging from 27% to 41% (Andersson et al. 2013; Sears et al. 2003). Factors that predicted persistence or relapse of asthma in these cohorts include sensitization to house dust mites, airway hyper-responsiveness, female sex, smoking at age 21 years, early age at onset (Sears et al. 2003), sensitization to furred animals, and more severe asthma (Andersson et al. 2013).

Further characterization of children experiencing remission versus persistence/relapse of asthma has been explored in the Tucson Children's Respiratory Study (TCRS). The TCRS, a birth cohort study of 1246 newborns followed through age 16 years, sought to identify the factors affecting wheezing before age 3 years and their relationship to wheezing and asthma through adolescence (Martinez et al. 1995; Morgan et al. 2005; Taussig et al. 2003). Participants were separated into three groups: (1) "transient infant wheezers," (2) "nonatopic wheezers," and (3) "atopic wheezers." The first group (transient infant wheezers) developed wheezing within the first 3 years of life. However, the majority (80%) of those with wheezing within the first year of life did not wheeze after age 3 years; this decreased to 60% and 40% with wheezing that persisted through years 2 and 3, respectively. These infants were not atopic, had diminished airway function at birth, and had either a mother who smoked during pregnancy or a younger mother; they did not have an increased risk of asthma later in life (Taussig et al. 2003). The second group (nonatopic wheezers) had lower respiratory infections

early in life (with strongest association noted with respiratory syncytial virus (RVS)) and continued to wheeze after age 3 years; it was felt that this group was more susceptible to acute airway obstruction following infection due to alterations in airway smooth muscle control, possibly virally induced or present at birth (Taussig et al. 2003). The third group (atopic wheezers) had wheezing that started both before and after age 3 years, but before age 6 years, most of these children had allergic sensitization noted by age 6 years, and most developed atopic asthma (Taussig et al. 2003).

Subsequently, the Isle of Wight Birth Cohort (IWBC) study, a whole population birth cohort, followed 1456 infants at 1 year, 2 years, 4 years, 10 years, and 18 years (Kurukulaaratchy et al. 2012). These participants were classified as "never asthma" (no asthma since birth), "adolescent-onset asthma" (asthma at age 18 years but not prior), "persistent-adolescent asthma" (asthma at both age 10 years and 18 years), and "recurrence of childhood asthma" (asthma in first 4 years of life, not at age 10 years, but again at age 18 years) (Kurukulaaratchy et al. 2012). Of asthmatics who had data available at both 10 years and 18 years, 63.1% had persistent-adolescent asthma, 28.3% had adolescent-onset asthma, and 8.6% had recurrence of earlier childhood asthma (Kurukulaaratchy et al. 2012). The IWBC study demonstrated that asthma remission was associated with mild disease before adolescence defined by few symptoms, low level of initial bronchial hyper-responsiveness (BHR), male sex, higher FEV_1 in boys, and low sputum eosinophil count (<3%) (Kurukulaaratchy et al. 2012).

The natural history of asthma in children might be schematically presented as in Fig. 1.

13.4 Risk Factors for Childhood Asthma

13.4.1 Genetic Risk Factors

Hereditary studies of families and twins indicate that genetics play a crucial role in development of childhood asthma (Willemsen et al. 2008). During the last decade, many studies have sought to delineate the role genetic factors play in the pathogenesis of asthma, especially childhood asthma, and whether these genes may correlate to airway inflammation, congenital BHR, and response to target treatment. Currently, by studying genome-wide linkage (GWL) or genome-wide association (GWA), more than 100 genes associated with asthma have been identified, and the number is growing.

The GABRIEL study a large meta-analysis of GWA studies in European populations genotyped 10,365 asthmatic patients and 16,110 control subjects to analyze the association between 582,892 single-nucleotide polymorphisms (SNPs) and asthma-identified genes on chromosomes 2 *(IL1RL1/IL18R1)*, 6 *(HLA-DQ)*, 9 *(IL33)*, 15 *(SMAD3)*, 17 *(ORMDL3/GSDMB)*, and 22 *(IL2RB)* (Moffatt et al. 2007). Especially, *ORMDL3* gene was associated with early-onset asthma in about 38% of all cases of childhood-onset asthma (Moffatt et al. 2007). A more recent meta-analysis evaluated >2 million SNPs in North American populations (European Americans, African Americans/African Caribbeans, and Latinos). This showed that SNPs near the 17q21 locus and the *IL1RL1*, *TSLP*, and *IL33* genes were associated with asthma risk in these ethnic groups, while the *PYHIN1* gene was associated with asthma in individuals of African descent (Torgerson et al. 2011).

Although GWA studies have discovered loci associated with childhood-onset asthma, the contribution of polygenic influences is more difficult to assess. The use of "genetic risk scores" may provide a useful tool to predict the link between genetic risks discovered in GWAS and the development or persistence of asthma in an individual.

13.4.2 Prenatal Risk Factors

13.4.2.1 Fetal Immune Response

Overall, maternal allergy impacts the development of allergic disease, presumably through alteration of the in utero environment and influence on prenatal immune development via placental transfer of immunoallergic factors (Lockett et al. 2015). Collectively, a multitude of studies

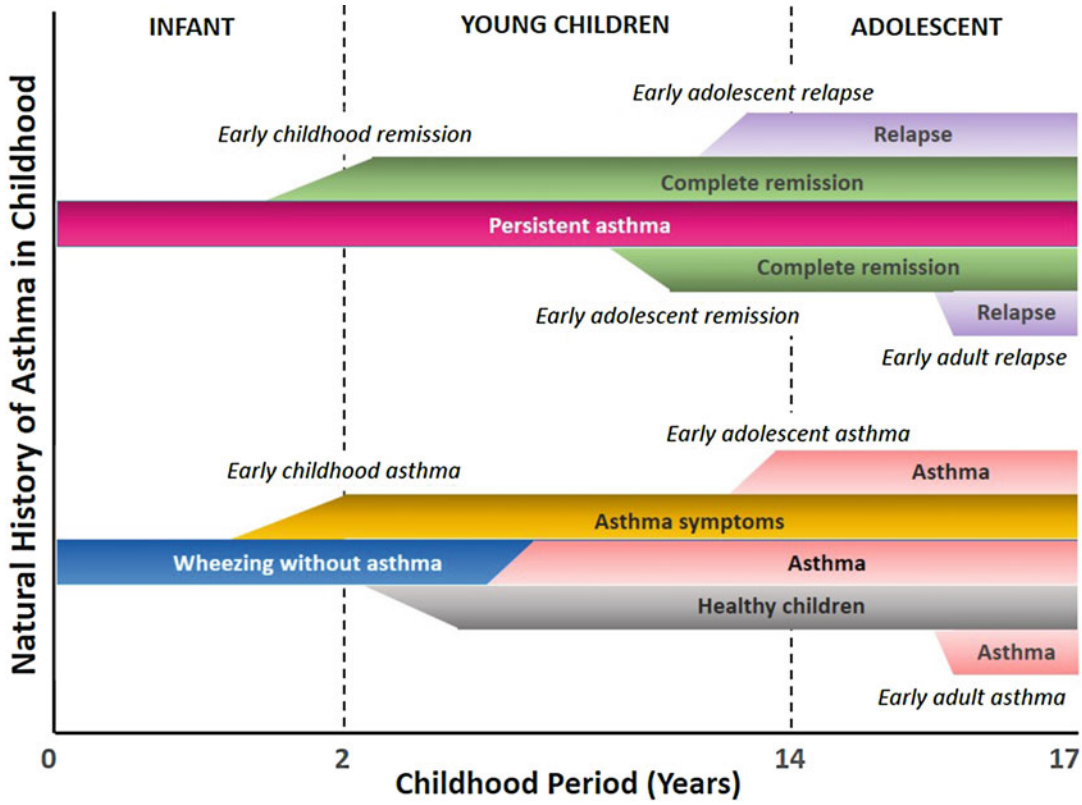


Fig. 1 Natural history of childhood asthma: persistent asthma in early childhood may have a complete remission in later childhood or remit and relapse later during childhood (top); early infants with wheezing without asthma may develop asthma symptoms/asthma or become healthy children without wheezing (bottom)

indicate that both innate and adaptive immune responses may be altered in utero in allergy-prone individuals through varied effects from immunoglobulin transfer, chemokine effects, toll-like receptor genotypes, Treg gene expression/development, Th2 cytokine levels, and methylation signals, among others (Bullens et al. 2015; Lockett et al. 2015; Fu et al. 2013; Liu et al. 2011; Martino et al. 2014). For example, in one study, maternal atopy status influenced Treg marker gene expression and Th2 cytokine levels in cord blood through interaction with toll-like receptor genotypes (Liu et al. 2011). In others, elevated cord blood levels of long-chain polyunsaturated fatty acids dose-dependently predicted the development of childhood respiratory allergies by age 13 years (Barman et al. 2013), and a cord blood CD4+ T cell DNA methylation signature at 96 CpGs sites predicted the development of food allergy by 12 months of age (Martino et al. 2014). The impact of such factors and other epigenetic changes induced by environmental exposures (de Planell-Saguer et al. 2014) on the development of asthma are still being explored.

13.4.2.2 Fetal Growth Restriction

There may be a causal link between fetal growth restriction and development of asthma, although the exact mechanism underlying this link is not well-demonstrated. Abnormalities in maternal-fetal circulation and development of the placenta, umbilical cord, and lung, as well as epigenetic alterations have all been suggested as pathways that explain fetal growth restriction during pregnancy (Martino and Prescott 2011).

The results of the Aberdeen birth cohort showed that for each millimeter increase in fetal crown-rump length (CRL), measured by ultrasound in

the first trimester, the odds of ever having wheezing decreased by 4%, and the odds of ever having asthma decreased by 5% (Turner et al. 2010). Additionally, this study revealed that reduced fetal size in the first trimester may be associated with reduced lung function and increased asthma symptoms at age five. Furthermore, the correlation between fetal dimension (by measuring CRL in the first trimester and biparietal diameter in the second trimester) and asthma remained at 10 years follow-up (Turner et al. 2011). The authors state that a continuous high fetal growth (high CRL at the first trimester and high biparietal diameter in the second trimester) may be a protective factor for future asthma development in childhood (odds ratio (OR) 2.8) (Turner et al. 2011).

13.4.2.3 Maternal Tobacco Smoke

Evidence-based data suggest that prenatal maternal smoking is associated with early childhood wheezing and reduced lung function in newborn infants compared to those of non-smoking mothers (Dezateux et al. 1999). Prenatal maternal smoking increases the risk of both asthma and impaired lung function throughout childhood as well as illness-related school absenteeism (Burke et al. 2012; Gilliland et al. 2003; Grabenhenrich et al. 2014); risk of childhood wheeze is increased with postnatal smoke exposure and is also noted with prenatal secondhand smoke exposure (Burke et al. 2012).

13.4.2.4 Maternal Drug Use

In the last decades, relationships between prenatal/infancy medication use and asthma in childhood have been reported. Longitudinal cohort studies and meta-analysis show that use of antibiotics during pregnancy increases risk of persistent wheeze and asthma in early childhood with a dose-response correlation between number of antibiotic courses and the risk of respiratory symptoms (wheeze or asthma) (Bisgaard et al. 2007; McKeever et al. 2002). In addition, this risk is further increased if the antibiotic is used during the last two trimesters of pregnancy (Jedrychowski et al. 2006). It has been hypothesized that an imbalance between pathogenic and beneficial bacteria due to antibiotic use plays a role in this asthma effect (Bisgaard et al. 2007).

Data assessing the association of prenatal and infancy use of paracetamol (acetaminophen) with increased risk of childhood asthma are mixed (Castro-Rodriguez et al. 2016; Hoeke et al. 2016; Migliore et al. 2015). A subsequent study involving 53,169 children at 3 years and 25,394 children at 7 years found a modest association between prenatal maternal paracetamol use and use of paracetamol in infancy with the development of asthma at both time points (Magnus et al. 2016). However, a systematic review and meta-analysis of 11 observational cohort studies found insufficient evidence to link paracetamol use to the development of childhood asthma due to confounding (Cheelo et al. 2015). Further studies are needed to better define the role that paracetamol may play in the development of asthma and to provide clarification of potential confounders.

13.4.2.5 Maternal Diet and Weight Gain

While no specific maternal dietary patterns have been associated with asthma in childhood, several ingestions during pregnancy seemingly reduce the risk of asthma or wheezing. These include "allergenic" foods (such as peanut, tree nuts, milk, and/or fish) (Bunyavanich et al. 2014; Maslova et al. 2012), long-chain fatty acid supplements (Bisgaard et al. 2016), and, in some studies, vitamin D and vitamin E (Nurmatov et al. 2011). Notably, results regarding vitamin D supplementation were not confirmed by randomized controlled trials (Chawes et al. 2016).

On the other hand, data currently suggest that maternal obesity and high gestational weight gain result in increased risk of development of wheezing or asthma (Forno et al. 2014; GINA 2017). However, unguided weight loss or dietary restriction in pregnancy is strongly not recommended due to concern for deleterious fetal and maternal effects.

13.4.2.6 Breastfeeding

Many studies report a beneficial effect of breastfeeding on asthma prevention and on reduction of wheezing in early life (Arbes

et al. 2007; Martinez et al. 1995). However, while breastfeeding should be encouraged, caution should be taken in advising families that breastfeeding will prevent asthma.

13.4.3 Childhood Risk factors

13.4.3.1 Aeroallergen Sensitization

Sensitization to allergens is one of the strongest determinants of subsequent development of asthma (Arbes et al. 2007; Martinez et al. 1995), and an increase in IgE level, a surrogate marker for allergen sensitivity, is associated with the incidence of childhood asthma (ISSAC 1998). Both the ISSAC study and the Childhood Asthma Management Program (CAMP) reveal that allergy-associated asthma is the most common asthma phenotype in children (CAMP Research Group et al. 2000; Strachan et al. 2015).

To date, studies focusing on single indoor allergen exposure (e.g., cat, dust mite, mold) and asthma development have been mixed, showing positive, negative, and no effect (Bufford and Gern 2007; Halonen et al. 1997; Lau et al. 2000; Lødrup Carlsen et al. 2012; Melén et al. 2001; Ownby et al. 2002; Quansah et al. 2012; Sporik et al. 1990; Takkouche et al. 2008). However, birth cohort studies suggest that a multifaceted allergen reduction strategy approach seems to reduce the incidence of asthma if applied in children, even up to age 18 years in some cases (MacDonald et al. 2007; van Schayck et al. 2007). Overall, evidence is insufficient to recommend increasing or decreasing exposure to common sensitizing allergens early in life as a means of primary prevention of asthma. Furthermore, the roles that a pro-allergic immune response in childhood, immature neonatal immune response, and innate system influences in atopic children play on the development of asthma require further clarification.

13.4.3.2 Presence of Food Allergy

Having food allergy increases a child's risk of asthma fourfold (Liu et al. 2010) and has also been associated with increased rates of hospitalization, exacerbations necessitating mechanical ventilation, and corticosteroid use in asthmatics (Liu et al. 2010; Roberts et al. 2003; Simpson et al. 2007). One study suggests that asthma may present at a younger age in children with food allergies (Schroeder et al. 2009).

13.4.3.3 Presence of Atopic Dermatitis

In children with recurrent wheezing, the coexistence of atopic dermatitis (AD) increases the risk for developing asthma (Castro-Rodríguez et al. 2000). Severity and age of onset of AD may also play an informative role. In one study, only 26% of children with mild to moderate AD developed an allergic respiratory disease (mainly asthma) compared to 75% with severe AD (Patrizi et al. 2000). Early-onset AD (before age 2 years) is associated with increased risk of onset of asthma at an earlier age (at age 6 years), whereas late-onset AD (after age 2 years) is associated with increased risk of onset of asthma at a later age (at age 12 years) (Lowe et al. 2017).

13.4.3.4 Gender

Multiple studies support the finding that males have more wheeze and asthma in childhood, but females have more wheeze and asthma in adolescence and thereafter. Additionally, asthma after childhood is more severe in females than in males (Almqvist et al. 2008). In one study, childhood asthma hospitalization rates were highest for boys between 2 and 12 years of age (peak hospitalization rate at 4 years) but were higher for girls between 16 and 18 years of age (peak hospitalization rate at 17 years) (Debley et al. 2004). Although hormonal changes have been suggested as a possible explanation for this trend, one study could not link pubertal stages with gender shift in asthma prevalence (Vink et al. 2010). Furthermore, in adolescent girls, but not adolescent boys, development of wheeze was associated with current smoking or being overweight (Tollefsen et al. 2007), suggesting a multifaceted explanation for the reversal of gender predominance noted through adolescence. Further exploration of factors driving gender differences in childhood asthma is ongoing.

13.4.3.5 Postnatal Smoking Exposure and Outdoor Pollutants

Tobacco smoke exposure is strongly associated with wheezing (Akinbami et al. 2013), although postnatal maternal tobacco smoke exposure is most relevant in the development of asthma in older children (GINA 2017). Children with asthma exposed to tobacco smoke (passive smoking or second-hand smokers) are at higher risk for uncontrolled asthma, with more severe asthma symptoms, and asthma exacerbations (Burke et al. 2012; Wang et al. 2015). Likewise, exposure to outdoor pollutants, such as living near a main road, is also associated with increased risk of asthma in childhood, especially for those who are also exposed to tobacco smoke in infancy (Gasana et al. 2012).

13.4.3.6 Microbial Effects

Recently, results from studies on hygiene and microflora suggest that interactions with microbiota may be beneficial in preventing asthma in childhood. The prevalence of asthma is higher in children born by Caesarean section than those born vaginally, suggesting that exposure of an infant to the mother's vaginal microflora through vaginal delivery (Huang et al. 2015) or differences in the infant gut microbiota according to their mode of delivery (Azad et al. 2013) may also be important in prevention of asthma. Moreover, the risk of asthma is also reduced in children whose bedrooms have high levels of bacterial-derived lipopolysaccharide endotoxin (Karvonen et al. 2012), and children raised on farms with exposure to stables and consumption of raw farm milk have a lower risk of asthma than children of nonfarmers (Riedler et al. 2001).

13.4.3.7 Parental History of Asthma

Family history of asthma is a known risk factor for development of asthma. Children with parents reporting a history of asthma in childhood may have decreased lung function and increased respiratory symptoms such as wheezing in early infancy and in later childhood (Camilli et al. 1993). One study of 306 children found that the odds of having a child with asthma were threefold greater in families with one asthmatic parent and sixfold greater in families with two asthmatic parents than in families where only one parent had inhalant allergy without asthma (Litonjua et al. 1998). Additionally, in a larger study comprising 2552 children, children were almost twice as likely to have asthma if they had a parent with asthma and more than four times likely to develop asthma if both a parent and grandparent had asthma (Valerio et al. 2010). Interestingly, more recently, the Isle of Wight Cohort analysis, after stratification of child's sex, demonstrated that maternal asthma was associated with asthma in girls but not in boys, whereas paternal asthma was associated with asthma in boys but not in girls (Arshad et al. 2012). Parental asthma also increases the risk of aeroallergen sensitization, a strong association for asthma development in early childhood (Crestani et al. 2004).

13.4.3.8 Respiratory Tract Infections

The role of respiratory tract infections in early childhood asthma development has been the source of debate over the last decades. It is hypothesized that repeated lower respiratory tract infections in childhood induce airway injury and increase susceptibility to inhalant allergens and other environmental risk exposures for asthma or provide the stimulus needed for gene-by-environment interactions (Busse et al. 2010).

A study of 154,492 European children followed from birth through age 15 years showed that both upper and lower respiratory tract infection before age 5 years increase asthma risk later in childhood (van Meel 2017). Children with upper respiratory infections (sinusitis, laryngitis, tonsillitis, or pharyngitis) by age 5 years had a 1.5-fold increased risk of developing asthma later in life, while those who had lower respiratory tract infections (bronchitis, bronchiolitis, or pneumonia) experienced a two to fourfold increased risk of developing asthma later in life. Interestingly, young children with both aeroallergen sensitization and viral respiratory infection may have synergistic risk for development of asthma at age 6 years, increasing ninefold if both aeroallergen sensitivities and at least two viral infections with wheezing occurred compared to only twofold if only aeroallergen sensitivity developed (without

viral infection with wheezing) and fourfold if only viral infection with wheezing noted (without aeroallergen sensitivity) (Kusel et al. 2007).

The relationship between respiratory syncytial virus (RSV) infection and the development of asthma is documented (the ISSAC study; Sigurs et al. 2000; Wu et al. 2008; Kusel et al. 2007; Jackson et al. 2008), although not all studies support the connection between RSV and asthma later in life. Infants from the Avon Longitudinal Study of Parents and Children with a history of severe RSV bronchiolitis necessitating hospitalization were 2.5 times more likely than controls to develop asthma by age 7.5 years (Henderson et al. 2005). The TCRS found that RSV infection before age 3 years was associated with wheezing and asthma in early childhood but not after age 11 years (Stein et al. 1999). Another study of twins suggested that RSV does not cause asthma but that genetic factors coupled with RSV infection are responsible for the development of asthma (Thomsen et al. 2009).

Studies assessing the impact of RSV prophylaxis or treatment on the development of asthma suggest an impact on the development of asthma but are limited in number and design. A retrospective investigation of 13 children treated with RSV immunoprophylaxis showed improved spirometry (FEV_1/FVC) and less atopy and were less likely to have an asthma attack 7–10 years after receiving immunoprophylaxis compared to those who did not receive immunoprophylaxis (Wenzel et al. 2002). An open-label compassionate-use RSV immunoprophylaxis (using palivizumab) study in a European cohort of 191 preterm infants suggested decreased wheeze at 19–43 months follow-up in those receiving prophylaxis (Simoes et al. 2007). One open-label study showed a reduction in the risk of asthma and allergic sensitization at 6 years of age among children less than 2 years old who were hospitalized and received ribavirin for RSV bronchiolitis (Chen et al. 2008).

The role of rhinovirus (RV) infection in predicting future asthma and severe asthma exacerbation has only been reported in more recent years. In the Childhood Origins of Asthma (COAST) birth cohort study, 90% of children with RV-associated wheezing episodes at age 3 years had asthma at age 6 years (Jackson et al. 2008). In this study, there was a 2.6 odds ratio (OR) for asthma by age 6 years if RSV infection occurred by age 3 years; this increased to a 9.8 OR if the infection was RV (Jackson et al. 2008). Additionally, similar to a prior study, Jackson et al. found that infants with both aeroallergen sensitization and RV wheezing had the highest incidence of asthma at age 6 years compared to populations with only RV wheezing or aeroallergen sensitization (Jackson et al. 2008).

13.4.3.9 Miscellaneous Risk Factors

Studies are ongoing regarding the aforementioned childhood asthma risk factors. Generally, it is not easy to identify the cause-effect of each risk factor for asthma development in childhood because children are usually exposed to multiple risk factors in early life that interfere with the control of gene-by-environment interactions (epigenetic factors) (Subbarao et al. 2009). Furthermore, the relationship between asthma in childhood and risk factors may change over time due to changes in living environment and/or modification of susceptibility. To date, the roles of maternal stress during pregnancy, mode of delivery, or breastfeeding on the risk of childhood asthma remain controversial. Other risk factors such as family socioeconomic status, air pollution, or microbiome remain to be clarified.

13.5 Asthma Phenotypes in Childhood

13.5.1 Background

Asthma in childhood is a heterogeneous disease with clinical manifestations varying from early infancy through later childhood. The phenotypes of asthma in childhood depend on molecular mechanism characteristics, or endotypes, epigenetic factors, and environmental exposures. The main molecular mechanism of childhood asthma is chronic inflammation resulting from inhalant

allergen-induced inflammation driven by the T-helper type 2 (Th2) pathway and mediated by the related cytokines IL-4, IL-5, and IL-13. These cytokines stimulate inflammatory cells such as eosinophils, basophils, and mast cells as well as injure epithelial and smooth muscle cells, thus contributing to the pathophysiology of asthma (Wenzel 2012). Asthma phenotyping in childhood related to Th2 pathophysiology mainly includes allergic asthma (early-onset asthma). However, there is a large body of evidence showing that non-Th2, or Th2-low, pathways may trigger asthma by alternative means such as neutrophilic, Toll-like receptor (TLR), Th1, and Th17 related-mechanisms. Examination of cellular components and biomarkers of airway inflammation are helpful in delineating Th2-high (eosinophilic) or Th2-low (non-eosinophilic) and for informing treatment. Better understanding of such phenotypes is imperative for initiating asthma treatment, monitoring of compatible biomarkers, and targeting treatment strategies.

13.5.2 Asthma Phenotypes in Childhood

13.5.2.1 Asthma Phenotypes in Infancy

Asthma in infancy is mostly Th2-related disease characterized by early-onset asthma. The diagnosis of asthma in infancy and in preschool age is based on wheezing as the main presenting clinical symptom. However, some children have wheezing early in life but do not have asthma, contributing to the challenge of diagnosing asthma in early childhood. Therefore, both pre- and postnatal risk factors should be considered in addition to wheezing in the classification of asthma phenotypes in this population. Of note, most infants with asthma also display other atopic diseases, such as atopic dermatitis and aeroallergen sensitization (Burgess et al. 2008; Guilbert et al. 2004; Shaaban et al. 2008). Currently, there is no consensus on classification of asthma phenotypes in early childhood (early infancy through preschool age), although several clusters have been proposed (Table 1).

Table 1 Asthma phenotypes in early infant (early childhood)

Phenotypes	Features
Phenotype 1: Recurrent wheezing with risk factor	
	Atopy: allergic dermatitis, allergic rhinitis, or skin prick test (+) Recurrent wheezing: unrelated to airway infection Pre- or postnatal risk factors of asthma: see Sect. 4
Phenotype 2: Persistent wheezing with risk factor	
	Atopy: allergic dermatitis, allergic rhinitis, or skin prick test (+) Persistent wheezing: unrelated to airway infection Pre- or postnatal risk factors of asthma: see Sect. 4
Phenotype 3: Recurrent or persistent wheezing with high rate of hospitalization	
	Atopy: allergic dermatitis, allergic rhinitis, or skin prick test (+) Recurrent or persistent wheezing High rate of annual hospitalization: ≥4 times/years
Phenotype 4: Recurrent or persistent wheezing with risk factor and high rate of hospitalization	
	Atopy: allergic dermatitis, allergic rhinitis, or skin prick test (+) Recurrent or persistent wheezing High rate of annual hospitalization: ≥ 4 times/years Pre- or postnatal risk factors of asthma: see Sect. 4

13.5.2.2 Asthma Phenotypes After Infancy

In children 5 years of age or older, clinical manifestations of asthma are often more diverse and follow the trends of diagnosis similar to adult patients. Furthermore, in these older children, the interaction between genetic factors and environmental factors may modify the clinical presentation of asthma. The Childhood Asthma Management Program (CAMP) study, evaluating 1041 children aged 5–12 years over 48 months, suggested 5 asthma phenotypes based on 3 main features: allergy status, degree of airway obstruction, and history of exacerbations (Howrylak et al. 2014); these are summarized in Table 2. These clusters were consistent with those identified in

Table 2 Asthma phenotypes in children according to Howrylak et al. (2014)

Phenotypes	Features
Phenotype 1: Mild asthma with low atopy, obstruction, and exacerbation rate	
	Largest subgroup of patients (28.8%) No history of allergic disease, lowest prevalence of hay fever or skin prick test reactivity, lowest IgE levels Preserved lung function (highest FEV_1/FVC ratio) Lowest bronchodilator response, intermediate airway hyper-responsiveness No prior hospitalization for asthma and lowest reported prevalence of emergency department visits Lowest risk of exacerbation[a]
Phenotype 2: Atopic asthma with low levels of obstruction and medium rates of exacerbation	
	Universally report allergic disease, high prevalence of allergic rhinitis, and skin test reactivity Preserved lung function (highest FEV_1) Intermediate bronchodilator response and airways hyper-responsiveness No prior hospitalization, low rates of prior emergency department visits Low-to-intermediate risk of exacerbations[a]
Phenotype 3: Atopic asthma with high levels of obstruction and medium rates of exacerbation	
	Rarely self-report allergic disease (in contrast to cluster 2) but have the highest prevalence of allergic rhinitis and skin test reactivity Most reduced lung function (lowest FEV_1 and FEV_1/FVC ratio) High bronchodilator response and most severe airways hyper-responsiveness Few prior hospitalizations but intermediate rates of prior emergency department visits (similar to cluster 4) Intermediate risk of exacerbations[a]
Phenotype 4: Moderately atopic asthma with high levels of obstruction and high exacerbation rates	
	No history of allergic disease, intermediate prevalence of hay fever (52.9%), lower IgE levels Reduced lung function (low FEV_1/FVC ratio, similar to cluster 5) High bronchodilator response and high airways hyper-responsiveness Most reports of prior hospitalization but intermediate rates of prior emergency department visits but intermediate rates of prior emergency department visits Intermediate-to-high risk of exacerbation[a]
Phenotype 5: Highly atopic asthma with high levels of obstruction and high exacerbation rates	
	Smallest subgroup of patients (9.3%) Nearly universal allergic disease, highest prevalence of skin test reactivity, highest IgE levels, highest eosinophilia, intermediate prevalence of allergic rhinitis Reduced lung function (low FEV_1/FVC ratio, similar to cluster 4) Highest bronchodilator response and severe airways hyper-responsiveness Most reports of prior hospitalization and highest rate of emergency department visits Highest risk of exacerbation[a]

[a]Poor long-term asthma exacerbation risk is defined from prospective survival analysis of time to first course of oral prednisone. This variable was derived by using the defined cluster groupings and was therefore not considered in spectral cluster analyses used to define the clusters (Howrylak et al. 2014)

the Severe Asthma Research Program (SARP) study (Fitzpatrick et al. 2011).

The SARP study also sought to better characterize the phenotypes of severe childhood asthma in children and identified 4 clusters in 161 severe asthmatic children greater than 5 years old based on symptom frequency, medication usage, lung function abnormalities, and comorbidities such as atopy (Fitzpatrick et al. 2011): (1) relatively normal lung function and less atopy; (2) slightly lower lung function, more atopy, and increased symptoms/medication usage; (3) greater comorbidity, increased bronchial responsiveness, and lower lung function; and (4) lowest lung function and the greatest symptoms/medication usage. The most severe phenotype in SARP study (phenotype 4) is consistent with the severe "Th2-high" phenotype in adults, characterized by IL-13-induced epithelial gene expression (high levels of periostin), immunoallergic airways inflammation

(increased eosinophil counts), and high risk of exacerbation (Woodruff et al. 2009).

13.6 Diagnosis of Asthma in Childhood

13.6.1 Clinical Manifestations of Childhood Asthma

Recurrent wheezing is the main symptom of asthma in children ≤5 years old, although not all wheezing in this age group indicates asthma (see Sect. 6.2 below). Parent or family report of symptoms may include recurrent or persistent nonproductive coughing accompanied with wheezing episodes and/or breathing difficulties, cough without cold symptoms, and recurrent breathlessness described as "difficult breathing," "heavy breathing," or "shortness of breath" during exercise. Atypical symptoms such as unwillingness to walk and play, irritability, tiredness, and mood changes may also be present and signal uncontrolled asthma in young children. Hence, review of a child's wheezing, daily activities, and behavior are important keys when assessing children with asthma.

Asthmatic children older than 5 years usually report shortness of breath, chest congestion or tightness, and sometimes non-focal chest pain that may be triggered by viral infection, inhaled allergens, and/or exercise. Respiratory symptoms may be worse at night, causing sleep disturbance and increased incidence of obstructive sleep apnea (OSA). Daytime respiratory symptoms are often linked with physical activities, especially in children with exercise-induced asthma. Other nonspecific asthma symptoms in school-age children may include school absence, decreased quality of learning, and general fatigue.

Physical examination in children is most informative during an acute asthma exacerbation. Expiratory wheezing, prolonged expiratory phase, and rhonchi may be auscultated. Additionally, physical examination may reveal labored breathing, respiratory distress, suprasternal and intercostal retractions, nasal flaring, and accessory respiratory muscle use. In the case of severe exacerbation, physical exam may be falsely reassuring when severe airflow limitation results in a "silent chest." A normal lung examination without acute asthma exacerbation does not rule out the diagnosis of asthma in childhood. Just as family history of asthma and atopic diseases such as eczema, atopic dermatitis, allergic rhinitis, or food allergy are useful for supporting the diagnosis of asthma, so are the concomitant findings of nasal polyposis, atopic dermatitis, and rhinitis.

Lung function testing or bronchial responsiveness testing (see below) are useful in defining impaired lung function or reversible obstruction consistent with asthma. These measures, coupled with history and physical exam, aid in the diagnosis of asthma in childhood.

13.6.2 Differential Diagnoses of Childhood Asthma

Many conditions in childhood have respiratory symptoms and signs similar to those of asthma. In early life, chronic coughing and wheezing might suggest gastroesophageal reflux (GER), rhinosinusitis, recurrent aspiration, laryngotracheobronchomalacia, airway anatomic abnormality (e.g., vascular ring), foreign body aspiration, cystic fibrosis, or bronchopulmonary dysplasia. Suspected asthma with chronic cough and recurrent upper and lower airways infections should be differentiated from primary cilliary dyskinesia, bronchiolitis obliterans, Churg-Strauss vasculitis (eosinophilic granulomatosis with polyangiitis), and immunodeficiency.

13.6.3 Laboratory Tests

13.6.3.1 Pulmonary Function Testing

Forced Oscillation Technique

Forced oscillation technique (FOT), also referred as the impulse oscillometry (IOS), is a useful tool for diagnosing young children with asthma (<5 years) because it requires only passive tidal breathing. FOT measures respiratory system resistance and reactance at several frequencies. It involves the application of a miniature loudspeaker

placed proximal to the device's flow sensor and produces forced oscillations of flow with a range of frequencies into the airway via a mouthpiece. Technically, children will be asked to breathe normally (tidal breathing) through a mouthpiece over a 30-s interval during which 10 stable respiratory rhythms are obtained (Fig. 2). Children must sit still with a mouthpiece in mouth and nose clips in place. The technician's or parent's hands should support the child's cheeks and floor of the mouth. The tongue cannot move around or obstruct the mouthpiece. In children with asthma, FOT can be used to measure bronchodilator response and perform methacholine challenges. Due to its relative ease of use, FOT is a reproducible and suitable method of lung function testing in younger children and especially in children who cannot perform spirometry (Delacourt et al. 2001).

Interrupter Technique (Rint)

The interrupter technique (Rint) is an alternative method that measures airway resistance (Raw) in very young asthma children. Similar to FOT, it also involves passive tidal breathing through a mouthpiece in a seated child wearing a nose clip (Beydon et al. 2007). Technically, the mouthpiece has to be held between the teeth, and the lips must be sealed around its circumference. The child's neck should be slightly extended with the cheeks supported by the operator's hands to decrease upper airway compliance. With passive breathing, the respiratory cycle is automatically "interrupted" multiple times (no more than 100 ms at a time) at a preset trigger to allow equilibration of alveolar and mouth pressure. "Rint" is defined as this pressure divided by the airflow measured immediately before interruption. Rint measurements may be obtained during either inspiratory or expiratory cycle with no significant difference between values obtained in either phase (Beydon et al. 2007). Rint measurements are useful to evaluate bronchodilator response and may be helpful in methacholine challenge, although Rint sensitivity in diagnosing bronchial hyper-responsiveness is lower than that of other more conventional methods such as methacholine challenge or histamine challenge (Beydon et al. 2007). To date, this technique is used extensively in Europe but remains primarily a research technique in the United States.

Spirometry Testing

Spirometry is the most common pulmonary function testing performed in school-age children and may be utilized in some younger children who are able to meet technical criteria. However, children

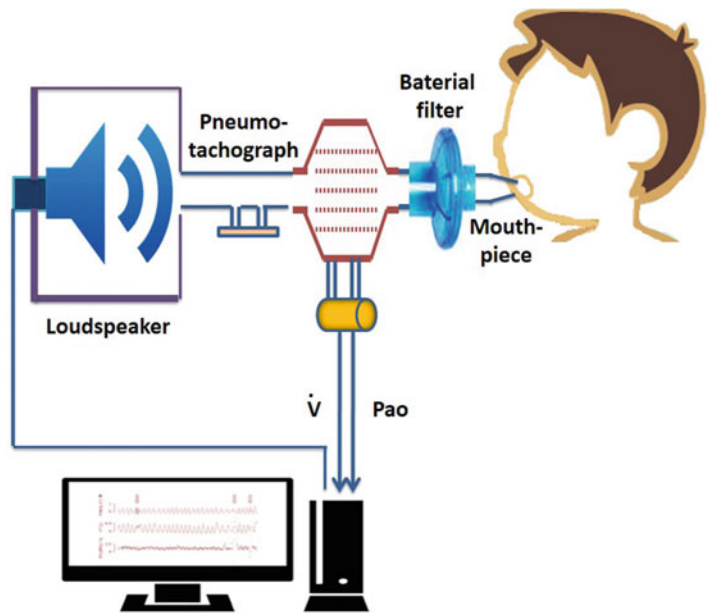


Fig. 2 Model of forced oscillation technique system (FOT)

of all ages may have difficulty meeting quality-control criteria outlined by the American Thoracic Society (ATS) and European Respiratory Society (ERS) (Miller et al. 2005); hence, as is true in all patients, attention to test performance is crucial in interpreting results. Most asthmatic children can perform spirometry with adequate technique and repeatability by age 5 years. Technically, spirometry is performed with the child in a standing or seated upright position wearing nose clips. The child's lips must be sealed around the mouthpiece, and the maneuver should begin with minimal hesitation. As recommended, a minimum of three maneuvers should be recorded (Beydon et al. 2007). For some children, if technique is improving with successive maneuvers, then more attempts may be helpful, although results should note number of technically satisfactory maneuvers and the repeatability of results.

Measures of spirometry include forced expiratory volume in 1 s (FEV_1), forced vital capacity (FVC), FEV_1/FVC ratio, and peak expiratory flow (PEF). In children with asthma, the goals of performing spirometry are to identify the presence of airflow limitation (obstructive defect) based on FEV_1/FVC ratio $<80\%$, to quantify the severity of airflow limitation based on FEV_1 (mild, FEV1 $>80\%$; moderate, $60\% \leq FEV_1 \leq 80\%$; and severe, $FEV_1 <60\%$ of predicted values), and to measure the response to bronchodilator (with short acting β_2-agonist) or a bronchial provocation test (with methacholine or histamine) by comparing the change of FEV_1 pre- and posttests. Spirometry is especially useful in children who are poor perceivers of airflow obstruction or when physical signs or symptoms of asthma do not occur until airflow obstruction becomes severe.

13.6.3.2 Bronchial Responsiveness Tests

Bronchodilator Reversibility Testing

Measure of bronchodilator responsiveness, also called reversibility testing (BRT), aims to determine evidence of reversible airflow limitation by comparing baseline spirometry with that obtained after short-acting bronchodilator administration. To perform BRT, children should avoid short-acting β_2–agonists (SABA) for 4 h prior to testing and long-acting β_2-agonists (LABA), slow release β_2-agonists, or oral therapy with aminophylline at least 12 h prior to testing (Miller et al. 2005). After obtaining baseline spirometry (as per above), two inhaled doses of 100 mcg of albuterol/salbutamol, separated by 30 s, through a spacer device are administered. Each dose should be followed by holding the breath for 5–10 s, and post-bronchodilator spirometry should be performed 10–15 min after the second dose. The improvement of FEV1 $\geq 12\%$ or >200 mL is consistent with asthma in children (Miller et al. 2005).

Bronchial Challenge Testing (BCT)

Bronchial challenge testing (BCT) utilizes pharmacological therapy or other challenge mediums to determine bronchial hyper-responsiveness in children with nonspecific respiratory symptoms who have normal pulmonary function testing, including response to bronchodilators. BCT can be performed with methacholine, histamine, carbachol, adenosine 5′-monophosphate (AMP), cold air, dry air, or exercise (Beydon et al. 2007).

In asthmatic children, children eligible for BCT are those free of respiratory infections for at least 3 weeks, free of wheezing, with normal oxygen saturation ($>95\%$), and with near-normal pulmonary function parameters in the setting of doubtful asthma (Crapo et al. 2000). Current guidelines recommend against use in preschool-age children (Crapo et al. 2000). Medications known to influence bronchial responsiveness should be withheld before the test (β_2-agonists, leukotriene modifiers, cromolyn sodium, and nedocromil).

The five-breath dosimeter method is generally used to deliver methacholine (or histamine) in BCT for children. The minimal inspiratory time required to inhale a dosimeter-delivered dose of solution is at least 3–5 s (deep inhalation) with a maximal nebulization time of 0.6 s. The interval between two inhalations should be 5 min (American Thoracic Society 2000). The provocative concentration (PC) or provocative dose (PD) is the accumulated inhaled concentration necessary to obtain a given pulmonary function test change from baseline. The dose that provokes a 20% baseline decrease of FEV_1 (or $PtcO_2$) is referred

as PD20-FEV_1 (or PD20-$PtcO_2$, transcutaneous partial pressure of oxygen), and the concentration that induces a 40% baseline increase in Rrs (total resistance of the respiratory system) is PC40-Rrs. Exercise induced-BCT is positive when FEV_1 decreases during or after exercise by >15%.

At the end of BCT, bronchodilators (β_2-agonist) should be administered even if the child does not demonstrate significant bronchoconstriction (wheezing or dyspnea), and the child should be monitored until the FEV_1 has returned to baseline. Oxygen, resuscitation equipment, and bronchodilators should be readily available throughout the provocation challenge.

13.6.3.3 Measure of Exhaled Nitric Oxide in Childhood Asthma

Role of Exhaled Nitric Oxide in Childhood Asthma

In the human respiratory system, nitric oxide (NO) is a biological mediator produced by the airways and lung (Dinh-Xuan et al. 2015). NO is present in the exhaled breath and implicated in the pathophysiology of lung diseases, including asthma. Currently, NO is considered a biomarker of Th2 or T2 airway inflammation and is synthesized by inducible nitric oxide synthase (iNOS) in epithelial cells, macrophages, neutrophils, eosinophils, and mononucleated cells (Prado et al. 2011). The levels of NO in exhaled air (fractional exhaled nitric oxide: F_ENO) is significantly increased in the majority of asthma phenotypes and can be detected with portable devices by using a chemical electrolytic technique. The measurement of F_ENO is a noninvasive, easy to perform, and safe technique for assessing airway inflammation in asthma. Since the early 1990s when F_ENO was first measured, many studies show close correlations between F_ENO levels and eosinophil counts in peripheral blood, sputum, bronchoalveolar lavage fluid, and in biopsied lung tissue. Therefore, F_ENO can be used as a relevant biomarker of airway inflammation in management of adult as well as childhood asthma. The measure of F_ENO also helps to predict asthma exacerbations, ICS response (decreases with ICS), and compliance to ICS (Dweik et al. 2011). Recently, F_ENO measurement has been recommended by GINA in monitoring patients with asthma (GINA 2017). Moreover, as recommended by the ATS, F_ENO predicts the likelihood of response to ICS more consistently than spirometry, bronchodilator response, peak flow variation, or airway BCT to methacholine (Dweik et al. 2011). Thus, high levels of F_ENO in children with asthma are a reliable marker for T2 or Th2 airway inflammation mediated by eosinophils and suggest a robust response to ICS.

Technical Issues Related to Measurement of Exhaled Nitric Oxide

Fractional exhaled nitric oxide (F_ENO), as measured in parts per billion (ppb), can be obtained by chemiluminescence or an electrochemical method. The technique using an electrochemical method has been developed recently for ambulatory use with portable devices. In children <12 years old, F_ENO should be obtained at a single flow rate of 50 mL/s for a duration of exhalation lasting at least 4 s (with 3 s at a plateau curve) (Dweik et al. 2011). The use of a nose clip to avoid the risk of contamination from NO produced in the nasal and sinus cavities is not necessary in children (Dinh-Xuan et al. 2015). It is recommended that F_ENO measurements be obtained before performing forced expiratory maneuvers for spirometry and at least 30 min after sustained exercise, as these may impact F_ENO results. In children, F_ENO may also be affected by age. However, it is suggested that in children (<18 years), F_ENO <20 ppb indicates non-eosinophilic inflammation with less likely responsiveness to ICS, and F_ENO >35 ppb is suggestive of eosinophilic inflammation to which ICS responsiveness is more likely. The values of F_ENO between 20 ppb and 35 ppb in children should be interpreted cautiously and with reference to clinical context. Moreover, when using F_ENO in monitoring airway inflammation in children with asthma, variation of F_ENO of 20% (if F_ENO >50 ppb at baseline) or 10 ppb (if F_ENO <50 ppb at baseline) may be considered significant (Dweik et al. 2011).

13.6.3.4 Other Laboratory Test in Childhood Asthma

Allergy Tests

Allergy tests are necessary examinations in childhood asthma. The presence of allergic status (atopy) increases the probability of asthma in children with respiratory symptoms. Children with atopic status can be identified by skin prick testing (SPT) or by measuring the level of specific immunoglobulin E (sIgE) in serum. SPT with standard environmental allergens is easily performed in children, is inexpensive, and has high sensitivity. Measurement of sIgE is more expensive than SPT and may be preferred for uncooperative patients, those with widespread skin disease, or if history suggests a risk of anaphylaxis to aeroallergens (GINA 2017). However, the presence of a positive SPT or sIgE does not mean that the allergen is responsible for respiratory symptoms, and the relevance of allergen exposure and its relationship to symptoms must be confirmed by the patient's history.

Radiology

Chest radiographs are not often indicated in childhood asthma except for eliminating different diagnoses such as foreign-body aspiration, abnormal airway structure, or parenchymal diseases. Chest radiographs (posteroanterior and lateral views) can help identify abnormalities that are hallmarks of asthma masqueraders (aspiration pneumonitis or bronchiolitis obliterans) and complications during acute asthma exacerbations (atelectasis or pneumothorax). The abnormalities in chest radiographs can be better analyzed with high-resolution (HR), thin-section, and low-dose CT scans. HR-CT scans may suggest the diagnosis of bronchiectasis, cystic fibrosis, or allergic bronchopulmonary aspergillosis.

13.7 Assessment of Asthma in Childhood

13.7.1 Assessment of Asthma Severity

Assessment of asthma severity informs treatment strategies and provides information regarding potential future risk. Asthma severity has traditionally been divided into intermittent or persistent categories with the latter being further subdivided into mild, moderate, and severe asthma, based on guidelines from the National Asthma Education and Prevention Program (NAEPP): Expert Panel Report 3 (NAEPP 2007). These guidelines have distinct criteria for three groups of childhood asthma (4 years, 5–11 years, and $\geq$12 years). In assessing asthma severity, data concerning daytime and nighttime symptoms, short-acting beta$_2$-agonist (SABA) usage for quick relief, ability to engage in daily activities, airflow limitation evaluated by spirometry in children 5 years of age and older, and risk of severe asthma exacerbations is recorded. Recommendations for initial treatment(s) follow this characterization of asthma severity (NAEPP 2007). The reader is referred to the NAEPP-Expert Panel Report 3 (NAEPP 2007), or its associated asthma care quick reference (NHLBI 2017), for further detail.

While assessment of asthma severity continues to play a role in the provision of asthma care, emphasis has more recently been placed on assessment of asthma control.

13.7.2 Assessment of Asthma Control

Asthma control is defined as the reduction or removal of respiratory manifestations of asthma symptoms with or without treatment (Reddel et al. 2009). In children, for whom pulmonary function testing may not be a reliable method for monitoring changes in FEV_1, asthma control refers to minimal symptoms, lung function impairment, and risk of adverse events while obtaining goals of treatments (Reddel et al. 2009). Assessment of asthma control includes two components: a child's asthma status (symptom control and lung function if measurable) and future risk of adverse events (loss of control, acute exacerbation, accelerated decline of lung function, and adverse effects of treatment). According to the National Heart, Lung, and Blood Institute (NHLBI) guidelines, it is recommended that symptom control, lung function if measurable, and risk be monitored regularly to allow for the characterization

of asthma as well controlled, not well controlled, or very poorly controlled and to inform strategies for adjusting therapy and reducing asthma morbidity (NHLBI 2011).

In children, symptoms such as wheeze, chest tightness, shortness of breath, and cough usually vary in frequency and intensity throughout time. However, poor asthma symptom control is strongly associated with an increased risk of asthma exacerbations (Reddel et al. 2009). Assessment of symptoms in children varies by age. In younger children, symptoms are most often reported by caregivers. However, caregivers may under- or overestimate asthma symptoms in the child or may fail to recognize symptoms. Of importance, a child's daily activities, including sports, play, and social life, should be carefully reviewed as some children with poorly controlled asthma avoid strenuous exercise; as such, their asthma may appear well controlled when it really is not. In addition, other potential symptoms related to uncontrolled asthma in children, such as irritability, tiredness, and changes in mood, should be queried and monitored.

The second component of asthma control is assessment of asthma risk. Here the goal is to identify whether the child is at risk of adverse asthma outcomes, particularly exacerbations, fixed airflow limitation, and side effects of medications. While the relationship between symptom control and future risk of adverse outcomes such as exacerbations has not been sufficiently studied in young children (GINA 2017), the risk is greater if current symptom control is poor (Meltzer et al. 2011). Furthermore, acute asthma exacerbations may occur after months of apparently good symptom control, may have different causes, and may require different treatment options. Therefore, it is imperative that the asthma provider remain attune to changes in symptoms and potential triggers and take steps to counter these changes. In young children with asthma, especially in infancy, "fixed" airflow limitation is very difficult to evaluate. In children >5 years of age who can perform spirometry, a persistent and accelerated decline in lung function (mainly FEV_1) associated with airflow limitation (FEV_1/FVC <75% in children) that is not fully reversible is a relevant functional marker of fixed airflow obstruction. Medication side effects are also considered risks for adverse outcomes due to systemic and local effects (e.g., changes in growth rate or facial rash due to inhaled corticosteroid use); thus, medication choices must strive to balance these types of risks with the benefit of impacting asthma control.

13.7.2.1 Current Guidelines for Assessment of Asthma Control

The 2017 Global Initiative for Asthma (GINA) guidelines have suggested a schema for assessing asthma control in children ≤5 years old (Table 3) and in those 6–11 years old (Table 4) (GINA 2017). In addition, the NHLBI guidelines also have distinct criteria for three childhood age groups (0–4 years, 5–11 years, and ≥12 years) for the assessment of asthma control (NAEPP 2007). These guidelines have integrated lung function and validated numeric scales to classify the control of asthma. The reader is referred to the NAEPP-Expert Panel Report 3 (NAEPP 2007), or its associated asthma care quick reference (NHLBI 2017), for further detail.

13.7.2.2 Asthma Control Assessment Tools for Children

In addition to the guidelines reported above, a variety of validated scoring tools have been developed to aid physicians in assessing asthma control in children. These numeric tools are useful for monitoring patient progress and are more sensitive to change in symptom control than categorical tools (O'Byrne et al. 2010). While these tools usually correlate significantly with each other, results are not identical (O'Byrne et al. 2010). Additionally, respiratory symptoms in children with asthma may be non-specific; therefore, when assessing changes in symptom control, it is important to clarify whether these symptoms are due to asthma or other diseases/comorbidities.

These tools include the Childhood Asthma Control Test (c-ACT), the Asthma Control Test (ACT), the Asthma Control Questionnaire (ACQ), the Test for Respiratory and Asthma Control in Kids (TRACK), the Composite Asthma Severity Index (CASI), and the Asthma Therapy

Table 3 Assessment of asthma control in children under 5 years (GINA 2017). (Reprinted with permission)

A. Asthma symptom control			**Level of asthma control**		
In the past 4 weeks, has the child had	**Yes**	**No**	**Well controlled**	**Partly controlled**	**Uncontrolled**
Daytime asthma symptoms for more than a few minutes, more than once a week?	c	c	None of these	1–2 of these	3–4 of these
Any activity limitation due to asthma? (Runs/plays less than other children, tires easily during walks/playing?)	c	c			
Reliever medication needed[a] more than once a week?	c	c			
Any night waking or night coughing due to asthma?	c	c			
B. Future risk for poor asthma outcomes					
Risk factors for asthma exacerbations within the next few months Uncontrolled asthma symptoms One or more severe exacerbation in previous year The start of the child's usual "flare-up" season (especially if autumn/fall) Exposures: tobacco smoke; indoor or outdoor air pollution; indoor allergens (e.g., house dust mite, cockroach, pets, mold), especially in combination with viral infection Major psychological or socioeconomic problems for child or family Poor adherence with controller medication or incorrect inhaler technique					
Risk factors for fixed airflow limitation Severe asthma with several hospitalizations History of bronchiolitis					
Risk factors for medication side effects Systemic: Frequent courses of OCS; high-dose and/or potent ICS Local: Moderate/high-dose or potent ICS; incorrect inhaler technique; failure to protect the skin or eyes when using ICS by nebulizer or spacer with face mask					

ICS inhaled corticosteroids, *OCS* oral corticosteroids
[a]Excludes reliever taken before exercise

Assessment Questionnaire (ATAQ). Comparison of these tools, including recommended ages, scoring scale, assessment interval, and score noting well-controlled asthma, is highlighted below in Table 5.

13.8 Treatment of Asthma in Childhood

13.8.1 Goals of Asthma Treatment in Childhood

Overall, the goals of asthma treatment include symptom control, maintaining normal daily activities, and minimizing exacerbations, fixed lung impairment, and treatment side effects (GINA 2017). Asthma management should include a cycle of assessment (diagnosis, symptom control, risk factors, inhaler technique, adherence, parent preference), treatment adjustment (medications, non-pharmacological strategies, and modification of risk factors), and review of response (including medication effectiveness and adverse effects) (GINA 2017). This is carried out in combination with education of parents/caregivers and child (depending on the child's age), skills training for effective use of inhaler devices, treatment adherence encouragement, monitoring of symptoms by parents/caregivers, cost considerations, and a written asthma action plan (GINA 2017).

13.8.2 Choosing Medications for Childhood Asthma

Asthma control requires a multimodal approach. In most cases, pharmacological treatment aids in achieving control, even in infancy, and should be established after partnership between parents/caregivers and healthcare providers. The GINA guidelines recommend that both general and individual questions should be utilized when recommending treatment (GINA 2017): (1) What is the "preferred" medication option at each

Table 4 Assessment of asthma control in children 6–11 years and adolescents (GINA 2017). (Reprinted with permission)

A. Asthma symptom control			**Level of asthma control**		
In the past 4 weeks, has the children had	**Yes**	**No**	**Well controlled**	**Partly controlled**	**Uncontrolled**
Daytime asthma symptoms more than twice a week?	c	c	None of these	1–2 of these	3–4 of these
Any night waking due to asthma?	c	c			
Reliever medication needed for symptoms[a] more than twice a week?	c	c			
Any activity limitation due to asthma?	c	c			
B. Future risk for poor asthma outcomes					
Assess risk factors at diagnosis and periodically, particularly for patients experiencing exacerbations Measure FEV_1 at start of treatment, after 3–6 months of controller treatment to record the patient's personal best lung function, then periodically for ongoing risk assessment					
Potentially modifiable independent risk factors for flare-ups (exacerbations) Uncontrolled asthma symptoms High SABA use (with increased mortality if >1 × 200-dose canister/month) Inadequate ICS: not prescribed ICS; poor adherence; incorrect inhaler technique Low FEV_1, especially if <60% predicted Major psychological or socioeconomic problems Exposures: smoking; allergen exposure if sensitized Comorbidities: obesity; rhinosinusitis; confirmed food allergy Sputum or blood eosinophilia *Other major independent risk factors for flare-ups (exacerbations)* Ever intubated or in intensive care unit for asthma. ≥1 severe exacerbation in last 12 months					**Having one or more of these risk factors increases the risk of exacerbations even if symptoms are well controlled**
Risk factors for developing fixed airflow limitation Lack of ICS treatment Exposures: tobacco smoke;93 noxious chemicals; occupational exposures Low initial FEV1;94 chronic mucus hypersecretion; sputum or blood eosinophilia					
Risk factors for medication side effects Systemic: Frequent courses of OCS; long-term, high-dose, and/or potent ICS; also taking P450 inhibitors[b] Local: high-dose or potent ICS; poor inhaler technique					

ICS inhaled corticosteroids, *OCS* oral corticosteroids, *SABA* short-acting $beta_2$-agonist
[a]Excludes reliever taken before exercise
[b]P450 inhibitors: cytochrome P450 inhibitors such as ritonavir, ketoconazole, and itraconazole

treatment step to control asthma symptoms and minimize future risk? These decisions are based on data for efficacy, effectiveness, and safety from clinical trials and on observational data; (2) How does this particular child differ from the "average" child with asthma, in terms of response to previous treatment, parental preference (goals, beliefs, and concerns about medications), and practical issues (cost, inhaler technique, and adherence)? Additionally, all clinical, functional, and biological characteristics or phenotypes that predict the child's response to treatment should be evaluated carefully.

GINA guidelines (see below) recommend a stepwise treatment approach, inclusive of reliever medications for as-needed symptom relief and daily use of controller medications or other add-on therapies, if needed, to keep asthma well controlled. In children with asthma, daily controller treatment initiated after the diagnosis of asthma is made affords the best results (GINA 2017). Previous studies, including a more recent Cochrane review of 1211 patients (Chauhan et al. 2013), have shown that early initiation of low-dose ICS in asthma patients leads to a greater improvement in lung function when compared to later treatment initiation using higher doses of ICS (Busse et al. 2008; Selroos 2008; Chauhan et al. 2013). However, the Childhood Asthma Management Program (CAMP), following 1041 children aged 5–12 years for a total of

Table 5 Asthma control assessment tools

Asthma control assessment tools				
	Ages validated	Scoring range	Score for well controlled	Assessment interval
Childhood Asthma Control Test (ACT-c)	4–11 years	0–27	>19	Month
Asthma Control Test (ACT)	≥12 years	5–25	>19	Month
Asthma Control Questionnaire (ACQ 5/6[a]/7[b])	≥11 years[c]	0–6	<0.75	Week
Test for Respiratory and Asthma Control in Kids (TRACK)	1–5 years	0–100	≥80	Month-year
Composite Asthma Severity Index (CASI)	6–17 years	0–20	Not defined[d]	2 weeks, symptoms; 2 months, exacerbations
Asthma Therapy Assessment Questionnaire (ATAQ)	5–17 years	"Other" 0–5; "control" 0–7	<1	Month

[a]ACQ-6 comprises all questions from ACQ-5 and adds a question about inhaler use
[b]ACQ-7 comprises all questions from ACQ-6 and includes spirometry in the score
[c]Has been used down to age 6 years if questionnaire administered by a trained interviewer (Juniper et al. 2010)
[d]Used to follow an individual's asthma. Lower score is better controlled

4–6 years, showed that, while inhaled corticosteroids reduce the risk of exacerbation, improve symptoms, and improve baseline lung function overall, these effects disappear after therapy is stopped (Covar et al. 2012). Furthermore, CAMP results suggest that ICS therapy does not prevent reduction in lung function nor does it seem to affect the natural history of childhood asthma (Covar et al. 2012).

13.8.3 Choice of Inhaler Device

The use of inhaled treatment constitutes a cornerstone of asthma therapy in children. A pressurized metered dose inhaler (pMDI) with a valved spacer (or chamber) is preferred; in children ≤3 years old, a low-volume spacer (<350 mL) should be used. A face mask should be added to the spacer for patients up to 3 years of age. The pMDI with spacer should be used during tidal breathing with approximately 5–10 breaths per actuation or enough to empty the spacer.

13.8.4 Reviewing Response and Adjusting Treatment

In children with asthma, symptom control, risk factors for exacerbation, and adverse treatment effects should be monitored at every visit. For those treated with ICS, especially with moderate to high doses, height should be measured regularly. Importantly, the ability to step-down therapy and even the need for long-term therapy with controller treatment should be evaluated every 3 months as some children have remission of asthma. The clinical benefit from ICS may be seen at low doses, and the evidence of dose-response relationships is controversial (Busse et al. 2008; Selroos 2008). Therefore, once asthma control is achieved, the ICS dose should be carefully titrated to the minimum dose (Table 6). If therapy is discontinued, children should be followed within 1–3 months, and, if asthma symptoms recur, asthma treatment should be reinstated.

13.8.4.1 Treatment of Asthma in Children 5 Years of Age or Younger

The stepwise approach to asthma treatment recommended by GINA for children ≤5 years old comprises four steps (Fig. 3).

Step 1 includes a short-acting beta-agonist (SABA) which should be prescribed to all children with wheezing; SABA should be used every 4–6 h as needed for one or more days until symptoms disappear. If wheezing episodes are frequent or severe, symptoms are not controlled, inhaled

Table 6 Low, medium, and high daily doses of inhaled corticosteroids (GINA 2017). (Reprinted with permission)

Drug	Daily dose (mcg)		
	Low	Medium	High
Children 12 years and older			
Beclometasone dipropionate (CFC)[a]	200–500	>500–1000	>1000
Beclometasone dipropionate (HFA)	100–200	>200–400	>400
Budesonide (DPI)	200–400	>400–800	>800
Ciclesonide (HFA)	80–160	>160–320	>320
Fluticasone furoate (DPI)	100	n.a.	200
Fluticasone propionate (DPI)	100–250	>250–500	>500
Fluticasone propionate (HFA)	100–250	>250–500	>500
Mometasone furoate	110–220	>220–440	>440
Triamcinolone acetonide	400–1000	>1000–2000	>2000
Children 6–11 years			
Beclometasone dipropionate (CFC)[a]	100–200	>200–400	>400
Beclometasone dipropionate (HFA)	50–100	>100–200	>200
Budesonide (DPI)	100–200	>200–400	>400
Budesonide (nebules)	250–500	>500–1000	>1000
Ciclesonide	80	>80–160	>160
Fluticasone furoate (DPI)	n.a.	n.a.	n.a.
Fluticasone propionate (DPI)	100–200	>200–400	>400
Fluticasone propionate (HFA)	100–200	>200–500	>500
Mometasone furoate	110	≥220- < 440	≥440
Triamcinolone acetonide	400–800	>800–1200	>1200

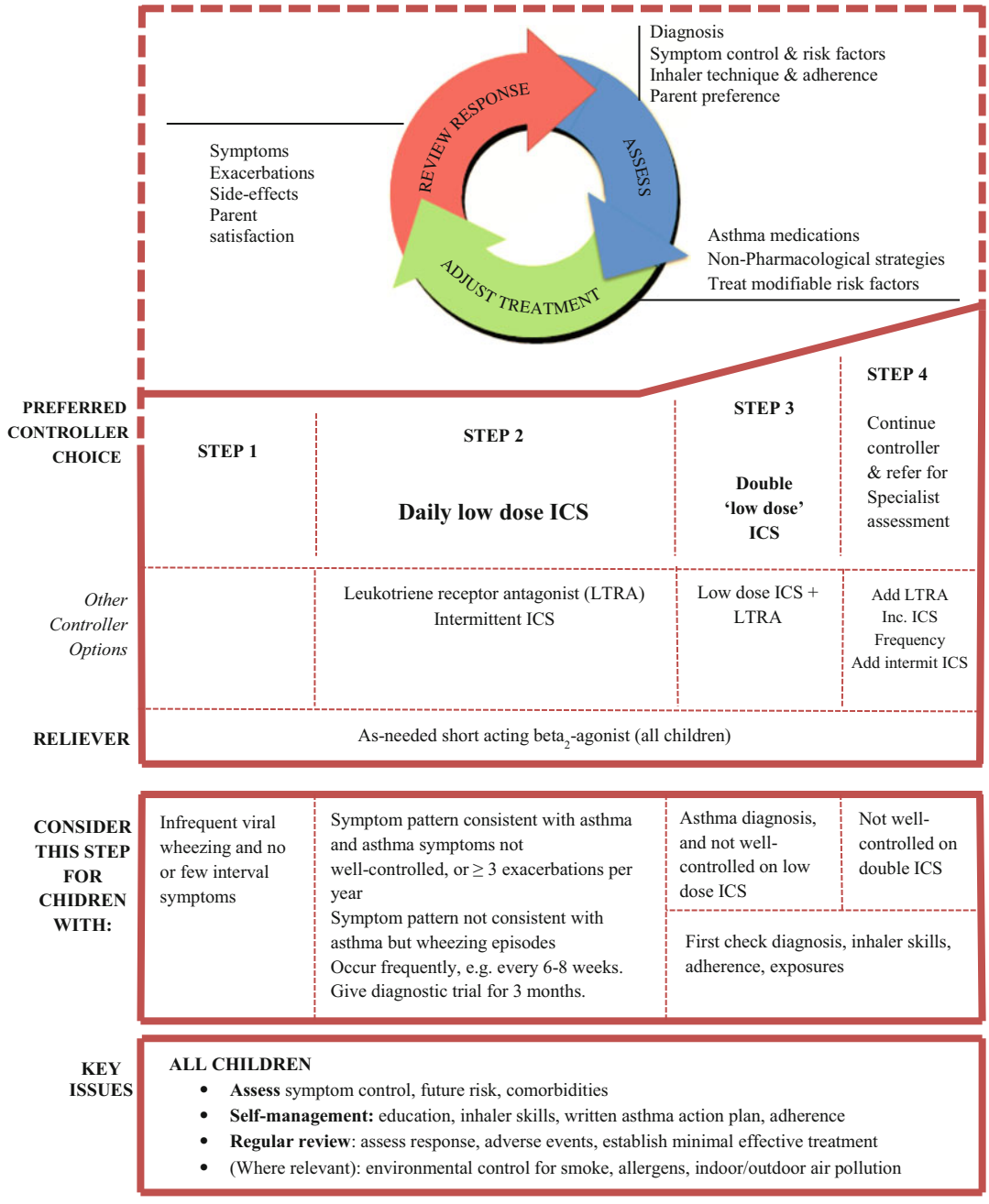
CFC chlorofluorocarbon propellant, *DPI* dry powder inhaler, *HFA* hydrofluoroalkane propellant, *n.a.* not applicable
[a]Beclometasone dipropionate CFC is included for comparison with older literature

SABA therapy needs to be repeated more than every 6–8 weeks, or wheezing episodes associated with viral infection are severe, escalation of therapy to Step 2 should be considered.

Step 2 includes use of a daily controller medication (inhaled corticosteroid, ICS, or leukotriene receptor antagonist, LTRA) as well as continued use of SABA as needed. Use of regular daily low-dose ICS (see Table 7) is recommended as the preferred initial treatment and should be administered for at least 3 months to establish efficacy. In young children with persistent asthma, regular treatment with LTRA modestly reduces symptoms and need for oral corticosteroids compared with placebo. In young children with recurrent virally induced wheezing, regular LTRA use improves some asthma outcomes compared with placebo but does not reduce the frequency of hospitalizations, courses of prednisone, or number of symptom-free days (Bisgaard et al. 2005). For preschool children with frequent virally induced wheezing and interval asthma symptoms existing in-between viral infection, as-needed episodic ICS may be considered, but a trial of regular ICS should be undertaken first. However, in one meta-analysis, while there was no statistically significant difference in the rate of asthma exacerbations between these types of patients using daily versus intermittent ICS, those using daily ICS had significantly more asthma-free days (Rodrigo and Castro-Rodríguez 2013).

When asthma symptoms or exacerbations are not controlled after 3 months on Step 2 therapies, Step 3 strategies are recommended, starting with review of modifiable factors (inhaler technique, treatment adherence, and environmental/allergen exposures). It is also important to confirm that symptoms are due to asthma rather than a concomitant or alternative condition; if the diagnosis of asthma is in doubt, there should be a low threshold to refer for expert assessment. Once these topics are reviewed and addressed, doubling the low-dose ICS (to medium dose) for another 3 months is preferred, although an acceptable alternative is to add a LTRA to the initial low-dose ICS.

If Step 3 strategies fail to achieve and maintain asthma control or side effects of treatment are



ICS: inhaled corticosteroid; intermit; intermittent; LTRA: leukotriene receptor antagonist.

Fig. 3 Stepwise treatment recommended by GINA 2017 for children 5 years and younger (GINA 2017). (Reprinted with permission)

Table 7 Low daily doses of inhaled corticosteroids for children 5 years and younger (GINA 2017). (Reprinted with permission)

Drug	Low daily dose (mcg)
Beclomethasone dipropionate (HFA)	100 200
Budesonide pMDI + spacer	500
Budesonide nebulized	100
Fluticasone propionate (HFA)	160
Ciclesonide	Not studied below age 4 years
Mometasone furoate	Not studied in this age group
Triamcinolone acetonide	

This is not a table of clinical equivalence. A low daily dose is defined as the dose that has not been associated with clinically adverse effects in trials that included measures of safety

HFA hydrofluoralkane propellant, *pMDI* pressurized metered dose inhaler

observed, the child should be referred for expert assessment. Step 4 options include further increase in ICS dose (perhaps combined with more frequent dosing) for a few weeks until asthma improves; addition of LTRA (if not already employed), theophylline, or low-dose oral corticosteroid (for a limited time only); and/or addition of intermittent high-dose ICS to the regular daily ICS if exacerbations are the main problem. The need for additional controller treatment should be re-evaluated at each visit and maintained for as short a period as possible, taking into account potential risks and benefits. Treatment goals and their feasibility should be reconsidered and discussed with the child's family/caregiver; it may become necessary to accept a degree of persisting asthma symptoms to avoid excessive and harmful medication doses. While there has been prior debate regarding use of LABA in a pediatric population and GINA guidelines do not include use of LABA, more recent studies and meta-analysis demonstrate that the addition of LABA to baseline ICS can reduce exacerbations when compared to ICS use alone without significantly increased adverse effects (Nelson et al. 2006; Rodrigo et al. 2009; Tal et al. 2002). The use of LABA in young remains an issue of debate (Malone et al. 2005).

13.8.4.2 Treatment of Asthma in Children 6 Years and Older

The stepwise approach to asthma treatment recommended by GINA for children >5 years old comprises five steps (Fig. 4) (GINA 2017). These guidelines recommend an approach similar to that used in adults.

Step 1, as in younger children, includes use of SABA as needed. However, in special circumstances, it is appropriate to immediately start an ICS; these cases include children with more frequent symptoms, FEV_1 <80% predicted or personal best, or an exacerbation within the past 12 months (GINA 2017). When asthma remains uncontrolled with Step 1 therapies, escalation to Step 2 is warranted.

Step 2 preferred option consists of adding a low-dose ICS to the as-needed SABA. In some (those unable/unwilling to use ICS, with intolerable side effects to ICS, or with concomitant allergic rhinitis), LTRA may be appropriate initial Step 2 therapy, although LTRAs are less effective than ICS (GINA 2017). Likewise, while low-dose ICS/LABA could be considered in controller-naive patients, these combinations are generally more expensive and do not further reduce the risk of exacerbations compared to ICS alone (GINA 2017). Additionally, for patients with purely seasonal allergic asthma and no interval asthma symptoms, ICS should be started immediately when symptoms commence and continued for 4 weeks after the relevant pollen season ends.

As in children <5 years old, when symptoms persist, the first recommendation for Step 3 treatment includes review of modifiable factors (inhaler technique, treatment adherence, and environmental/allergen exposures), and confirmation of asthma rather than alternative conditions are again recommended. If evaluation continues to suggest uncontrolled asthma, the Step 3 preferred option differs by age and includes one to two controller medications plus an as-needed reliever medication. For children 6–11 years, identical to those ≤5 years, the preferred option is to increase ICS to medium dose as this is similar to or more effective than adding a LABA. However, in adolescents (children >11 years), adding LABA to

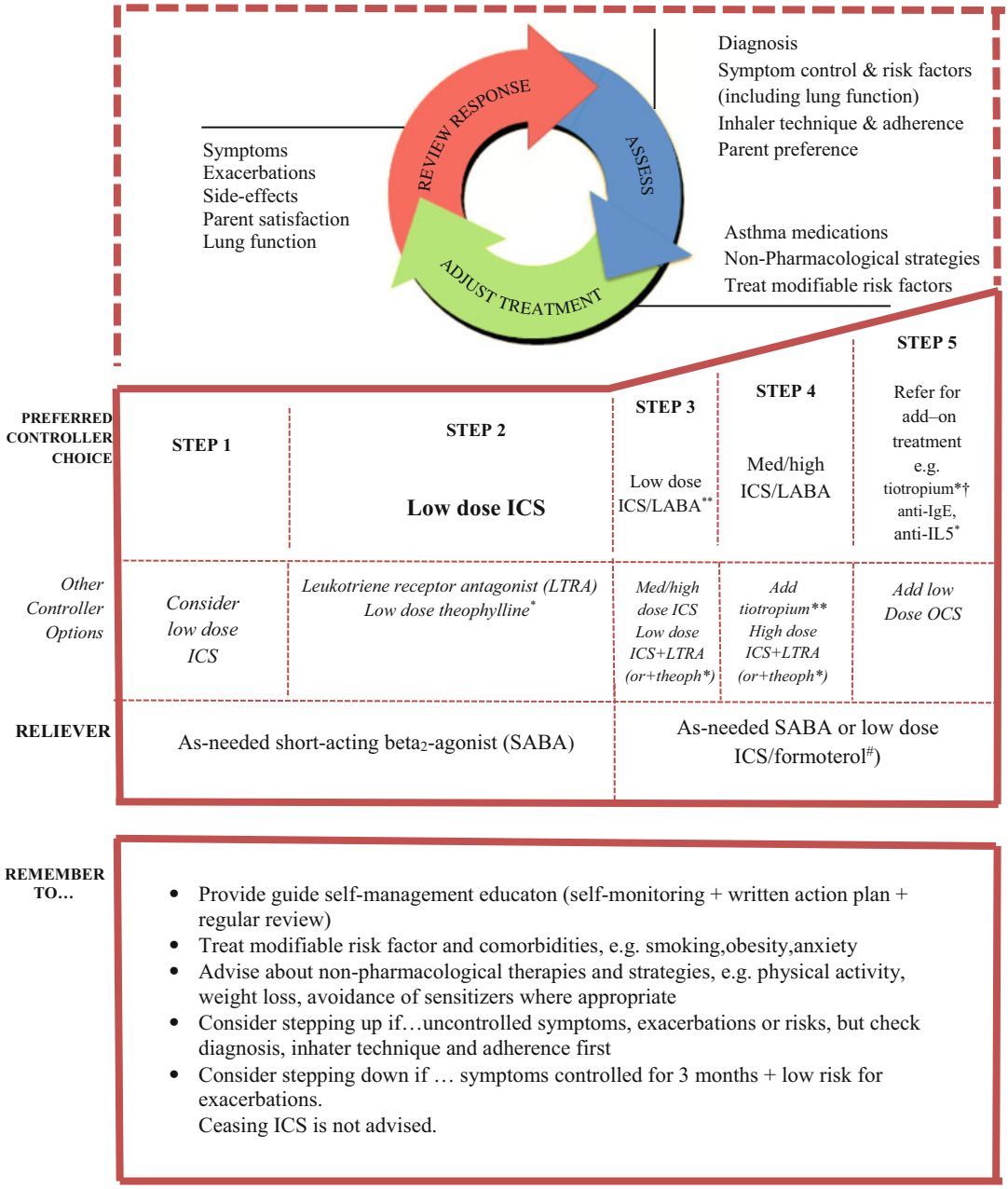


Fig. 4 Stepwise treatment recommended by GINA 2017 for children 6 years and older (GINA 2017). *ICS,* inhaled corticosteroids, *LABA* long-acting beta2-agonist, *med* medium dose, *OCS* oral corticosteroids. *Not for children <12 years. **For children 6–11 years, the preferred Step 3 treatment is medium-dose ICS. # Low-dose ICS/formoterol is the reliever medication for patients prescribed low-dose budesonide/formoterol or low-dose beclometasone/formoterol maintenance and reliever therapy. † Tiotropium by mist inhaler is an add-on treatment for patients with a history of exacerbations; it is not indicated in children <12 years. (Reprinted with permission)

the same dose ICS improves symptoms and lung function, reduces risk of exacerbations, and is more effective than increasing to medium-dose ICS (GINA 2017). One strategy using a single ICS/LABA inhaler for both maintenance and reliever treatment (using an overall lower-dose ICS/LABA as maintenance since additional corticosteroid will be administered with rescue doses using the same inhaler) has been employed. This strategy has been shown to increase time to first asthma exacerbation (Papi et al. 2013); result in fewer exacerbations requiring oral corticosteroids, ED visit, or hospitalization compared to higher fixed-dose combination inhaler (Kew et al. 2013); and reduce risk of exacerbation requiring oral corticosteroids compared to fixed higher dose of ICS (Cates and Karner 2013). Therefore, the preferred option in this age group is low-dose ICS/LABA (suggested as beclomethasone or budesonide with formoterol due to onset of action of formoterol similar to albuterol) as both maintenance and reliever treatment or low-dose ICS/LABA as maintenance with SABA as needed. Alternative controller options for adolescents include increase to medium-dose ICS, low-dose ICS plus LTRA, or low-dose ICS plus low-dose, sustained-release theophylline; however, all these are again less efficacious than ICS/LABA combination in this age group.

The selection of Step 4 treatment depends on the prior selection at Step 3 but generally consists of review of the modifiable factors mentioned in Step 3 (see above) and the preferred use of two controller medications plus as needed reliever medication. In children aged 6–11, it is recommended to refer for expert assessment and advice at Step 4. For adolescents on low-dose ICS/LABA with as needed SABA in Step 3, treatment may be increased to medium-dose ICS/LABA with as needed SABA or may be altered to low-dose ICS/LABA as maintenance and reliever with consideration for additional add-on therapy. In those with more than one asthma exacerbation in the past year, low-dose ICS/LABA as maintenance and reliever medication has been shown to be more effective in reducing exacerbations than the same dose of maintenance ICS/LABA or higher doses of ICS (GINA 2017).

Alternative add-on options in children include LTRA and in adolescents include LTRA, tiotropium (long-acting muscarinic antagonist or LAMA), high-dose ICS/LABA (although increase in ICS generally provides little additional benefit and increases risk of side-effects), and low-dose sustained-release theophylline. High-dose ICS is only recommended for a 3–6-month trial basis when asthma remains uncontrolled on medium-dose ICS/LABA and/or third controller such as LTRA.

Step 5 treatment options should be directed by a specialist with expertise in management of severe asthma. These add-on treatments include omalizumab (Xolair™; anti-immunoglobulin E) in children $\geq$6 years and tiotropium (Spiriva™; anticholinergic) and mepolizumab (Nucala™; anti-interleukin-5) in children $\geq$12 years. Another anti-IL-5 agent, reslizumab (Cinqair™), has not been approved for use in children $<$18 years. Omalizumab is a subcutaneous injection for those with moderate to severe asthma not well controlled on conventional therapies; currently dosing recommendations stratify individuals based on IgE level and weight to receive 75, 150, 225, 300, or 375 mg at every 2- or 4-week dosing intervals (Xolair™ Prescribing Information 2017). Mepolizumab is utilized in severe eosinophilic asthma and is given as a 100 mg injection every 4 weeks (Nucala™ Prescribing Information 2017).

13.9 Treatment of Acute Exacerbation Asthma in Childhood

13.9.1 Treatment of Acute Asthma Exacerbation in Children 5 years and Younger

13.9.1.1 Diagnosis of Acute Asthma Exacerbations in Children 5 Years and Younger

Acute asthma exacerbation (AAE) in children $\leq$5 years old is defined as an acute deterioration in symptom control that may cause respiratory

distress and death in some severe cases (Swern et al. 2008). Young children with AAE must be evaluated by a healthcare provider to determine the severity of exacerbation and to modify treatment, including starting systemic corticosteroids, if needed. Early symptoms of an AAE may include increased wheezing, worsened shortness of breathing, increased coughing (especially while the child is asleep), and poor response to reliever medication. While no single symptom is predictive of exacerbation in children aged 2–5 years, the combination of increased daytime cough or wheeze and nighttime beta$_2$-agonist use is a strong predictor for exacerbation (Swern et al. 2008). Frequently, viral respiratory tract infection precedes the onset of an asthma exacerbation in young children.

13.9.1.2 Assessment of Acute Asthma Exacerbation Severity in Children 5 Years and Younger

In children ≤5 years old, the presence of any of the following features may suggest a severe acute exacerbation requiring urgent treatment and immediate transfer to the hospital: altered consciousness (agitation, confusion, or drowsiness), desaturation (oximetry on presentation <92%), tachycardia (pulse rate >200 beats/minute for infant 0–3 years or >180 beats/minute for children 4–5 years), central cyanosis, or "quiet chest" on auscultation. Several clinical scoring systems such as PRAM (Preschool Respiratory Assessment Measure) and PASS (Pediatric Asthma Severity Score) are available for assessing the severity of acute asthma exacerbations in children (Gouin et al. 2010). PRAM scores are used in children aged 1–17 years and include pulse oximetry, substernal muscle retraction, scalene muscle retraction, air entry, and wheezing; scores range from 0 to 12 with "severe" at 8–12 and "mild" as 0–3 (Chalut et al. 2000; Ducharme et al. 2008). PASS scores are used in children aged 1–18 years and include respiratory rate, pulse oximetry, auscultation, retractions, and dyspnea; scores range from 5 to 15 with "severe" at ≥12 and "mild" at ≤7 (Maue et al. 2017).

13.9.1.3 Emergency Treatment and Initial Pharmacotherapy for Children 5 Years and Younger

The initial management of acute asthma exacerbations (AAE) in children 5 years and younger recommended by GINA 2017 is presented in Table 8 below and summarized here:

Oxygen

In young children with AAE and hypoxemia (SpO_2 <92%), urgent treatment with oxygen

Table 8 Initial management of asthma exacerbations in children 5 years and younger recommended by GINA (GINA 2017). (Reprinted with permission)

Therapy	Dose and administration
Supplemental oxygen	24% delivered by face mask (usually 1 L/minute) to maintain oxygen saturation 94–98%
Short-acting beta$_2$-agonist (SABA)	2–6 puffs of salbutamol by spacer or 2.5 mg of salbutamol by nebulizer, every 20 min for first hour[a], and then reassess severity. If symptoms persist or recur, give an additional 2–3 puffs per hour. Admit to hospital if >10 puffs required in 3–4 h
Systemic corticosteroids	Give initial dose of oral prednisolone (1–2 mg/kg up to a maximum 20 mg for children <2 years old; 30 mg for children 2–5 years) or intravenous methylprednisolone 1 mg/kg 6-hourly on day 1
Additional options in the first hour of treatment	
Ipratropium bromide	For children with moderate-severe exacerbations, 2 puffs of ipratropium bromide 80 mcg (or 250 mcg by nebulizer) every 20 min for 1 h only
Magnesium sulfate	Consider nebulized isotonic magnesium sulfate (150 mg) 3 doses in the first hour of treatment for children aged ≥2 years with severe exacerbation

[a]If inhalation is not possible, an intravenous bolus of terbutaline 2 mcg/kg may be given over 5 min, followed by continuous infusion of 5 mcg/kg/h. The child should be closely monitored, and the dose should be adjusted according to clinical improvement and side effects

by face mask is warranted to maintain oxygen saturation 94–98%. To avoid hypoxemia during changes in treatment, children who are acutely distressed should be treated immediately with oxygen and SABA delivered by an oxygen-driven nebulizer.

Bronchodilator Therapy

The initial dose of SABA may be given by a pMDI with spacer and mask/mouthpiece, an air-driven nebulizer, or, if oxygen saturation is low, an oxygen-driven nebulizer. For most children, pMDI plus spacer is favored as it is more efficient than a nebulizer for bronchodilator delivery. In acute severe asthma, 6 puffs of salbutamol (100 mcg per puff) or equivalent should be given. If a nebulizer is used, a dose of 2.5 mg salbutamol or albuterol solution is recommended. The frequency of dosing depends on the response observed over 1–2 h. For children with moderate-severe exacerbation and a poor response to initial SABA, ipratropium bromide may be given as 2 puffs (80 mcg per puff) or nebulizer treatment (250 mcg) every 20 min for 1 h only (Griffiths and Ducharme 2013a).

Magnesium Sulfate

There are few studies evaluating the role of magnesium sulfate in children <5 years old. However, nebulized isotonic magnesium sulfate may be considered as an adjuvant to standard treatment with nebulized salbutamol/albuterol and ipratropium in the first hour of treatment for children ≥2 years old with acute severe asthma, particularly those with symptoms lasting <6 h (Powell et al. 2013). One study enrolled 62 patients aged 5–17 years presenting to the emergency room with mild-to-moderate asthma exacerbation to receive either nebulized albuterol 2.5 mg mixed with 2.5 mL of normal saline or nebulized albuterol 2.5 mg mixed with 2.5 mL of isotonic magnesium supplied as 6.3% solution of magnesium heptahydrate (Mahajan et al. 2004). Patients randomized to receive albuterol mixed with magnesium had statistically improved FEV1 at 10 min, but not at 20 min, compared to the group that received albuterol mixed with normal saline, suggesting that nebulized magnesium may have short-term, but not necessarily long-term, benefit in the treatment of acute exacerbation (Mahajan et al. 2004). Further review of five trials in 2009 suggested IV magnesium (25–75 mg/kg) resulted in improved pulmonary function (FEV1, FVC, PEFR), clinical asthma score, and decreased hospitalization, although another trial found no evidence to support use of IV magnesium in addition to B2-agonist therapy in treatment of moderate to severe childhood asthma exacerbations (Bichara and Goldman 2009). Additional study suggests that a single dose of 40–50 mg/kg (maximum 2 g) by slow infusion (20–60 min) may be beneficial (Powell et al. 2013).

Oral Corticosteroids

For children with severe AAE, the sooner therapy is started in relation to the onset of symptoms, the more likely the impending exacerbation may be clinically attenuated or prevented (Rowe et al. 2001). A 3–5-day course of oral corticosteroids (OCS) equivalent to prednisolone 1–2 mg/kg/day (to a maximum of 20 mg/day for children <2 years and 30 mg/day for children 2–5 years) is recommended and can be stopped abruptly (Rowe et al. 2001).

13.9.1.4 Assessment of Treatment Response and Follow-up for Acute Asthma Exacerbation Severity in Children 5 Years and Younger

As recommended by GINA guidelines, children with a severe AAE must be observed for at least 1 h after initiation of treatment, at which time further treatment can be planned depending on the following scenarios:

1. If symptoms persist after initial bronchodilator, 2–6 additional puffs (depending on severity) of salbutamol/albuterol may be given 20 min after the first dose and repeated at 20-min intervals for an hour. Failure to respond at 1 h, or earlier deterioration, should prompt urgent admission to hospital and a short course of oral corticosteroids.
2. If symptoms have improved by 1 h but recur within 3–4 h, the child may be given more frequent doses of bronchodilator (2–3 puffs each hour), and oral corticosteroids should be

given. The child may need to remain in the emergency room, or, if at home, should be observed by the family/caregiver and have ready access to emergency care. Children who fail to respond to 10 puffs of inhaled SABA within a 3–4 h period should be referred to the hospital.

3. If symptoms resolve rapidly after initial bronchodilator and do not recur for 1–2 h, no further treatment may be required. Further SABA may be given every 3–4 h (up to a total of 10 puffs/24 h), and, if symptoms persist beyond 1 day, other treatments including inhaled or oral corticosteroids are indicated, as outlined below. Before being allowed to go home, the child's condition must be stable.

Children who have had an AAE within the past 3 months are at risk of further episodes and require close follow-up. Prior to being allowed to go home from the emergency department or hospital, family/caregivers should receive the following advice and information: instruction on recognition of signs of recurrence and worsening of asthma and the factors that precipitated the AAE; a written, individualized action plan, including details of accessible emergency services; careful review of inhaler technique; a supply of SABA and, where applicable, the remainder of the course of oral corticosteroid, ICS, or LTRA; and a follow-up appointment within 2–7 days and another within 1–2 months, depending on the clinical, social, and practical context of the exacerbation.

The summary of primary care management of acute asthma exacerbation in children 5 years and younger is summarized in Fig. 5.

13.9.2 Treatment of Acute Asthma Exacerbation in Children 6 Years and Older

13.9.2.1 Diagnosis of Acute Asthma Exacerbations in Children 6 Years and Older

In children 6 years and older, AAE represents a change in symptoms and lung function from a stable status with suddenly decreasing peak expiratory flow (PEF) or FEV_1 compared with previous lung function or predicted values. In these children, the frequency of symptoms may be a more sensitive measure of the onset of an exacerbation than PEF; however, in some children, the change in symptoms may not be perceived or reported, and change should be measured by lung function testing, especially in children with a history of near-fatal asthma. Similar to younger children, AAE in children >5 years is potentially life threatening, and treatment requires prompt medical evaluation with careful assessment and close monitoring.

13.9.2.2 Assessment of Acute Asthma Exacerbation Severity in Children 6 Years and Older

A brief focused history and relevant physical examination should be conducted concurrently with the prompt initiation of therapy. Medical history should include timing of onset and cause of the present exacerbation, severity of asthma symptoms including any exercise limitation or sleep disturbance, symptoms of anaphylaxis, current reliever and controller medications (including current doses, recent changes to dosing, and devices used), adherence pattern, and risk factors for asthma-related death. Risks for asthma-related death include hospitalization or emergency care visit for asthma in the past year, not currently using ICS, SABA use of more than one canister (200 actuations) per month, or a history of near-fatal asthma requiring intubation and mechanical ventilation.

Physical examination should assess signs of exacerbation severity (temperature, blood pressure, pulse oximetry (SpO2), PEF, pulse rate, respiratory rate, level of consciousness, ability to complete sentences, use of accessory muscles, wheeze), complicating factors (anaphylaxis, pneumonia, pneumothorax), and alternative conditions that could explain acute breathlessness (upper airway dysfunction or inhaled foreign body). In children with AAE, SpO_2 <92% is a predictor of the need for hospitalization, and <90% signals the need for aggressive therapy. Arterial blood gas (ABG) measurements and

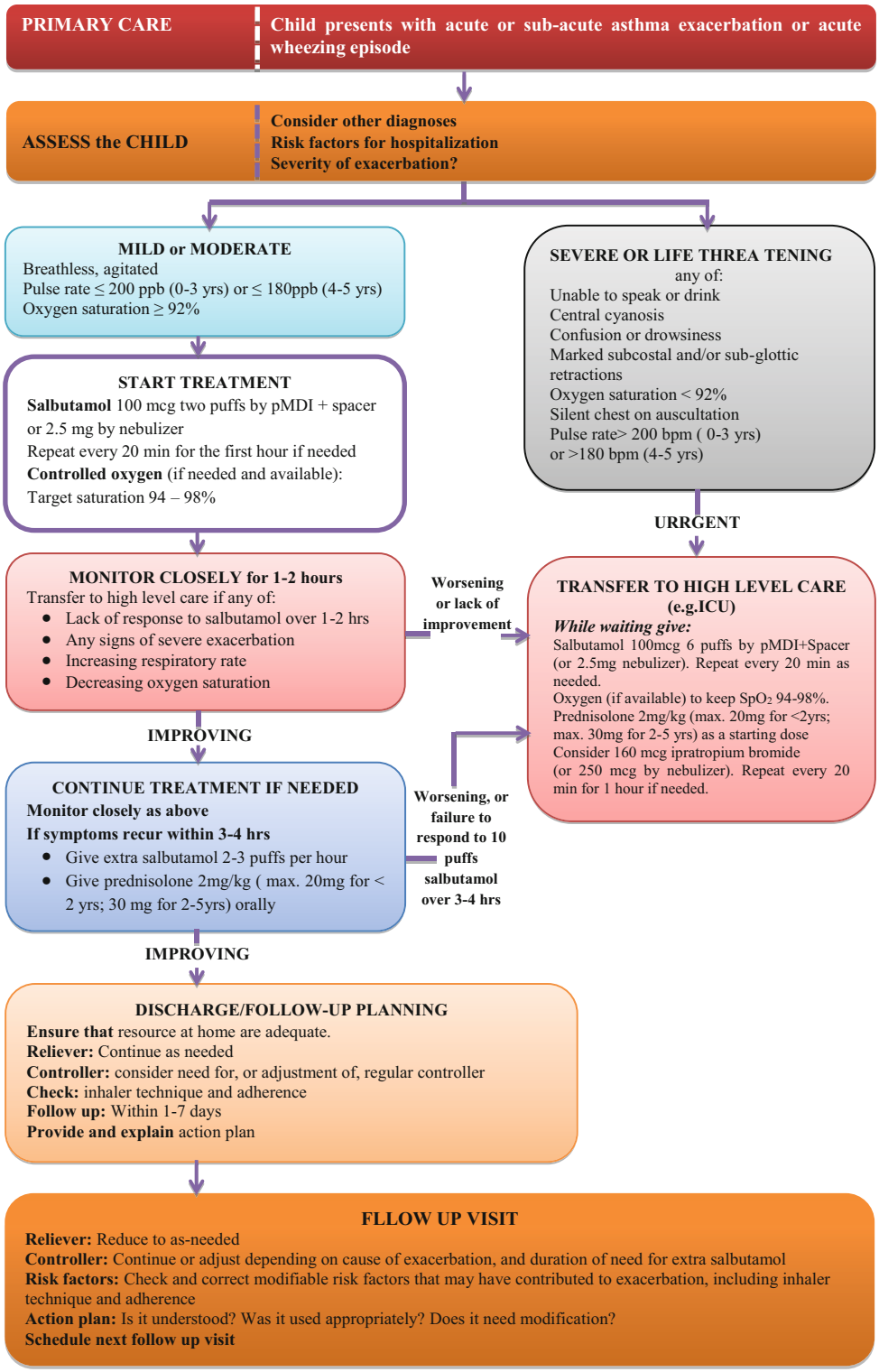


Fig. 5 Primary care management of acute asthma exacerbation in children 5 years and younger (GINA 2017). (Reprinted with permission)

chest radiographs are not routinely required in children with AAE except in the cases of severe AAE when PEF or FEV1 is <50% predicted or when a complicating or alternative diagnosis is suspected such as pneumothorax, parenchymal disease, or an inhaled foreign body, respectively (GINA 2017).

If the patient shows signs of a severe or life-threatening exacerbation, treatment with SABA, controlled oxygen (to maintain SpO_2 between 94% and 98% in asthmatic children), and systemic corticosteroids should be initiated while arranging for the patient's urgent transfer to an acute care facility or for hospital admission. Milder exacerbations can usually be treated in a primary care setting, depending on resources and expertise.

PRAM and PASS scoring tools are also used in children up to age 17 and 18, respectively (see Sect. 9.1.2).

13.9.2.3 Management of Acute Asthma Exacerbation in Children 6 Years and Older

The initial therapies in an AAE for children 6 years of age and older are similar to those in younger children, although dosing strategies differ slightly. GINA provides an algorithmic approach for both ambulatory (Fig. 6) and emergency care settings (Fig. 7), summarized here. The basic approach includes repetitive administration of SABA, early introduction of systemic corticosteroids, and oxygen supplementation. The aims of treatment include rapid relief of airflow obstruction and hypoxemia, addressing the underlying inflammatory pathophysiology, and preventing relapse.

Oxygen Therapy

Oxygen therapy should be titrated against pulse oximetry to maintain oxygen saturation at 94–98% for children 6–11 years and younger. Controlled or titrated oxygen therapy gives better clinical outcomes than high-flow 100% oxygen therapy (Perrin et al. 2011). Oxygen should not be withheld if oximetry is not available, but children should be monitored for deterioration, somnolence, or fatigue.

Inhaled Short-Acting $Beta_2$-agonists

For mild to moderate exacerbations, repeated administration of inhaled SABA (up to 4–10 puffs every 20 min for the first hour) is usually the most effective and efficient way to achieve rapid reversal of airflow limitation. After the first hour, the dose of SABA required varies from 4 to 10 puffs every 3–4 h up to 6–10 puffs every 1–2 h or more often. No additional SABA is needed if there is a good response to initial treatment (PEF >60–80% of predicted values). Delivery of SABA via pMDI and spacer or a DPI leads to a similar improvement in lung function as delivery via nebulizer (Selroos 2014). Currently, there is no evidence to support the use of intravenous $beta_2$-agonists in children with severe AAE (GINA 2017).

Systemic Corticosteroids

Systemic corticosteroids may improve exacerbations and prevent relapse; they should be utilized in mild-to-moderate exacerbations in children 6–11 years (Edmonds et al. 2012). Where possible, systemic corticosteroids should be administered promptly with the preferred route being oral, especially using liquid formulations in children. Intravenous corticosteroids can be administered when patients are too dyspneic to swallow, are vomiting, or are requiring noninvasive ventilation. The use of systemic corticosteroids is particularly important when initial SABA treatment fails to achieve lasting improvement in symptoms, exacerbation developed while the patient was taking OCS, or there is a history of previous exacerbations requiring OCS (GINA 2017). In children with AAE, an OCS dose of 1–2 mg/kg/day up to a maximum of 40 mg/day for 3–5 days is adequate; GINA guidelines recommend once-daily dosing. A duration of 3–5 days is usually considered sufficient, although longer duration (5–7 days) is recommended if the patient is being treated in the ambulatory setting (GINA 2017).

Ipratropium Bromide

For children with moderate-severe exacerbations, treatment in the emergency department with both SABA and ipratropium, a short-acting anticholinergic, was associated with fewer hospitalizations

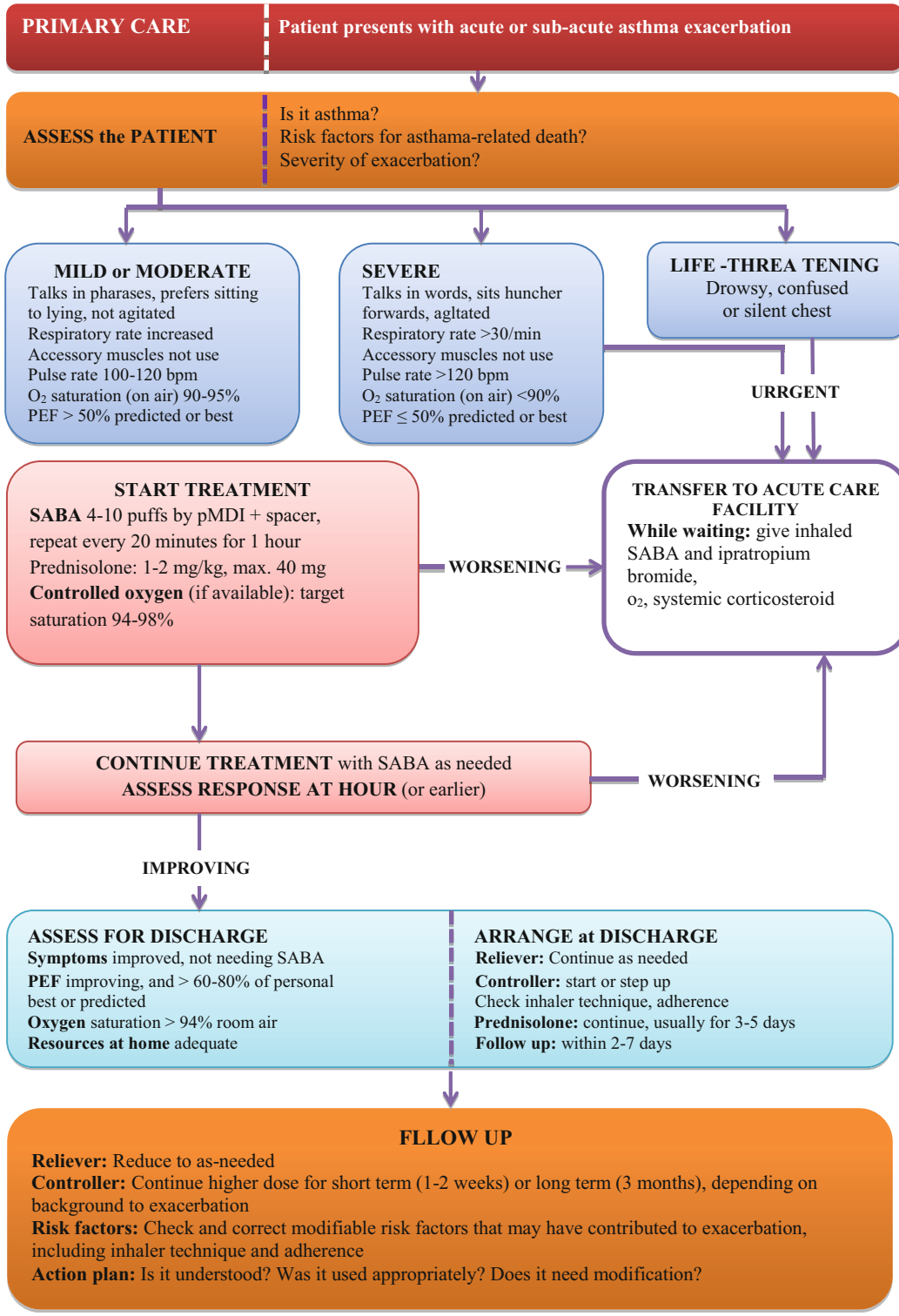


Fig. 6 Management of asthma exacerbations in primary care for children 6–11 years and adolescents (GINA 2017). *O_2* oxygen, *PEF* peak expiratory flow, *SABA* short-acting beta2-agonist (doses are for salbutamol). (Reprinted with permission)

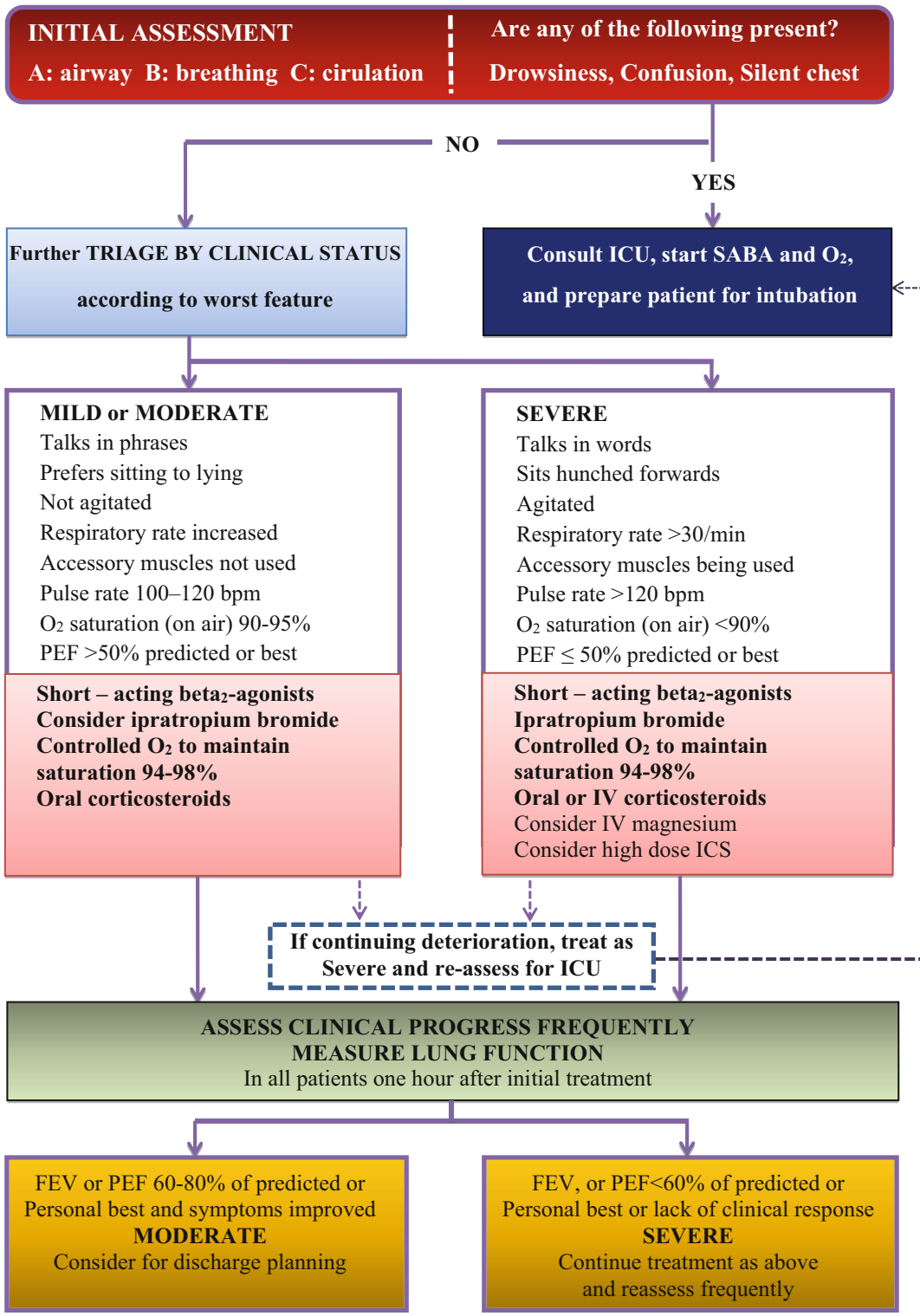


Fig. 7 Management of asthma exacerbations in emergency department for children 6 years and older (GINA 2017). *ICS* inhaled corticosteroids, *ICU* intensive care unit, *IV* intravenous, O_2 oxygen, *PEF* peak expiratory flow, *FEV1* forced expiratory volume in 1 s. (Reprinted with permission)

and greater improvement in PEF and FEV_1 compared with SABA alone (Griffiths and Ducharme 2013b). However, in children hospitalized for acute asthma, no benefits were seen from adding ipratropium to SABA, including no reduction in length of stay (Vézina et al. 2014).

Magnesium Sulfate

Intravenous magnesium sulfate is not recommended for routine use in asthma exacerbations in children. However, when administered as a single 2 g infusion over 20 min, it reduces hospital admissions in some children who fail to respond to initial treatment, who have persistent hypoxemia, or whose FEV_1 fails to reach 60% predicted after 1 h of care. Moreover, nebulized salbutamol/albuterol can also be administered in isotonic magnesium sulfate (Powell et al. 2012). While the overall efficacy of this practice is unclear, pooled data from three trials suggest possible improved pulmonary function in those with severe asthma exacerbations (FEV_1 <50% predicted). However, the efficacy of combined treatment of magnesium by both nebulized and IV route in children with AAE remains controversial.

Epinephrine

Intramuscular (IM) epinephrine (adrenaline) is indicated in addition to standard therapy only in cases for which AAE is associated with anaphylaxis or angioedema. IM dose of epinephrine 1:1000 at 0.01 mg/kg (with a maximum dose of 0.5 mg) should be administered (Chipps et al. 2005). Parenteral epinephrine is a consideration when other more expensive therapies are not available. IV epinephrine must be given very cautiously and slowly. Add 1 mg of epinephrine (1 mg in 1 cc, 1:1000 dilution) to an IV bag of saline or D5W, and run this drip through a microdrip chamber at 15 microdrops per minute (Chipps et al. 2005).

Inhaled Corticosteroids

High-dose ICS given within the first hour after presentation to an emergency room reduces hospitalizations in patients not receiving systemic corticosteroids (GINA 2017). The evidence for the impact of ICS in addition to systemic corticosteroids during this early evaluation and treatment is conflicting (GINA 2017). Patients already prescribed ICS should be provided with advice about increasing the dose for the next 2–4 weeks. Patients not currently taking controller medication should usually be commenced on regular ICS-containing therapy, as an exacerbation requiring medical care indicates that the patient is at increased risk of future exacerbations.

13.9.2.4 Assessment of Treatment Response and Follow-up for Acute Asthma Exacerbation in Children 6 Years and Older

During treatment of AAE, children should be carefully monitored and treatment adapted according to their response. Children with AAE who present to the ambulatory setting with severe or life-threatening symptoms, who fail to respond to pharmacotherapy, or who continue to deteriorate should be transferred immediately to an acute care facility. Children with weak response to SABA treatment should be closely monitored and evaluated. Lung function, including FEV_1 if the child can perform spirometry and it is available, should be monitored before and at regular intervals starting at 1 h after SABA therapy. Moreover, additional treatment should continue until PEF or FEV_1 reaches a best value or returns to previously stable values.

When children with AAE are discharged after having favorable treatment response, medications should include as-needed reliever medication, usually OCS and, for most patients, regular controller treatment. Inhaler technique and adherence should be reviewed before discharge. GINA guidelines recommend a follow-up appointment in 2–7 days depending on the clinical and social-familial situation. At the follow-up visit, the healthcare provider should assess the patient's level of symptom control and risk factors, explore the potential cause of the exacerbation, and review the written asthma action plan. Previous maintenance controller regimens can generally be resumed at 2–4 weeks after the exacerbation unless the exacerbation was preceded by symptoms suggestive of chronically poorly controlled asthma. In this situation, provided inhaler technique and adherence have been checked, a step up in treatment is indicated.

13.10 Severe Therapy-Resistant Asthma in Childhood

13.10.1 Background

Severe asthma, also called severe therapy-resistant (STRA) or refractory asthma, accounts for less than 5% of all childhood asthma (Lang et al. 2008) and has become less common over time, possibly due to the effectiveness of asthma guideline implementation worldwide and the use of controller medications. STRA in childhood constitutes a poorly controlled asthma group and represents a significant challenge for healthcare due to associated morbidity and mortality as well as high utilization of healthcare resources. In addition, STRA in childhood has long-term negative impact on adult lung function, and an association with chronic obstructive pulmonary disease (COPD) in later life has emerged (McGeachie et al. 2016).

13.10.2 Nomenclature and Definition

There is a lack of international consensus regarding the definition of severe and resistant (or refractory) asthma. Severe treatment-resistant asthma (STRA) in childhood refers to children having three main criteria (Reddy et al. 2014): (1) chronic uncontrolled symptoms, defined as the use of SABAs on at least 3 days/week for at least 3 months, combined with high-dose ICS and in association with LABAs, LTRAs, and/or low-dose theophylline; (2) severe acute exacerbation in the previous year, defined as one admission to pediatric intensive care with the need for more than two intravenous treatments or the use of two or more high doses of OCS; (3) fixed or persistent airflow limitation, defined as FEV_1 (or PEF) of $<80\%$ after SABA withhold or an FEV_1 (or PEF) of $<80\%$ despite a trial of OCS and acute administration of SABA.

STRA must be differentiated from difficult-to-treat asthma, as the former is a candidate for immunosuppressive or other anti-inflammatory modalities. Difficult-to-treat asthma is characterized by poor asthma control due to nonadherence, persistent triggers, inadequate inhalation, and other comorbidities (Bush et al. 2008; Martin Alonso et al. 2017). Unlike difficult asthma, severe asthma patients remain symptomatic after these factors are addressed.

13.10.3 Approach to the Childhood with Severe Therapy-Resistant Asthma

13.10.3.1 Confirm Diagnosis of Severe Therapy-Resistant Asthma

Before labeling a child as having STRA, the first step is to confirm the diagnosis of asthma with a full history, physical examination, and directed testing. Once the diagnosis of asthma is confirmed, comorbidities and modifiable factors should be identified and addressed. Additional testing may then be undertaken as directed by prior findings.

13.10.3.2 Identify Comorbidities

Comorbidities may contribute directly to the severity of asthma, may complicate the assessment of asthma, or may be a coincidental finding. These include atopic diseases, obesity, gastroesophageal reflux (GER), and obstructive sleep apnea (OSA). Other potential comorbidities such as dysfunctional breathing, vocal cord dysfunction, and mental health disorders such as anxiety and depression have not been well studied in children.

Inadequate treatment of common atopic diseases such as allergic rhinitis, food allergy, and atopic dermatitis is usually associated with worse asthma control (Bush et al. 2008; Martin Alonso et al. 2017). However, more data are needed to more fully evaluate the relationship between these atopic conditions and asthma severity and to determine whether their treatment improves asthma control.

In children, obesity may cause breathlessness and "wheeze" without evidence of asthma, leading to the wrong diagnosis and inappropriate treatment. However, although some studies have found no difference (Brenner et al. 2001; Schachter et al. 2003; Story 2007), the majority of studies demonstrate an increased prevalence of asthma in overweight children (Castro-Rodríguez

et al. 2000; Ogden et al. 2002; Schaub and von Mutius 2005; Scholtens et al. 2010). In addition, according to one meta-analysis, obesity is a minor risk factor for asthma exacerbation and, as such, should also be addressed in the child with severe asthma (Ahmadizar et al. 2016).

GER is typically considered a comorbid condition in asthma patients; however, it is not clear if treatment for GER improves asthma control (Writing Committee for the American Lung Association Asthma Clinical Research Centers et al. 2012). One study showed improvement in asthma exacerbations on protein pump inhibitor (PPI) while another showed decreased nighttime symptoms while taking ranitidine (Gustafsson et al. 1992; Khoshoo and Haydel 2007). However, a double-blind study from the American Lung Association showed that, in children without GERD symptoms, treatment with PPI made no difference in asthma control even if pH studies showed GER (Holbrook et al. 2012). Hence, the impact of GER treatment on asthma control and severity remains controversial.

Obstructive sleep apnea (OSA) is an additional comorbid condition that contributes to bronchial hyperreactivity/inflammation (Janson et al. 1996; Lewis 2001) and is associated with increased likelihood of uncontrolled asthma (Teodorescu et al. 2010) and more severe asthma (Julien et al. 2009). These effects may be due to increased GER, leptin dysregulation (in obese subjects), and pro-inflammatory cytokine milieu in asthmatic patients with OSA (Salles et al. 2013). It is estimated that nearly 60% of children with severe asthma have OSA (Kheirandish-Gozal et al. 2011). Some argue that the ICS treatments used in more severe asthma contribute to OSA rather than OSA contributing to severe asthma (DelGaudio 2002; Teodorescu et al. 2010; Williams et al. 1983). The relationship of OSA and asthma is explored in more detail in the review by Salles et al. (2013).

13.10.3.3 Review Modifiable factors

After identifying and addressing potential comorbidities, modifiable factors such as incorrect inhaler technique, poor treatment adherence, or harmful environmental exposures should be reviewed and improved. In childhood asthma, correct inhaler technique is a cornerstone to assure treatment success, and the majority of children make mistakes when inhaler technique is assessed (Alexander et al. 2016). Direct assessment of inhaler technique with the use of appropriate spacer devices (nasal mask or mouthpiece) in young children should be reviewed carefully by a specialist nurse or physician in the presence of child's family/caregiver.

In addition, treatment adherence also should be reviewed systematically in childhood with STRA as the impact of poor adherence on asthma-related morbidity is also well-described (Levy 2015; Lindsay and Heaney 2013).

Among harmful environmental exposures, passive (second-hand) and active smoking in children should be identified and eliminated prior to diagnosis of STRA. Passive tobacco smoke exposure is common in children with asthma and usually associated with corticosteroid resistance (Kobayashi et al. 2014). Therefore, exposure to tobacco smoke must be eliminated before the diagnosis of refractory asthma can be made. Besides tobacco smoke exposure, persistent exposure to indoor and outdoor allergens in a sensitized child with STRA should also be identified and addressed if possible. A home visit by a specialist nurse may help to identify objective evidence of allergen exposure before confirming the diagnosis of STRA.

13.10.3.4 Perform Laboratory and Pulmonary Testing

Finally, in children with a clinical diagnosis of STRA, laboratory testing results should be reviewed to re-evaluate the concordance between skin prick tests, fungal sensitization, total and specific IgE concentrations, blood (or sputum) eosinophil counts, and F_ENO. Spirometry should be done to confirm fixed airway limitation (obstruction) with bronchodilator responsiveness testing. While bronchial challenge testing (BCT) is not routinely performed in children with a clinical diagnosis of STRA due to typically poor baseline spirometry with low FEV_1 and/or an extreme bronchial hyper-responsiveness, BCT may be helpful in cases with suspected STRA

with reported chronic severe symptoms but normal spirometry. Other sophisticated examinations such as Th2-related cytokine level and gene expression studies may be performed in some severe acute exacerbations or resistant asthma in childhood (Nguyen-Thi-Dieu et al. 2017). Low-dose high-resolution computed tomography (HRCT) scanning is rarely done in childhood asthma except for those with suspected bronchiectasis or for analyzing bronchial remodeling or distal airway structures in special cases (Jain et al. 2005; Tillie-Leblond et al. 2008). Invasive investigation such as bronchoscopy with possible bronchoalveolar lavage and endobronchial biopsy or brushing may be indicated and performed in select cases (Bossley et al. 2012).

13.10.4 Treatment of Severe Therapy-Resistant Asthma in Childhood

Currently, there is a lack of high-quality evidence and international consensus for treating childhood STRA. Therefore, children with STRA need add-on "beyond guidelines" therapies because of poor control despite maximal conventional treatments and optimization of basic asthma management (Bush et al. 2011).

13.10.4.1 Optimization of Conventional Medications

High Dose of Corticosteroids

Before starting add-on "beyond guidelines" therapies for children with STRA, standard therapies should be optimized. Bush et al. suggest a sequence for consideration of therapy for severe corticosteroid-resistant asthma in childhood (Bush et al. 2011). Children with STRA may be treated with increasing dose of ICS (up to 1000–2000 mcg/day for fluticasone propionate or equivalent). A small percentage of children with STRA may benefit from increasing the dose to as high as 2000 μg/day. If asthma symptoms and frequency of asthma exacerbation improve, ICS dose should be gradually reduced to the lowest dose which maintains significant benefits. If there is no response to ICS dose escalation, it is recommended that maximal dose ICS be promptly stepped down to a lower dose. If no benefit is seen with maximal high dose of ICS, systemic oral corticosteroids, starting at prednisolone 0.5 mg/kg, should be tried preferentially to extra fine particle ICS in most patients (except in those with proven distal airway inflammation by transbronchial biopsy or high level of alveolar nitric oxide) (Bush et al. 2011). If significant clinical benefit is seen with oral corticosteroid, this must be stepped down to the lowest dose (or alternate day dosing) needed to control disease; importantly, potential adverse side effects of systemic long-term treatment must be assessed and appropriately treated if possible.

Anti-IgE Antibody

Omalizumab reduces the frequency of asthma exacerbation (Busse et al. 2011; Deschildre et al. 2013; Kulus et al. 2010; Lanier et al. 2009; Milgrom et al. 2001) and ICS dose (Milgrom et al. 2001) as well as increases symptom-free days (Busse et al. 2011; Deschildre et al. 2013) in children with severe allergic asthma. Long-term (>1 year) safety and efficacy data are not available in children. At this time, omalizumab is included in GINA guidelines as a possible step 5 add-on therapy in children ≥6 years old who are not controlled on step 4 therapies (GINA 2017). However, while omalizumab is primarily indicated for allergic asthma, it may also be administered in rare cases of nonatopic STRA when IgE is in range for described omalizumab dosing (Milgrom et al. 2001).

Anti-interleukin-5

Mepolizumab has been studied in individuals aged 12 years and older with severe eosinophilic asthma (Castro et al. 2015; Haldar et al. 2009; Pavord et al. 2012). GINA guidelines recommend mepolizumab as a possible Step 5 add-on therapy if criteria (absolute eosinophil count) threshold is met (GINA 2017).

Other Therapies

Other treatments have been used in childhood with STRA, but their efficacy is still controversial. These include use of the SMART regimen (symbicort™ maintenance and reliever therapy)

by using budesonide/formoterol as maintenance and reliever dry powder inhaler device or a trial of low-dose theophylline (Bush et al. 2011).

13.10.4.2 Trials with Unconventional Medications

Antibiotic and Antifungal Therapy

Macrolides, such as azithromycin and clarithromycin, with immunomodulatory properties may be indicated for children with STRA, especially for those with suspected atypical bacterial infection (Brusselle and Joos 2014). Recently, the diagnosis of severe asthma with fungal sensitization (SAFS) has been described; this is defined as severe asthma combined with sensitization to at least one fungus as evidenced by skin prick test (SPT) or IgE testing (Denning et al. 2009). If a diagnosis of SAFS is being considered in childhood with STRA, treatment with oral itraconazole or voriconazole may be considered in association with reducing fungal exposures in the environment. The side effects of antifungal drugs (including loss of appetite, vomiting, diarrhea, headache, muscle and joint pain, and anemia) should be monitored regularly, particularly since these therapies interfere with corticosteroid metabolism.

Immunosuppressant and Immunoglobulin Therapy

There is a lack of randomized, controlled trials or strong evidence for the benefits of cytotoxic or immunosuppressive drugs in childhood STRA. Immunosuppressants have been used in children with oral corticosteroid (OCS)-dependent asthma on the basis of small case series (Aaron et al. 1998; Marin 1997). A trial with methotrexate or cyclosporine may be considered in children with eosinophilic STRA with persistent inflammation despite OCS therapy or in those who require very high dose of OCS (>2 mg/kg or 60 mg/day of prednisone) to maintain control of asthma (Bush et al. 2011). The use of nebulized cyclosporine, an attractive and alternative way of drug delivering the immunosuppressant to avoid systemic toxicity, may be a consideration in children with STRA, but data from randomized controlled studies are still needed. Finally, after attempts with previously described therapies, immunoglobulin administration could be considered in children with OCS-dependent STRA, although there is no adequately powered pediatric trial to support its use (Bush et al. 2011).

13.11 Prevention of Asthma in Childhood

Studying the natural history of asthma in childhood may assist in the development of a vision and strategy for prevention of the disease (primary prevention). Asthma is a heterogeneous disease with the inception and persistence driven by gene-environment interactions. While these interactions may occur in early life and even in utero, a "window of opportunity" may exist during childhood for influencing asthma development (GINA 2017). Asthma prevention focuses on addressing the risk factors for asthma development both in utero and throughout childhood (see above). While this knowledge base continues to increase, clear recommendations are guarded at this time, due to the complexity of gene-environment interplay. Preventative strategies should remain at the forefront of future childhood asthma research.

13.12 Conclusion

Asthma is the most common chronic respiratory disease in childhood and is the leading cause of childhood morbidity from chronic disease. While much progress has been made over the past years in the understanding of childhood asthma, clearly there remains work to be done. The factors contributing to asthma development (both genetic and environmental), preventative strategies addressing these risks, and novel treatment options will be crucial clinical considerations in the years to come. Not only will these pursuits strengthen our understanding of a complex disease process, but they will also inform the manner in which the lives of millions of children with asthma worldwide are impacted. It is no small goal but one certainly worthy of the effort.

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14 Aspirin or Nonsteroidal Drug-Exacerbated Respiratory Disease (AERD or NERD)

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Contents

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Abstract

Nonsteroidal anti-inflammatory drug (NSAID)-exacerbated respiratory disease (N-ERD) is a chronic eosinophilic inflammatory condition of the airways characterized by chronic severe asthma, rhinosinusitis, and nasal polyposis in which symptoms are aggravated by the intake of aspirin or NSAIDs. Its pathogenesis is not completely understood, although alterations of the metabolism of arachidonic acid with decreased production of prostaglandin E_2 (PGE_2) and increased release of cysteinyl leukotrienes are proposed as responsible for the immediate respiratory symptoms induced by NSAIDs. In addition, abnormalities of the immune system with generation of particular cytokine profiles result in the chronic eosinophilic inflammation observed in the disease. A role for chronic viral infections and specific IgE to *Staphylococcus aureus* enterotoxins may be involved in the maintenance of the chronic stages of N-ERD. The diagnosis of N-ERD is based on a medical history suggestive of the typical clinical manifestations, and in some patients, confirmation by an oral provocation test with aspirin can be performed when necessary. Treatment of N-ERD includes patient education for careful avoidance of COX-1 inhibitors, the use of alternative non-COX-1-inhibitor NSAIDs for relief of pain and inflammation, treatment of asthma and chronic rhinosinusitis according to current guidelines, and sinus surgery and aspirin (ASA) desensitization when indicated.

Keywords

Aspirin · Asthma · Cyclooxygenases · Nasal polyps · NSAIDs · Rhinosinusitis

14.1 Introduction and Historical Perspective

Aspirin (acetylsalicylic acid, ASA) and nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most commonly used drugs worldwide. After antibiotics, ASA and NSAIDs are the most frequent cause of drug hypersensitivity. Natural salicylates from white willow's bark were mentioned in texts from ancient Sumer, Egypt, Mesopotamia, Lebanon, and Assyria. Approximately in 3000 BC, ancient Egyptians recorded the medicinal value of willow bark and myrtle. The decoction of sheets of willow is already mentioned in the famous Egyptian Papyrus, *Ebers Papyrus*, a medical text from 1543 BC. The Roman, Greek, and Chinese civilizations employed willow bark as medication more than 2000 years ago.

Hippocrates described "a bitter powder that came from the bark and leaves of the willow tree which was able to relief pain and fever." The active extract of the bark, salicin (from the Latin name of the white willow tree, *Salix alba*), is the glycoside of salicylic acid, also used by Celsus, Pliny the Elder, Dioscorides, and Galen.

The roman encyclopedist Celsus, in his *De Medicina* of circa 30 BC, suggested willow leaf extracts as anti-inflammatory. By the time of Galen, willow was commonly used throughout the Roman and Arab worlds. In the middle ages, Hildegard of Bingen, a nun, and Henrik Harpestreng used salicylates for the treatment of fever and rheumatism. Native Americans and the Hottentots of South Africa used for centuries an infusion of the bark for fever and other purposes.

The first clinical trial on the therapeutic use of willow bark against fever was reported to the Royal Society of Medicine on April 25, 1763, by Reverend Edward Stone, a vicar from Chipping Norton in Oxfordshire, England, who noted that it was effective in reducing malarial fever. He collected, dried, and powdered willow bark and tested it on people with fever, pain, and fatigue related to malaria. Lewis and Clark used willow bark tea for therapy of fever between 1803 and 1806, and in 1824 Bartolomeo Rigartelli used willow bark extract as an antipyretic drug. Brugnatelli and Fontana obtained salicin in impure form in 1826, and Johann Andreas Buchner isolated in 1828 a tiny amount of bitter-tasting, yellow needlelike crystals from willow tree which he called "salicina" (salicin).

In 1829, French pharmacist Henri Leroux isolated salicin in crystalline form. He boiled

the powder of white willow bark in water and, while trying to concentrate the preparation, obtained the soluble crystals that he named salicylic acid. At the same time, Löwig found salicylic acid in meadowsweet. It had unpleasant taste and caused gastric irritation and nausea. In 1830 the Swiss pharmacist Johann Pagenstecher isolated a pain-reducing substance in meadowsweet (*Spiraea ulmaria*), and in 1838 Raffaele Piria was able to convert salicin to salicylic acid.

A major research breakthrough in the field of pharmacology occurred in 1853 when Gerhardt, a French chemist, first synthesized acetylsalicylic acid by buffering salicylic acid with acetyl chloride and sodium salicylate. The resulting product was unstable and impure. In 1859 Hermann Kolbe prepared salicylic acid from sodium phenate and carbon dioxide, and von Gilm called ASA as acetylated salicylic acid. In 1869 Schröder, Prinzhorn, and Kraut assigned the correct structure of ASA with the acetyl group connected to phenolic oxygen. A few years later, in 1876, Mac Laghan described the antirheumatic effect of salicin and Stricker and Riess that of salicylic acid.

In 1886 a German chemical company, Kalle & Co., discovered the antipyretic properties of acetanilide, which was called antifebrin. Carl Duisberg developed phenacetin (acetophenetidin), and in 1897 Felix Hoffman, working at Friedrich Bayer & Co., discovered a better method to synthesize pure, stable, and palatable ASA, the first modern and truly synthetic drug. He neutralized salicylic acid buffering it with sodium and acetyl chloride. The unpleasant sweet taste of sodium salicylate was refined by acetylation of the free phenolic hydroxyl group of salicylic acid through substitution of the hydrogen atom with a methyl group.

In 1899, Heinrich Dreser set up animal experiments showing anti-inflammatory and analgesic effects of ASA, and Bayer & Co. patented it on March 6, 1899. The name aspirin comes from "a" in "acetyl chloride," "spir" from spirsäure (salicylic acid) in *S. ulmaria* (the plant they derived the salicylic acid from), and "in," a familiar name ending for medicines (Sánchez-Borges 2014).

14.2 Hypersensitivity Reactions to ASA and NSAIDs

The first description of a hypersensitivity reaction triggered by ASA was made by Hirschberg in 1902. He described a patient with acute angioedema and urticaria occurring immediately after aspirin intake (Hirschberg 1902). Gilbert recognized for the first time an asthmatic reaction to ASA in 1911 (Gilbert 1911), whereas Reed and Cooke repeated the same observation in 1919. In 1920 van der Veer described the first ASA-induced fatal asthmatic reaction.

M. Fernand Widal, Pierre Abrami, and Jacques Lermoyez observed in 1922 the association between aspirin sensitivity, aspirin-induced asthma, and nasal polyposis, the ASA triad (Widal et al. 1922), which was rediscovered more than 40 years later by Samter (Samter and Beers 1968).

Different terminologies have been proposed for aspirin-induced asthma, such as aspirin-intolerant asthma, aspirin sensitivity, aspirin-sensitive asthma, aspirin-exacerbated asthma, and aspirin-exacerbated respiratory disease. Presently, the designation of nonsteroidal anti-inflammatory drug-exacerbated respiratory disease (N-ERD) is the most accepted, because it includes other NSAIDs, the involvement of upper and lower airways, and reflects the fact that the disease progresses independently of any ASA or NSAID exposure (Kowalski et al. 2013).

14.3 Classification of Hypersensitivity Reactions to Aspirin and NSAIDs

ASA and NSAIDs are routinely used for the treatment of pain, fever, and inflammation. By definition NSAIDs are drugs which, although having different chemical structure, share a common mechanism of action consisting in the inhibition of the cyclooxygenases (COX) that convert arachidonic acid into potent inflammatory mediators such as prostaglandins and thromboxanes (Table 1).

Two cyclooxygenase isoenzymes have been described. COX-1 is the constitutive enzyme,

Table 1 Chemical classification of "classic" NSAIDs

Group	Drugs
Salicylic acid derivatives	Aspirin, sodium salicylate, choline magnesium trisalicylate, salsalate, diflunisal, salicylsalicylic acid, sulfasalazine, olsalazine
Para-aminophenol derivatives	Acetaminophen
Indole and indene acetic acids	Indomethacin, sulindac, etodolac
Heteroaryl acetic acid	Tolmetin, diclofenac, ketorolac
Arylpropionic acid	Ibuprofen, naproxen, flurbiprofen, ketoprofen, fenoprofen, oxaprozin
Anthranilic acid (fenamates)	Mefenamic acid, meclofenamic acid
Enolic acid	Oxicams (piroxicam, tenoxicam), pyrazolidinediones (phenylbutazone, oxyphenbutazone)
Alkanones	Nabumetone
Pyrazolic derivatives	Antipyrine, aminopyrine, dipyrone

present in all cells, whereas COX-2 is the inducible form, restricted to inflammatory cells and expressed following cell activation by cytokines, bacterial lipopolysaccharide, and other stimuli. According to their ability to inhibit COX, NSAIDs are divided into three groups: the older "classic" NSAIDS inhibit both enzymes, COX-1 and COX-2. Meloxicam and nimesulide are preferential COX-2 inhibitors that can inhibit COX-1 only if administered in high doses. The third group of NSAIDs is constituted by the coxibs, celecoxib, rofecoxib, etoricoxib, lumiracoxib, and valdecoxib which are selective or specific COX-2 inhibitors. In that group rofecoxib marketing was stopped due to cardiovascular adverse effects judged to be unacceptable by the manufacturer, lumiracoxib because of hepatotoxicity, and valdecoxib was retired because its use was associated with severe systemic allergic manifestations such as Stevens-Johnson syndrome and toxic epidermal necrolysis (Sánchez-Borges et al. 2004). Acetaminophen (paracetamol) and pyrazolones are analgesic and antipyretic drugs with lower anti-inflammatory strength that are regarded as weak COX inhibitors. Acetaminophen is generally well tolerated in N-ERD patients, but increased doses (more than 1000 mg) can induce respiratory symptoms in some individuals.

The European Academy of Allergy and Clinical Immunology proposed a comprehensive classification of hypersensitivity reactions to NSAIDs based on the timing of symptom initiation, the clinical picture, the pattern of drugs inducing the reaction, and the presence or absence of other chronic underlying conditions (Kowalski et al. 2013). Three types of immediate reactions, including N-ERD, nonsteroidal drug-exacerbated cutaneous disease (N-ECD), and multiple NSAID-induced urticaria and angioedema, are observed in subjects who react to structurally diverse COX-1 inhibitors. On the other hand, two other clinical pictures are truly allergic, that is, mediated by immunological mechanisms. These include urticaria/angioedema and anaphylaxis of immediate type induced by a single NSAID and drugs structurally similar, purportedly mediated by drug-specific IgE antibodies, and delayed reactions to a single NSAID chemical group, putatively mediated by drug-specific T cells (Table 2).

14.4 Definition of NSAID-Exacerbated Respiratory Disease (N-ERD)

NSAID-exacerbated respiratory disease is a chronic eosinophilic inflammatory disorder of the respiratory tract occurring in patients with asthma and/or rhinosinusitis with nasal polyps, whose symptoms are aggravated by NSAIDs, including aspirin. This terminology substitutes previous designations such as aspirin-exacerbated respiratory disease (AERD), aspirin-induced asthma, aspirin-intolerant asthma, aspirin triad, and Samter's disease.

14.5 Epidemiology and Natural History

Respiratory symptoms triggered by exposure to NSAIDs are observed in 1.8% of the general population (Makowska et al. 2016) and in asthmatic individuals between 5.5% and 12.4%.

Table 2 Phenotypes of hypersensitivity reactions to nonsteroidal anti-inflammatory drugs

Type of reaction	Clinical picture	Comorbidities	Cross-reactivity with COX-1 inhibitors
NSAID-exacerbated respiratory disease (N-ERD)	Asthma, rhinosinusitis, nasal polyposis	Asthma/rhinosinusitis	Yes
NSAID-exacerbated cutaneous disease (N-ECD)	Urticaria and/or angioedema	Chronic spontaneous urticaria	Yes
NSAID-induced urticaria and angioedema	Urticaria and/or angioedema	None	Yes
Single NSAID-induced urticaria, angioedema, and anaphylaxis	Urticaria, angioedema, anaphylaxis	None	No
Single NSAID-induced delayed reactions	Various (e.g., fixed drug eruption, Stevens-Johnson, toxic epidermal necrolysis)	None	No

Modified from Kowalski et al. (2013)
NSAID nonsteroidal anti-inflammatory drug, *N-ERD* nonsteroidal anti-inflammatory drug-exacerbated respiratory disease, *N-ECD* nonsteroidal drug-exacerbated cutaneous disease

However, in asthmatics challenged with ASA, this figure increases to 21%, and in severe asthmatics, the prevalence of NSAID hypersensitivity doubles (Rajan et al. 2015).

In patients with chronic rhinosinusitis with nasal polyps, the prevalence of N-ERD ranges between 9.69% and 40%, and up to 2% of asthmatic children may suffer N-ERD, although this figure increases between 3.3% and 12.5% when oral challenges are performed (Jenkins et al. 2004). Risk factors for the development of N-ERD include a positive family history of N-ERD, nasal polyposis, and asthma. The prevalence of atopy among N-ERD subjects is greater than in the general population (Kupczyk et al. 2004; Berges-Gimeno et al. 2002), and a higher prevalence of N-ERD is observed in females (Steinke and Borish 2015).

Symptoms usually begin between adolescence and 40 years of age. The initial manifestations simulate those of a viral upper respiratory infection and are accompanied by rhinitis and nasal congestion. Chronic nasal congestion and rhinorrhea develop, while hyposmia and anosmia occur in about 55% of those affected. Finally, a chronic eosinophilic and hyperplastic sinusitis ensues, and in about 70% of patients, nasal polyps will develop. This clinical picture is associated with intercurrent episodes of infectious rhinosinusitis.

After a variable period of time, between 3 months and 5 years, asthma and acute respiratory reactions induced by ASA and other NSAIDs are observed. Severity of asthma is mild in about 20% of cases, moderate in 30%, and severe in 50% (Szczeklik et al. 2000).

14.6 Clinical Picture

Typically, N-ERD presents as moderate to severe asthma with concomitant chronic persistent rhinosinusitis and nasal polyposis. Compared to aspirin-tolerant asthma, N-ERD patients exhibit more severe asthma, decreased lung function, increased requirements for systemic glucocorticoids, poor response to standard asthma treatment, and a greater risk of life-threatening asthma exacerbations. NSAID hypersensitivity (N-ERD) constitutes a significant risk factor for severe chronic and near-fatal asthma (Mascia et al. 2005).

Intense eosinophilic infiltrates are present in the upper and lower airway mucosa of affected subjects. When challenged with NSAIDs, N-ERD patients develop within 1–3 h respiratory symptoms (bronchospasm, rhinitis), sometimes accompanied by ocular (conjunctival injection), cutaneous (flushing, urticaria, and/or

angioedema), or gastrointestinal symptoms (nausea, epigastric pain).

This condition is usually accompanied by significant blood, nasal, and sputum eosinophilia, as well as eosinophilic infiltration and increased numbers of IL-5 positive cells in bronchial biopsies. Polypoid hypertrophy and severe inflammation of sinus mucosa are present, and patients complain of severe nasal obstruction, postnasal drainage, and anosmia (Fig. 1). Decreased smell usually is associated with nasal polyposis and repeated sinus surgery, and polypectomies are often needed. Also, recurrent sinus infections are common. An additional recent observation is the induction by alcoholic beverages, especially red wine, of upper and lower respiratory symptoms in patients suffering N-ERD (Cardet et al. 2014).

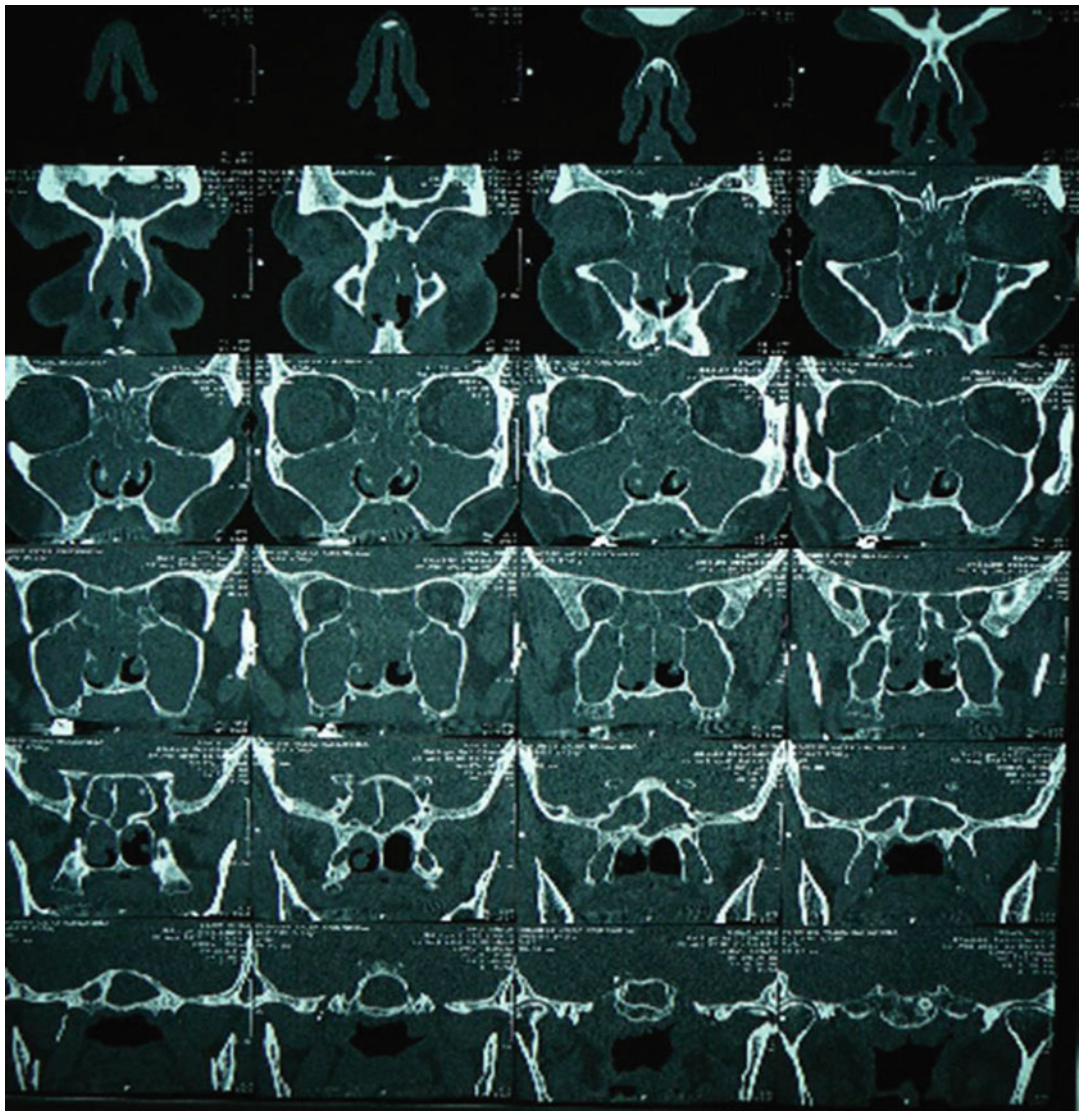

Fig. 1 CT scan of a 73-year-old female patient presenting nonsteroidal anti-inflammatory drug-exacerbated respiratory disease associated with chronic rhinosinusitis and nasal polyps. Arrows indicate full opacification of sinuses

14.7 Pathophysiology of N-ERD

14.7.1 Mechanisms of Acute Respiratory Reactions in N-ERD

The ability of NSAIDs to induce symptoms in asthmatics with N-ERD is dependent on its potency for inhibition of cyclooxygenase-1 (COX-1), the enzyme responsible of the production of prostaglandins. NSAIDs that do not inhibit (or weakly inhibit) COX-1 are generally tolerated (Szczeklik and Stevenson 2003).

According to the cyclooxygenase hypothesis, the inhibition of COX-1, the enzyme that metabolizes arachidonic acid derived from the phospholipids of cell membranes to prostaglandins, thromboxanes, and prostacyclins, would lead to a decreased generation of protective PGE_2, activation of inflammatory cells, release of inflammatory mediators, and bronchial and nasal symptoms (Szczeklik 1990) (Fig. 2).

Supporting this theory, a local deficiency of PGE_2 synthesis in nasal polyp epithelial cells and bronchial fibroblasts has been observed in N-ERD. This observation suggests that decreased baseline levels of the anti-inflammatory prostaglandin PGE_2 are further decreased acutely with NSAID ingestion, resulting in enhanced airway inflammation and bronchospasm. This hypothesis is supported by the finding that inhalation of PGE_2 or oral pretreatment with misoprostol (a synthetic PGE_2 analog) prevents ASA-induced bronchoconstriction. Thus, the reduced protective role of PGE_2 is critical to N-ERD pathogenesis (Hamilos et al. 1998; Kowalski et al. 2003).

14.7.2 Pathogenesis of Chronic Inflammation in the Airways

Eosinophil airway inflammation is a typical feature of N-ERD, linked to a distinctive profile of cytokine expression, with upregulation of cytokines related to eosinophil activation and survival (IL-5, GM-CSF, RANTES, eotaxin), as well as increased IL-4, IL-33, TSLP, and interferon-γ in the airway mucosa (Souza et al. 1997; Pods et al. 2003).

Increased numbers of activated T cells and mast cells and platelet adherent granulocytes are also present in the airway mucosa (Kowalski et al. 2005).

Regarding the metabolism of arachidonic acid, several abnormalities are present in N-ERD, including a decreased production of PGE_2, a decreased expression of PGE_2 receptors, increased PGD_2, decreased expression of COX-2 isoenzyme, increased production of cysteinyl leukotrienes (LT) with increased LTE4 levels in the urine and nasal polyps, increased expression of cysteinyl leukotriene 1 (Cys-LT1) and Cys-LT2 receptors in the bronchial mucosa, increased expression of LTC4 synthase and 5-lipoxygenase in bronchial mucosa and nasal polyps, and decreased other lipoxygenase products such as lipoxin A4 in peripheral blood leukocytes and nasal polyp tissue.

The pathogenesis of persistent eosinophilic inflammation of the airway mucosa in N-ERD is not related to the intake of NSAIDs because in most patients the airway disease precedes the development of hypersensitivity to ASA and NSAIDs, and complete avoidance of NSAIDs does not lead to clinical improvement. Putative viral factors have been proposed as both primary triggers of ASA hypersensitivity and as a cause of the underlying chronic inflammation in the airways of subjects with N-ERD (Szczeklik 1988). Supporting this hypothesis, human rhinovirus RNA transcripts occur in bronchial epithelial cells from 100% of subjects with N-ERD but only in 73% of ASA-tolerant subjects with well-controlled asthma (Wos et al. 2008).

Additionally a role for IgE antibodies specific for *Staphylococcus* enterotoxin in perpetuating chronic eosinophilic inflammation in the airways has been suggested. This possibility is supported by increased enterotoxin antibodies in the nasal polyp tissue of patients with N-ERD, and the concentration of these antibodies correlates with eosinophilic-related products, such as eosinophil cationic protein, eotaxin, and IL-5 (Suh et al. 2004).

14.8 Genetics

Approximately 6% of subjects with N-ERD have a family history of aspirin hypersensitivity (Lockey et al. 1973; Szczeklik et al. 2000). A number of single nucleotide polymorphisms

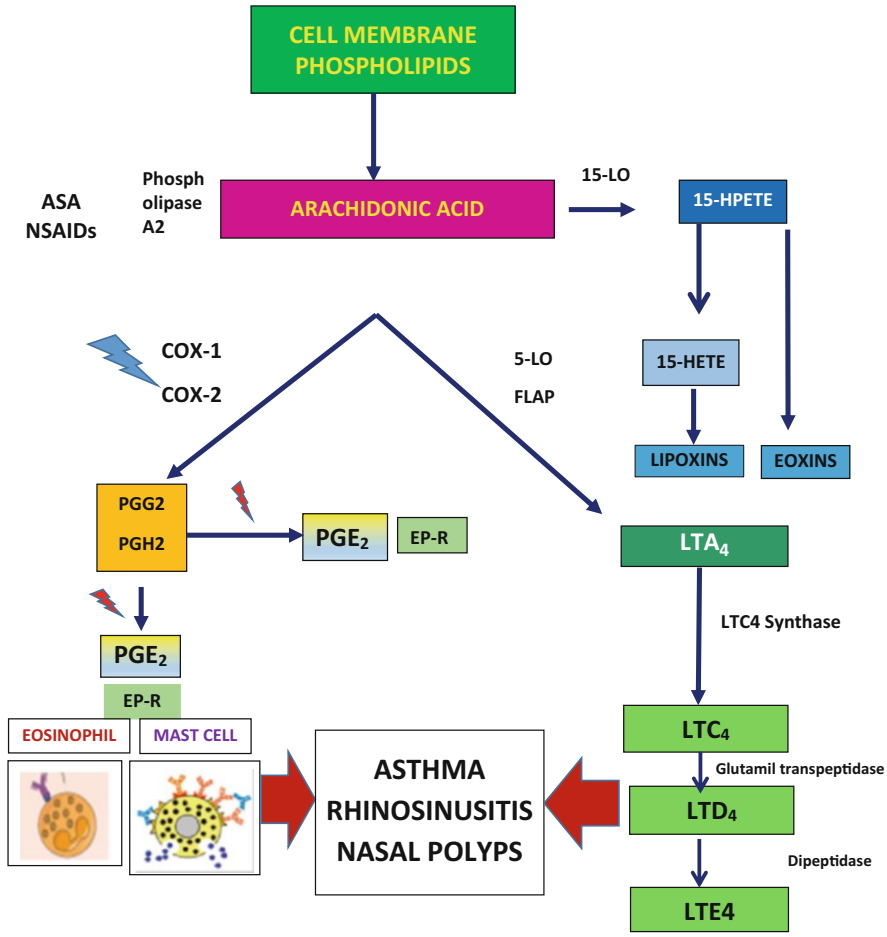

Fig. 2 Metabolism of arachidonic acid and pathogenesis of nonsteroidal anti-inflammatory drug-exacerbated respiratory disease. Pathways inhibited by ASA and NSAIDs are represented with the symbol ↘. COX-1, cyclooxygenase-1; COX-2, cyclooxygenase-2; PGG_2, prostaglandin G_2; PGH_2, prostaglandin H_2; PGE_2, prostaglandin E_2; EP-R, prostaglandin E_2 receptor; 15-LO, 15-lipoxygenase; 5-LO, 5-lipoxygenase; FLAP, 5-lipoxygenase activating protein; 15-HETE, hydroxyperoxyeicosatetranoic acid; LTA_4, leukotriene A_4; LTC_4, leukotriene C_4; LTD_4, leukotriene D_4; LTE_4, leukotriene E_4

associated with leukotriene or prostaglandin metabolisms, genetic control of immune responses, tissue remodeling, or neural physiology have been described in subjects with N-ERD (Table 3). Since these polymorphisms are often limited to specific ethnic groups or reports have been derived from studies of small groups of patients, it is difficult at this time to propose the utilization of genetic markers for the diagnosis, risk assessment, or prognosis (Park et al. 2013; Ledford et al. 2014).

14.9 Diagnosis

A history of repeated respiratory symptoms occurring 1–2 h after taking NSAIDs in a patient with adult-onset asthma and nasal polyposis is strongly suggestive of N-ERD. In patients without a clear history, the diagnosis can be confirmed by means of the gold standard test, oral provocation with aspirin (Table 4) (Berges-Gimeno et al. 2002). Alternatively, bronchial and nasal challenges with lysine-aspirin are employed in some centers

Table 3 Potential genetic markers of nonsteroidal anti-inflammatory drug-exacerbated respiratory disease (N-ERD)

	Gene	Polymorphisms	Ethnic group	Mechanisms
Arachidonic acid metabolism	CysLTR1	_634C > T, _475A > C, _336A > G	Korean	CysLTR1 expression
	CysLTR2	_819T > G, 2078C > T, 2534A > G	Korean	CysLTR2 expression, LTC4S gene interaction
	EP2	uS5, uS5b, uS7	Japanese	Decreased transcription level of EP2, PGE_2 braking
	PTGER	PTGER2: _616C > G, _166G > A PTGER3: _1709T > A, PTGER4: _1254A > G	Korean	PGE_2, TXA2 receptor polymorphism
	TXA2R	_4684C>, 795T > C	Korean	
	PTGER	PTGER3: rs7543182, rs959	Korean	PGE_2 receptor polymorphism
Eosinophil-associated gene	CRTH2	_446T > C	Korean	Decreased CRTH2 expression and increased eotaxin-2 production
	CCR3	_520T > C	Korean	Higher mRNA expression of CCR3
HLA	HLA-DPB1	DPB1∗0301	Polish	Genetic regulation of immune responses
	HLA-DPB1	DPB1∗0301	Korean	
	HLA-DPB1	rs3128965	Korean	
	HLA-DPB1	rs1042151	Korean	

Modified from Park et al. (2017)
CysLTR Cys-leukotriene receptor, *EP2* E prostanoid 2, *PTGER* prostaglandin E receptor, *TxA2R* thromboxane A2 receptor, *CRTH2* chemoattractant receptor-like molecule expressed on Th2 cells, *CCR3* chemokine receptor 3, *LTC4S* leukotriene C4 synthase

Table 4 Single-blind oral ASA challenge for evaluation of N-ERD (Berges-Gimeno et al. 2002)

Time	Day 1	Day 2	Day 3
First dose	Placebo	ASA 30 mg	ASA 100–150 mg
Second dose (after 3 h)	Placebo	ASA 45–60 mg	ASA 150–325 mg
Third dose (after 6 h)	Placebo	ASA 60–100 mg	ASA 325–650 mg

ASA acetylsalicylic acid

(Makowska et al. 2015; Nizankowska-Mogilnicka et al. 2007). Intranasal challenge with ketorolac has also been proposed, although it is less sensitive than oral aspirin challenge (White et al. 2006).

For oral and inhalation challenges, patients should be in a stable clinical condition and their basal FEV_1 should be at least 70% of the predicted value after withdrawal of short- acting β2-agonists, ipratropium bromide, long-acting β2-agonists, long-acting theophylline, tiotropium bromide, antihistamines, cromolyn sodium, nedocromil sodium, and leukotriene modifiers. These challenges should be performed in a specialized center under supervision of a physician experienced in their technique and able to manage severe reactions.

In vitro tests for the diagnosis of N-ERD, including sulfidoleukotriene release assay, 15-HETE generation assay (ASPITest), and basophil activation test have not been validated.

The diagnosis of chronic rhinosinusitis in patients with N-ERD is based on a history of sinonasal symptoms (nasal obstruction, nasal discharge, and olfactory dysfunction) for more than 12 weeks, nasal endoscopy, and/or computed tomography scan of paranasal sinuses (Fokkens et al. 2012a). Ledford et al. have recently proposed diagnostic criteria for N-ERD that are intended to substitute the need for provocation tests (Ledford et al. 2014) (Table 5).

14.10 Management

The management of patients with N-ERD is complex and includes pharmacological and nonpharmacological measures. Pharmacologic

Table 5 Suggestive diagnostic criteria for N-ERD[a] (Ledford et al. 2014)

History of respiratory symptoms (upper or lower) within 4 h of ingestion of aspirin or other
NSAID
Chronic rhinosinusitis
Nasal polyps
Peripheral blood eosinophilia
Onset of respiratory symptoms >20 years of age

N-ERD nonsteroidal anti-inflammatory drug-exacerbated respiratory disease, *NSAID* nonsteroidal anti-inflammatory drug

[a]The presence of four out of five criteria without a clinical history of aspirin or other NSAIDs that cause exacerbation of symptoms is sufficient for diagnosis

treatment of asthma and chronic rhinosinusitis should follow general recommendations for the underlying eosinophilic inflammation of the respiratory tract (Global Initiative for Asthma. Global strategy for asthma management and prevention 2017; Bateman et al. 2008; Fokkens et al. 2012b).

14.10.1 Management of NSAID Hypersensitivity

Education on strict avoidance of cross-reactive COX-1 inhibitors is mandatory for subjects with N-ERD (Table 6). Selective COX-2 inhibitors (coxibs, celecoxib, etoricoxib, rofecoxib) are tolerated by most patients, whereas acetaminophen and preferential COX-2 inhibitors (nimesulide, meloxicam) given at low recommended doses do not usually cross-react with other NSAIDs and may be used in N-ERD patients, generally after a tolerance test is performed. Reactions to low doses of acetaminophen (<500 mg) occur in 0–8.4% of patients, while nimesulide and meloxicam are tolerated by 86–96%.

Opioids, azapropazone, choline magnesium trisalicylate, and salsalate are also well tolerated by the majority of affected subjects. Alcohol avoidance should be advised as it may intensify the reactions.

14.10.2 Management of Asthma

In most patients asthma treatment that includes combination therapy with inhaled corticosteroids and long-acting β2-agonists according to GINA/NIAID guidelines is effective. However, some patients exhibit difficult to control asthma requiring additional measures. Those include leukotriene modifiers (pranlukast, montelukast, zileuton) and oral corticosteroids. Omalizumab, mepolizumab, dupilumab, and reslizumab are potential therapies for N-ERD that are currently under investigation (Bachert et al. 2015; Tuttle et al. 2018; Bergmann et al. 2015).

14.10.3 Management of Chronic Rhinosinusitis and Nasal Polyps

Eosinophilic rhinosinusitis in patients affected by N-ERD is difficult to treat. Standard treatment includes long-term high doses of topical corticosteroids applied in the form of nasal sprays or drops, antibiotics, and occasional short courses (5–10 days) of oral glucocorticoids to reduce inflammation, control symptoms, and delay nasal polyp recurrence (Palikhe et al. 2009). Leukotriene modifiers, nasal and oral decongestants, and antihistamines may provide additional relief.

Nasal saline irrigation, both isotonic and hypertonic, may help to alleviate nasal symptoms, and macrolides for a period of 3 months are sometimes utilized in severe cases. Anti-IgE (omalizumab) may be effective in relieving nasal symptoms and preventing polyp recurrence after surgery (Bachert et al. 2015), and biologic therapies interfering with eosinophilic inflammation (mepolizumab, dupilumab, reslizumab) possibly are effective for the treatment of chronic rhinosinusitis with nasal polyps in N-ERD patients (Bachert et al. 2017; Rivero and Liang 2017).

14.10.4 Surgical Treatment

In patients with severe chronic sinusitis with multiple nasal polyps and nasal passage obstruction, surgical treatment, including polypectomy, functional endoscopic sinus surgery, or ethmoidectomy, may be needed to relieve symptoms and to remove polyp tissue from the sinuses. Sinonasal surgery is indicated in patients with severe or uncontrolled symptoms and in those

Table 6 NSAID tolerance in patients with N-ERD

NSAIDs cross-reacting in a majority of patients with N-ERD (60–100%)	Ibuprofen Indomethacin Sulindac Naproxen Fenoprofen Meclofenamate Ketorolac Etodolac Diclofenac Ketoprofen Flurbiprofen Piroxicam Nabumetone Mefenamic acid
NSAIDs cross-reacting in a minority of N-ERD patients (2–10%)	Acetaminophen (at doses below 1000 mg)[a] Meloxicam Nimesulide
NSAIDs well tolerated by most patients with N-ERD	Selective cyclooxygenase-2 inhibitors Trisalicylate Salsalate

Modified from Kowalski et al. (2011)
[a]Generally not considered an NSAID

with inadequate responses despite intranasal and oral corticosteroid therapy. Nasal polyposis recurrence rate after surgery is up to ten times higher in N-ERD patients.

Endoscopic sinus surgery improves nasal symptoms, quality of life, endoscopic and computed tomography scores, bronchial symptoms, and requirement for asthma medications. After surgery, patients should continue under observation and medical treatment.

14.10.5 Aspirin Desensitization

The administration of increasing doses of ASA to patients with N-ERD results in cross-tolerance to ASA and other NSAIDs, which can be maintained indefinitely with daily drug intake. ASA treatment after desensitization is effective in improving symptoms of chronic rhinosinusitis and asthma in these patients. It also induces improvement of the sense of smell and quality of life and reduces purulent sinus infections, the requirement for systemic corticosteroids, recurrence of nasal polyps, and the need for further polyp surgery and hospitalizations. Decreased asthma symptoms and improved asthma control also occur in some patients. After omitting ASA during 2–5 days, tolerance disappears (Hope et al. 2009; Berges-Gimeno et al. 2003).

Indications for ASA desensitization include respiratory symptoms that are not controlled with maximal treatment, patients who require intermittent or continuous high doses of systemic corticosteroids, patients requiring multiple polypectomies (3 or more), and patients who require using ASA/NSAIDs for the treatment of other diseases such as ischemic cardiopathy and chronic arthritis.

Other physiologic effects of ASA desensitization are the return of urinary LTE4 to basal levels, decrease of CysLTR1, decrease of LTB4 synthesis, reduction of IL-4 y MMP-9 in the airways, and disappearance of LTC4 and histamine from nasal secretions.

The incidence of adverse effects induced by chronic ASA administration varies between 0% and 34%, and those can be prevented or reduced by additional measures such as *Helicobacter pylori* eradication, proton pump inhibitors, and H2 blockers. The rate of discontinuation of ASA treatment after desensitization is 14%.

14.11 Conclusions

Hypersensitivity reactions to ASA have been known for more than one century and were reported soon after the discovery of acetylsalicylic acid. The first description of the association of asthma, nasal polyposis, and ASA sensitivity, the ASA triad, was published in 1922, and since then numerous investigators have studied the clinical features, epidemiology, and pathogenesis and have proposed strategies to deal with this severe chronic respiratory disease, now designated as nonsteroidal anti-inflammatory drug-exacerbated respiratory disease (N-ERD).

In spite of the recent advances in the knowledge of this condition, there are still many unanswered questions to be addressed, and there is an important proportion of patients who exhibit difficult-to-treat symptoms in the upper and lower airways.

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Occupational Asthma

15

Justin Greiwe and Jonathan A. Bernstein

Contents

Abstract

Allergic respiratory diseases in the workplace, like occupational asthma (OA), represent a significant public health concern leading to long-term health consequences and socioeconomic costs for the affected worker, employer, and society as a whole. The lungs are particularly vulnerable to contact with these types of exposures due to their extensive surface area, high blood flow, and thin alveolar epithelium. Occupational asthma is the most prevalent occupational lung disease in industrialized countries and since undiagnosed OA can cause considerable medical and economic consequences, aggressive prevention strategies are essential. Despite an increase knowledge of sensitizing agents in the workplace as well as improvements in workplace safety and

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reporting, OA continues to afflict workers worldwide. Various health surveillance programs have been implemented over the years with varying degrees of success. Greater collaboration between employers, employee organizations, legislators and researchers should be encouraged to determine the most effective and economically feasible interventions for preventing OA in the workplace.

Keywords
Occupational asthma · Irritant-induced asthma · Reactive airways dysfunction syndrome · Work-aggravated asthma · Immunologic stimuli · High molecular weight · Low molecular weight

15.1 Introduction

With the onset of industrialization in the nineteenth century, workers have borne the brunt of an endless array of hazardous airborne exposures in the workplace. While worker's rights, increased regulations, and technological advancements have significantly reduced these exposures, occupational respiratory diseases continue to affect millions of workers in the USA and abroad. The lungs are particularly vulnerable to contact with these types of exposures due to their extensive surface area, high blood flow, and thin alveolar epithelium. Allergic respiratory diseases in the workplace represent a significant public health concern leading to long-term health consequences and socioeconomic costs for the affected worker, employer, and society as a whole. There are numerous examples in the recent past where recognition of occupational risk factors has led to important public health and policy changes. While the general public is aware of well-reported occupational lung disorders such as silicosis and asbestosis, occupational asthma (OA) is the most prevalent occupational lung disease in industrialized countries, accounting for approximately 5–15% of asthma in adults (Galdi and Moscato 2002a; Bernstein et al. 2013; Tarlo 2014). According to the Occupational Safety and Health Administration (OSHA), "an estimated 11 million workers in a wide range of industries and occupations are exposed to at least one of the numerous agents known to be associated with occupational asthma."

15.2 Definitions of Work-Related Asthma

Occupational asthma is a "disease characterized by variable airway obstruction and/or airway hyperresponsiveness due to causes or conditions attributable to a particular occupational environment and not to stimuli encountered outside the workplace (Bernstein et al. 2013)."OA is a subset of a larger category of diseases known as occupational respiratory diseases detailed in Table 1. There are various definitions of work-related asthma which can sometimes be confusing to understand. In general, work-related asthma is a non-specific term used to describe asthmatic symptoms identified to increase during or after work exposure and that usually improve after leaving (Bernstein n.d.).

Work-related asthma can further be divided into three groups.

1. **Occupational asthma (OA)** is caused by some exposure unique to the work environment often in workers with no pre-existing history of asthma. It can be further divided into hypersensitivity-induced OA, indicating a specific immune response can be identified. Hypersensitivity-induced OA is the most common form of OA and is typically characterized by exposure to workplace allergens or chemicals characterized by a latency period between first exposure to a substance at work and the onset of symptoms. Mechanistically this can manifest as a specific IgE-mediated immune response caused by either high molecular weight (HMW) or low molecular weight (LMW) chemical agents or as non-IgE mediated when a specific immune response can't be identified (i.e., western red cedar).
2. **Irritant-induced OA or irritant-induced asthma (IIA)** is a non-immunologic form of OA where there is no latency period

Table 1 Classification of occupational respiratory diseases

Airway disorders
Occupational rhinitis (often coexists with OA)
Occupational asthma
Sensitization: high molecular weight (HMW)/low molecular weight (LMW) agents
Irritant induced, RADS (irritant gases)
Byssinosis (cotton dust)
Grain dust effects (grain)
Chronic bronchitis/COPD (mineral dusts, coal)
Acute inhalation injury
Toxic pneumonitis (irritant gases, metals)
Metal fume fever (metal oxides like zinc and copper)
Smoke inhalation (combustion products)
Hypersensitivity pneumonitis (bacteria, fungi, animal proteins)
Infections disorders (tuberculosis, virus, bacteria)
Pneumoconiosis (asbestos, silica, coal, beryllium, cobalt)
Malignancies (lung cancer, mesothelioma)

RADS = reactive airways dysfunction syndrome, *COPD* = chronic obstructive pulmonary disease

resulting from single or multiple high-dose exposures to irritant products (Fig. 1) (Lemière et al. 2018a). When a single, high-dose exposure is identified as causative, terms **reactive airways dysfunction syndrome (RADS)** or "acute onset IIA" are often used (Vandenplas et al. 2014). For RADS, respiratory symptoms develop within minutes or hours after a single, high-level exposure to an irritant gas, aerosol, vapor, or smoke (Bernstein et al. 2006). The diagnostic criteria for RADS are summarized in Table 2. The initial symptoms are followed by airway hyperresponsiveness and asthma-like symptoms that can persist for a prolonged period (Brooks et al. 1985a). For "subacute IIA," onset of symptoms occurs greater than 24 h after multiple irritant exposures and/or chronic low levels of exposure to irritants in the workplace over time (Smith 2011). The diagnosis of these forms of OA is usually made retrospectively as patients often do not present to a facility early on where there is expertise to recognize and diagnose this variant form of OA (Tan and Bernstein 2014).

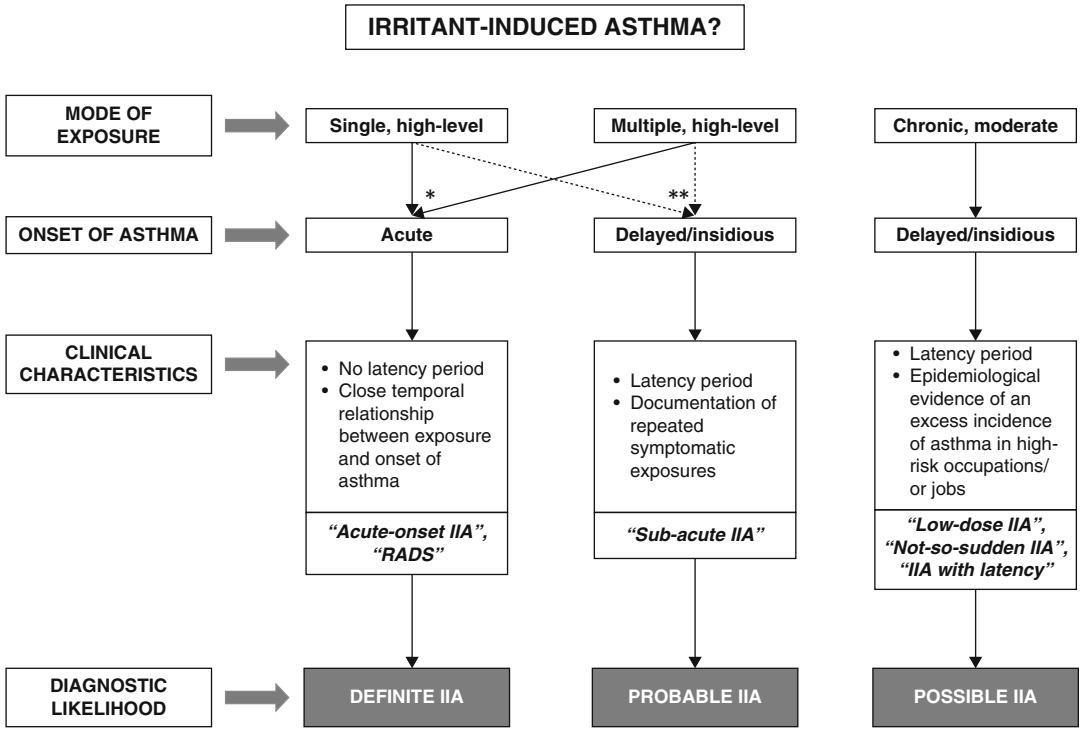
3. **Work-aggravated asthma (WAA)** refers to worsening of pre-existing asthma due to non-specific irritants or physical workplace triggers often requiring increased use of rescue bronchodilators (e.g., inhaled albuterol). Potential triggers include irritant chemicals, dust and fumes, common allergens, secondhand smoke, worksite temperature, physical exertion, and emotional stress. Work-aggravated asthma can often be prevented by avoiding workplace triggers or adjusting asthma medications and often doesn't require relocation or a job change. A broad overview of WAA is provided in Fig. 2.

15.3 Immunologic Stimuli of Occupational Asthma

Traditionally, immunologic sensitizers to OA have been divided into HMW and LMW compounds. Occupational asthma due to immunologic stimuli typically has a latency period between exposure and symptom onset. This latency period is associated with HMW agents and some LMW agents. A detailed synopsis of the most relevant causes of high and low molecular weight occupational agents is summarized in Table 3.

15.4 Prevalence of Occupational Asthma

The incidence of OA varies depending on the type of exposure and geographic location around the world. For example, OA has been reported in 8–12% of laboratory animal workers, 7–9% of bakers, and 1.4% of healthcare workers exposed to natural rubber latex; however, these latter rates vary depending on the study cited (Aronica 2014). Overall, males have the higher attributable risk for OA (14%) compared to women (7%); however, women have a higher risk for OA in certain occupations such as drivers, cleaners, nurses, and hairdressers (Lillienberg et al. 2013). The use of spray products, especially chlorine bleach, ammonia, and air freshening sprays, in occupations like spray-painters and janitorial cleaning seems to put these workers at greatest risk for developing OA and other respiratory disorders (Aronica 2014; Kogevinas et al. 1999; Zock et al. 2010).



Acute onset IIA (or RADS) be called "definite" IIA, sub-acute IIA be called "probable" IIA, and other types of moderate or low dose exposure associated IIA be called "possible" IIA
*Onset of asthma symptoms often occurs after one more severe high-level exposure incident
**There is some evidence that asthma may develop within days to weeks after an acute high-level exposure incident
Directly Copied from EAACI position paper: Vandenplas O, Wiszniewska M, Raulf M, et al. EAACI position paper: irritant-induced asthma. Allergy. 2014 Sep;69(9):1141-53.

Fig. 1 European Academy of Allergy and Clinical Immunology (EAACI) proposed diagnostic algorithm for identifying the various clinical phenotypes of irritant-related asthma

Table 2 Diagnostic criteria for RADS

1. Documented absence of previous respiratory complaints/asthma
2. Acute high-level exposure to a single respiratory irritant like a gas, smoke, fume or vapor
3. Onset of lower respiratory symptoms within 24 h after irritant exposure and should persist for at least 3 months
4. Pulmonary function tests may or may not show airflow obstruction
5. Positive methacholine test demonstrating airway hyperresponsiveness
6. Other types of pulmonary diseases should be ruled out.

Adapted from Brooks et al. (1985)

Probably the best data on OA prevalence and occupational exposures comes from a public health surveillance program (Work-Related Lung Disease (WoRLD) Surveillance Report 2007) performed by the National Institute for Occupational Safety and Health (NIOSH) which identified >4000 cases of work-related asthma from 1993 to 2002 in four states (California, Massachusetts, Michigan, and New Jersey) with ~68% caused by occupational exposure and 20% represented pre-existing asthma aggravated by occupational exposure (Work-Related Lung

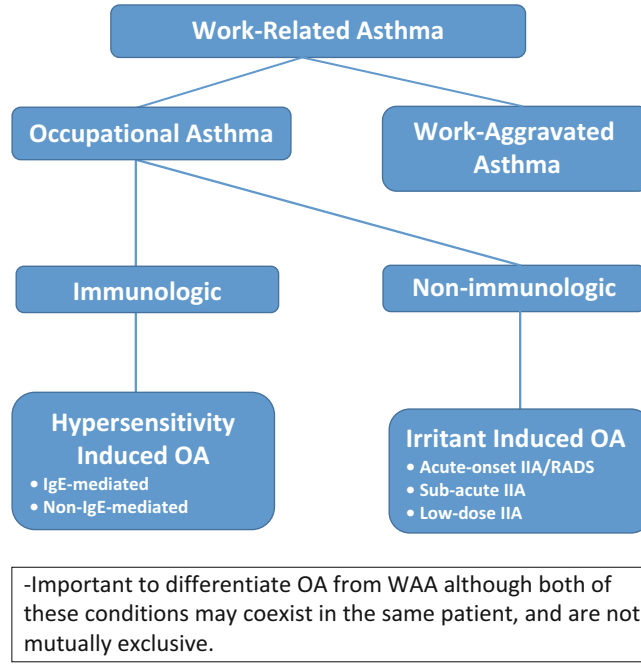


Fig. 2 Classification of work-related asthma

Disease Surveillance Report 2007). Of all the work-related asthma cases from these states, ~20% were associated with miscellaneous chemicals, 13% with mineral and inorganic dust, 12% with cleaning materials, 11% with indoor air pollutants, and 4% with exposures to polymers, among others (Work-Related Lung Disease Surveillance Report 2007). Within agent categories, isocyanates and hydrocarbons, not otherwise specified, accounted for the greatest proportion of cases classified as occupational asthma, at 89% and 83%, respectively; pyrolysis products had the greatest proportion of cases classified as work-aggravated asthma, at 29% (Work-Related Lung Disease Surveillance Report 2007).

15.5 Risk Factors for Occupational Asthma

While it is possible to develop OA in almost any workplace environment, there are certain occupations that put workers at much higher risk. Table 4 identifies some of the riskiest occupations for OA and inciting sensitizing agents. Irritants generated at higher concentrations tend to be associated with an increased risk for developing OA, especially when the offending agent is a vapor or wet aerosol. While the concentration, chemical and physical properties of the offending agent can increase a worker's susceptibility for developing OA, there are certain host factors for some inciting agents that can increase this risk which include having a pre-existing history of allergies or asthma (atopy), active smoking history, rhinitis, gender, and possible genetic factors, such as leukocyte antigen class II alleles (Vandenplas 2011).

15.6 Clinical History and Evaluation

It is important to remember that OA can improve or even be cured if it is recognized and treated early on after onset. Therefore, a detailed clinical history and evaluation focusing on work-related triggers is of utmost importance. Making an appropriate diagnosis of OA can have a significant impact not only on the worker's health but on their future employment and earning power. If left unrecognized and untreated, asthma symptoms can progress and persist for years even after

Table 3 High and low molecular weight immunologic causes of occupational asthma and their characteristics (Chan-Yeung and Malo 1995; Malo and Vandenplas 2011)

High molecular weight compounds (>1.0 Kd)	Low molecular weight compounds (<1.0 Kd)
• Proteins/polysaccharides of animal, vegetable, bacterial, or insect origin - Flour and cereal dusts - Enzymes (amylases, lipases, proteases) - Animal proteins (domestic and laboratory animals, fish and shellfish) - Plant proteins (coffee beans, tobacco dust, cotton, tea, latex, psyllium) • Prevalence related to amount of exposure • Atopy modest risk factor • Induced specific IgE antibodies, tends to be eosinophilic inflammation • Smoking is a risk factor • Bakers asthma most common cause of OA. - Animal laboratory workers take 2 years to sensitize - Flour workers take significantly longer • Longer latency period than with LMW compounds	• Chemicals - Isocyanates, wood dusts, acid anhydrides, amines, fluxes, chloramine, metals, drugs, dyes, persulfate, acrylate, formaldehyde, glutaraldehyde, other chemicals (incomplete antigens: haptens) • Lower prevalence • Atopy generally not a risk factor • Tends to be neutrophilic inflammation • Smoking increases incidence • 5–10% of workers exposed to diisocyanates develop OA • IgE response by serving as haptens - Response against the hapten, protein carrier, or a newly formed antigenic determinant • Toluene diisocyanate (TDI) and plicatic acid (red cedar wood dust): - Direct B-receptor blockade, non-immunologic mast cell degranulation, activate complement, direct toxic effects on airway (cedar wood processing).

Table 4 Professionals at risk for occupational asthma (Lemière et al. 2018b; Song et al. 2013; Goeminne et al. 2013; Galindo-Pacheco et al. 2013; Hougaard et al. 2012; Barranco et al. 2012; Delclos et al. 2007)

Occupation	**Sensitizing agent (LMW chemicals)**
Adhesive handlers, plastic manufacturers	Glues and resins (acrylates, epoxy)
Platers, welders, metal, and chemical workers	Metals (nickel sulfate, chromic acid, potassium dichromate, platinum salts)
Spray-painters, insulators, roofers, polyurethane workers	Isocyanates (diisocyanates)
Manufacturers of paint, plastics, epoxy resins	Acid anhydrides
Chemists, cleaners, shellac handlers, plastic manufacturers	Amines
Pharmaceutical workers, health professionals	Drugs (beta-lactams, opiates)
Textile workers, hairdressers	Dyes and bleaches (carmine, henna, persulfate)
Carpenters, woodworkers, forest workers	Wood dust (western red cedar, maple, oak)
Lab workers, textile workers, spray-painters, health professionals	Miscellaneous (formaldehyde, glutaraldehyde, pyrethrin, ethylene oxide)
Occupation	**Sensitizing agent (HMW chemicals)**
Veterinarians, farmers, poultry, fish and shellfish processors	Animal proteins (domestic and lab animals, fish, and shellfish)
Bakers, millers, food processors	Flours and cereal grains
Bakers, food processors, pharmaceutical workers, plastic workers, detergent manufacturers	Enzymes (pancreatic extracts, papain, trypsin, amylase, lipase)
Bakers, farmers, food and plant processors, health professionals, textile workers	Plant proteins (wheat, grain dust, coffee beans, tobacco dust, cotton, tea, latex, psyllium)

the patient leaves work resulting in significant lung impairment. Therefore, the general approach is to define and characterize the nature and extent of the respiratory illness by performing a detailed medical history followed by thorough physical exam and supportive testing if indicated. An occupational and environmental history is an essential part of any diagnostic workup for OA in order to determine the extent to which the disease is caused or exacerbated by one or more exposures in the workplace. The history should include a meticulous assessment of the following:

1. Type of industry and job title.
2. Description of jobs performed including specific workplace exposures (i.e., work process).
3. Details about the workplace environment including overall hygiene, personal exposure protective clothing and respiratory equipment worn by the worker, and ventilation/exhaust systems.
4. Improvement or worsening of symptoms away from the workplace: do symptoms improve or worsen during the weekend and over vacations?

(a) It is important to note that patients can sometimes have late-phase responses to workplace triggers that begin at home and not during the work day. Failure to recognize a late-phase response could lead to a missed diagnosis.

5. When do symptoms develop during the work shift or workweek?
6. Pre-existing asthma and/or associated rhinitis, sinusitis, and conjunctivitis symptoms.
7. Do other workers have similar symptoms?
8. Years employed.
9. Past employment history in chronological order which should include their work process and any pertinent occupational exposures.
10. Additional nonwork-related history such as nonoccupational environmental exposures, smoking, diet, and hobbies.

Information about workplace exposures can be supplemented with material safety data sheets (MSDSs) which by law must be provided by the workplace supervisor. The OSHA requires that SDSs, also known as MSDSs or material safety data sheets, be readily displayed and accessible to all employees potentially exposed to harmful substances in the workplace under the Hazard Communication Standard (OSHA 2009). Safety data sheets include information about each workplace substance including their physical and chemical properties, known health effects with different environmental exposure durations, recommended personal protective measures, and safety precautions for handling, storing, and transporting the chemical (OSHA 2009). It is important to note that materials present in concentrations $<1\%$ as well as HMW compounds from animal/plant sources are often omitted (Lemière et al. 2018b). Furthermore, limited information may be listed about specific chemical compounds if they proprietary and in these instances it may be necessary to contact the safety officer to obtain additional information if these are suspected to be causing adverse health effects for the worker. It should also be realized that SDSs are not standardized, and therefore the content may vary between workplaces. Workers are entitled to receive copies of SDSs at no cost upon request which can be shared with their treating healthcare provider.

Symptoms of OA are similar to non-occupational asthma and include shortness of breath, chest tightness, wheeze, and cough which can be productive or nonproductive of sputum. The primary difference between OA and non-OA is the patterns in which they emerge over time. Whereas non-OA exhibits no obvious relationship to workplace exposures, patients with OA experience worsening symptoms immediately or within a few hours after starting work with improvement a few hours after leaving work or over the weekend and while vacationing. However, the absence of this pattern does not exclude the possibility of OA. For example, workers exposed to toluene diisocyanate may exhibit an isolated late-phase airway response which may not manifest until later in the evening after returning home which could be missed if the treating physician is not familiar with the heterogenous physiologic presentations of different workplace asthmagens. In addition, for more severe cases of OA in workers who don't have prolonged breaks away from work or in workers who only have intermittent exposure to the inciting agent(s), a diagnosis of OA can sometimes go unrecognized.

While respiratory complaints are the hallmark manifestation for OA, many patients with OA may experience a number of extrapulmonary symptoms that precede symptoms of OA. Most notably, occupational rhinitis with or without conjunctivitis often appears before OA and may include a spectrum of symptoms including itchy eyes, ocular tearing, sneezing, nasal congestion, and posterior or anterior rhinorrhea. The risk for developing OA is highest in the year after work-related rhinitis symptoms start, especially among workers exposed to HMW agents (Vandenplas et al. 2005). Diseases that mimic OA should also be considered, especially for those workers who smoke or with pre-existing health conditions like COPD. Other conditions that mimic OA include nonoccupational allergic asthma, hyperventilation syndrome, vocal cord dysfunction, hypersensitivity pneumonitis, bronchiolitis obliterans, endotoxin-induced asthma-

like syndromes (e.g., grain fever or byssinosis), pneumoconiosis, and chronic cough caused by either seasonal/perennial allergic rhinitis or nonallergic rhinitis secondary to postnasal drainage. Many of these conditions can present with cough and wheeze triggered by physical factors such as cold or hot temperatures and non-specific irritants such as chemical volatile organic compounds (cVOCs) and airborne particulate matter.

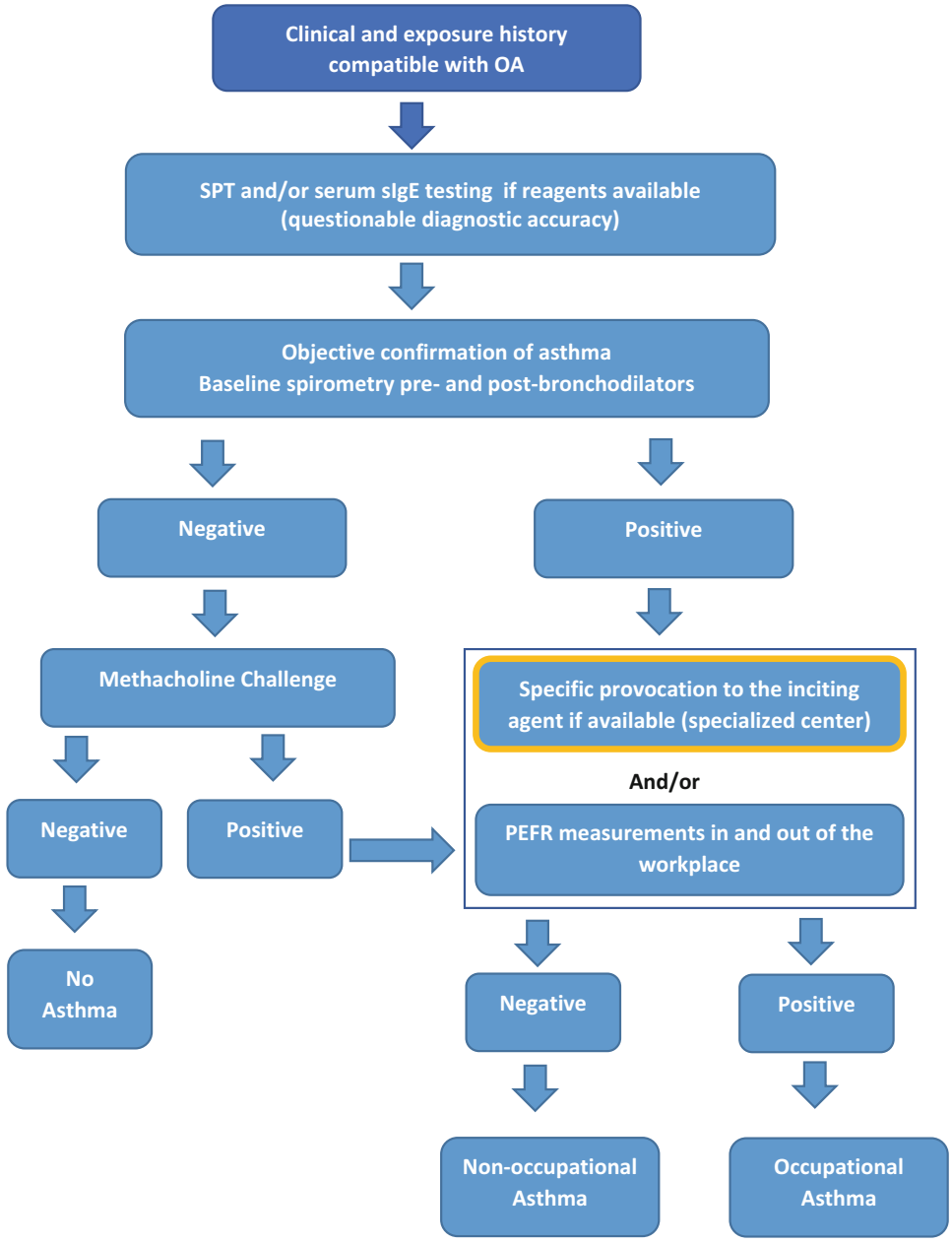
15.7 Diagnosis

The diagnosis of OA can sometimes be challenging. A diagnostic algorithm for OA in workers with active exposure in the workplace is provided (Fig. 3) for further clarification. First and foremost, OA should be considered in the differential diagnosis in all working-age individuals with new-onset asthma or worsening asthma as accurate, early recognition is crucial to minimize the health and economic impact on the worker as well as reduce costs to the employer in the context of worker's compensation and disability. While the physical exam is generally unrevealing about specific causes of respiratory symptoms, it can be helpful in ruling out nonoccupational causes of respiratory symptoms or diseases including cardiac or connective tissue disorders.

15.7.1 Pulmonary Function Testing

Objective testing with pulmonary function testing to assess the severity of airway obstruction and the presence of airway reversibility is the most important first step in an OA evaluation. If asthma is not confirmed with spirometry and there is high suspicion for OA, then additional provocation testing using direct approaches such as methacholine challenge or indirect methods (i.e., adenosine challenge) can help determine the presence of airway hyperresponsiveness (AHR) which is an essential characteristic for the diagnosis of asthma. It is important to recognize that a positive provocation test does not confirm a diagnosis of OA and neither does a negative test exclude AHR especially if performed when the patient is off work for a prolonged period of time and symptom free. Furthermore, a positive non-specific provocation test only indicates the presence of AHR suggestive for asthma but is not diagnostic of OA. However, if a challenge is performed when the patient is working and actively exposed to the suspected inciting agent(s) and is negative, then diagnosis of OA can in most circumstances be excluded. In some cases a non-specific provocation test can be negative, whereas a specific provocation test can be positive, but this is uncommon and should only be pursued if the history is very compelling. If there is evidence of a restrictive pattern on screening spirometry, then additional testing should include full pulmonary function testing with lung volumes and a diffusion capacity (DLCO). In addition, radiographic imaging with a chest x-ray or if necessary a chest CT should be performed to rule out other conditions that can confound a diagnosis of OA.

Once a diagnosis of asthma is confirmed, the next step is to establish a relationship between objective changes in lung function and symptoms in the workplace. There are various approaches to help accomplish this goal; however, their sensitivity and validity are variable. Peak expiratory flow rate (PEFR) measurements at work and at home while the worker is awake are a helpful tool to track breathing over time and in different environments, but compliance can be an issue. However, electronic PEFR meters that can mitigate this problem are now available as they can assess expiratory effort and reproducibility and record the time and date of the measurements. Furthermore, some of the electronic PEFR meters have now been validated to correlate with FEV1 which provides a more accurate reflection of lung function variability in and out of the workplace. Serial measurements of lung function by spirometry have also been used to diagnose OA, but this approach is typically only available during working hours and may not accurately reflect the physiologic variability of some OA causes. Neither of these approaches are useful for patients who have already left the workplace. Additional diagnostic tools to analyze lung function and airway inflammation at work are detailed in Table 5.



- For subjects no longer in the workplace where clarification of possible occupational exposures causing OA is still indicated, a specific inhalational challenge should be completed if possible. If positive the subject has OA. If negative the patient may return to work but work-up to identify non-OA causes for clinical symptoms should be pursued. If symptoms still persist, proceed with PEFR measurements in and out of the workplace following the algorithm above.

Fig. 3 Diagnostic algorithm for occupational asthma in subjects with active exposure in the workplace

Table 5 Recommendations for diagnostic tools to help establish a relationship between objective changes in lung function and symptoms in the workplace

Peak expiratory flow rate (PEFR) (Tan and Bernstein 2014) • PEFR measurements should be recorded every 2 h in the workplace and every 3–4 h at home while awake for at least 2 weeks • If feasible, PEFRs should be performed for 2 weeks while the worker is out of the workplace as well. • To improve worker adherence and the reliability of data, paper-free electronic devices that time and date stamp each reading in addition to quantifying effort are recommended • PEFRs with ≥20% variability between workplace and home confirm workplace exposure airway hyperresponsiveness
Cross-shift FEV1 (Tan and Bernstein 2014) • Cross-shift FEV1 measurements require the worker to undergo spirometry before and after the work-shift. • Reduction in FEV1 ≥15–20% is suggestive of workplace exposure. • This method is currently not validated to confirm diagnosis of OA
Fractional concentration of exhaled nitric oxide (FeNO) and induced sputum eosinophil counts (Girard et al. 2004; Lemière et al. 2010) • Noninvasive testing can identify increased inflammation within the airways. • Increased inflammation at the end of a period at work provides indirect evidence of OA • These methods are currently not validated to confirm diagnosis of OA

If possible, for workers with irritant-induced asthma (a.k.a. RADS), measurement of an irritant exposure index which has previously been shown to be correlated with AHR may be a useful adjunctive tool but is not validated (Brooks et al. 1985b). This could potentially allow comparison of days when there is documented irritant exposure(s) with work-related symptoms and changes in lung function. While not readily available or feasible in many clinical settings, specific provocation testing in challenge chambers with the suspected inciting agent is considered the gold standard for confirming the diagnosis of OA. Specific provocation testing is rarely available due to cost related to development and maintenance of a challenge chamber. Specific provocation should only be performed, whether to HMW or LMW agents, by experienced individuals in facilities with emergency therapy readily available in case of a severe asthma exacerbation. Due to these limitations, only a few academic centers have the capacity to perform these procedures.

15.7.2 Skin prick testing (SPT) or serologic testing for specific IgE (sIgE)

The first association between asthma and work-related exposures was documented by Hippocrates for occupations including metal workers, fishermen, farmhands, horsemen, and tailors (Tan and Bernstein 2014). Over the ensuing centuries, greater than 400 agents have been described to cause OA, but only very few are characterized on the molecular level and available for routine diagnosis (Raulf 2016). A more thorough understanding of the relevant allergen components would significantly improve the diagnostic capability of testing. Both SPT and serum sIgE testing to aeroallergens to assess the worker's atopic status can sometimes be useful especially when considering certain forms of OA where atopy is a risk factor. Skin prick testing is generally most useful for the diagnosis of OA caused by HMW agents, but there are circumstances where skin testing can also be useful for LMW agents such as acid anhydrides. If performed properly, these tests correlate very well with serologic testing for confirming sensitization (Bernstein et al. 2011). However, many workers may demonstrate sensitization to various HMW allergens by skin or serum testing but lack corresponding clinical symptoms, and therefore it is always important to correlate test results with exposure and symptoms. Sensitization or allergenic cross-reactivity to allergens or epitopes from unrelated sources may interfere with specific IgE assays resulting in false-positive results (Quirce 2014). However, skin testing and/or serologic testing has been used very successfully as part of immunosurveillance programs. Enzymes and trimellitic anhydride (TMA) are two examples of HMW and LMW agents, respectively, where skin testing and serum-specific IgG and IgE assays have been effective at identifying sensitized workers

who are at risk for subsequently developing OA. Early removal of these workers from further workplace exposure has been very effective at preventing development of OA (Ghosh et al. 2018). However, for most causes of OA, skin testing and specific serum assays are not available, and the approaches used for testing in these circumstances have not been well characterized or validated (van Kampen et al. 2009, 2013; Sander et al. 2004). Further knowledge of molecules relevant for some of the most prevalent causes of OA would allow for development of standardized in vitro IgE antibody assays that could aid in diagnosis (Hamilton and Williams 2010; Sander et al. 2015). Component-resolved diagnosis is an attempt to address this unmet need by identifying relevant HMW molecules for OA like wheat flour components for baker's asthma, wood dust allergens, and laboratory animal allergens. Interestingly, Sander et al. analyzed the most important IgE binding to wheat flour components with the goal of discriminating between grass pollen allergy, wheat-induced food allergy, and baker's asthma. Unfortunately, their attempt to classify relevant single-wheat allergens failed to outperform whole wheat sIgE extract currently in use.

15.8 Treatment

Management of OA requires removing the worker from further exposure and subsequent treatment with medications similar to non-OA. If simple avoidance fails to manage symptoms or is not feasible, workers may need medications to better control OA and prevent asthma attacks. Both the National Asthma Education and Prevention Program (NAEPP) and the Global Initiative for Asthma (GINA) provide guidelines that can be used to help guide therapy in a stepwise manner (National Asthma Education and Prevention Program 2007; Global Initiative for Asthma (GINA) 2018). The two major categories of asthma medications are quick-relief and long-term control medications. Quick-relief medications (a.k.a rescue medications) are used as needed for rapid, short-term symptom relief during an asthma attack. Short-acting beta agonists (albuterol, levalbuterol) act as smooth muscle bronchodilators within minutes to relieve symptoms. Ipratropium bromide is a long-acting M3 muscarinic receptor antagonist that is approved as a bronchodilator for acute COPD exacerbations. Long-term medications including inhaled corticosteroids (ICS), long-acting beta-2-agonists (LABA), leukotriene modifiers, combination ICS/LABA inhalers, long-acting muscarinic antagonists (LAMA), and biologics have all been approved for the treatment of asthma and should be used in a similar capacity in OA cases as appropriate.

Oral and intravenous corticosteroids (prednisone, methylprednisolone) are reserved to treat more severe OA to aggressively relieve airway inflammation and as adjunctive therapy during an acute asthma exacerbation. Severe or poorly controlled cases of OA might require more frequent or prolonged use of oral corticosteroids in order to better control symptoms even after removal from the workplace exposure.

15.9 Prognosis

While complete avoidance of the triggering agent is the gold standard treatment for OA, a certain proportion of patients will continue to experience asthmatic symptoms even after cessation of work. Symptom improvement seems to correlate with the duration of exposure to the inciting agent prior to removal from the workplace (i.e., shorter duration of exposure leads to quicker resolution of symptoms) (Gautrin et al. 2008; Rachiotis et al. 2007; Miedinger et al. 2010). Recovery can be gradual, taking several years or longer to resolve or improve. Some cases can be confounded by lingering conditions unrelated to the respiratory tract including depression and anxiety secondary to their illness and the economic impact of not being able to work which can affect approximately 50% of workers with OA (Perfetti et al. 1998; Malo and Ghezzo 2004; Yacoub et al. 2007; Malo et al. 1993). Early recognition, well-preserved lung function, and less airway hyperreactivity are all characteristics associated with a

better long-term prognosis, whereas longer duration of exposure and symptoms before onset of asthma, baseline airway obstruction, dual airway response after specific provocation and persistence of airway inflammatory markers in sputum, bronchoalveolar lavage, or bronchial biopsy are all characteristics for more persistent sensitization and long-term bronchial hyperresponsiveness: (Paggiaro et al. 1994)

15.10 Prevention

Since undiagnosed OA can cause considerable medical and economic consequences, aggressive prevention strategies are essential. Most preventive interventions focus on early recognition and removal of the worker from further exposure which can significantly improve overall outcomes. While worker-focused interventions are crucial, additional efforts directed at improving the workplace environment to reduce risk of exposure by other workers is also critical. Many public health-based and population-based interventions over the years have started with recognition of individual cases of occupational exposures causing health issues. These cases serve to increased clinical awareness that have led to the development of health surveillance programs which have been effective at defining the extent of these public health concerns (Tarlo et al. 2008). Several voluntary reporting programs have been established in the USA including the NIOSH Sentinel Event Notification System for Occupational Risk (SENSOR) program. The mission of the SENSOR program is to build and maintain occupational illness and injury surveillance registries within state health departments. Other countries have similar programs whose mission is to protect workers' safety and health. While NIOSH is not a regulatory agency, it may conduct thorough worksite evaluations, also referred to as Health Hazard Evaluations (HHEs) in selected situations if requested by a worker or employer. Workers can also request that the employer and/or workers compensation insurer take actions to attempt to reduce current exposure or undertake preventative actions including screening programs and improved exposure control (Tarlo et al. 2008). Under guidelines established by OSHA, employers have a legal responsibility to help protect workers in high-risk professions from hazardous chemicals. These companies are required to inform workers that they will be working with hazardous chemicals; train workers how to safely handle these chemicals; train workers how to respond to an emergency, such as a chemical spill; provide protective gear, such as masks and respirators; and offer additional training if a new chemical is introduced to the workplace.

An anonymous tip-line (800-321-OSHA) is also available to request an on-site inspection if workers are concerned about unsafe and unhealthy working conditions not being addressed by supervisors.

Optimal control of workplace sensitizers and irritants can only be accomplished by complete elimination of the triggering agent. This intervention is often not possible in real-world work environments; therefore, reducing exposures to the lowest practical or feasible level is encouraged. The efficacy of reducing exposure levels on OA rates has been demonstrated for a number of high and LMW compounds including acid anhydrides, detergent enzymes, isocyanates, laboratory animals, and latex (Lemière and Bernstein 2018; Allmers et al. 2002; Tarlo et al. 2001, 2002). In order to create a more suitable workplace environment, there are a number of sensible interventions and resources available including aforementioned elimination, process modification, respirator use, and engineering controls (Tarlo et al. 2008). Improved ventilation and use of personal protection devices are obvious first steps but do not completely protect against development of OA. However, various reports have demonstrated significant reduction of exposure levels and reduced incidence of OA after introduction of respiratory protective equipment (Lemière and Bernstein 2018; Grammer et al. 2002; Petsonk et al. 2000).

More complicated and costly interventions such as modification and/or automation of tasks to reduce worker exposure to sensitizing agents and substituting or altering the inciting agents used in the work process are also

options. Unfortunately, as mentioned, controlling workplace exposures is not that simple. What complicates these efforts is the limited information known about exposure levels that induce sensitization to both high and LMW agents (Galdi and Moscato 2002b). Continuous monitoring systems are currently available to measure ambient levels of several LMW chemicals including acid anhydrides, isocyanates, and formaldehyde; however, the concentrations of these chemicals required to provoke respiratory symptoms in susceptible workers are often below the limits of detection (Lemière and Bernstein 2018). Thus, further research is necessary to identify levels of exposures for the most common inciters of OA that correlate with sensitization. Furthermore, although workers with a history of atopy are at greater risk for developing OA from HMW agents (Jonaid et al. 2017), the clinical characteristics that place workers at risk for OA to LMW agents are still incompletely understood. In some OA studies, smoking has been reported to be a clear risk factor but not in others. Regardless of whether smoking is a risk factor or not, workers should be encouraged to stop smoking to reduce or prevent related health effects (Siracusa et al. 2006).

15.11 Conclusion

Despite an increase knowledge of sensitizing agents in the workplace as well as improvements in workplace safety and reporting, OA continues to afflict workers worldwide. Various health surveillance programs have been implemented over the years with varying degrees of success. In some industries using HMW or LMW agents known to induce OA, immunosurveillance programs have been very successful in monitoring worker exposure and development of potential sensitization so they can be immediately removed from further exposure to prevent the development of OA (Bernstein 2016). In order to encourage industry-wide changes in health surveillance programs, occupational health professionals need to provide overwhelming evidence that early intervention leads to improved worker health in a cost-efficient manner. To date there is conflicting evidence on whether these programs lead to reduced disease incidence and thus for some employers implementing these programs may not be economically feasible (Szram and Cullinan 2013). However, for detergent enzyme and trimellitic anhydride manufacturers, immunosurveillance have been overwhelmingly successful in preventing OA or other work-related respiratory conditions. Greater collaboration between employers, employee organizations, legislators, and researchers should be encouraged to determine the most effective and economically feasible interventions for preventing OA in the workplace (Szram and Cullinan 2013).

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Differential Diagnosis of Asthma

16

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Abstract

Asthma is one of the most common chronic syndromes worldwide (Moorman et al., Vital Health Stat 3(35), 2012). It is not a diagnosis but a clinical syndrome based on a constellation of signs and symptoms (Li et al., Ann Allergy Asthma Immunol 81:415–420(IIa), 1998). The classic symptoms of asthma include chest tightness, wheeze, cough, and dyspnea (Moorman et al., Vital Health Stat 3(35), 2012). The term asthma encompasses a spectrum of pulmonary diseases sharing the hallmark of reversible airway obstruction and can be classified as allergic or non-allergic (Löwhagen, J Asthma. 52 (6):538–44, 2015). Asthma designated allergic is due to an immunoglobulin E (IgE)-mediated process, but as noted not all asthma is allergic in etiology (Romanet-Manent et al., Allergy 57:607–13, 2002). The differential diagnosis for asthma is broad and requires a detailed history with supportive pulmonary function tests to be properly diagnosed.

Keywords

Asthma · Differential diagnosis · Pathophysiology

16.1 Introduction

16.1.1 History of Asthma

The word asthma is derived from the Greek verb, aazein, which means to pant (Marketos 1982). Hippocrates was the first to use asthma as a medical term referring to lung spasm in his teachings entitled, The Corpus Hippocraticum (Marketos 1982). In ancient China, inhaled preparations of ephedrine containing plants were used to stimulate beta-adrenergic receptors within the lung, which continues to be a mainstay mechanism for the treatment of asthma (Chang et al. 2013). In the 1860s, Dr. Henry Salter of London described the classic characteristics associated with asthma, such as airway hyperresponsiveness to cold and exercise, as well as environmental particulates (Sakula 1985).

16.1.2 Background of Asthma

Asthma is one of the most common chronic syndromes worldwide, and it is characterized by chronic inflammation of the pulmonary airway (Moorman et al. 2012). It is not a diagnosis but a clinical syndrome based on a constellation of signs and symptoms (Li et al. 1998). The classic symptoms of asthma include chest tightness, wheeze, cough, and dyspnea, which may resolve spontaneously or in response to treatment (Moorman et al. 2012) (Table 1). Definitive criteria for the diagnosis of asthma do not exist (Li et al. 1998). The term asthma encompasses a spectrum of pulmonary diseases sharing the hallmark of reversible airway obstruction and can be classified as allergic or non-allergic (Löwhagen 2015). Asthma resulting from an IgE-mediated immunologic mechanism is designated allergic,

Table 1 Common symptoms of asthma

Wheeze
Cough
Dyspnea
Chest tightness

while those not associated with IgE are classified as non-allergic and consist of many phenotypes (Romanet-Manent et al. 2002).

16.1.3 Pathology/Histopathology

The pathophysiology of asthma is characterized by reversible airway obstruction, non-specific airway hyperreactivity, and chronic inflammation (Kudo et al. 2013). Recurrent airflow limitation is driven by inflammatory mediators leading to bronchoconstriction, airway edema, hyperresponsiveness, and airway remodeling. Bronchoconstriction is the result of bronchial smooth muscle contraction in immediate response to an inhaled irritant or allergen (National 2007). While classically complete reversal of airway obstruction is indicative of asthma, many cases of asthma may only have a partial reversal in airflow and in some cases no reversal of obstruction. The fixed airway obstruction may in part be due to airway remodeling. Investigations are still underway to understand the exact pathophysiology of this; however, upregulation of growth factors by the bronchial epithelium seems to be the key in the persistent inflammation, smooth muscle hypertrophy, collagen production, neovascularization, basement membrane thickening, and increased myofibroblast and fibroblast activity (Busse et al. 2000).

In allergic asthma, activation of mast cells and T helper (Th2) cells by inhaled antigens leads to production and secretion of histamines, leukotrienes, and cytokines (National 2007). Key cytokines in this cascade include IL-4, IL-13, and IL-5, the latter of which is the primary signal for the differentiation of eosinophils. Eosinophils prolong and potentiate persistent airway inflammation by releasing leukotrienes, granule proteins, and GM-CSF. This is consistent with postmortem histopathology showing eosinophilic infiltration into the mucosa and the airway and mucous plugging of the airway lumen (Busse et al. 2000).

In all classifications of asthma severity, mild, moderate, or severe, there are consistent histopathologic changes. In both the proximal and distal airways, epithelial detachment, goblet cell hyperplasia, subepithelial fibrosis, infiltration of inflammatory mediators, bronchial smooth muscle hypertrophy, and vascular changes are all observed (Hamid 2003). Despite these consistent changes, the course of asthma is variable in its severity and progression over an individual's life and between individuals. For the majority of patients, asthma begins early in life with risk factors for development including atopic disease, recurrent wheezing, and parental history of asthma (2).

16.1.4 Common Asthma Triggers

Common asthma triggers are environmental factors such as air pollution, tobacco smoke, occupational exposures, indoor allergens (dust mites, molds, pets, rodents, and cockroaches) and outdoor allergens (tree, grass, and weed pollen), exercise, and infections (CDC 2012; Yang et al. 2017) (Table 2). Viral infections and airborne allergens are two of the most important environmental factors leading to asthma development, persistence, and possibly asthma severity (NHLBI 2007). Though allergens and other environmental factors are a strong trigger for many with asthma, complete avoidance is often impossible, and despite avoidance asthma often remains active. For those not responding to avoidance, treatment is based on symptom frequency and severity of disease. Quick relief medications are inhaled short-acting beta2-agonists and anticholinergics. Long-term control medications are used to treat persistent asthma and include inhaled long-acting beta2- agonists, anticholinergics, corticosteroids, cromolyn sodium, and oral leukotriene modifiers and methylxanthines. Those that fail to respond to conventional therapy noted above may respond to biologic agents depending on their phenotypic classification of asthma (AAAAI 2017). Allergen

Table 2 Common asthma triggers

Perennial allergens
Outdoor allergens
Infections
Occupational exposures
Air pollution
Exercise

immunotherapy is also an option when there is a clear association between asthma symptoms and perennial and/or seasonal allergens (NHLBI 2007). Vaccination schedules should be adhered to in order to decrease infectious triggers.

16.1.5 Chronic Obstructive Pulmonary Disease (COPD)

Like asthma, the term COPD encompasses numerous phenotypes. One phenotype is chronic bronchitis, which is a diagnosis of exclusion characterized by a chronic cough occurring for 3 continuous months a year for at least 2 consecutive years (Monetes 2012). Emphysema is another subtype resulting from the permanent loss of alveoli (Montes de Oca et al. 2012). Without the alveoli the airway loses the recoil from the parenchyma necessary to keep the airway patent. The asthma-COPD overlap syndrome (ACOS) is a phenotype inclusive of both clinical syndromes (Foreman et al. 2007). The diagnosis of ACOS is clinical, and with most of the key symptoms being shared between pure COPD and asthma, it further adds to the challenge of accurately making this diagnosis (Saetta et al. 1994; Barnes 2002) (Fig. 1).

COPD is considered by most to be a less reversible obstructive airway disease; however, COPD can reverse and even to the same degree as asthma. The symptoms experienced by patients with COPD are common to asthma as well; these include wheezing, coughing, and dyspnea. Both diseases are diagnosed similarly by taking into account the patient's history as well as pulmonary function tests (PFTs). Chronic obstructive lung disease is defined by having a forced expiratory volume in 1 s (FEV1) to forced vital capacity (FVC) ratio of 0.7 or less after reversal with albuterol (Alpert et al. 2016).

Characteristics distinguishing COPD from asthma include failure to reverse to normal with therapy, a strong association with cigarette smoke or inhalation of smoke from indoor burning of organic material for cooking, and a reduced diffusing capacity of the lung for carbon monoxide (DLCO) (Stoller et al. 1994). Cigarette smoke exposure is dose-dependent making it important to determine the smoker's total pack-years (the number of cigarette packs smoked per day multiplied by the number of years the individual smoked) (Montes de Oca et al. 2012). Secondhand cigarette exposure is a risk factor as well, which has more recently gained significant recognition for its role in the development of COPD (Guerra et al. 2009).

Emphysema increases dead space ventilation by destroying the alveolar membranes. This leads to an imbalance in the amount of inhaled air relative to the surface area of the lung capable of gas exchange (Miravitlles et al. 2000). Emphysema may be ascertained by using a CT scan of the

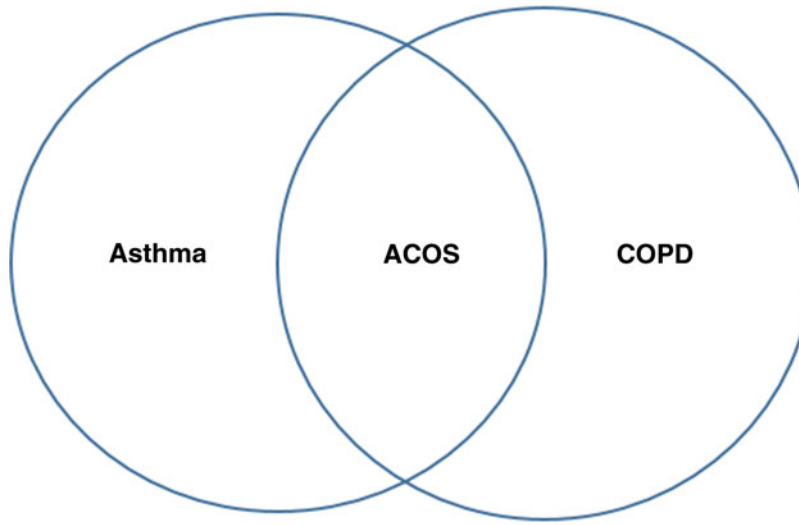

Fig. 1 Asthma-COPD overlap syndrome

chest, demonstrating classic COPD findings of emphysema such as vast destruction and dilation of alveoli. By comparison in asthma, the alveoli are not destroyed, but instead air is trapped within the alveoli due to bronchial obstruction. The result in asthma is decreased ventilation, but the surface area capable of gas exchange remains intact with a normal DLCO (Miravitlles et al. 2000).

16.2 Differential Diagnosis for Asthma

16.2.1 Pneumonia

Patients given the diagnosis of asthma that is refractory to treatment should be evaluated for an alternative diagnosis (Aguilar et al. 2014) (Table 3). Acute respiratory symptoms, tachypnea, fever, or radiologic evidence of parenchymal infiltrates defines pneumonia. Pneumonia is often initiated by colonization of the nasopharynx with subsequent infection of the lower respiratory tract and can be caused by bacteria, viruses, or fungi (Browne 2010) (Table 4).

Viral etiologies are the main triggers for asthma exacerbations. Respiratory viruses are the etiologic agent in nearly 15% of all patients presenting with pneumonia (Johnstone et al. 2008). Viral causes of pneumonia include the influenza virus, especially during influenza outbreaks (Musher 2014). It is important to maintain a high index of suspicion for a secondary bacterial infection in these patients as well. Respiratory syncytial virus, parainfluenza virus, human metapneumovirus, adenovirus, coronavirus and rhinovirus can also be detected in patients with community acquired pneumonia (CAP) (Musher 2014). In children, respiratory viruses are the most common causes of pneumonia (Jain et al. 2015). Syndromes suggestive of a viral etiology are usually treated with symptomatic measures. If there are symptoms suggestive of influenza as the culprit, oseltamivir, a viral neuraminidase inhibitor, should be administered within the first 48 h of symptoms (Musher 2014).

Patients who develop acute lung infections, have not been recently hospitalized, and also do not have routine exposure to the health-care system fall under the category of community-acquired pneumonia (CAP) (Musher 2014). Common bacterial causes of CAP are *Streptococcus pneumoniae* (the most common), *Haemophilus influenzae,* and *Staphylococcus aureus* (Musher 2014). *Mycoplasma pneumoniae*, an atypical species, has also been implicated and occurs in both early- and late-onset asthma (Yeh et al. 2016). Compared with typical bacterial pneumonia, atypical pneumonia usually presents with less severe symptoms, such as headache, malaise, and low grade fever, with a more gradual onset (Browne 2010). The mainstay of therapy for bacterial pneumonias is the administration of antimicrobial agents that are appropriate for the overall clinical condition of the patient and the suspected microorganism in question.

Table 3 The differential diagnosis of asthma

Common
COPD
Infectious etiologies
(1) Bacterial
(2) Viral
(3) Fungal
Gastroesophageal reflux disease (GERD)
Chronic rhinosinusitis (CRS)
Congestive heart failure (CHF)
Vocal cord dysfunction (VCD) and other disorders of the upper airway
Less frequent
Idiopathic anaphylaxis with predominant respiratory manifestations
Aspirin or nonsteroidal exacerbated respiratory disease (AERD or Samter's triad)
Malignancy
Sarcoidosis and other autoimmune processes
Hypersensitivity pneumonitis
Pulmonary hypertension
Drug induced bronchospasm
Uncommon
Lymphangioleiomyomatosis (LAM)
Cystic fibrosis
Loeffler's syndrome and other eosinophilic lung diseases
Vasculitides
(1) Churg-Strauss vasculitis (eosinophilic granulomatosis with polyangiitis [EGPA])
(2) Wegener's granulomatosis (chronic granulomatosis with polyangiitis [GPA])
(3) Microscopic polyangiitis

Table 4 Most common pneumonic etiologies with asthma-like symptoms

Bacterial	Viral	Fungal
Streptococcus pneumoniae	Respiratory syncytial virus (RSV)	Histoplasma, sCoccidioidomycosis in endemic areas
Haemophilus influenzae	Parainfluenza and influenza virus	Candida, Aspergillus, Zygomycetes in ICU setting
Staphylococcus aureus	Human metapneumovirus	
Mycoplasma pneumoniae		

Uncommon causes of CAP can present as subacute infections due to fungal etiologies, such as *Histoplasma* and *Coccidioides* species in endemic areas. This type of an infection is characterized by cough, fever, and pulmonary infiltrates and should be treated with appropriate antifungal therapy (Musher 2014). Candida, aspergillus, and zygomycete are the main fungal isolates obtained from respiratory secretions of ICU patients (Shamim et al. 2015). While these more commonly occur in neutropenia, non-neutropenic patients with appropriate risk factors in the intensive care unit develop this type of pathology and should be treated with appropriate antifungal therapy as determined by the identified microorganism (Shamim et al. 2015).

16.2.2 Gastroesophageal Reflux Disease

Gastroesophageal reflux disease (GERD) classically presents with symptoms of persistent heartburn or metallic taste (NIH); however, either of these symptoms is only present 40% of the time. Extraesophageal symptoms may include chronic cough, wheezing, bronchospasm, sore throat, laryngitis, and hoarseness (NIH, Badillo 2014). Symptoms of GERD may be triggered by a select number of foods and drinks such as coffee, chocolate, citrus fruits, tomato-based foods, spicy foods, fatty foods, and alcohol. GERD can present in several different ways and at times can resemble asthma as suggested by the extraesophageal manifestations. In some asthmatics, reflux serves as a potential trigger or contributing factor for asthma (Harding 1999). There is no gold standard diagnosis for GERD. Upper endoscopy shows characteristic esophageal changes in only 40% of cases (Nwokediuko 2012). GERD may be differentiated from asthma with pH probe and/or barium swallow (King 2008). However, there is no definitive test to reliably confirm the diagnosis of GERD. GERD can coexist with asthma in up to 80% of patients (Sontag 2006). Treatment of GERD should be pursued if the patient is symptomatic, although it does not appear that GERD worsens asthma (NEJM 2009;160:1487–1499).

Thus, the diagnosis is made predominantly on clinical suspicion in combination with medication trials. Patients with significant asthma symptom improvement with proton pump inhibitor therapy likely have GERD, but GERD treatment is ineffective for persistent asthma without GERD symptoms (NEJM 2009;160:1487–1499). Asthma should be considered when extraesophageal symptoms of cough, wheeze, and bronchospasm persist despite maximal GERD treatment.

16.2.3 Chronic Sinusitis

Sinusitis is essential to the differential of asthma. Sinusitis exhibits respiratory symptoms similar to asthma, such as shortness of breath from extensive turbinate edema and cough from postnasal drip (Bucca et al. 1995). Additionally, both conditions share many inflammatory mediators, which may be triggered by infections and air pollution and by allergens in allergic subjects (Frieri 2003).

The prevalence of sinusitis is 15% of the population in the United States (Moss 1986). Symptoms include nasal congestion, sinus discharge, facial pressure, and diminished sense of smell (Wald et al. 2013). In addition to symptoms, for

formal diagnosis patients must have evidence of sinus inflammation demonstrated by either endoscopy or computerized tomography (CT) scan (Wald et al. 2013). Sinusitis is termed chronic once the symptoms have been present for 12 weeks or longer (Wald et al. 2013). Chronic sinusitis often has longer duration but diminished severity of symptoms compared to acute sinusitis (Wald et al. 2013).

A variety of etiologies contribute to the syndrome of chronic sinusitis. Allergic rhinosinusitis due to perennial allergens is relatively common and associated with sneezing and itching (Williams 1996). Continuous exposure to perennial allergens such as dust mite, animal dander, mold, and cockroach contribute to the chronicity of the disease (Williams 1996). Intranasal corticosteroids are the treatment of choice for allergic rhinitis (Ratner et al. 2007). The most common isolates of bacterial sinusitis include *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis* (Zimmerman 1991). Amoxicillin, with or without clavulanate, is the first-line therapy for bacterial sinusitis (Lund 1194). Recurrent episodes of bacterial sinusitis should prompt an evaluation for immunologic and anatomic abnormalities (Zimmerman 1991).

16.2.4 Congestive Heart Failure

Congestive heart failure (CHF) is due to a variety of etiologies, which result in systolic or diastolic ventricular dysfunction (Figueroa 2006). The diagnosis is based on a thorough history and physical exam and supported by appropriate ancillary testing such as an echocardiogram, electrocardiogram, and chest X-ray (Figueroa 2006). CHF is the leading cause of acute dyspnea in elderly patients, and one-third of those affected experience cardiac wheezing, which could be confused with asthma (Jorge et al. 2007). In non-elderly patients, the rate of wheezing in patients with CHF is 10–15%. On the basis of these statistics, CHF should be considered in the differential diagnosis of patients with dyspnea and wheezing.

The underlying pathophysiologic mechanism for a cardiac wheeze seems to arise from the left ventricular (LV) dysfunction itself. As LV function deteriorates, there is an increase in pulmonary vascular pressure, which causes a leakage of plasma into the interstitial space (Dominguez 2002). As the interstitial pressure rises, there is resultant narrowing of the bronchioles that in return causes impedance of the conducted air, resulting in the wheezing sound (Dominguez 2002). Diuresing these subjects presumably improves the clinical picture by reducing the extravascular lung water and overall general improvement in pulmonary and bronchial lung volumes (Jorge et al. 2007).

Once the diagnosis of CHF is made, treatment comprises both pharmacologic and non-pharmacologic measures. Pharmacologic treatment combines the use of afterload reduction with angiotensin-converting enzyme inhibitors, reduction catecholamine surges with beta-blockers, and preload reduction with diuretics for the relief of dyspnea and signs of water and sodium retention (Figueroa 2006). Non-pharmacologic treatments include ventricular synchronization via biventricular pacing devices as well as implantable defibrillators. The most important key in determining appropriate treatment for patients with CHF is to clinically stratify them in the appropriate New York Heart Association Classification system. This system provides a yardstick for the comparison of CHF treatment (Figueroa 2006).

16.2.5 Vocal Cord Dysfunction

Vocal cord dysfunction (VCD) occurs when the vocal cords do not open properly or close inappropriately, particularly during inspiration. Specifically, there is inappropriate adduction of the vocal cords usually during inhalation caused by vocal cord hyperresponsiveness. Symptoms can resemble asthma, and the two diagnoses can be confused leading to misdiagnosis, inappropriate treatment, and persistence of uncontrolled respiratory symptoms (Dunn 2005; AAAAI 2017).

The clinical presentation of vocal cord dysfunction can vary from asymptomatic, to mild dyspnea, to symptoms suggesting an acute asthma exacerbation (Maillard et al. 2000). Symptoms of wheezing, hoarse voice, difficulty breathing, coughing, dysphagia, throat tightness, globus sensation, and chest pain can occur. Similar to asthma, VCD can be triggered by temperature changes, upper respiratory infections, emotional stressors, physical exertion or exercise, acid reflux, ingestion of specific foods, laughing, talking, singing, strong odors, and inhalation of respiratory irritants (Andrianopoulos et al. 2000; Morrison et al. 1999). Features that may distinguish VCD from asthma are inspiratory wheeze triggered by odors, dysphonia, and throat tightness. Further, there is no absolute distinguishing feature between VCD and asthma if the two disorders coexist (AAAAI 2017).

The diagnosis of VCD should begin with a thorough clinical history and physical exam to assess for characteristic features. Often, patients will point to their throat when asked where symptoms originate. The vocal cord dysfunction questionnaire (VCDQ) is a 12-item questionnaire developed by Fowler and colleagues that may help assess severity and symptom improvement. This instrument demonstrates improvement in scores following speech therapy (Fowler et al. 2015). The Pittsburgh VCD index is another tool developed by Traister and colleagues to help distinguish between VCD and asthma. Scores are assigned based on symptoms of throat tightness (score of 4), dysphonia (score of 2), absence of wheezing (score of 2), and presence of odors as a trigger (score of 3). A score $\geq$4 is 83% sensitive and 95% specific for the diagnosis of VCD (Traister et al. 2014).

Spirometry may help differentiate VCD and asthma. Flattening, sawtooth pattern, and/or truncation may be seen on the inspiratory flow loop indicating a variable extrathoracic obstruction (Balkissoon 2002; Miller 1973). These characteristics may occur while the patient is asymptomatic but are more likely during an acute VCD attack (Balkissoon 2002).

Laryngoscopy showing paradoxical vocal fold movement on inhalation is the gold standard for the diagnosis of VCD. Although, between attacks, the vocal cords may be normal, the condition cannot be excluded by a normal examination when symptoms are minimal or absent. In severe cases, the airway can become so compromised that only a small star-shaped orifice, often termed "chink," may be available for inhalation leading to acute respiratory distress. Treatment of VCD focuses on patient reassurance of the benign nature of the condition, speech therapy and deep breathing techniques, all of which may reduce the laryngeal hyperreactivity. Inappropriate, high-dose inhaled therapy, particularly with corticosteroids, may contribute to the condition by irritating the larynx or result in reversible laryngomalacia.

16.2.6 Anaphylaxis

Anaphylaxis is a systemic, potentially life-threatening, immediate reaction that is most commonly induced by allergy to medication or foods. This is classically the result of an IgE-mediated mechanism that may affect the cutaneous, respiratory, cardiovascular, and gastrointestinal systems. Anaphylactic events can resemble asthma if respiratory symptoms precede other organ system manifestations. Approximately 40–60% of anaphylactic reactions present with respiratory manifestations, such as shortness of breath, wheeze, and nasal congestion. It is therefore important to perform a thorough physical examination as well as obtain an adequate history to distinguish between this multisystem, life-threatening reaction and an acute asthmatic attack. Subjects with asthma are at risk of more severe anaphylaxis, particularly if the asthma is not well controlled at the time of the anaphylaxis.

Exercise-induced anaphylaxis (EIA) may be misdiagnosed as an exercise-induced asthma. The trigger of exercise-induced may not be obvious, since it is inconsistently reproducible. EIA occurs when a patient engages in rigorous physical activity and the symptoms progress with the duration of activity. A subset of EIA is the food-dependent, but the majority of EIA episodes are non-food-dependent. In food-dependent EIA, the trigger is more elusive, since the patient must

exercise within 4–6 h of ingesting a specific food. The initial symptoms may include wheezing and dyspnea although other manifestation may soon follow, including pruritus, urticaria, and dizziness, or other manifestations of hypotension. An accurate history of the events before, during, and after the reaction is necessary to differentiate EIA from exercise-induced asthma.

Idiopathic anaphylaxis is in the differential diagnosis of patients suspected of having asthma. Both conditions can present with acute onset of dyspnea, wheezing, cough, anxiety, and a sense of impending doom (Simons et al. 2011). Classically, anaphylaxis refers to a systemic, IgE-mediated hypersensitivity reaction due to the release of mediators from basophils and mast cells (Johansson et al. 2006). Anaphylaxis is a clinical diagnosis and does not require specific testing for confirmation, but identification of specific-IgE to culprit causes is necessary to establish allergic anaphylaxis (Bacal et al. 1978). The term idiopathic anaphylaxis refers to the absence of identifiable triggers to account for the often multiple, systemic reactions (Kemp et al. 1995). This may cause clinicians to overlook anaphylaxis as the etiology of a patient's symptoms, since a history of exposure to a typical allergen is not reported.

Idiopathic anaphylaxis is a diagnosis of exclusion, as is true for all idiopathic disorders. While the exact incidence is unknown, it is estimated to affect 20,592–47,024 individuals annually in United States (Patterson et al. 1995). It is more common among adults than in children and women more than men. Approximately 50% of subjects with idiopathic anaphylaxis are atopic (Patterson et al. 1995). While by definition subjects with idiopathic anaphylaxis have no identifiable cause for their anaphylactic reactions, eventually exercise and certain foods are identified as triggers in 11% and 5% of cases, respectively (Ditto et al. 1996). Other organic, systemic diseases involving mast cells must be considered as well; for instance, up to 50% of those initially diagnosed with idiopathic anaphylaxis ultimately are found to have systemic mastocytosis (Akin et al. 2007).

The management of idiopathic versus non-idiopathic anaphylaxis is significantly different. The goal is to prevent future reactions from occurring through medical management in idiopathic anaphylaxis, as opposed to avoidance of known triggers in non-idiopathic anaphylaxis (Blatman et al. 2012). Patients can be treated with prophylactic H1 and H2 antagonists for long-term control and in rare cases with the addition of systemic corticosteroids (Blatman et al. 2012; Wong et al. 1991). These patients should also be prescribed epinephrine auto-injectors, the only effective treatment for anaphylaxis. Preliminary data for the use of omalizumab, an anti-IgE monoclonal antibody, is promising (Warrier et al. 2009). The successful use of rituximab, a monoclonal antibody specific for B lymphocytes, to induce remission has also been reported (Borzutzky et al. 2014).

16.2.7 Samter's Triad

Aspirin-exacerbated respiratory disease (AERD) is often referred to as Samter's triad. This triad includes asthma, sinus disease with recurrent nasal polyposis, and sensitivity to aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) (Pongdee 2017). The hallmark of this chronic medical condition is exacerbation of upper and/or lower airway disease following the ingestion of aspirin or other NSAIDs (Aguilar et al. 2014). These reactions may include nasal congestion, frontal headache, sinus pressure, coughing, wheezing, chest tightness, and less commonly skin flushing, rash, abdominal pain, or vomiting (Pongdee 2017). Because of the predominant respiratory symptoms of wheezing and chest tightness, most experts consider AERD as a phenotype of asthma rather than a separate diagnosis.

Epidemiologically, 9% of all asthmatics and 30% of patients with asthma and concurrent nasal polyps have AERD (Pongdee 2017). Patients with this condition commonly develop symptoms in adulthood, between the ages of 20 and 50 years (Pongdee 2017; Aguilar et al. 2014). Usually these patients will present with adult onset asthma that is preceded by years of sinonasal symptoms (Aguilar et al. 2014).

The primary mediators of AERD inflammation are in the arachidonic acid pathway. Arachidonic acid is metabolized by either cyclooxygenase to yield prostaglandins or by lipoxygenase to yield proinflammatory cysteinyl leukotrienes, which are significantly overproduced in patients with AERD (Aguilar et al. 2014; Laidlaw 2013). The relative excess of cysteinyl leukotrienes and prostaglandin-D2 leads to a shift toward a pro-inflammatory state (Laidlaw 2013; Moebus 2012). The inhibition of PgE2 may be the explanation for the rapid deterioration with the ingestion of NSAIDs.

The diagnosis of AERD is confirmed with an oral aspirin challenge and may be treated with aspirin desensitization which involves dose escalation into a therapeutic range, 325–650 mg bid, and then continued daily (Aguilar et al. 2014). The goals of desensitization are to control upper and lower respiratory symptoms, reduce the use of systemic corticosteroids, decrease the rate of growth and recurrence of nasal polyps, and improve the patient's quality of life (Moebus 2012). Continual aspirin therapy decreases bronchial hyperreactivity and improves nasal symptoms in addition to reducing polyp growth.

The asthmatic patient who does not respond to traditional asthma therapies and is difficult to control should be evaluated for AERD (Aguilar et al. 2014). These patients can experience severe exacerbations and often require control with inhaled corticosteroids, leukotriene modifying drugs, as well as aspirin desensitization (Aguilar et al. 2014; Moebus 2012).

16.2.8 Malignancy

Malignancies may resemble asthma and in some cases mask the underlying diagnosis. It is important to consider malignancy as a differential diagnosis in patients with persistent respiratory symptoms despite adequate asthma therapy.

Lung cancer accounts for 1.3 million deaths worldwide (WHO 2003). Lung parenchyma has limited sensory innervation, and primary lung cancers may reach a considerable size before becoming symptomatic (Ganie et al. 2013). The most common early symptom is cough, which occurs due to bronchial irritation or obstruction in up to 70–90% of patients. Dyspnea occurs in approximately 60% of patients as an early symptom. Hemoptysis can result from ulceration of bronchial tissue from tumor invasion or tumor necrosis and is an early symptom in 25–40% of patients. Wheezing can occur in 2–10% of lung cancer patients due to partial bronchial obstruction, usually from a hilar tumor (Ganie et al. 2013).

Carcinoid tumors are rare, occurring in 1.9 per 100,000, are slow growing, and may be either benign or malignant (Crocetti 2003). Pulmonary carcinoid tumors compromise 2–5% of all lung cancers and are most commonly located centrally in the main or lobar bronchi (Hage et al. 2003; Filosso et al. 2002). Symptoms of pulmonary carcinoid tumors include hemoptysis, cough, wheezing, dyspnea, and lower respiratory tract infections (Schrevens et al. 2004; Zuetenhorst 2005). There is typically a delay in onset of symptoms to time of diagnosis, and patients are often misdiagnosed with asthma (Walusiak 2002; Dipaolo 1993; Wynn et al. 1986). Diffuse idiopathic pulmonary neuroendocrine hyperplasia (DIPNECH) is classified as a premalignant condition. It causes wheezing, cough, and dyspnea with relatively poor response to inhaled therapy but with improvement in systemic corticosteroids. Thus, this premalignant lung condition may be confused with asthma. Octreotide or other somatostatin analogs can reduce symptoms.

16.2.9 Sarcoidosis

Pulmonary sarcoidosis is in the differential diagnosis of suspected asthma. Sarcoidosis can present with dyspnea and cough, thereby mimicking asthma (Ungprasert 2017). Sarcoidosis is a non-caseating, granulomatous disease involving multiple organ systems (Iannuzzi et al. 2007; Thomas 2003). The annual incidence rate for sarcoidosis is 35.5–70 per 100,000 among African-Americans versus 5–19 per 100,000 among Caucasians

(Thomas 2003; Ungprasert 2017; Ungprasert et al. 2016). Ninety-seven percent will have evidence of intrathoracic sarcoidosis, and 43% will have respiratory symptoms (Ungprasert et al. 2016). A definitive diagnostic test does not exist for sarcoidosis. It is a diagnosis of exclusion, and it is dependent on clinical, radiographic, and histopathologic findings consistent with the disease (Judson 2012).

The pathogenesis of sarcoidosis has been extensively studied; however, the inciting etiologic stimulus has not been established (Iannuzzi et al. 2007; Thomas 2003). The majority of sarcoidosis patients have pulmonary involvement, which accounts for a majority of morbidity and mortality (Iannuzzi et al. 2007; Thomas 2003). The initial pulmonary lesions are comprised of CD4+ T cells, and they subsequently develop into the classic noncaseating granulomas characteristic of sarcoidosis (Tazi et al. 1992; Lecossier et al. 1991).

Many patients with sarcoidosis do not require treatment (Iannuzzi et al. 2007). Patients with severe pulmonary disease are treated to reduce the granulomatous inflammation and the development of irreversible lung damage (Iannuzzi et al. 2007). Glucocorticoids can be used as an initial therapy after the presence of *Mycobacterium tuberculosis* is excluded (Baughman et al. 2008). Prednisone at a maintenance dose of 0.25–0.4 mg/kg may prevent progression of disease (Baughman 2015). Experts recommend a minimum of 3–6 months of therapy to prevent relapse (Wijsenbeek 2015). Most patients will respond to glucocorticoid therapy.

Patients who do not respond to glucocorticoids will require alternative immunosuppressive agents (Baughman 2004). Alternative agents should be considered when sarcoidosis progresses despite adequate glucocorticoid therapy or when patients cannot tolerate or refuse glucocorticoids (Sharma 1993). Methotrexate is the most commonly used alternative but is avoided in liver disease (du Bois 1994). Other immunosuppressive agents such as azathioprine, leflunomide, or TNF-alpha antagonists can be considered as options (du Bois 1994).

16.2.10 Hypersensitivity Pneumonitis

Hypersensitivity pneumonitis (HP) is a respiratory syndrome in the differential diagnosis of asthma. The clinical overlap with asthma is due to great variability in symptom, severity, and clinical presentation of the various stages of the disease. Hypersensitivity pneumonitis, also known as extrinsic allergic alveolitis, is the result of an inflammatory response from repeated exposure to a variety of antigenic particles in the environment. These particles affect the lung parenchyma, specifically the alveoli, terminal bronchiole, and alveolar interstitium (Sforza 2017; Ohshimo et al. 2012). The dispersed antigens must be a size that is appropriate for reaching the alveolar spaces (5 μm or less) (Selman 2012). These antigens include mammalian and avian proteins, fungi, thermophilic bacteria, and chemical compounds that can combine with host proteins to form haptens (Selman 2012). These same antigens can be the cause or trigger of asthma, and this can add to the difficulty of distinguishing between the two diseases.

The clinical presentation of HP is classified into acute, subacute, and chronic stages (Ohshimo et al. 2012). The acute form presents with a flu-like prodrome including fevers, chills, and malaise with concomitant respiratory features of cough, dyspnea, chest tightness, and tachypnea. These symptoms usually present 4–12 h after exposure to the antigen (Ohshimo et al. 2012). Acutely, this disease stage is nonprogressive and improves with antigen avoidance; however, it recurs following reintroduction of the etiologic antigen (Ohshimo et al. 2012).

The subacute form usually results from continuous, low-level exposure to the antigen and is usually the result of progression from undiagnosed acute HP (Selman 2012). Clinical findings include dyspnea and productive cough progressing over weeks. In this subacute stage, fatigue, anorexia, and weight loss are also common (Selman 2012).

Chronic HP may be the result of continued low level exposure to inhaled antigens from either unrecognized acute or subacute episodes, known as recurrent chronic HP. Insidious chronic HP

would describe patients without a previous history of acute HP. These patients experience progressive dyspnea on exertion, cough, fatigue, malaise, and weight loss, and the condition often progresses to diffuse fibrosis and end-stage lung disease.

The pathophysiology of this disease process is not clearly understood; however, it seems to be due to both humoral and cellular mechanisms (Selman 2012). In the acute phase, inflammation is due to immune complex-mediated reactions with high titers of antigen-specific serum immunoglobulin G, termed precipitins, and elevated neutrophils. Subacute and chronic HP has an amplified T-cell-mediated immune response (Selman 2012). Migration, proliferation, and decreased apoptosis of lymphocytes contribute to the pathogenesis of the classic T-lymphocytic alveolitis. HP is classically understood to be a Th1 disease (Ohshimo et al. 2012). However, the evolving fibrosis seen in the chronic forms of HP may be driven by a Th2 mechanism. Understanding of the mechanism of HP is evolving, and further studies are needed to explain why this disease develops in a minority of exposed individuals (Ohshimo et al. 2012).

The diagnosis of HP relies on a thorough history and physical examination with particular attention to the environmental and occupational history (Sforza 2017; Ohshimo et al. 2012). While there are several diagnostic criteria that have been proposed, none have been validated. Therefore, a high level of clinical suspicion, recognition of inhaled antigen exposure, and relevant clinical investigations including imaging, laboratory, and pathologic findings help to confirm the diagnosis of HP (Ohshimo et al. 2012).

16.2.11 Pulmonary Arterial Hypertension

The symptoms of pulmonary arterial hypertension (PAH) can be misinterpreted as asthma. Symptoms of PAH include breathlessness, dyspnea on exertion, cardiac palpitations, fatigue, syncope, and chest discomfort. PAH is an incurable and progressive disease characterized by elevated pulmonary arterial pressures leading to right ventricular failure (Chin 2008). A personal history of heart disease, congenital heart defects, scleroderma, and HIV and family history should be assessed, as these may contribute to PAH.

The physical examination may show signs of right heart failure, such as lower extremity edema and prominent jugular veins. Echocardiogram is used as a screening tool to assess ventricular function, while right ventricular catheterization remains the gold standard for diagnosis (Rich 2014). The hemodynamic diagnostic criteria for PAH include a mean pulmonary arterial pressure of >25 mmHg, pulmonary capillary wedge or left ventricular end-diastolic pressure <15 mm Hg, and pulmonary vascular resistance >3 Wood units (Chin 2008).

16.2.12 Lymphangioleiomyomatosis

Lymphangioleiomyomatosis is a progressive, rare cystic lung disease that predominantly affects young women of reproductive age (Pais 2017). As respiratory findings are common, this disease process is in the differential diagnosis of asthma, especially in the premenopausal female. LAM should be considered in a patient with dyspnea, cough, and chest pain (Johnson et al. 2016; Zhou et al. 2016). LAM can often mimic COPD, asthma, and bronchitis, which may lead to a delay in diagnosis. The natural course of this disease is usually varied, and affected women are at high risk of developing pneumothorax, rapid decline of lung function, progressive respiratory failure, and death (Taylor; Johnson et al. 2016).

The lung lesions in LAM are identified on chest CT and appear as numerous scattered thin-walled cysts that are evenly distributed throughout all lung fields (Johnson et al. 2016). Histologically, the lung lesions are small clusters of proliferated smooth muscle-like cells that are distributed along the peripheral vessels, bronchioles, and lymphatics (Taylor et al. 1990). Due to these changes, the conducting airways are compressed and obstructed causing the clinical respiratory findings described above.

To diagnose LAM, a thorough history and physical examination are combined with findings of angiolipomas and lymphatic disease on chest CT. Serum VEGF-D testing may be helpful, and lung biopsies may be employed if other clinical information is inconclusive (Johnson et al. 2016; Zhou et al. 2016). Once the diagnosis has been made, the patient should undergo a complete pulmonary function test and receive pneumococcal and influenza vaccinations, pulmonary rehab, and appropriate drug treatments with bronchodilators if obstructive symptoms are present (Johnson et al. 2016; Zhou et al. 2016; Taylor et al. 1990). Patients should also be made aware of the potential risks associated with the role of estrogen in this disease and take appropriate precautions in terms of estrogen containing pharmacotherapies (Johnson et al. 2016; Taylor et al. 1990). Once the diagnosis of LAM has been established, patients should be managed closely by a pulmonary team and be made aware of the chronicity of the disease (Johnson et al. 2016).

16.2.13 Cystic Fibrosis

Cystic fibrosis can mimic asthma due to coughing and dyspnea similar to asthma. It is an autosomal recessive disorder. Currently there are 30,000 people in the United States living with cystic fibrosis, and approximately 1000 new cases are diagnosed each year. More than 75% of patients are diagnosed with the disorder by the age of 2 years because of newborn screening programs (Cystic Fibrosis News Today 2017).

Cystic fibrosis is caused by a mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. This gene regulates anion transport and mucociliary clearance in the airways. Due to the dysfunction of the CFTR gene, mucous retention leads to chronic infections and local airway inflammation. This often results in progressive lung damage and decreased life expectancy (Elborn et al. 1991).

Symptoms include salty tasting skin, persistent coughing with production of thick mucus, wheezing, dyspnea, frequent sinusitis, bronchitis and pneumonia, digestive problems including malabsorption, and failure to gain weight (NIH 2017).

All newborns in the United States are screened for cystic fibrosis via genetic testing or blood test. If these tests suggest cystic fibrosis, the diagnosis is then confirmed with a sweat test. Goals of treatment focus on decreasing infections, pulmonary hygiene, and optimizing digestive health.

16.2.14 Eosinophilic Pulmonary Diseases

Pulmonary eosinophilia encompasses a group of heterogeneous diseases. These diseases must be considered in the differential of asthma, since they may present with dyspnea, wheezing, and cough (Loffler 1956). Eosinophilic lung disease may be characterized by peripheral eosinophilia with supportive pulmonary radiographic findings, eosinophils demonstrated on lung biopsy, or increased eosinophils in a bronchoalveolar lavage (BAL) (Allen 1994; Bain 1996). Peripheral eosinophilia with an absolute eosinophil count of 500 cells per microliter or greater supports an eosinophilic pulmonary disease (Valent et al. 2012). The degree of eosinophilia does not enable diagnosing the precise etiology (Umeki et al. 1992). A high-resolution CT scan of the chest can provide significant findings early in the course of the disease (Johkoh et al. 2000). Löffler syndrome is one of many diseases classified as an eosinophilic pulmonary disease. It occurs when helminth larvae migrate to the lungs of an infected individual to mature before ascending the airways and return to the gastrointestinal tract (Wilson 2006). There are four types of helminths with life cycles within the lung: *Ascaris lumbricoides*, *Ancylostoma duodenale*, *Necator americanus*, and *Strongyloides stercoralis* (Wilson 2006). The syndrome was originally described by Löffler when patients presented with fleeting pulmonary opacities with peripheral eosinophilia after being exposed to soil contaminated with human waste (Löffler 1956).

Chronic eosinophilic pneumonia (CEP) is characterized by increased pulmonary eosinophils (Jederlinic et al. 1988). It is an idiopathic disease

occurring predominantly in non-smokers and women (Marchand et al. 1998). Symptoms of weight loss and night sweats may occur in addition to respiratory symptoms and laboratory findings, which mimic asthma. In addition to mimicking asthma, 50% of cases of CEP will have a concurrent or historical diagnosis of asthma (Jederlinic 1998). Peripheral eosinophilia is a typical feature and is present in up to 90% of cases (Marchand et al. 1998). A virtually pathognomonic finding on chest X-ray is peripheral pulmonary infiltrates, described as the photographic negative of pulmonary edema, and may be observed in up to one-third of CEP cases (Jederlinic 1998). The clinical diagnosis of CEP is based on the combination of peripheral or BAL eosinophilia, subacute presentation, and characteristic radiographic findings (Jederlinic 1998). CEP is treated with corticosteroids.

16.2.15 Eosinophilic Granulomatosis with Polyangiitis

Churg-Strauss syndrome (CSS), also known as eosinophilic granulomatosis with polyangiitis, is a rare, granulomatous eosinophilic vasculitis. It is characterized by a diffuse necrotizing vasculitis with extravascular granulomas seen almost exclusively in patients with asthma and tissue eosinophilia (Greco et al. 2015). Treating difficult to control asthma with corticosteroids can mask this diagnosis. Given the increased mortality in delaying the diagnosis until the active vasculitis phase, clinicians should keep the diagnosis of Churg-Strauss in the differential diagnosis of asthma (D'Cruz 1999; Aguilar 2014).

Churg-Strauss classically follows a triphasic pattern. The first phase is the initial prodrome and consists of upper airway disease such as rhinosinusitis with asthma. The second phase is the eosinophilic phase, characterized by significant peripheral eosinophilia and myocardial, pulmonary, and gastrointestinal involvement. The final phase is the vasculitis phase. This phase is the progression of the disease to multisystem, small vessel vasculitis (Greco et al. 2015; D'Cruz et al. 1999; Aguilar et al. 2014).

Patients with CSS typically present with dyspnea, cough, and wheeze that is refractory to traditional asthma treatment or a peripheral manifestation of vasculitis in a subject with a history of asthma. The diagnosis of CSS relies on radiologic, laboratory, and pathologic findings. CSS is a small vessel vasculitis that is associated with perinuclear-antineutrophil cytoplasmic antibody (p-ANCA) in approximately 40% of patients. The antigen recognized by the autoantibody is usually myeloperoxidase (MPO). The absence of ANCA does not exclude the diagnosis (Greco et al. 2015; Aguilar et al. 2014). Four or more of the following criteria aid in the diagnosis of CSS: presence of asthma, greater than 10% peripheral eosinophilia, mononeuropathy multiplex or polyneuropathy, nonfixed lung infiltrates, sinus abnormalities, and extravascular eosinophils on tissue biopsies, particularly in blood vessel walls or perivascular localization (Aguilar et al. 2014). Some authors suggest that any patient with asthma and concurrent features of multisystem disease should be considered to have an underlying vasculitis such as CSS (D'Cruz et al. 1999).

16.2.16 Other Pulmonary Vasculitis Syndromes

The triad of Wegener's granulomatosis, or granulomatosis with polyangiitis (GPA), consists of necrotizing granulomatous inflammation of the upper and lower airways, necrotizing glomerulonephritis, and an autoimmune necrotizing vasculitis (Lamprecht 2004). GPA is a vasculitis affecting medium- and small-sized vessels.

GPA usually presents in middle age but can occur in older adults. It is rare in childhood. This disease can affect almost any site in the body; however, the classic sites of involvement include the upper respiratory tract, lungs, and kidneys. Patients may present with a multitude of complaints such as fever, fatigue, unintentional weight loss, hearing changes, recurrent sinusitis, persistent rhinorrhea, eye problems, nasal crusts and ulcerations, epistaxis caused by local inflammation, dyspnea and hoarseness caused by subglottic stenosis, cough with bloody sputum, wheezing

caused by upper or lower airway inflammation, joint pain, and hematuria.

The diagnosis may be delayed by months because early clinical symptoms of GPA are similar to milder and more common respiratory problems. The combination of c-ANCA (cytoplasmic-ANCA)/anti-proteinase 3 (PR3) (~80%) or p-ANCA/anti-MPO (10–15%) has high specificity (>95%) for the diagnosis of GPA. The diagnosis of GPA is confirmed with biopsy. Tissue from the upper respiratory tract can be obtained with less risk; however, the yield of upper airway biopsies is relatively low. Lung biopsy or renal biopsy, if kidney involvement suspected, is often the best way to diagnose this disorder. Treatment is focused on long-term immunosuppression.

Microscopic polyangiitis is another systemic vasculitis with pulmonary involvement. Generally the manifestation is dyspnea and cough with generalized alveolitis and alveolar hemorrhage. The CT scan usually demonstrates ground-glass changes rather than nodules as is typical of GPA. Microscopic polyangiitis is usually ANCA positive, although not as reliably as GPA. Eosinophilia is not typical with microscopic polyangiitis and it is not associated specifically with asthma. As with all vasculitic syndromes, the diagnosis requires tissue biopsy demonstrating small artery and arteriole damage with hemorrhage.

16.3 Summary

Although asthma is very common, other disease states can mimic asthma as emphasized in this chapter. The cardinal symptoms of asthma, cough, shortness of breath, wheezing, and chest tightness, are shared with many disorders, which can be confused with asthma or which may complicate asthma. Careful attention to history as well as the physical examination and selected imaging, spirometry, and/or laboratory facilitates the appropriate classification and diagnosis in the subject with suspected asthma. Corticosteroid therapy typically used for asthma may improve many of the conditions in the differential diagnosis. Clinical vigilance is essential, particularly when the clinical course is atypical for asthma or fails to resolve with appropriate asthma therapy.

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Asthma in Athletes

17

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Contents

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Abstract

Exercise-induced bronchoconstriction (EIB) is a very common disorder that may have considerable impact on the lives of those who suffer from its symptoms. Often, we contrast the significance of EIB on recreational versus competitive (or elite) athletes. Any athlete with EIB, from recreational to elite, Olympic, or competitive athletes, may have a comparable decrease in quality of life as a direct consequence of impaired overall exercise performance. EIB is an indicator of active and treatable airway pathophysiology consistent with asthma, identifying the presence of airway inflammation and sensitive airway smooth muscle. It also identifies airways that are treatable by pharmacotherapies that are successful in the treatment of asthma. It is important to identify objectively EIB in the athlete using standardized bronchial provocation tests as symptoms are not a useful diagnostic predictor of the presence or severity of EIB. It is important to treat EIB in a similar manner as treating asthma. Optimal treatment should not just decrease daily symptoms of asthma, but significantly attenuate or even abolish EIB. To achieve this, the health-care provider must understand the prevalence, pathophysiology, diagnostic modalities, and underlying mechanisms of EIB.

Keywords

Exercise-induced bronchoconstriction · Asthma · Athlete · Bronchial provocation testing

17.1 Introduction

The presence of active asthma in either a recreational or elite level athlete can manifest as exercise-induced bronchoconstriction (EIB). The presence of EIB can impact an individual's optimal exercise performance at best and at worst can put an individual at risk of a severe and possibly life-threatening attack of asthma. It is essential that the presence and severity of EIB be documented and treated optimally, with the goal to attenuate or abolish EIB.

EIB is the term used to describe the transient narrowing of the airways or bronchial hyperresponsiveness (BHR) that occurs either during exercise, although most commonly following, vigorous exercise. EIB can occur in persons with active asthma; however, it can also occur alone in the absence of daily asthma symptoms. Thus, EIB can commonly be seen in the elite or recreational athlete. Pharmacotherapy in the treatment of asthma is efficacious in the treatment of EIB, and there appear to be similarities in the airway pathophysiology. As EIB can be frequently documented in those with active asthma, it is thought to reflect insufficient control of the pathophysiology of underlying asthma. The prevalence of EIB can be difficult to determine in different populations and in different regions. However, in elite athletes the prevalence can be higher than observed in the general population. Further, the prevalence can also vary based on the intensity of the exercise or the environment (e.g., ambient conditions) where the exercise is performed.

Over the past two decades, significant advances in the understanding of the pathophysiology of EIB have been made. The increased hyperpnea caused by strenuous exercise is known to create a hyperosmolar airway surface via dehydration, resulting in compensatory water loss. This leads to a movement of water from the airway tissue into the lumen which is essential for heat loss. This leads to a hyperosmolar environment of the airway surface and likely to the submucosa, causing the release of bronchoconstricting mediators from inflammatory cells. Thus, the water content of the inspired air and the level of ventilation achieved and maintained during exercise are the major determinants of EIB. As a result of water loss, there are also alterations in airway temperature that can develop during exercise, but thermal factors are thought to have only a minor impact on the amount of bronchoconstriction that occurs. Thus, exercise per se is not needed to cause bronchoconstriction. Dry air hyperpnea in the absence of exercise, as well as the inhalation of an osmotic aerosol, can mimic the BHR that is observed with exercise.

Making the correct diagnosis of EIB is both challenging and essential. Overcoming these challenges is possible with a sound understanding of the advantages and limitations of diagnostic methods, combined with a good understanding of the pathophysiology of EIB. It is clear that symptoms alone are not sufficiently accurate to diagnose EIB. For example, dyspnea, a primary symptom of EIB, may exist due to poor exercise conditioning. Thus, objective testing of EIB has been recommended in order to document the presence and severity of BHR. These tests, also known as bronchial provocation tests (BPTs), include laboratory exercise testing using either treadmill running or a cycle ergometer, a surrogate hyperpnea test known as eucapnic voluntary hyperpnea (EVH), or challenging the airways in a dose-response manner with an osmotic aerosol (e.g., dry powder mannitol).

Therapeutic interventions for EIB have to consider both the acute protection and long-term treatment. Short-acting beta2-agonists (SABAs) are essential for reversal of bronchoconstriction and bronchoprotection. Additionally, anti-inflammatory medications including inhaled corticosteroids, leukotriene receptor antagonists (LTRAs), or combination therapy (with inhaled corticosteroids and long-acting beta2-agonists [LABAs]) are recommended for managing both BHR and airway inflammation. Unfortunately, the regular use of beta2-agonists can cause tolerance, limiting ability to provide optimal bronchoprotection, as well as complete and rapid rescue bronchodilation. A variety of alternative methods to prevent EIB have also been explored from exercise warm-up, use of face masks for minimizing airway water loss, and dietary modification. Alternative methods have shown different degrees of efficacy.

This review aims to be a guide for the successful identification and treatment of EIB. This chapter will focus on the athlete with asthma, but with relevance also regarding the athlete who does not have daily symptoms of asthma. It is both possible and essential for the correct diagnosis and treatment to be employed so that an athlete's performance is minimally impacted by the presence of BHR.

17.2 Prevalence of Exercise-Induced Bronchoconstriction

EIB is seen in either the presence or absence of chronic asthma in athletes or in individuals who are not otherwise competitive athletes. In most cases, exercise is the trigger for EIB so that many patients who otherwise have chronic asthma also have EIB when they exercise.

Often the criteria for the diagnosis of asthma also determine how many patients have EIB when tested. Thus, fall in FEV_1 with exercise, workload of exercise, and environmental conditions determine the percentage of patients diagnosed as having EIB. However, we must also take into consideration whether the subject being tested might have either a false-positive or false-negative diagnosis for EIB, which can be seen especially when symptoms rather than objective tests are used to make the diagnosis of EIB (Parsons et al. 2007, 2013; Rundell et al. 2001; Weiler et al. 2007). For these reasons, it has been recommended that indirect challenges such as exercise, EVH, or mannitol be performed to rule in or rule out EIB (Parsons et al. 2007, 2013; Rundell et al. 2001; Hallstrand et al. 2002; Weiler et al. 2016).

17.2.1 Prevalence in Nonathletes

When performing studies to estimate the prevalence of EIB in a nonathlete population, we must take into consideration the age, gender, and ethnicity of the subjects as well as their level of exercise performance (elite, competitive, or recreational). Season may also play a role in whether the challenge is positive (e.g., caused by exposure to ragweed or mountain cedar pollen) as well as environmental conditions (e.g., ambient temperature and humidity) (Parsons et al. 2013; Weiler et al. 2007; Mountjoy et al. 2015; Rundell et al. 2015).

In a study of 15,241 children that examined a 6-min free running test, participants recorded a fall in peak expiratory flow to diagnose EIB and a positive test was one in which the fall was at least 15%. It was observed that girls (8.5%) were

more likely than boys (6.4%) to have EIB and EIB was more prevalent in urban locations (8.9%) compared to rural settings (7.0%) (De Baets et al. 2005). Importantly, in all populations, symptoms alone poorly predicted a positive challenge. It is uncommon from other studies to observe gender differences in those having EIB, but, it has been shown that the frequency of EIB can decrease with increasing age (Bardagi et al. 1993).

It is unclear whether there are racial and ethnic differences in EIB prevalence. In one study using a standardized free running test and recording peak expiratory flow measurements, a higher prevalence of EIB was seen in African American (13%) compared with Caucasians (2%) (Kukafka et al. 1998). Using cycle ergometry, a study from Great Britain demonstrated that in 9-year-old children, those Asian children originating from the Indian subcontinent were 3.6 times more likely to have EIB than Caucasian inner-city children (Jones et al. 1996). A systematic review of 66 studies comprised of 55,696 participants assessing the prevalence of EIB in children confirmed findings of a high prevalence of EIB globally, with a 15% prevalence of EIB in children and adolescent athletes and 46% in children and adolescents with asthma (de Aguiar et al. 2018).

It has been reported that EIB in children may be the earliest symptom in the development of asthma (Sano et al. 1998; Cabral et al. 1999). In addition, the prevalence of EIB in school children may be 10–20% (Randolph 2013). EIB is significantly greater in children who are overweight and obese compared to non-overweight asthmatic children (Baek et al. 2011; van Veen et al. 2017). Further, BMI is a predictor of the severity of EIB in asthmatic boys (van Veen et al. 2017). Longitudinal studies have been performed that demonstrate increasing prevalence of asthma in children with EIB (Frank et al. 2008; Stern et al. 2008). Of interest are reports that parental observation of a history of exercise-induced wheezing and a presence of atopy are very strong predictors of asthma observed over 6 years of follow-up (Frank et al. 2008). In addition, a longitudinal birth cohort study reported that BHR to cold dry air in early childhood associated with an increased risk of chronic asthma was seen at 22 years of age (Stern et al. 2008).

An EVH challenge in adults may be a more potent test to identify EIB than a laboratory exercise challenge. A high prevalence of EIB in those who recreationally exercise (19% in 212 adults without a history of asthma) has been observed (Mannix et al. 2003), with another study finding a prevalence of 13% using EVH in 136 recreational athletes (Molphy et al. 2014). Further, a higher prevalence of EIB may be found in individuals with a family history of asthma (Godfrey and Konig 1975a). EIB is also more frequently documented in atopic individuals (Helenius et al. 1998; Sallaoui et al. 2009), including those who have allergic rhinitis (Brutsche et al. 1995). This was supported by studies showing EIB also occurs more frequently during and after respiratory viral infections and other respiratory diseases such as allergic rhinitis (Tilles 2003). Symptoms of EIB in some individuals vary depending on the time of year or season (Choi et al. 2012; Goldberg et al. 2005, 2012).

Microenvironments may play a role in the development of EIB so that exercise at an athletic field that has high air pollution or pollen counts may cause EIB (Mickleborough et al. 2007; Haverkamp et al. 2005). In one study, significant decreases in lung function in soccer players were related to months of daily measurements of air pollutants (Rundell et al. 2006). Emissions and particulate matter from vehicular traffic, as well as high levels of ambient ozone, can increase the airway responsiveness of EIB in asthmatics (McCreanor et al. 2007).

17.2.2 Prevalence in Athletes

EIB is commonly reported in athletes, especially in athletes who have asthma. The overall prevalence of EIB is reported to be from 30% to 60% (Cabral et al. 1999; Lazo-Velasquez et al. 2005; Benarab-Boucherit et al. 2011; Park et al. 2014). In patients with asthma, EIB in itself indicates lack of control of asthma and suggests the need to initiate or increase therapy or alternatively to encourage treatment adherence (Global Initiative

for Asthma 2007a). Depending on the sport and environment, the prevalence of asthma symptoms in elite athletes has been shown to vary from none to 61% (Rundell et al. 2000, 2001, 2004a; Parsons and Mastronarde 2005; Mannix et al. 1996; Rundell 2003; Wilber et al. 2000; Weiler et al. 1998; Weiler and Ryan 2000; Fitch and Morton 1971; Sue-Chu et al. 1999a; b; Pohjantahti et al. 2005; Randolph et al. 2006).

Both summer and winter elite endurance athletes have considerably more symptoms than athletes participating in non-endurance sports (Weiler et al. 1998; Weiler and Ryan 2000). However, it is difficult to determine if EIB is more common in winter compared to summer sporting activity. History forms required by the US Olympic Committee and completed by athletes participating in the 1996 Summer Olympic Games showed as many as 45% of summer athletes, depending on sport, answered questions compatible with having EIB (Weiler et al. 1998). Different sports showed varied prevalence, with endurance sports having higher prevalence rates and non-endurance sports having minimal levels. The same researchers found that as many as 61% of athletes participating in Nordic skiing events responded to questions that suggested they had EIB (Weiler and Ryan 2000).

17.2.2.1 Winter Athletes

High prevalence of EIB is reported in elite endurance athletes who perform exercise in cold environments such as competitive skaters and cross-country skiers (Pohjantahti et al. 2005; Anderson et al. 2003; Fitch et al. 2008). A similar high prevalence of EIB in Winter Olympic athletes has been reported based on objectively assessing EIB using an exercise BPT (Wilber et al. 2000). Ice skaters have a reported prevalence of EIB of 20–35%, which may be attributed to regular exposure of high emission pollution from ice cleaning equipment and cold dry air (Rundell 2003; Rundell et al. 2004a, 2007; Rundell and Caviston 2008). However, in cross-country skiers, the prevalence of EIB has been shown to be as high as 30–50% (Rundell et al. 2003). Others have found as many as 78% of elite cross-country skiers have symptoms of EIB and/or BHR (Larsson et al. 1993). The prevalence of both asthma and EIB may vary by gender in winter sport elite athletes. Frequency of EIB in females appears to exceed that of males. The prevalence of EIB by exercise challenge test was 26% in female and 18% in male athletes with a combined percentage of 23% in US Olympic winter sports (Wilber et al. 2000).

17.2.2.2 Summer Athletes

There also may be a high prevalence of EIB in summer athletes, dependent upon the type of sporting activity performed. In athletes who participated in the 1996 Summer Olympic Games, long-distance runners were found to have a prevalence of 17%, whereas speed runners had a prevalence of 8% (Helenius et al. 1997). For athletes who expend a similar amount of work, however, these differences may depend on how the test was performed rather than on a difference in the sports. None of the US Olympic divers and weightlifters had symptoms (by survey), while 45% of mountain bikers experienced symptoms. This difference in prevalence is consistent with the hypothesis that a higher prevalence of associated EIB during sport participation is found with endurance sports (Weiler et al. 1998). There is limited evidence to show differences in gender in athletes when using EVH as a surrogate challenge for EIB (Parsons et al. 2007; Couillard et al. 2014).

A high prevalence of EIB in summer athletes may also be associated with poor air quality (Helenius and Haahtela 2000). For swimmers, the chloramines used in swimming pools, which may be in high concentration in the air above the water, may trigger EIB. Swimmers with greater than 100 h of chlorinated pool exposure showed a higher prevalence of EIB (Bernard et al. 2009). Decreased incidence of EIB resulted from discontinuation of swimming (Helenius et al. 2002).

Seasonal variation of EIB is also described in Olympic summer athletes (Helenius et al. 1998). When using a reduced cutoff value for EIB of 6.5% fall in FEV_1 with running, 28% of runners had probable EIB. Of these athletes, 22% had EIB that happened only in the winter, and 7% reported EIB only during the pollen season (Helenius et al.

1998). It has also been shown that 35% of runners training in the cold reported a greater prevalence of EIB compared with a lower prevalence during the summer season (Ucok et al. 2004).

17.3 Mechanisms of Exercise-Induced Bronchoconstriction

The mechanisms of EIB have been elucidated over the last 55 years with significant controversy over the primary mechanisms of airway drying. Specifically, the controversy is between the "airway drying" or osmotic theory of EIB and the "airway cooling" or thermal theory of EIB (Godfrey and Fitch 2013). Currently it is thought that a period of high ventilation causes respiratory water loss along with cooling of the airways (Fig. 1). The result is a transient increase in the osmolarity of the airway surface liquid that occurs with a loss in volume of this liquid. These transient changes in osmolarity are rapidly resolved by the movement of water from the luminal side of the osmotically sensitive epithelium. The subsequent water loss from cells is thought to cause reduction in cell volume and the resulting regulatory volume increase, which includes increases in intracellular concentrations of calcium and inositol triphosphate, and is a requirement for the release of intracellular mediators (Eveloff and Warnock 1987). Cooling could provide a different stimulus which could induce reactive hyperemia of the bronchial vasculature (McFadden and Pichurko 1985). The response of the epithelium and other cells to the changes in airway surface liquid volume and the subsequent changes in osmolarity is the most likely trigger for the bronchoconstricting mediator release. Further, this mediator release is likely the primary stimulus for sustained bronchoconstriction following vigorous exercise (Hallstrand et al. 2012). Thus, it is important to consider that there may be some

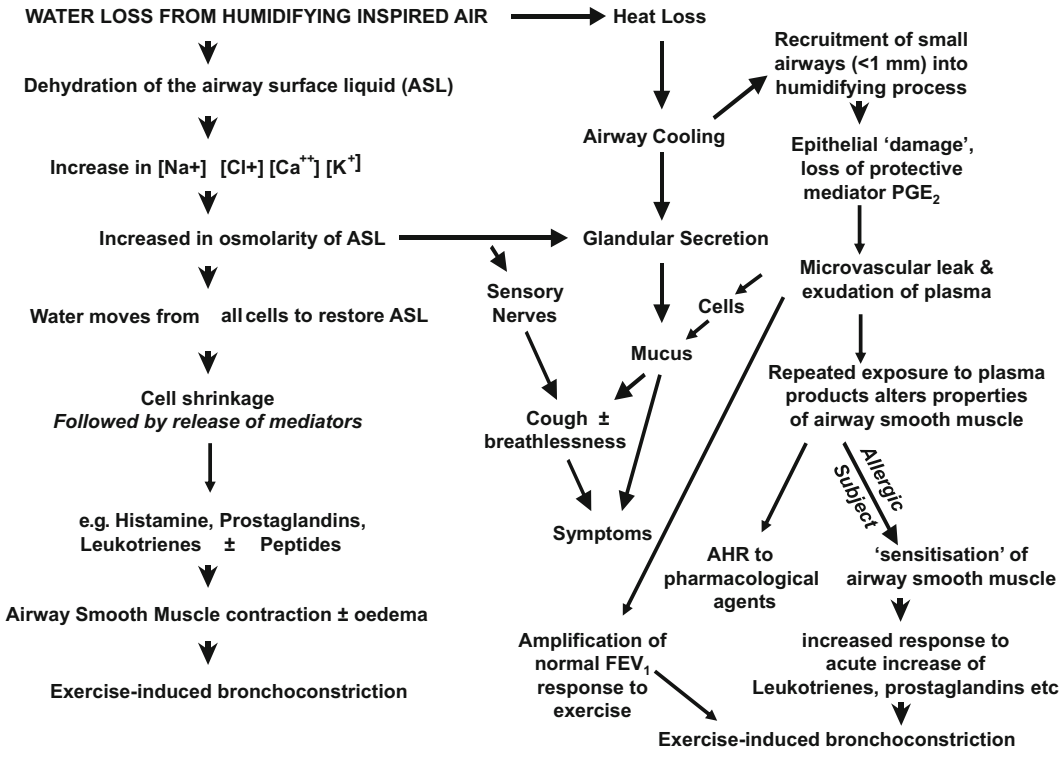


Fig. 1 Flow chart describing the acute events leading to EIB in the subject with classic asthma (left) and the events leading to the development of EIB in the athlete (right). (Reproduced with permission from (Anderson and Kippelen 2005))

contribution in certain extreme conditions of both the thermal and the osmotic theories of EIB. Under conditions of breathing cold dry air, vascular effects may result in airway edema and amplify the contractile effect of mediator release. Thus, the osmotic and vascular theories of EIB may operate together. It should be recognized that osmotic effects of water loss are more important than cooling, particularly as the temperature of the inspired air increases toward body temperature (Aitken and Marini 1985; Eschenbacher and Sheppard 1985; Tabka et al. 1988).

The thermal theory of EIB may be more relevant when subfreezing air is inspired during exercise. Then, airway cooling could induce vasoconstriction of the bronchial vasculature (McFadden and Pichurko 1985). When exercise ceases and ventilation falls, the airways rewarm, and reactive hyperemia with vascular engorgement and edema of the airway may occur (McFadden et al. 1986). The thermal theory of EIB is not sufficient to explain many of the events that occur in the airways following exercise challenge, in particular the sustained airway response and prolonged recovery of bronchoconstriction (Freed et al. 1995; Anderson and Daviskas 1992). Studies in canine models demonstrate that ligation of the bronchial circulation does not attenuate hyperpnea-induced bronchoconstriction, bringing into question the role of the bronchial vasculature (Freed et al. 1995). Studies in humans demonstrated that inspiring warm air following a BPT with cold air only had a modest effect on the degree of bronchoconstriction over 15 min after exercise (McFadden et al. 1986).

Because it was demonstrated that cooling of the airways was not a prerequisite for EIB, the osmotic theory of EIB was developed (Anderson 1992). Changes in airway surface osmolarity, with direct delivery of dry air (Freed and Davis 1999) or inhalation of osmotically active aerosols, were sufficient to cause BHR (Argyros et al. 1993; Freed et al. 1994; Brannan et al. 2003). Airway surface dehydration causes a temporary increase in ion content and osmolarity when water from the airway surface liquid is evaporated faster than it is returned by either condensation or via the epithelium or submucosa (Daviskas et al. 1991; Davis et al. 2003a). The exact mechanism by which the loss of water and resulting transient osmotic gradients lead to activation of inflammatory cells and mediator release is unclear. Mast cells (bound with cross-linked IgE) and eosinophils release mediators in response to changes in osmolarity (Gulliksson et al. 2006; Eggleston et al. 1987; Moloney et al. 2003). However, it is also now appreciated that changes in both airway surface volume and osmolarity also activate cellular signaling events in epithelial cells (Hallstrand et al. 2012). The release of regulatory epithelial proteins could lead to direct activation of other cells.

Voluntary hyperpnea of dry air induces bronchoconstriction similar to exercise in susceptible individuals; thus, exercise itself is not necessary to cause bronchoconstriction (Eliasson et al. 1992; Phillips et al. 1985). For athletes, EVH of dry air containing approximately 5% carbon dioxide can be used as a surrogate for exercise in the diagnosis of EIB in athletes (Parsons et al. 2007; Dickinson 2006; Stadelmann et al. 2011). Osmotic aerosols of hypertonic saline and mannitol can also cause bronchospasm in both asthmatic and athletic individuals and also can be used to aid in the EIB diagnosis. The relationship of the airway responses to these "surrogate" stimuli for EIB, and to an exercise provocation challenge test, is good in both asthmatic and athletic individuals with EIB (Brannan et al. 1998; Holzer et al. 2003; Munoz et al. 2008).

Many studies indicate that subjects with increased cellular inflammation are susceptible to EIB, supporting the concept that mediator release is important for EIB to occur. Inflammatory lipid mediators that have the capacity to cause bronchoconstriction via specific receptors on the airway smooth muscle are implicated in EIB. The induced sputum of adults and exhaled breath condensate (EBC) of children show the concentration of cysteinyl leukotrienes (CysLTs) C_4, D_4, and E_4 is increased with EIB (Hallstrand et al. 2005a; Carraro et al. 2005). CysLTs are elevated in EBC following exercise challenge (Bikov et al. 2010). Urinary LTE4 has been demonstrated to be released, and this release is sustained after exercise (Reiss et al. 1997;

Hallstrand et al. 2005b) (Fig. 2). Prostaglandins also play a significant role; specifically, prostaglandin D_2 (PGD_2) has been shown to be excreted in the urine after exercise (O'Sullivan et al. 1998a) and in association with the presence of leukotrienes in the airway response to dry air hyperpnea (Kippelen et al. 2010a) (Fig. 3). In contrast, prostaglandin E_2 (PGE_2) inhibits EIB when administered by inhalation (Melillo et al. 1994). The balance of these mediators may be important, as there is a possible reduction in the production of PGE_2 relative to CysLTs in patients with EIB (Hallstrand and Henderson 2010). Other mediators that may have a role in EIB but are not well understood are the nonenzymatic products of phospholipid oxidation, 8-isoprostanes, which are increased in EBC of individuals who have asthma with EIB (Barreto et al. 2009). Reduction in the formation of lipoxin A4, which is known to be a protective lipid mediator that may also play some role in the mechanism of EIB (Tahan et al. 2008). Individuals who have asthma who are susceptible to EIB, especially patients with atopy, often have elevated fraction of exhaled nitric oxide levels (Scollo et al. 2000; Malmberg et al. 2009).

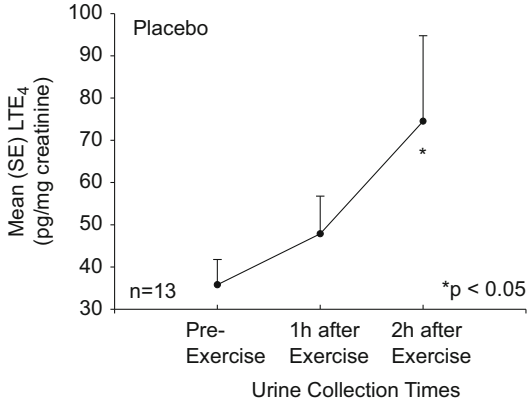


Fig. 2 The increase in the urinary excretion of metabolites of the leukotriene pathway, leukotriene E4 (pg per mg of creatinine), following a treadmill exercise challenge in 13 asthmatics; on a day placebo was administered in a study assessing the effectiveness of montelukast in the protection of EIB. (Reproduced with permission from (Reiss et al. 1997))

The formation of inflammatory eicosanoids such as CysLTs and PGD_2 is largely restricted to the myeloid cells; thus suggesting the intensity of airway inflammation in the airways may be an important factor in both EIB susceptibility and severity. There is an association with the degree of sputum eosinophilia and the severity of EIB (Duong et al. 2008). The severity of EIB is reduced after treatment with inhaled corticosteroid (ICS), which occurs with a reduction in percentage of eosinophils in sputum (Duong et al. 2008). Using genome-wide methods in patients with asthma has identified increased expression of mast cell genes in patients with EIB based on

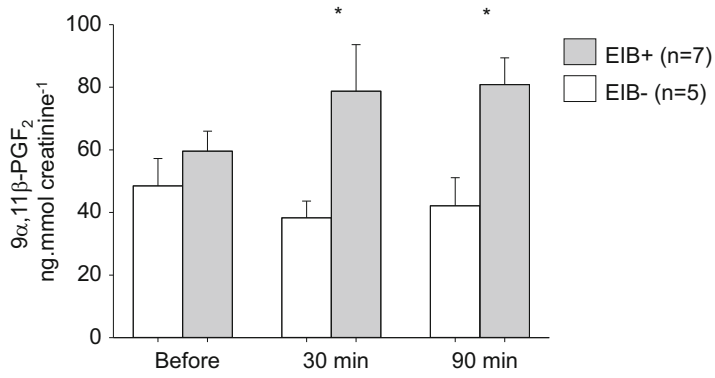


Fig. 3 The increase in the urinary excretion of a metabolite of prostaglandin D_2 and marker of mast cell activation, 9a,11b-PGF_2 (ng.mmol creatinine), following a cycle ergometer exercise challenge in seven asthmatics with EIB compared to five subjects who did not have EIB. (Reproduced with permission from (O'Sullivan et al. 1998b))

induced sputum and epithelial brushings (Lai et al. 2014). Increased expression of tryptase and carboxypeptidase A3, in the presence of relatively low chymase expression from epithelial brushings, indicates EIB is associated with Th2 high asthma (Woodruff et al. 2007; Dougherty et al. 2010). In patients who are susceptible to EIB, the density of intraepithelial mast cells per volume of the airway epithelium in endobronchial tissue of asthmatics is markedly elevated, suggesting a defining feature of EIB is mast cell infiltration of the airways (Lai et al. 2014). These more recent findings support a hypothesis that was developed in the early study of inhaled asthma drugs, where these drugs were thought to inhibit EIB acutely by inhibiting mast cells (Anderson et al. 1976). The rapid action of these drugs suggested to the investigators that the mast cell must have been located close to the airway surface.

Mast cells and eosinophils are well established as the major source of mediators in EIB (Reiss et al. 1997; Hallstrand et al. 2005b; O'Sullivan et al. 1998a). Mast cells generate de novo prostaglandin D_2 and leukotrienes and release stored histamine. Eosinophils are also a major source of leukotrienes and if present in high number may contribute to the increased severity of EIB (Duong et al. 2008). The immediate effect of these mediators is to constrict airway smooth muscle; however, they play other roles in activating sensory nerves, mucus secretion, and increasing microvascular permeability leading to airway edema (Hallstrand and Henderson 2010). It is not clear that they play a role in worsening airway inflammation acutely as there are no known late phase responses to exercise (Gauvreau et al. 2000). The first observations suggested small increases in arterial histamine in response to exercise (Hartley et al. 1981; Anderson et al. 1981). More recent studies using modern sampling methodology that allow more direct sampling of the airway using induced sputum found mast cell degranulation occurs with the release of histamine and tryptase during EIB (Hallstrand et al. 2005b; Haverkamp et al. 2007; Anderson and Brannan 2002).

Pharmacological treatments have played an important role in elucidating the mechanism of EIB and the role of bronchoconstricting mediators. Histamine antagonists have incomplete protection against EIB, suggesting histamine is a relatively weak mediator (Hallstrand et al. 2005b; Patel 1984; Baki and Orhan 2002; Dahlén et al. 2002). The development of leukotriene receptor antagonists revealed that leukotrienes play an important role in EIB, particularly in sustaining the airway response after exercise (Reiss et al. 1997; Leff et al. 1998). Thus, the response of a $CysLT_1$ receptor antagonist in EIB is to reduce both the maximum fall in FEV_1 and the time of recovery to baseline lung function after EIB (Leff et al. 1998; Pearlman et al. 2006). The 5-lipoxygenase inhibitor, zileuton, when administered four times daily over 2 days, also reduced the fall in FEV_1 after exercise challenge by approximately 50% (Meltzer et al. 1996). A role for CysLTs in the pathogenesis of EIB is clearly demonstrated by these results, but they also indicate the protection from EIB is incomplete. This again suggests that other mediators may play a role (e.g., PGD2) (Brannan et al. 2006; Simpson et al. 2016). The cromolyn drugs are thought to protect primarily via stabilizing mast cells and preventing mediator release (Kippelen et al. 2010a; Brannan et al. 2006). Following EVH challenge, the metabolite of PGD2, 9α, 11beta-PGF2 is increased in the urine, and the release of PGD2 can be inhibited by either pretreatment with a high dose of inhaled steroid or with a cromone (Kippelen et al. 2010a, b).

Sensory nerves also are thought to play a role, but there is less direct evidence for effects on EIB. Sensory nerve endings within the epithelium may be activated directly by a variety of mechanisms such as changes in osmolarity, the mechanical effects of bronchospasm, or in response to other mediators in the airways that could cause the release of neurokinins. Sensory nerves could send signals from the airways to the central nervous system, but they can also act locally via retrograde axonal transmission that could lead to bronchoconstriction and the production of mucus. Sensory nerves can either be directly activated or have the activation threshold altered by eicosanoids such as CysLTs (Taylor-Clark et al. 2008). Animal models of hyperpnea-induced

bronchoconstriction (HIB) have shown leukotriene antagonists inhibit both the release of neurokinins and HIB. Neurokinin receptor antagonists inhibit the development of HIB without changing neurokinin levels consistent with leukotriene-mediated bronchoconstriction that occurs via sensory nerve activation (Freed et al. 2003; Lai and Lee 1999). Human studies of neurokinin 1 antagonists have given varied results in the presence of BPTs using exercise and hypertonic saline (Fahy et al. 1995; Ichinose et al. 1996), which may be due to the predominance of the neurokinin 2 receptor (Naline et al. 1989). Release of the major gel-forming mucin MUC5AC following exercise challenge is associated with the levels of CysLTs in the airways and the levels of CysLTs and neurokinin A are correlated after exercise (Hallstrand et al. 2007).

Following exercise there is an interval of refractoriness lasting approximately 1–3 h during which additional exercise produces less bronchoconstriction in approximately half of patients who have EIB (Mickleborough et al. 2007; Haverkamp et al. 2005; Edmunds et al. 1978). This protection has been shown to be additive to the protective effect of pretreatment with a SABA (Mickleborough et al. 2007). Thus, warm-up exercise prior to competition may be useful to further attenuate EIB (Elkins and Brannan 2013). The mechanism of the refractory period is not well understood, and there could be multiple pathways and explanations. An early explanation for the refractory period was that it induces the generation of protective prostaglandins (e.g., release of PGE_2). It was found that when nonsteroidal anti-inflammatory drugs were administered that inhibit the cyclooxygenase pathway, the refractoriness to both exercise and leukotriene D_4 challenge was reduced (Manning et al. 1993; Wilson et al. 1994). There is now evidence for PGE2 being released in the urine during the refractory period to EVH challenge that supports these earlier observations (Bood et al. 2015). However, two separate studies using mannitol or EVH found that the protective effect to a repeat challenge could be explained by possible tolerance at the site of the airway smooth muscle (Bood et al. 2015; Larsson et al. 2011).

17.3.1 The Regular Effect of Vigorous Exercise: The Potential Role of Airway Damage

Athletes engaged in swimming, mountain biking, rowing, biathlon, cross-country skiing, and skating events (i.e., either winter or summer sports with high ventilation rates) may develop respiratory symptoms compatible with EIB alone. These athletes also may or may not demonstrate a positive exercise, EVH, or mannitol challenge test result indicative of EIB or asthma (Sue-Chu et al. 2010). Changes in the contractile properties of the bronchial smooth muscle as a result of exposure to plasma-derived products from exudation may result from the repetitive epithelial injury repair cycle that arises in response to breathing high volumes of unconditioned air over long periods (Sue-Chu et al. 1999a; Anderson and Kippelen 2008; Karjalainen et al. 2000) (Fig. 1). In contrast to EIB, which results from airway smooth muscle constriction from the osmotic release of bronchoconstricting mediators from resident inflammatory cells (e.g., mast cells, eosinophils), this may be representative of an "airway injury" resulting in a form of "overuse syndrome." With winter athletes, it is common to see a low prevalence of BHR to indirect tests but high prevalence of BHR to direct challenge tests such as methacholine, which in this situation suggests the presence of airway damage (Sue-Chu et al. 2002, 2010; Stensrud et al. 2007). Treatment recommendations for suspected airway injury in an athlete may include the limitation of activity, rather than the introduction of the pharmacological agents used in the treatment of asthma and EIB (Bougault et al. 2010; Hull et al. 2009).

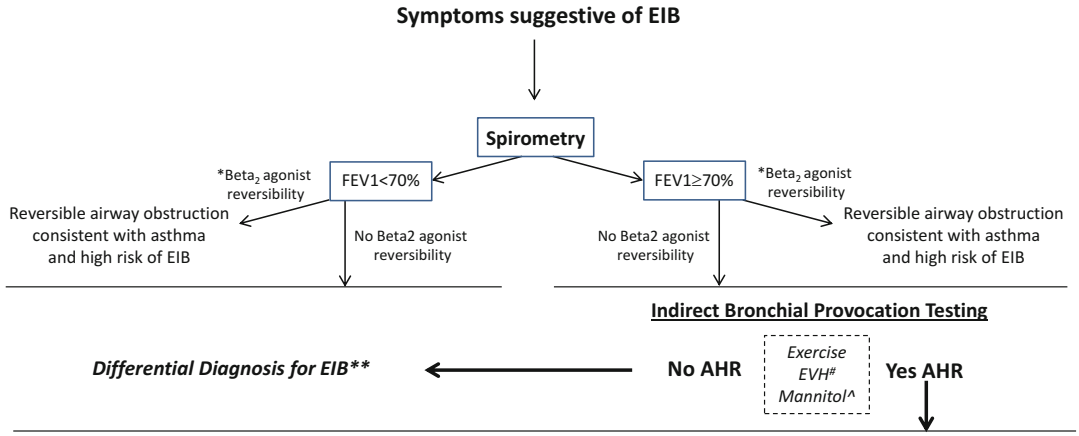
For summer athletes with allergic sensitization, the conditioning of large volumes of air may lead to airway inflammatory cell recruitment as well the consequences of plasma exudation leading to passive sensitization of the bronchial smooth muscle, possibly due to higher levels of seasonal airborne allergen (Anderson and Kippelen 2008). In contrast to the winter athlete, summer athletes generally demonstrate lower rates of BHR to direct tests (Holzer et al. 2002; Pedersen et al. 2008) and higher rates of BHR to indirect tests,

which has led to suggestions that elite level exercise in these environments may promote EIB in susceptible individuals (Kippelen and Anderson 2013).

17.4 Diagnosis of Exercised-Induced Bronchoconstriction

Wheeze, chest tightness, shortness of breath (dyspnea), and cough are the primary symptoms of EIB. Symptoms can also include chest pain in children as well as excessive mucous production. Some patients will report feeling unfit despite being in good physical condition (Parsons et al. 2007; Rundell et al. 2001; Weiler et al. 2007; Carlsen et al. 2000; Weinberger and Abu-Hasan 2009). A diagnosis of EIB based on symptoms is not reliable to predict a positive exercise challenge in either adults or children, because these symptoms also occur with other conditions (Rundell et al. 2001; De Baets et al. 2005; Anderson et al. 2010; van Leeuwen et al. 2013; Simpson et al. 2015). Given the lack of diagnostic sensitivity and specificity, symptom-based diagnosis alone should be avoided, and it is preferable that it be accompanied by data from an objective exercise or surrogate BPT such as EVH or mannitol (Parsons et al. 2007; Rundell et al. 2001; Weiler et al. 2007; Carlsen et al. 2000; Rundell and Slee 2008; Crapo et al. 2000; Cockcroft and Davis 2009) (Figs. 4 and 5).

There are two types of BPTs used to identify airway hyperresponsiveness based on mechanism of action: direct and indirect challenges. Direct challenges involve the exogenous administration of a single pharmacological agent as a provoking substance (such as methacholine), which acts directly via receptors on airway smooth muscle to cause contraction. For indirect challenges, the provoking agent causes the endogenous release of bronchoconstricting mediators that target specific receptors to cause the airway smooth muscle to contract. Indirect challenges include exercise or a surrogate, such as EVH, or an inhaled osmotic agent such as mannitol or hypertonic saline. It is now clear that a variety of mediators are released with indirect stimuli, such as leukotrienes, prostaglandins, and histamine (Anderson et al. 2018). BHR that is caused by the presence of airway inflammation is reflected more specifically in indirect challenges; thus indirect challenges are preferred as a way to confirm underlying asthma and potentially the need for regular inhaled corticosteroids (Parsons et al. 2007; Rundell et al. 2001; Weiler et al. 2007; Carlsen et al. 2000; Rundell and Slee 2008; Crapo et al. 2000; Cockcroft and Davis 2009). Indirect challenges additionally are recommended for monitoring asthma therapy because BHR is caused by airway inflammation (Parsons et al. 2007; Rundell et al. 2001; Carlsen et al. 2000; Rundell and Slee 2008; Crapo et al. 2000; Cockcroft and Davis 2009) which is diminished by ICS therapy (Weiler et al. 2007; Cockcroft and Davis 2009; Koh et al. 2007; Subbarao et al. 2006; Lipworth et al. 2012). In contrast, direct challenges are used as a screening test for chronic asthma, especially to rule out asthma. Direct challenges reflect the effect of only a single agonist or mediator and can have a low sensitivity and specificity to detect EIB, thus limiting their use (Weiler et al. 2007; Rundell and Slee 2008; Crapo et al. 2000; Cockcroft and Davis 2009; Anderson et al. 2009; Holley et al. 2012). An individual who has a positive direct BPT, current active symptoms of asthma, demonstrated airway reversibility with spirometry, and/or has other markers of airway inflammation (e.g., raised exhaled nitric oxide, sputum eosinophils) will likely have EIB. While there is an association with FeNO and percent fall in FEV_1 to exercise in atopic patients (Rouhos et al. 2005), FeNO should be used with caution to predict EIB when considering FeNO as a substitute for an indirect challenge. FeNO is a weak predictor of a positive EVH challenge in athletes (Voutilainen et al. 2013). Further, some ICS-naïve asthmatics with BHR to mannitol can have normal FeNO values (Porsbjerg et al. 2008). It is for this reason that guidelines recommend the use of physiological tests to assess BHR, in particular indirect tests to document both the presence and severity of EIB (Weiler et al. 2016).



Grade Severity of AHR

Laboratory Exercise		Eucapnic Voluntary Hyperpnea		Mannitol	
Fall in FEV1	*Classification*	*Fall in FEV1*	*Classification*	*PD15*	*Classification*
>50%	severe	>50%	severe	< 35mg	severe
25-50%	moderate	25-50%	moderate	35-155mg	moderate
>10-25%	mild	>10-25%	mild	155-635mg	mild
< 10%	no EIB	< 10%	no AHR If Ve >60%MVV	No PD_{15}	No AHR
				PD10 only may suggest mild EIB	

Legend:

FEV1 – Forced expiratory volume in 1 second, AHR – Airway hyperresponsiveness, EVH – Eucapnic Voluntary Hyperpnea , PD15 – the provoking dose of mannitol to cause a 15% fall in FEV1, PD10 – the provoking dose of mannitol to cause a 10% fall in FEV1. * Demonstrating reversibility in FEV1 of 12% and 200mL or greater., # FEV1≥75% for EVH challenge, ^Subject to availability in the USA, **Very mild AHR may cause variable responses to all tests and if EIB is still strongly suspect a repeat test may be warranted.

Fig. 4 An algorithm for the decision to perform an indirect bronchial provocation test in persons with symptoms suggestive of EIB, including the test options and test outcomes, which include the cutoff values for a positive test and the classification of the airway response to grade severity of AHR. (Adapted from (Weiler et al. 2016) and taken from (Brannan and Porsbjerg 2018)) (*FEV1* Forced expiratory volume in 1 s, *AHR* Airway hyperresponsiveness, *EVH* Eucapnic Voluntary Hyperpnea, *PD15* the provoking dose of mannitol to cause a 15% fall in FEV1, *PD10* the provoking dose of mannitol to cause a 10% fall in FEV1. * Demonstrating reversibility in FEV1 of 12% and 200 mL or greater, # FEV1 $\geq$ 75% for EVH challenge, ^Subject to availability in the USA, **Very mild AHR may cause variable responses to all tests and if EIB is still strongly suspect a repeat test may be warranted)

17.4.1 Exercise Challenge Testing

Exercise challenge testing should be conducted only by trained personnel and using standardized protocols, which also often require the presence of trained medical personnel. Exercise BPTs in a laboratory should be performed as described in the consensus statement published by the American Thoracic Society (ATS) and American Academy of Allergy, Asthma, and Immunology (AAAAI) (Parsons et al. 2013; Weiler et al. 2016; Crapo et al. 2000). For all BPTs, in order to avoid influencing the airway response, treatments that are effective at attenuating or inhibiting BHR should be withheld for an appropriate time prior to testing to ensure sufficient washout of the drug. Withholding times have been reviewed in recent guidelines (Weiler et al. 2016).

It is essential that adequate exercise laboratory challenges control minute ventilation and water content of inhaled air (Parsons et al. 2013; Weiler et al. 2007; Rundell and Slee 2008; Crapo et al. 2000). If this is not achieved, it will lead to a decreased sensitivity of the testing procedure. Exercise ramp-up should be rapid, within 2–3 min, to reach quickly a heart rate of 85% of

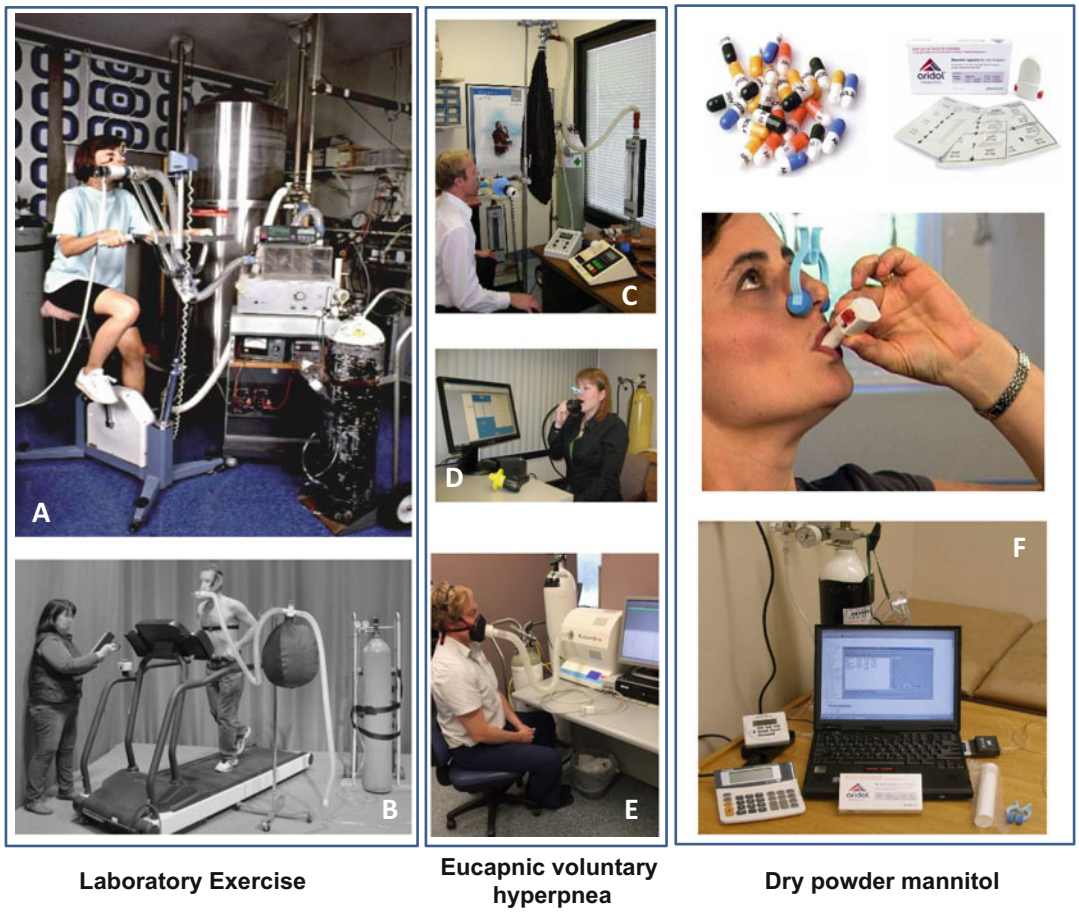


Fig. 5 An example of equipment required to perform laboratory exercise, eucapnic voluntary hyperpnea or inhaled mannitol challenge testing. Exercise challenge testing; (**a**) cycling exercise using a cycle ergometer; (**b**) running exercise using a treadmill, eucapnic voluntary hyperpnea; (**c**) noncommercial system using sourced equipment; (**d**) commercial device known as the hyperventilometer; (**e**) commercial device known as the EucapSys system; (**f**) mannitol challenge test kit and supporting equipment. (Adapted from (Brannan and Porsbjerg 2018))

maximum for adults and up to 95% for children. Exercise should continue at this rate for an additional 6 min, at 20–25 °C, while breathing dry (medical grade) air to provide a surrogate for at least 40% of maximum voluntary ventilation (MVV) (Parsons et al. 2013; Weiler et al. 2007; Rundell and Slee 2008; Crapo et al. 2000). However, the exercise ventilation ideally should be above 60% of predicted maximum (i.e., greater than 21 times FEV_1) (Parsons et al. 2013; Rundell and Slee 2008; Crapo et al. 2000). Medical air can be supplied to a balloon reservoir bag (e.g., Douglas bag) fitted with a two-way non-rebreathing valve before being attached to a mouthpiece or face mask. Alternatively it can be supplied directly from a compressed air tank with a demand valve that delivers air at high flow rates (Anderson et al. 2001; Weiler et al. 2005). The level of ventilation reached and sustained is key to providing a maximal stimulus, and thus the measurement of ventilation should be encouraged (Anderson and Kippelen 2013). Minute ventilation of expired air may be measured in real time by using a high flow spirometer or metabolic cart. Maximal heart rate (HR) may be used alternatively and is estimated using the formula

220 – age (in years). A more accurate equation to predict HRmax (208 – 0.7 × age) was recently recommended (Weiler et al. 2016). The exercise intensity may be required to be above a 90% HRmax for very well-conditioned individuals. Adolescent children may need to reach a higher target HRmax of 95% as one study in 9–17-year-olds demonstrated the fall in FEV_1 was 25.1% at 95% HRmax but 8.8% when only 85% HRmax was reached (Carlsen et al. 2000).

Spirometry should be obtained at baseline, before exercise challenge, and at predetermined times after exercise, usually at 5, 10, 15, 30, and occasionally 45–60 min after exercise. Spirometry should be performed seated. For reasons of safety, a measurement at 1 and/or 3 min post exercise may be warranted in persons who may be suspected of having large falls in FEV_1. To avoid causing the patient to become tired by the spirometry efforts and thus limiting the quality of subsequent measurements, FEV_1 measures are often performed by the patient without full forced vital capacity (FVC) maneuvers at the post-exercise time points. FEV_1 should be recorded beginning as soon as 3 min after completion of the exercise challenge to overcome the problem of posttest respiratory fatigue. To obtain a pre-exercise value, a full FVC maneuver is performed at baseline (Parsons et al. 2013; Weiler et al. 2007; Rundell and Slee 2008; Crapo et al. 2000). EIB may be diagnosed with a 10% or greater fall in FEV_1 from the pre-exercise value at any two consecutive time points within 30 min of ceasing exercise (Parsons et al. 2013; Weiler et al. 2007; Rundell and Slee 2008; Crapo et al. 2000; Anderson and Kippelen 2013). A fall at only one time point may be considered diagnostic of EIB if a greater fall in FEV_1 is required (such as an FEV_1 fall of 20% as in some pharmaceutical studies) (Anderson et al. 2001).

To determine whether the fall is sustained and not the product of a single measurement that may represent an artifact due to inadequate spirometry effort at one or more time points, the profile of the fall in FEV_1 following an exercise or EVH challenge should be carefully examined. In those with milder BHR, it is important to note that there may be variability in the airway response to exercise when more than one test is performed. Thus, in some cases where EIB is strongly suspected or when the patient is treated optimally and evidence of the abolition of EIB is required, repeat testing may need to be considered (Weiler et al. 2016; Anderson et al. 2010; Anderson and Kippelen 2013; Price et al. 2015).

All individuals who have EIB cannot be identified with any single test (Weiler et al. 2007). Individuals who are subsequently found to have other conditions may show falls in FEV_1 that are consistent with EIB (Weiler et al. 2007). For example, an upper airway dysfunction may be suggested by a flat or "truncated" inspiratory flow volume loop on the flow volume curve rather than EIB (Weiler et al. 2007). EIB may occur independently or coexist with exercise-induced laryngeal dysfunction. It may be important to document changes in FVC in some cases to identify if a fall in FEV_1 is due to upper airway dysfunction limiting the patient's inhalation to total lung capacity (TLC). Protocols to identify potential exercise-induced laryngeal dysfunction may need to be followed and this condition to be investigated separately (Weiler et al. 2016).

Exercise challenge by treadmill is easily standardized for office practice, though more commonly performed in a hospital laboratory. Alternative exercise challenges using cycle ergometry or rowing machine may be performed. Compared to the treadmill challenge, cycle exercise may provide a suboptimal exercise stimulus (Anderson and Kippelen 2013). Further, field and free running challenge tests are an option and have been used to screen larger numbers of patients. These protocols are more difficult to standardize and present difficulties in both documenting and guaranteeing an optimal exercise intensity and airway dehydration stimulus (Parsons et al. 2013; Weiler et al. 2007; van Leeuwen et al. 2013; Rundell and Slee 2008; Crapo et al. 2000).

In spite of sport governing bodies requiring specific cutoff values to diagnose EIB, there is no single absolute cutoff for a fall in FEV_1 or change in some other spirometry measure that clearly and unequivocally distinguishes between the presence of EIB and the absence of EIB (Weiler et al. 2007). The ATS criteria suggest the

post-exercise fall in FEV_1 required to make the diagnosis must be at least 10%, whereas other groups have suggested a fall of 13–15% is necessary to make the diagnosis (Parsons et al. 2013; Rundell and Slee 2008; Crapo et al. 2000). Other recommendations also include a fall in FEV_1 of 15% after a "field" challenge and a fall of 6–10% in the laboratory (Parsons et al. 2013; Weiler et al. 2007; Rundell and Slee 2008; Crapo et al. 2000).

17.4.2 Surrogate Tests for EIB

Organizations that regulate drug use by elite athletes or professional bodies needing to assess the presence of EIB by occupation are increasingly recommending the use of surrogate challenges for exercise such as EVH (ungraded challenge) or an inhaled hyperosmolar agent such as mannitol (graded challenge). While EVH is a challenge test that should be used for the investigation of EIB alone, inhaled mannitol may be useful in identifying both EIB and the presence of active asthma (Anderson 2010, 2016) (Fig. 6). Inhaled mannitol, commercially available as a disposable kit (Aridol™ or Osmohale™) (Aridol™ 2017), has undergone extensive phase 3 testing (Anderson et al. 2009; Brannan et al. 2005) establishing safety and has been recognized by regulatory authorities in Australia, the United States, European Union, Korea, and other regions. At the time of writing, Aridol™ will be reintroduced into the wider US market in late 2018.

17.4.3 Eucapnic Voluntary Hyperpnea

The EVH challenge was developed based on the understanding that the ventilation reached and sustained and the water content of the air inspired are the most important determinants of EIB (Anderson and Daviskas 2000). The EVH test was developed initially to evaluate military recruits for EIB (Argyros et al. 1996). The European Respiratory Society/European Academy of Allergy and Clinical Immunology Task Force (Carlsen et al. 2008a) recommend EVH to identify EIB in athletes, and EVH is included in the World Anti-Doping Agency assessment of asthma.

All safety precautions should be observed during an EVH test and should only be performed by highly trained specialists. For those with

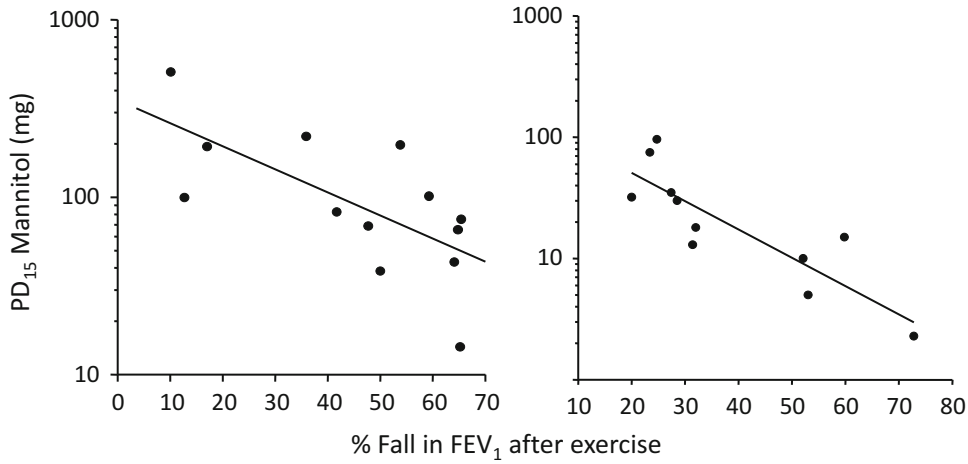


Fig. 6 In steroid-naïve asthmatics, the relationship demonstrating satisfactory agreement between the percent fall in FEV_1 after a cycle exercise challenge and the airway sensitivity to inhaled mannitol (PD_{15}) in two separate studies (Brannan et al., $n = 13$, rp 0.68, $p < 0.01$ and Munoz et al., $n = 11$ rp $= 0.86$, $p < 0.001$). These studies highlighted further the safety of mannitol challenge testing, only requiring a 15% fall in FEV_1 compared to significant falls in FEV_1 to exercise in some of these asthmatic subjects. (Reproduced with permission from (Brannan et al. 1998))

established asthma who are experiencing frequent symptoms and require beta2-agonists to alleviate those symptoms, the EVH test should be performed with caution knowing that the stimulus may cause significant bronchospasm in these susceptible patients. The EVH test should not be performed on patients in whom the FEV_1 is less than 75% of predicted (Parsons et al. 2013; Weiler et al. 2007, 2016; Rundell and Slee 2008; Crapo et al. 2000).

When performing the EVH test, the patient voluntarily hyperventilates a source of dry air containing approximately 5% carbon dioxide to maintain eucapnia, with the remainder of the gas mixture containing 21% oxygen and the balance nitrogen (Phillips et al. 1985). The characteristics of the airway response to EVH are very similar to exercise. The patient's maximum level of ventilation can be reached more rapidly with voluntary hyperventilation, reducing the required time for the EVH test in comparison to the exercise challenge.

An EVH challenge requires less space and equipment than an exercise challenge. Noncommercial or homemade systems similar to those that were first developed for EVH are still in use (Anderson and Kippelen 2013). The required apparatus can be easily sourced, and the initial setup is relatively inexpensive compared with exercise challenge equipment. Real-time measurement of ventilation is recommended, and a pre-prepared gas mixture is required which adds to the cost of the test. This system requires a large meteorological balloon as a gas reservoir, and the balloon is filled with at least 90 L of the dry air mixture containing 5% CO_2. The patient inhales the air via a two-way valve and is encouraged to hyperventilate sufficiently to keep the balloon at a constant volume, while the gas from the cylinder refills the balloon via a rotameter at the target ventilation. This system provides constant feedback to patient on their ventilation rate, while the investigator can encourage "deeper" or "faster" breathing if required. This mixture keeps end-tidal CO_2 levels within the normal or eucapnic range between 40 and 105 L/min in patients with FEV_1 values greater than 1.5 L (Phillips et al. 1985). If a subject, such as an elite athlete, has a level of ventilation value beyond this range, then a mixing device can be used to adjust and monitor the CO_2 concentration to maintain eucapnia. It is important that eucapnia (38–42 mmHg) is maintained during an EVH challenge as hypocapnia has long been known as a stimulus for bronchoconstriction (O'Cain et al. 1979). Commercial systems now exist that also require gas mixtures that use a demand valve directly attached to the source of gas, with incentive devices on computer screens to help the subject achieve the target ventilation. Another commercial system permits the breath-by-breath delivery of dry air with the addition of CO_2 (SMTEC 2014). These systems may be cheaper to run in the long term as separate sources of dry air and CO_2 are cheaper than a pre-prepared gas mixture.

While there are a number of different protocols for EVH, the most accepted standardized protocol uses a pre-prepared gas mixture inhaled at room temperature for 6 min (Parsons et al. 2013; Weiler et al. 2016). The target ventilation is 30 times the baseline FEV_1, and it has been demonstrated that the majority of patients are able to achieve this target. The minimum level for a valid test may be set as low as 17.5 times the FEV_1 for 6 min to be consistent with exercise ventilation. If the minimum ventilation is not reached, however, the test may be invalid and need repeating. Cooling the air can reduce the time of the challenge, but it is an expensive addition that is unnecessary for most assessments. At the end of the period of ventilation, FEV_1 is measured in duplicate immediately post-challenge and at 3, 5, 10, 15, and 20 min.

In susceptible patients, in particular those with known asthma, more severe falls in FEV_1 could be achieved with this 6-min protocol, and it is for this reason these patients are recommended to be excluded from performing EVH (Weiler et al. 2016). For known asthmatics a 4-min protocol at 21 times the FEV_1 has been used as well as a multistage protocol requiring 3-min periods of ventilation at 10.5, 21, and 31 times FEV_1 (Brannan et al. 1998). If using a multistage protocol in known asthmatic patients, measurements of FEV_1 are made following each EVH stage at 1, 3, 5, and 7 min. If there is no further fall at 7 min, the

subject proceeds to the next level of ventilation. Progressive protocols can induce refractoriness, which leads to an attenuated response at the next ventilation level in some patients. For this reason progressive protocols should not be used routinely. BHR may occur during ventilation, and any sudden falls in ventilation rate could be an indication of bronchoconstriction. In such cases the test may need to cease and FEV_1 be measured immediately, followed by the administration of rescue bronchodilator.

A fall in FEV_1 $\geq$10% from the pre-challenge value is defined as a positive test, and the severity of the fall in FEV_1 defines the severity of the BHR. It is recommended that the fall in FEV_1 should be sustained, with the subject having at least a 10% fall in FEV_1 recorded at two consecutive time points after the challenge (Parsons et al. 2013; Weiler et al. 2016). A fall of 15% has been suggested a more appropriate cutoff value to identify athletes and minimize potential false positives who have a single 10% in FEV_1 post exercise (Price et al. 2016).

EVH has been observed to identify more cases of EIB than laboratory exercise tests, and it is as sensitive as field exercise testing for athletes (Dickinson 2006; Mannix et al. 1999; Rundell et al. 2004b). This is likely due to the higher levels of ventilation that can be rapidly achieved and sustained using EVH compared with laboratory exercise on a bicycle or treadmill. Thus, persons with mild EIB with a negative response to an exercise protocol may have a positive response to the 6-min dry air EVH protocol. Assessments of the reproducibility of the airway response to EVH are limited to small populations of either athletes or nonathletes (Stadelmann et al. 2011; Price et al. 2015; Argyros et al. 1996; Williams et al. 2015). Variations around the diagnostic cutoff value of 10% with mild BHR occur, similar to the observed variations with exercise (Anderson et al. 2010), suggesting the possible need for two tests in borderline responses if EIB is still suspected (Weiler et al. 2016; Price et al. 2016). Those with moderate falls in FEV_1 to EVH appear to have adequate reproducible airway responses over 3 and 6 weeks (Argyros et al. 1996; Williams et al. 2015).

17.4.4 Inhaled Mannitol

The mannitol challenge test was developed in an attempt to make an indirect BPT more clinically accessible, so the test could move beyond the clinical laboratory to be performed safely in a clinical office setting (Anderson et al. 2018). Prior to development of mannitol, osmotic challenge testing was performed using aerosols of hypertonic saline generated by large volume ultrasonic nebulizers that were confined to clinical laboratories (Anderson and Brannan 2003). There were additional disadvantages with nebulization, such as variation in the delivered dose of aerosol, hygienic problems related to the patient expiration of the wet aerosols and exposure of technical staff, as well as the requirement to regularly clean and maintain equipment. Mannitol dry powder produced using spray drying in order to provide a uniform particle size was found to be stable and suitable for encapsulation (Anderson et al. 1997). The pre-prepared package of mannitol provides a common operating standard for BPTs with potential to compare results in different laboratories.

Following the establishment of reproducible baseline spirometry, the mannitol test requires the patient to inhale increasing doses of dry powder mannitol and has the FEV_1 measured in duplicate 60 s after each dose. The FEV_1 at each dose step should be within repeatable values within 5%. The test protocol consists of 0 mg (empty capsule), 5, 10, 20, 40, 80 mg (2 $\times$ 40 mg capsules), and three doses of 160 mg (4 $\times$ 40 mg capsules) of mannitol. The maximum cumulative dose of mannitol that is administered is 635 mg (Brannan et al. 2005).

A positive test result is defined as either a fall in FEV_1 of 15% from baseline (i.e., post 0-mg capsule) or a 10% fall in FEV_1 from baseline between two consecutive doses (Brannan et al. 2005). If a patient presenting with symptoms suggestive of EIB has a fall of greater than 10% but less than 15% following the maximum cumulative dose of 635 mg (i.e., only documenting a PD_{10}), then mild EIB could be considered (Holzer et al. 2003) (Fig. 7).

The mannitol test needs to be performed in a timely manner so that the osmotic gradient is

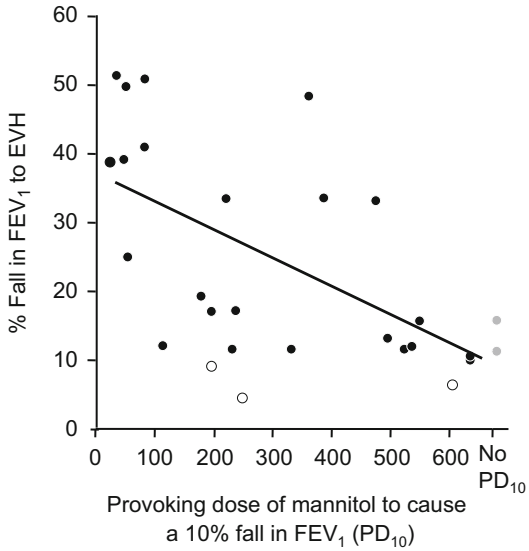


Fig. 7 In elite athletes, the relationship of the airway response to eucapnic voluntary hyperpnea (EVH) expressed as a percent fall in FEV_1 and the airway response to mannitol expressed as the cumulative dose to cause a 10% fall in FEV_1 (PD_{10}). The majority who responded to both tests (black dots) with those positive to EVH alone (gray dots) and those responsive to mannitol alone (white dots). In 24 subjects who had airway responses to both tests, there was a good relationship between percent fall in FEV_1 to EVH and the PD_{10} to mannitol ($r_p = 0.61$, $r_s = 0.70$, $p < 0.01$). (Reproduced with permission from (Holzer et al. 2003))

increased with each dose. The repeatability of the PD_{15} to mannitol is one doubling dose using a low-resistance dry powder inhaler (Anderson et al. 1997; Brannan et al. 2001). The time to complete a positive test as observed in a large phase 3 trial was 17 min (±7 min) for a positive test and 26 min (±6 min) for a negative test (Anderson et al. 2009).

It was also found that a test taking more than 35 min may lead to a false-negative result. Excessive cough may be a reason for delaying the duration of the challenge test; however, it has been demonstrated excessive cough to mannitol may indicate cough hypersensitivity syndrome (Koskela et al. 2018).

Inhaled mannitol has demonstrated adequate safety both in established phase 3 trials and in the field in epidemiology studies (Anderson et al. 2009; Brannan et al. 2005; de Menezes et al. 2018). Airway responses are reversed rapidly with a standard dose of bronchodilator (Brannan et al. 2005; Anderson et al. 1997). Not unlike that observed with other BPTs, prolonged recovery to a standard dose of bronchodilator can be observed in patients who use beta2-agonists regularly, which may be indicative of tolerance to beta2-agonist use (Haney and Hancox 2006). It is also becoming clearer that BHR to mannitol may be more sensitive than a laboratory exercise challenge. Mannitol has also been shown to identify BHR 1.4 times more than a 10% fall in FEV_1 to laboratory running exercise and 1.65 times more if a 15% fall to exercise is considered as an abnormal response in persons with newly diagnosed asthma (Anderson et al. 2009). Mannitol is also more sensitive at identifying BHR compared to a laboratory cycle exercise in known asthmatic individuals (Seccombe et al. 2018).

17.5 Therapy for Exercised-Induced Bronchoconstriction

EIB in those with asthma, even in the presence of minimal daily symptoms, may represent inadequacy of control of asthma (National Asthma Education and Prevention Program 2007; Global Initiative for Asthma 2007b). The goal of therapy for EIB in a person with asthma is to prevent symptoms induced by exercise while enhancing overall control of asthma. Pharmacotherapeutic agents that are useful in controlling chronic asthma usually have bronchoprotective activity for EIB as well. If asthma is otherwise well controlled, bronchoprotective therapy for EIB is administered only as needed, or in cases of optimal anti-inflammatory, bronchoprotective therapy for EIB may not be required. Considering this it should be noted that exercise symptoms may be one of the last manifestations of asthma that will resolve with routine longer-term treatment strategies.

Therapy for EIB may be delivered by inhalation or by oral administration minutes to hours before exercise, respectively. However, in general, acute treatments via the inhaled route provide

more rapid bronchoprotective effects. When used alone or in combination with pharmacotherapy, nonpharmacological therapies can also be helpful in preventing EIB. Pharmacological agents act to prevent or attenuate EIB often by different mechanisms and different degrees of protection among different individuals. No therapies when given acutely can be guaranteed to completely eliminate EIB. However, the attenuation of EIB minimizes bronchospasm during exercise and reduces the severity of the response following exercise (Rossing et al. 1982; Latimer et al. 1983).

Changes in airway responsiveness over time, environmental conditions, intensity of the exercise stimulus, and the frequency of use of existing asthma therapies may lead to the variability of effectiveness of treatments within an individual (Guidance for Industry 2002). The variability observed with different treatments may also result from differences in baseline airway responsiveness and susceptibility of tolerance to a specific treatment (Anderson et al. 2006). The most common and standardized primary end point for assessing the efficacy of a drug in the treatment of EIB either in a clinical trial or in clinical practice is the maximum percentage fall in FEV_1 (Guidance for Industry 2002). In addition to this maximum absolute fall in FEV_1, expressed as a percentage of baseline, the results may indicate a change in the percent fall in FEV_1 before and after either acute or long-term therapy. The percent protection for a drug on EIB can be determined permitting a comparison of efficacy between treatments (Kemp et al. 1998).

17.5.1 Pharmacological Therapy

The most effective therapeutic class for acute prevention of intermittent EIB are beta2-adrenergic receptor agonists (Spooner et al. 2003). For most patients they provide the best protection against EIB (Anderson et al. 1991, 2001; Spooner et al. 2003; Hendrickson et al. 1994; Ferrari et al. 2000, 2002; Bisgaard 2000). Alternatively, when administered following bronchoconstriction to exercise, they enhance recovery of FEV_1 to baseline values (Anderson et al. 1979; Godfrey and Konig 1975b). When inhaled between 5 and 20 min before exercise, SABA drugs which were initially developed for asthma were highly effective in protecting against EIB, as shown in early investigations (Anderson et al. 1976; Hendrickson et al. 1994; Godfrey and Konig 1976; McFadden and Gilbert 1994). This protection, however, does not occur when beta2-agonists are given in an oral formulation suggesting they must be administered topically to the airway surface (Anderson et al. 1976). The bronchoprotective effect lasts 2–4 h after inhalation, and there are no significant differences among the different SABAs currently in use, such as albuterol and terbutaline (Anderson et al. 1991; Woolley et al. 1990). The cromolyn drugs that are mast cell stabilizers have been used as add-on therapy to enhance SABAs in increasing bronchoprotection; however, it is important to recognize that part of the superior action of beta2-agonists is to also stabilize mast cells (Spooner et al. 2003; Tan and Spector 2002).

There are now a number of long-acting beta2-agonists (LABAs) in use. Many of the new LABAs (but none of the ultra-LABAs) have currently been formally assessed for their efficacy to inhibit EIB. LABAs differ in their actions, mainly in their onsets of effect. Salmeterol requires up to 30 min for its optimal action to take effect. In contrast, formoterol has a rapid onset of bronchodilator and bronchoprotective action similar to SABAs (Ferrari et al. 2000, 2002). In beta2-agonist-naïve patients, prolonged (up to 12 h) duration of bronchoprotective effect has been shown for these drugs after the first dose (Anderson et al. 1991; Bisgaard 2000; Kemp et al. 1994; Nelson et al. 1998; Carlsen et al. 1995; Newnham et al. 1993). Many patients are not protected for this entire dosing interval. The optimal dosing interval for EIB bronchoprotection may be closer to 6 h on average (Anderson et al. 1991; Kemp et al. 1994; Nelson et al. 1998; Newnham et al. 1993).

LABAs provide prolonged, sustained protection with intermittent use (Kemp et al. 1994; Newnham et al. 1993; Boner et al. 1994; Vilsvik et al. 2001; Bronsky et al. 2002), but daily maintenance use of LABAs (and SABAs) can result in "tolerance," i.e., some loss of bronchoprotection,

with cross-tolerance to other beta2-agonists (Nelson et al. 1998; Ramage et al. 1994; Simons et al. 1997; Haney and Hancox 2005; Villaran et al. 1999; Edelman et al. 2000; Hancox et al. 2002; Inman and O'Byrne 1996). Moreover, the severity of EIB may actually increase with daily use of LABAs and SABAs (Hancox et al. 2002; Inman and O'Byrne 1996). It is well established that regular beta2-agonists can increase BHR to both direct and indirect stimuli, suggesting regular beta2 stimulation can increase airway smooth muscle sensitivity (Haney and Hancox 2006). Further, the degree of tolerance may increase with increasing bronchoconstriction which could potentially put patients with severe asthma attacks at risk of experiencing even less bronchodilator responsiveness (Wraight et al. 2003). Therefore, adrenergic agonists are recommended for only intermittent use for bronchoprotection (Parsons et al. 2013; Weiler et al. 2007). Tolerance occurs in most patients who demonstrate EIB (Haney and Hancox 2005; Hancox et al. 2002; Inman and O'Byrne 1996; Wraight et al. 2003; Hancox et al. 1999, 2000; Haney and Hancox 2007); however, some individuals may have a greater propensity than others to develop tolerance. To assess if there was a genetic basis to beta2-agonist tolerance, patients with and without the Arg16Gly beta2-receptor polymorphism, which previously suggested a susceptibility to beta2-agonist tolerance, demonstrated that these polymorphisms do not influence tolerance to loss of bronchoprotection to beta2-agonists with EIB (Bonini et al. 2013). Notably, tolerance occurs even when patients are also receiving ICS suggesting attenuating airway inflammation is independent of the mechanism of beta2-receptor tolerance (Weiler et al. 2005; Simons et al. 1997).

Tolerance is demonstrated most noticeably by a decrease in protective effect of both SABA (Storms et al. 2004) and LABA (Weiler et al. 2005; Bisgaard 2000; Nelson et al. 1998; Boner et al. 1994; Simons et al. 1997) (Fig. 8). This tolerance has been demonstrated in one study to occur in less than 3 h (Garcia et al. 2001). In addition, tolerance manifests by prolongation of recovery from bronchoconstriction with a standard dose of rescue beta2-agonist (Haney and Hancox 2005; Hancox et al. 2002). It is possible that the presence of tolerance is often missed in a clinical setting because a patient rarely is evaluated for responsiveness to bronchodilator following bronchospasm. Thus, the shorter duration of bronchoprotection and prolonged recovery time can go unreported without objective measurement. Prescribing additional doses of SABA before exercise in an asthmatic patient taking intermittent to regular beta2-agonists for daily symptom control may unintentionally contribute to potential worsening of beta2-agonist tolerance.

The mechanisms by which regular long-term beta2-agonist use causes tolerance to acute use of beta2-agonist are not completely understood, but beta2-agonists can increase smooth muscle sensitivity (Haney and Hancox 2006; Anderson et al. 2006). Another possible explanation is that the long-term exposure of beta-receptors to beta2-agonists results in uncoupling and internalization or sequestration in the cells (Johnson 2006). "Downregulation" of receptors and decreasing responsiveness to beta2-agonists result from the net loss in the number of available functional beta2-receptors (Hayes et al. 1996) which manifests as an absence of optimal clinical protection to bronchoconstrictive stimuli. Thus, resynthesis of the receptor to the active state is required for restoration of sensitivity. Within 72 h of cessation of exposure to beta2-agonist, the restoration of sensitivity is observed clinically (Haney and Hancox 2005; Davis et al. 2003b).

Mediator release from mast cells is inhibited using beta2-agonists by stimulation by beta-receptors on the cell surface. The process of beta2-receptor desensitization varies between bronchial mast cells, which appear to be more readily desensitized when compared to bronchial smooth muscle cells, which have larger numbers of beta2-receptors (Johnson 2006; McGraw and Liggett 1997; Chong et al. 2003; Scola et al. 2004). The clinical effects of downregulation on mast cells are related more to bronchoprotection, than to smooth muscle and bronchodilation (O'Connor et al. 1992). It is also possible the downregulation of mast cell beta2-receptors could have a dual effect, boosting mediator release and increasing bronchoconstriction

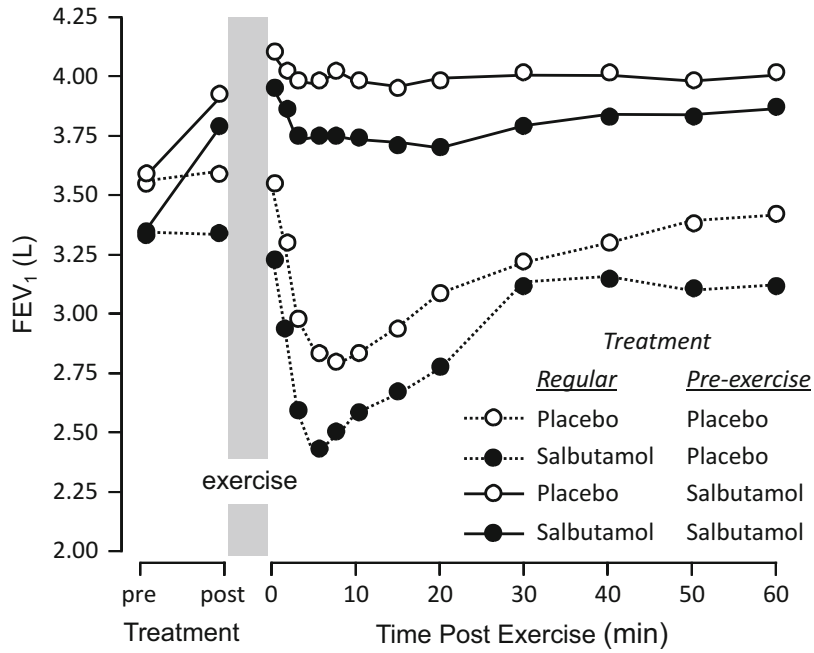


Fig. 8 Mean forced expiratory volume in 1 s (FEV_1) before and following a pre-exercise dose of 200 mcg of salbutamol or placebo followed by 5 min of constant workload exercise on a cycle ergometer in asthmatics with EIB. Exercise tests followed 7 days of regular treatment of 800 mcg per day of salbutamol and placebo. One week of regular treatment with salbutamol resulted in a decrease in baseline FEV_1, more marked EIB, and decreased protective effect of salbutamol on EIB. (Reproduced with permission from (Inman and O'Byrne 1996))

(Hancox et al. 2002; Chong et al. 2003; Scola et al. 2004; Swystun et al. 2000; Peachell 2006).

Beta2-receptor downregulation, or tolerance, is exhibited clinically as a decrease in duration of beta2-agonist bronchoprotection to stimuli such as exercise, which depends on mast cell mediator release for bronchoconstriction (Anderson et al. 2006). Tolerance to bronchodilation following EIB is shown by protraction of the time of recovery from bronchoconstriction in response to usual doses of beta2-agonists (Haney and Hancox 2005; Hancox et al. 2002; Inman and O'Byrne 1996).

Daily monotherapy use of LABAs to provide overall asthma control is not recommended (National Asthma Education and Prevention Program 2007). LABAs are often combined with ICS to provide effective maintenance therapy when ICS alone are not satisfactory in controlling chronic asthma; however, there is no persuasive clinical evidence that this combination reduces tolerance to the bronchoprotective effect of LABAs in asthma or EIB with asthma (Weiler et al. 2005; Simons et al. 1997; Kalra et al. 1996). LABAs alone, used intermittently up to three times a week, do not appear to be connected with tolerance (Davis et al. 2003b; FDA drug safety communication 2010).

Although their role appears to vary significantly among patients, leukotrienes in EIB sustain the bronchoconstrictive and inflammatory response. Inhibitors of the leukotriene pathway (leukotriene receptor antagonists or LTRAs and lipoxygenase inhibitors) are not only effective in enhancing recovery of airway narrowing but also reducing the severity of the fall in FEV_1. However, a limitation may be the variability in the effectiveness of LTRAs, from completely blocking EIB in some asthmatic individuals to little or no bronchoprotection at all in some individuals. However, most patients do not experience comprehensive protection (Raissy et al. 2008). Approximately 50% of patients can respond to these treatments, with a 30–80% protection of EIB (Kemp et al. 1998; Stelmach et al. 2008; Vidal et al. 2001). These percentages may differ, contingent in part on the FEV_1 fall required to make a diagnosis of EIB (>10%, >15%, or > 20%). Given that other mediators (e.g., PGD_2, histamine) (Hallstrand et al. 2005b; Finnerty and Holgate 1990) are involved in EIB, this incomplete protection is perhaps not surprising.

Several LTRAs have been found to be effective in reducing EIB (Leff et al. 1998; O'Byrne 2000;

Pearlman et al. 1999; Manning et al. 1990; Finnerty et al. 1992) (Fig. 9). Most studies have examined the $CystLT_1$ receptor antagonist, particularly montelukast, and zafirlukast and pranlukast can be used as well. Montelukast is approved by the FDA and many other health-care regulatory authorities worldwide for treatment of EIB in children, adolescents, and adults. As it is an oral formulation, its onset of action is not as fast as an inhaled treatment that can acutely protect against EIB. Montelukast has an onset of action within 1–2 h of oral administration (Pearlman et al. 2006; Finnerty et al. 1992; Philip et al. 2007a; Wasfi et al. 2011) but provides a duration of bronchoprotection for at least 24 h (Leff et al. 1998; Pearlman et al. 2006; Kemp et al. 1998; Wasfi et al. 2011; Philip et al. 2007b; Bronsky et al. 1997). It should be noted that maximum protection may not be maintained in some patients (Peroni et al. 2002a). LTRAs also speed the time to recovery to baseline lung function following EIB (Leff et al. 1998; Storms et al. 2004). While LTRAs do not have the same effectiveness overall in attenuating EIB as rapidly as beta2-agonists (Raissy et al. 2008), tolerance has not been observed with $CystLT_1$ antagonists with long-term use (Leff et al. 1998; Villaran et al. 1999; Edelman et al. 2000; de Benedictis et al. 2006). Populations of responders and nonresponders of leukotriene antagonists to EIB have been observed similar to that observed for these drugs on asthma control to daily symptoms (Drazen et al. 2000; Kang et al. 2008; Kim et al. 2008).

Lipoxygenase inhibitors, a second group of agents that affect the leukotriene pathway by inhibiting synthesis, are less widely used in the treatment of EIB and are not currently recommended for this indication. While lipoxygenase inhibitors have been shown to attenuate EIB when given orally (Meltzer et al. 1996; Coreno et al. 2000; Lehnigk et al. 1998; van Schoor et al. 1997), the duration of inhibition of these compounds is relatively short (Meltzer et al. 1996; Coreno et al. 2000). Early stage development studies suggest a 5-lipoxygenase activating protein (FLAP) inhibitor that can target different stages of the leukotriene synthesis pathway and can inhibit EIB (Kent et al. 2014).

Mast cell stabilizers such as cromolyn sodium and nedocromil sodium (not currently available as an MDI or DPI in the United States), two structurally unrelated compounds, have no bronchodilator action but have similar bronchoprotective action against EIB when inhaled (Spooner et al.

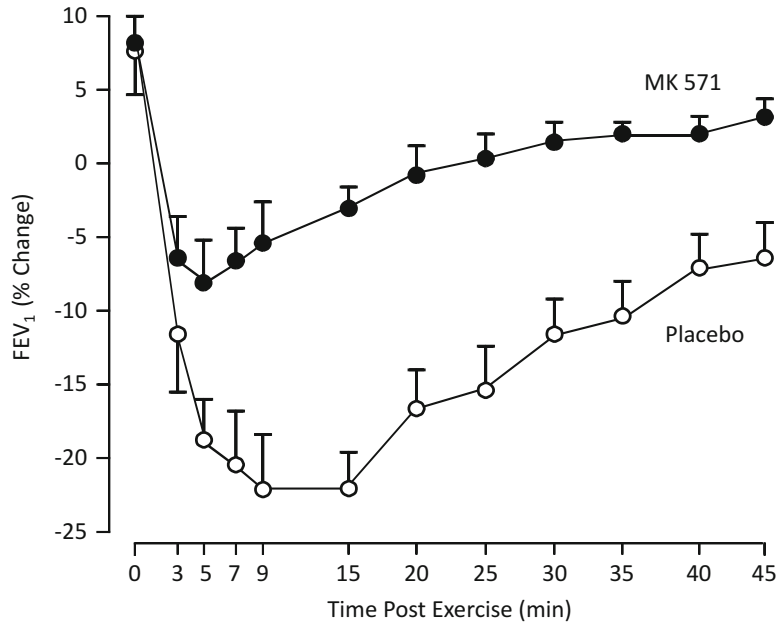


Fig. 9 The first evidence to demonstrate in asthmatics that the leukotriene receptor antagonist MK-571 (eventually known as montelukast) administered intravenously inhibits EIB by attenuating the reduction in forced expiratory volume in 1 s (FEV_1) following exercise and causing rapid recovery to pre-exercise FEV_1 values. (Reproduced with permission from (Manning et al. 1990))

2003; Kelly et al. 2001). A number of mechanisms have been suggested for these agents, including inhibition of mast cell mediator release of PGD_2 (Kippelen et al. 2010a; Brannan et al. 2006). The bronchoprotective effect is of short duration (1–2 h) (Woolley et al. 1990; Comis et al. 1993), but bronchoprotection is immediate, suggesting activity occurs on or close to the airway epithelium (Silverman and Andrea 1972). Further, these agents may be effective and may increase overall inhibition of EIB when combined with other drugs used to diminish EIB (Spooner et al. 2003; McFadden and Gilbert 1994; Comis et al. 1993; de Benedictis et al. 1998). Similar to other treatments for EIB, there is significant intersubject and between-study variability on bronchoprotection (Tullett et al. 1985; Patel and Wall 1986). The effectiveness of cromolyn appears to be dose related; however, while these drugs have few side effects, they may have been administered in insufficient doses (Patel and Wall 1986; Schoeffel et al. 1983; Patel et al. 1986). There is no evidence of tolerance with the cromolyn drugs. Due to observed safety profiles and rapid onset of action, these agents have been regularly used to attenuate EIB (Spooner et al. 2003; Kuzemko 1989).

In asthmatic patients EIB is best controlled by maintenance anti-inflammatory treatment using ICS (Subbarao et al. 2006; Hofstra et al. 2000; Jonasson et al. 2000) or in combination with other short-term preventive treatment (National Asthma Education and Prevention Program 2007; Stelmach et al. 2008; National Institutes of Health NH, Lung and Blood Institute 2007). ICS are the mainstay therapy for the improvement in asthma control in the majority of patients with persistent asthma symptoms; however, it is also effective at attenuating BHR to both direct and indirect stimuli, including exercise (Anderson and Holzer 2000; Brannan 2010). Adherence to ICS should be encouraged for the treatment of EIB, as it should be encouraged for the routine management of asthma. The dose-dependent effect of ICS has been noted shortly following the initial 3–4 weeks of treatment (Subbarao et al. 2006; Pedersen and Hansen 1995). The effects of ICS are time dependent, however, with longer treatment periods (12 weeks) showing no difference between different doses of ICS inhibiting EIB (Jonasson et al. 2000). There is no relationship between control of persistent asthma and severity of EIB (Madhuban et al. 2011). Nevertheless, the presence of EIB in the presence of regular ICS can be considered a reflection of the lack of pathophysiological control of asthma, even in the presence of good clinical control. In this case, if moderate to severe EIB is present with minimal symptoms suggestive of adequate asthma control, this should suggest a need to maintain therapy.

The mechanism of regular ICS may be different when administered acutely. Bronchoprotection against EIB with acute high-dose ICS has been documented as early as 4 h after the first dose in adults (Kippelen et al. 2010c; Thio et al. 2001; Driessen et al. 2011). In children, however, it has been demonstrated that lower doses consistent with the daily treatment of asthma can have a more immediate bronchoprotective effect on EIB (Visser et al. 2014). The mechanisms are unclear but possibly similar to other inhaled treatments by impacting epithelial function. After 1 week of ICS treatment, efficacy appears to plateau in studies of short treatment duration (Duong et al. 2008; Subbarao et al. 2006; Pedersen and Hansen 1995). However, bronchoprotection may increase further over weeks or even months until it reaches its final plateau, which may exist in the form of complete bronchoprotection (Koh et al. 2007; Hofstra et al. 2000; Henriksen and Wenzel 1984; Henriksen 1985) (Fig. 10). Bronchoprotection with regular ICS has been demonstrated to occur in 30–60% of asthmatic patients with EIB, with marked individual variability that can range from complete inhibition of EIB to minimal protection (Koh et al. 2007). It has yet to be determined if an individual who does not benefit from attenuated EIB with regular ICS is corticosteroid insensitive or poorly adherent to treatment. Without studies understanding the duration of effect of ICS on EIB and accounting for adherence to ICS, it will remain unclear whether this variability reflects distinct subpopulations of ICS responders and nonresponders (e.g., a reflection of genetic differences) or if this is a feature of the severity of EIB.

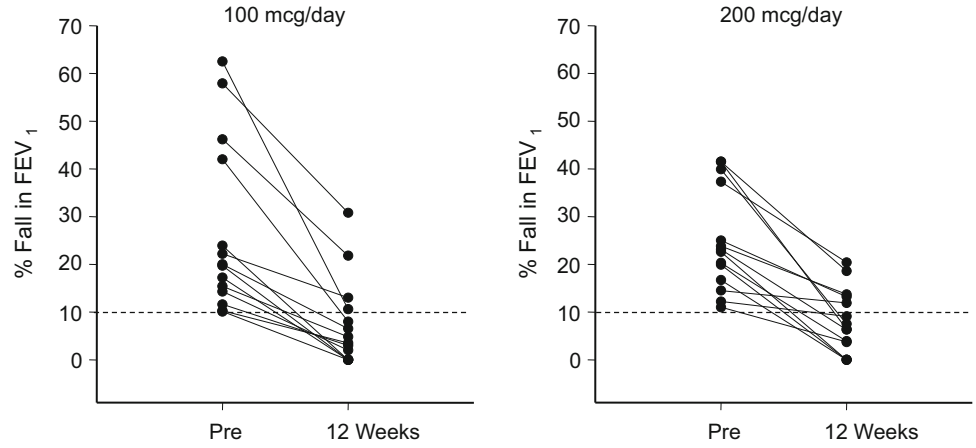


Fig. 10 Individual data of the effect of 12 weeks of treatment with low doses of inhaled corticosteroid (ICS) budesonide (100 mcg or 200 mcg, once daily) on the percentage fall in FEV_1 in children with asthma who have EIB. The majority of children were observed to have a negative exercise challenge test (<10% fall in FEV_1) with 71% (10 of 14) and 64% (9 of 14) following 100 mcg or 200 mcg, respectively. The data demonstrates that it is possible to treat with regular ICS over a longer time period and see resolution in airway sensitivity to an exercise challenge, independent of dose of ICS. (Reproduced with permission from (Jonasson et al. 1998))

Allergic rhinitis can be common in atopic asthmatic patients, and some evidence suggests that effective treatment of nasal congestion and obstruction by nasal ICS is related to at least mild protection of EIB (Henriksen and Wenzel 1984; Kersten et al. 2012; Shturman-Ellstein et al. 1978). These findings appear to validate the "unified airway" theory that considers allergic rhinitis and atopic airway inflammation in asthma are demonstrations of similar pathologic processes throughout the respiratory tract (Brozek et al. 2010). This suggests that treating EIB with both intranasal corticosteroids and ICS could lead to more effective attenuation of EIB in allergic asthmatics compared to ICS alone, however, as yet there is no evidence to support this conclusion.

As daily treatment with ICS may not completely inhibit EIB, this does not remove the need for acute bronchoprotection for EIB to aid for more complete protection. Beta2-agonists can be added when the need is required for additional short-term protection of EIB (Anderson et al. 1979; Godfrey and Konig 1975b). As an alternative, and considering beta2-agonist tolerance could be an issue, when maintenance ICS are not effective enough, LTRAs can be used to obtain added protection with low- and medium-dose ICS (Stelmach et al. 2008; Duong et al. 2012) while also using beta2-agonists for acute bronchoprotection if necessary (Fitch et al. 2008; Global Initiative for Asthma 2007b; Grzelewski and Stelmach 2009; Carlsen et al. 2008b).

The evidence shows little improvement by ICS of tolerance to beta2-agonist bronchoprotection, and a shortened duration of bronchoprotection remains when ICS and LABAs are given together (Weiler et al. 2005; Simons et al. 1997; Storms et al. 2004; Kalra et al. 1996; Yates et al. 1996). Nonetheless, one study that evaluated the combination of an ICS and LABA (fluticasone and salmeterol) for four weeks of maintenance therapy in adult patients showed better bronchoprotection at 1 and 8.5 h after dosing compared with the same dose of monotherapy fluticasone (Weiler et al. 2005). In that study, most patients taking the combined therapy also exhibited greater complete protection (<10% fall of FEV_1) and better overall asthma control. A similar study with the same agents in children and adolescents also demonstrated a small persistent effect of bronchoprotection when the combination was used compared with the monotherapy ICS (Pearlman et al. 2009). EIB is reduced by a similar magnitude over 6 weeks when comparing LABAs

in combination with ICS versus a low dose of ICS daily (Lazarinis et al. 2014).

Anticholinergic agents act to cause bronchodilation by blocking vagally mediated tone and have been used alone and in combination with SABAs with some success in treating acute exacerbations of asthma (Knopfli et al. 2005; Blake 2006). In double-blind trials, especially with placebo controls, the ability of anticholinergic agents to prevent EIB has not been consistent (Boulet et al. 1989). Not all patients seem to respond to anticholinergic agents (Spooner et al. 2003; de Benedictis et al. 1998; Poppius et al. 1986; Magnussen et al. 1992), and responsiveness may be variable within the same patient (Boner et al. 1989). There is no evidence to suggest these drugs would be useful in combination, and there is no study to date assessing any of the longer acting anticholinergics in EIB.

The methylxanthines theophylline and aminophylline have been used for long-term maintenance therapy in the treatment of asthma, and these agents have been used as adjunct therapy to ICS when an additional agent is required to improve asthma control (Global Initiative for Asthma 2007b; National Institutes of Health NH, Lung and Blood Institute 2007). The methylxanthines are nonselective phosphodiesterase inhibitors of the cyclic AMP and cyclic guanine monophosphate pathways active in the pathophysiology of asthma. Methylxanthines have been shown to modify EIB in only a subset of patients with EIB (Ellis 1984; Iikura et al. 1996; Seale et al. 1977). Selective phosphodiesterase inhibitors have a better safety profile than methylxanthines with one study using the phosphodiesterase 4 inhibitor, roflumilast, showing attenuation of EIB (Timmer et al. 2002).

The methylxanthine drug class also includes caffeine. Ingestion of caffeine can attenuate EIB in a dose response manner, with evidence of high doses of caffeine (6–10 mg/kg) inhibiting EIB (Duffy and Phillips 1991; Kivity et al. 1990; VanHaitsma et al. 2010). The recommendation to abstain from caffeine prior to performing BPTs to identify EIB is based on these studies (Weiler et al. 2016).

Antihistamines or H_1 antagonists can provide incomplete attenuation of EIB (Patel 1984; Baki and Orhan 2002; Finnerty and Holgate 1990; Clee et al. 1984; Magnussen et al. 1988; Wiebicke et al. 1988; Zielinski and Chodosowska 1977), but results have been inconsistent (Dahlén et al. 2002; Peroni et al. 2002b). This variability may relate to variances in the intensity and duration of the exercise stimulus, the severity of the EIB in the population studied, or the specific dose of the antihistamine. The antihistamine class is pharmacodynamically diverse as well. Greater intensity or more severe EIB may be required for participation of histamine in the pathogenesis of EIB (Anderson and Brannan 2002). Histamine is also less potent than the other two main mediators (leukotrienes and prostaglandins) that contribute to EIB (O'Byrne 1997). Antihistamines may have other actions such as an ability to inhibit mediator activation and release (Passalacqua et al. 2002). Dissimilar routes of administration and dosages of antihistamines may also be confounding factors in previous studies (Ghosh et al. 1991). The evidence to date suggests the effectiveness of oral antihistamines should not be considered a treatment to aid in the effective inhibition of EIB. Considering this, it will likely remain as a treatment option in allergic rhinitis in the hope that there will be some additional benefits in those with comorbid asthma and EIB.

Additional considerations to the management of EIB in elite athletes should include moderating relevant environmental exposures as much as possible (such as methods to reduce home or occupational allergen exposures, minimizing air pollution exposure), treating comorbid conditions that may have additional impacts on dyspnea, and patient education (Fitch et al. 2008; Boulet and O'Byrne 2015). The athlete and the specialist may need to consider an exercise prescription that has additional considerations such as the athlete's routine and exercise environment in order to provide adequate control of EIB (e.g., swimmers, ice hockey players).

It should be noted that similar to observations in asthmatic patients with EIB, the few studies in athletes with EIB alone have shown the same results for the acute protective effect of a beta2-

agonist, the mast cell stabilizer cromoglycate, the LTRA montelukast, and the inhibitory effect of high-dose ICS when given acutely (Kippelen et al. 2010a, c; Simpson et al. 2013; Rundell et al. 2005). These findings reinforce the concept that similar pathophysiological mechanisms occur in EIB with or without the daily symptoms of asthma.

17.5.2 Nonpharmacological Therapy and Dietary Modification

For some athletes, continuous warm-up before exercise has been shown to cause significant decrease in post-exercise bronchoconstriction (Stickland et al. 2012). The precise mechanisms for an about 50% reduction in airway responsiveness in 50% of persons with EIB with repeated exercise following an initial exercise stimulus are not well understood. Pre-exercise warm-up is not a useful treatment option in all patients, and there are currently no predictors of the response other than to objectively measure attenuated EIB after repeated exercise separated by 60–90 min. Pre-exercise warm-up at 60–80% maximum heart rate can be performed to provide partial attenuation of EIB for up to 4 h (Edmunds et al. 1978; Schoeffel et al. 1980; Anderson and Schoeffel 1982). Due to the incomplete protection, pre-exercise warm-up does not prevent the need for pharmacotherapy. Combination of pharmacotherapy and warm-up should be considered as it has been shown that SABA plus a warm-up gives better protection than the warm-up or SABA alone (Mickleborough et al. 2007; McKenzie et al. 1994).

Dietary modification as a treatment for EIB has generally been used as evidence of significant yet partial inhibition of the percent fall in FEV_1 following exercise with low-salt diets, omega-3 fatty acids, and ascorbic acid (vitamin C) with up to 3 weeks of modification (Mickleborough et al. 2001, 2003, 2005, 2006; Tecklenburg et al. 2007). If dietary supplementations are to be prescribed, they should not be seen as a substitute for established pharmacotherapies but should be used in association with maintenance therapy in the asthmatic athlete.

17.6 Conclusion

Asthma in athletes can have significant implications for exercise performance by causing EIB. For optimal treatment of EIB, it is important to have the presence and severity of EIB characterized using a standardized BPT that causes BHR via the release of bronchoconstricting mediators. Indirect tests are useful not only for identifying an airway that is sensitive to the treatments used in asthma, in particular ICS, but also to assess the efficacy of therapy after treatment. Understanding the advantages and disadvantages of the treatments and strategies for EIB can help diminish EIB while also aiding in the treatment of asthma. The optimal point to treatment in the asthmatic athlete is the significant attenuation and, if possible, the abolition of EIB. Based on the evidence of clinical trials, this attenuation and/or abolition would lead to improvements in exercise performance while significantly minimizing the likelihood for an attack of asthma with exercise.

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Asthma in Pregnancy

18

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Abstract

Asthma is a chronic inflammatory respiratory illness manifesting with intermittent or persistent symptoms and is frequently encountered in pregnant women, most of whom have been diagnosed prior to conception. The degree of control over the illness in pregnancy often changes compared to the pre-pregnant state. Some of this change is likely mediated by the modified physiologic and immunologic state of pregnancy. Another contributor is decreased treatment, a well-intentioned but erroneous approach stemming from concern in a proportion of mothers and health-care providers about adverse effects of medications on the fetus. Poorly controlled asthma has the potential to cause morbidity in the mother and fetus, the latter being particularly vulnerable to the effects of hypoxia. Effective treatments exist to reduce morbidity and mortality from asthma, and management algorithms emphasize maintenance of good control of symptoms. Key pharmacologic agents used to treat asthma in the general population, particularly bronchodilators and inhaled corticosteroids, have established safety profiles for use in pregnant women. While some studies have shown associations between asthma medications and adverse perinatal events and congenital defects, the confounding effect of underlying asthma severity remains a significant obstacle to drawing firm conclusions. The overwhelming consensus is that the risk of leaving asthma untreated is greater than any risk conferred by most pharmacologic interventions. Pregnant women with asthma should be assessed regularly throughout pregnancy, and medications should be optimized to prevent exacerbations and minimize risks of fetal hypoxia. Exacerbations should be treated aggressively, and concomitantly, fetal well-being must be monitored closely.

Keywords

Asthma · Pregnancy · Exacerbations · Control · Management guidelines · Spirometry · Peak expiratory flow rate · Hypoxia · Congenital anomalies · Birth defects · Perinatal complications · Corticosteroid · Inhaled corticosteroid · ICS · Drug safety

18.1 Introduction

The definition of asthma is the same in pregnancy as it is in the non-gravid state: asthma is a disease of chronic airway inflammation, manifesting with episodic wheeze, shortness of breath, chest tightness, and cough of varying intensity and demonstrating variable expiratory airflow limitation (Global Initiative for Asthma (GINA) 2018). It is the most common chronic respiratory condition to affect pregnant women, with prevalence in the USA between 3.7% and 8.4% as per data obtained from 1997 to 2001 (Kwon et al. 2003). These data and others (Berg et al. 2009) also pointed to a rise in prevalence over similar time frames. Prevalence rates for asthma in pregnancy in other areas of the world are estimated at between 4% and 8% in Europe (Murphy and Gibson 2011; Charlton et al. 2016) and, similarly, between 5% and 8% in Brazil (Mendes et al. 2013). In Australia, they are reported to be as high as 12%

(Clifton et al. 2009). Epidemiologic data from other areas of the world, such as the African continent, are sparse (Adeyemi et al. 2015).

While approximately one third to one half of asthmatic women who become pregnant will have stability of asthma during pregnancy, the remainder will experience a change in asthma control, with roughly one half improving and the other half worsening (Gluck and Gluck 2006; Pearce and Douwes 2013). Those with severe asthma prior to pregnancy are more prone to developing exacerbations or to have worsening while pregnant (Belanger et al. 2010; Schatz et al. 2003). Exacerbation rates during pregnancy as determined in one large, prospective study were 12.6% for patients with mild asthma, 25.7% for those with moderate asthma, and 51.9% for those with severe asthma (Schatz et al. 2003). Hospitalization rates in that study were 2.3%, 6.8%, and 26.9%, respectively. Asthma in pregnancy is therefore an important cause of morbidity. Furthermore, in addition to its impact on maternal well-being, asthma can adversely affect fetal outcomes if poorly controlled (GINA 2018). Frequent, regular assessment of pregnant asthmatic patients is recommended, as effective and safe treatment options exist for maintenance of control and managing exacerbations. These topics will be addressed in this chapter, as well as the physiologic changes occurring in the immune and respiratory systems related to the gravid state.

18.2 Pathophysiology of Asthma

Asthma is an inflammatory disease affecting the airways, anywhere from the upper respiratory tract down to small airways, i.e., peripheral membranous bronchioles with diameters under 2 mm (Contoli et al. 2010). There is great heterogeneity in its clinical manifestation, its response to treatment, and in the composition of inflammatory cells and mediators that may be sampled from the sputum of affected patients. Its pathophysiology has been the subject of much research, and our current understanding of it is well-explained in many publications, one of which is material produced by the Global Initiative for Asthma (2016). An overview of some salient points derived from this source follows and is applicable to asthma in general, not just as it affects pregnant patients. Points specific to pregnancy will be raised in a later section.

18.2.1 Implicated Immune Cell Types and Inflammatory Mediators

A wide range of cell types can be involved in the inflammation seen in asthma, including mucosal mast cells, eosinophils, T lymphocytes, dendritic cells, macrophages, and neutrophils. Allergens binding to cell-surface-bound IgE trigger mast cell activation leading to the release of mediators that induce bronchoconstriction, such as histamine, cysteinyl leukotrienes, and prostaglandin D2. Mast cells may also be activated by osmotic stimuli and interactions with neurons. Macrophages present in the airways may also be activated via allergen binding to surface IgE, resulting in the release of inflammatory molecules. Eosinophils are frequently present in greater concentration in the airways of patients with asthma and, in addition to producing cysteinyl leukotrienes, may release mediators with the potential to damage the epithelium. T lymphocytes are often of the T helper 2 (Th2) subtype, typically producing interleukins (IL) 4, 5, 9, and 13, which promote eosinophilic activity and IgE production by B cells. Other subtypes of T lymphocytes, such as Th1 and Th17 cells, may also be present in airway tissue when the asthma is severe. Indeed, although asthma associated with allergic sensitizations, i.e., atopic asthma, is largely a Th2-driven illness, Th1 cells and their hallmark cytokines interferon (IFN)-gamma and tumor necrosis factor (TNF)-alpha may also contribute to clinical manifestations (Tamási et al. 2005). Dendritic cells perform antigen-processing and antigen-presenting functions and, when activated, migrate to local lymph nodes where they interact with, and activate, T cells, particularly Th2 populations. The presence of neutrophils in the airways and in sputum is associated with severe asthma and is also seen in asthmatics who smoke. It has proven challenging to tease apart the relative

contributions of each cell type, as well as to understand the heterogeneity in the predominance, if any, of some cell types over others. Classification of asthma into distinct phenotypes based on sputum cell composition is referred to as subtyping, and at least two broad categories, eosinophilic and non-eosinophilic, are recognized. The latter can be further subdivided depending on the predominant cell population identified (Simpson et al. 2006). By and large, better responses to conventional treatments are seen with the eosinophilic subtype of asthma.

18.2.2 Implicated Local, Structural Cells

In addition to immune cells, other cell types found in airways contribute to the inflammation of asthma. Epithelial cells can react to environmental and mechanical stimuli, as well as to viruses, and produce pro-inflammatory molecules, including cytokines, chemokines that can recruit pro-inflammatory immune cells, and lipid mediators. Via the inducible nitric oxide synthase enzyme, epithelial cells are a major important source of nitric oxide (NO), an important vasodilator. Endothelial cells in the bronchial circulation promote the passage of inflammatory cells from the vasculature into the airway. Airway smooth muscle cells in asthma can also participate in inflammation, and hyperplasia and hypertrophy of these cells are classic findings. Fibroblasts and myofibroblasts contribute to airway remodeling via production of collagens and proteoglycans. Reflexes mediated by cholinergic neurons present in airways can induce bronchoconstriction and mucus secretion. The cough and sensation of chest tightness often experienced by patients with asthma are thought to stem from reflex changes and production of inflammatory peptides from sensory neurons.

18.2.3 Structural Changes

Structural changes seen in asthmatic airways are referred to as airway remodeling and are thought to reflect disease severity, possibly even representing irreversible narrowing of the airways. Features of these changes include subepithelial fibrosis, smooth muscle hypertrophy and hyperplasia, increased airway wall vascularity, and mucus hypersecretion.

18.2.4 Airway Narrowing and Hyperresponsiveness

Typical symptoms of asthma and classic findings of airflow limitation are felt to be direct consequences of airway narrowing that has resulted from airway smooth muscle contraction induced by bronchoconstricting mediators and neurotransmitters, airway edema provoked by inflammatory mediators, thickening of the airway due to the structural changes mentioned above, and the over-secretion of mucus which can obstruct airway lumina. The airway hyperresponsiveness that is a hallmark of asthma implies that the threshold of airways to react to stimuli is reduced compared to what is seen in non-asthmatic patients. This feature is the reason that airflow limitation is usually variable and intermittent.

18.3 Physiology of Pregnancy

The inflammatory process, central to asthma, is influenced by the hormonal milieu of pregnancy. This very complex area has been extensively reviewed (Robinson and Klein 2012), and several overarching principles can be identified.

18.3.1 Immune System Alterations in Pregnancy

In a successful pregnancy, the immune system of the mother adapts in order to tolerate rather than reject the fetus in which paternal antigens are expressed. This adaptation involves a shift away from pro-inflammatory responses toward anti-inflammatory responses. As a pregnancy progresses, rising concentrations of estradiol, estriol, and progesterone accompany this shift. Receptors for these hormones exist on immune cells and

other tissues in varying distribution: estrogen receptors are present in lymphoid tissue, lymphocytes, macrophages, and dendritic cells. In addition to being present on epithelial cells, progesterone receptors are present in mast cells, eosinophils, macrophages, dendritic cells, and lymphocytes. Increasingly as the pregnancy progresses, pro-inflammatory responses are reduced, while anti-inflammatory responses increase. The reduction in pro-inflammatory responses manifests with diminished activity of natural killer (NK) cells, M1 macrophages, and T cells of the Th1 and Th17 subtypes and decreased levels of IL-12, IL-2, and TNF-alpha among others. Concomitantly, augmented anti-inflammatory changes result in increased activity of tolerogenic dendritic cells, M2 macrophages, T helper cells of the Th2 subtype, and regulatory T cells and rising levels of IL-4, IL-10, and transforming growth factor-beta (TGF-beta), among others. Estrogens promote increased B-cell differentiation and antibody production (Namazy and Schatz 2008). Progesterone may have partial glucocorticoid agonist activity and curtail basophil histamine release (Namazy and Schatz 2008). Estrogen and progesterone can diminish the oxidative burst that occurs subsequent to phagocytosis (Namazy and Schatz 2008), and both are implicated in the migration of eosinophils to organs including the uterus, with estradiol potentiating eosinophilic adhesion within the microvasculature and inducing degranulation in concert with progesterone (Namazy and Schatz 2008).

How these profound changes influence asthma and how the changes may deviate in the context of asthma are not well established. One study found that numbers of IL-4- and IFN-gamma-producing T cells are increased in the blood of healthy pregnant patients and even more so in the blood of asthmatic pregnant patients (Tamási et al. 2005). Moreover, the rise in IFN-gamma-producing T cells surpasses that of the IL-4-producing T cells in asthmatic pregnant patients (Tamási et al. 2005). The data also show that, among the asthmatic pregnant patients, the greater the numbers of IFN-gamma+ or IL-4+ T cells, the worse the maternal pulmonary function as measured by peak expiratory flow rates (Tamási et al. 2005). Similar negative correlation was found with birth weight of newborns (Tamási et al. 2005).

Asthma subtyping among pregnant patients is not common practice currently, although it is possible that an asthmatic patient will have undergone typing investigations prior to pregnancy, in which case the information may be useful in her management. One study that examined asthma subtypes did so in the postpartum period and did not identify any predisposition to exacerbations based on subtyping determined by postpartum sputum analysis of women with and without exacerbations during pregnancy (Ali et al. 2017).

18.3.2 Respiratory Physiology Alterations in Pregnancy

In addition to influencing the immune system, hormones of pregnancy also affect respiratory physiology. In their review, Sathish et al. (2015) summarize the current state of knowledge in this regard. Salient points are that the roles of these hormones in normal lung physiology and in pathophysiology have not been fully elucidated, but there is evidence for expression of estrogen and progesterone receptors in the upper and lower airways. Roles are postulated in the function of airway smooth muscle and in nitric oxide effects on vasculature (Sathish et al. 2015). Progesterone contributes to the nasal congestion that is common in pregnancy, and alters smooth muscle tone, resulting in bronchodilation (LoMauro and Aliverti 2015). Estrogen potentiates some of its actions by increasing the number and sensitivity of progesterone receptors in the central nervous system (LoMauro and Aliverti 2015).

18.3.2.1 Dimensions and Mechanics of the Thoracic Cage

Hormonal and mechanical influences also change the anatomy and dynamics of the thoracic cage in the gravid state. As reviewed by Hegewald and Crapo (2011), early on in pregnancy, before significant uterine enlargement occurs, there are increases in the subcostal angle of the rib cage and the circumference of the lower thorax, likely mediated to some extent by hormonally induced

ligamentous effects, and the diaphragm moves superiorly. The subcostal angle widens from 68.5° to 103.5° during pregnancy (Hegewald and Crapo 2011), and the circumference at the lower rib cage level increases by 5–7 cm. Uterine-related upward displacement of the diaphragm may be in the order of 4 cm, but its overall effect on lung volumes is limited by the chest wall's increased size (Hegewald and Crapo 2011). Respiratory muscle strength is preserved in pregnancy (Hegewald and Crapo 2011).

18.3.2.2 Lung Volume Changes

Increased tidal volume (V_T), i.e., the volume of air in a single inspiration or expiration during regular breathing, and therefore increased minute ventilation, i.e., the volume of air inspired or expired in 1 minute of normal breathing, are attributed to the effect of progesterone on the respiratory center, which increases its sensitivity to CO_2 (LoMauro and Aliverti 2015), resulting in respiratory alkalosis (Namazy and Schatz 2008; Hegewald and Crapo 2011). This normal elevation in pO2 and decrease in pCO2 are important to keep in mind in view of interpretation of arterial blood gas testing in an acute asthma exacerbation, as abnormalities in measurements could reflect greater severity than in a non-gravid patient, given that a baseline alkalosis is already present (Namazy and Schatz 2008). Due to increases in negative pleural pressure caused by intra-abdominal pressure changes, there is earlier closure of small airways (LoMauro and Aliverti 2015), leading to decreased residual volume (RV), which represents the volume of air that remains in the lungs after a maximal expiration. Expiratory reserve volume (ERV), which represents the volume of air that can be exhaled from the lungs after normal expiration, also decreases for the same reasons as the RV, such that the sum of RV and ERV, the functional residual capacity (FRC), may be reduced by the order of 25% in the final weeks (Gluck and Gluck 2006). Vital capacity (VC), representing the volume of air exhaled after a maximum inspiration, i.e., the sum of inspiratory reserve volume (IRV), V_T, and ERV, is largely preserved (Namazy and Schatz 2008), while the total lung capacity, the volume of gas in the lungs at the end of a maximum inspiration, represented by the sum of VC and RV decreases slightly (Hegewald and Crapo 2011) (see Table 1).

Table 1 Respiratory changes in pregnancy

Parameter	Change observed in pregnancy
Tidal volume (V_T)	↑
Minute ventilation	↑
Respiratory rate	Unchanged
pO_2	↑
pCO_2	↓
Arterial pH	↑
Residual volume (RV)	↓
Expiratory reserve volume (ERV)	↓
Functional residual capacity (FRC)	↓
Vital capacity	≈ Unchanged

18.3.2.3 Spirometry and Peak Expiratory Flow Rates

Spirometry is used to evaluate airflow and can detect the airflow limitation or obstruction that is a crucial feature of asthma. The airflow parameter forced expiratory volume in 1 second (FEV_1) is unchanged in pregnancy (Namazy and Schatz 2008). Forced vital capacity (FVC), which represents the volume of air that can be exhaled forcibly following deep inspiration, and the mean forced expiratory flow during the middle half of forced vital capacity ($FEF_{25–75}$) are thought to remain unchanged as well by many experts in the field (Namazy and Schatz 2008), such that their use is prescribed by guidelines (National Asthma Education and Prevention Program (NAEPP) 2007; GINA 2018) for asthma assessment in pregnancy. However, there is controversy in the data with regard to peak expiratory flow rate (PEFR) measurement, another method of detecting airflow limitation that measures the maximal flow rate occurring during forceful expiration following full inspiration (DeVrieze and Bhimji 2018). Some data point to stability of PEFR (Bracanzio et al. 1997), while others show that FVC and PEFR increase at a certain gestational age (Grindheim et al. 2012). Yet others reported rates of decline in PEFR of 0.65 L/min per week with advancing gestational age, with

the decline being more pronounced when measurements were taken in a supine position (Harirah et al. 2005). The reasons for such variability in conclusions about lung function changes in pregnancy may lie in limitations and differences in study design, whether cross-sectional or longitudinal, as an example, sample sizes, statistical methods, and whether or not the effect of patient ethnicity was taken into consideration (Grindheim et al. 2012). Overall, national and international guidelines are accepting of data indicating that PEFR and spirometry parameters are reliable in pregnant asthmatic patient assessment (NAEPP 2007; GINA 2018). Therefore, demonstration of reversible airflow obstruction during spirometry, typically an improvement of 12% in FEV_1 following bronchodilator administration, with at least a 200 mL absolute increase, can confirm a diagnosis of asthma in the pregnant patient. Changes in spirometry over the course of pregnancy are useful indicators of the evolution of the disease and can help guide treatment decisions. PEFR measurements are most often used in comparison with a patient's personal best measurement (DeVrieze and Bhimji 2018) and can also be used to guide treatment decisions.

18.4 Asthma Exacerbations

Exacerbations of asthma are reported to occur most frequently in the second trimester (Murphy et al. 2006; GINA 2018). A pattern of improvement is noted in the third trimester, with exacerbations rarely occurring in the last month of gestation and at the time of labor (Murphy et al. 2006; Namazy and Schatz 2008; Pearce and Douwes 2013). The differential diagnosis of acute asthma during pregnancy includes pulmonary edema, cardiomyopathy, pulmonary embolism, and amniotic fluid embolism (Hanania and Belfort 2005).

18.4.1 Risk Factors for Exacerbation of Asthma During Pregnancy

Several factors can augment risks of exacerbation in pregnant asthmatic women.

18.4.1.1 Reduced Adherence to Pharmacologic Treatment

Cessation of medications in the first trimester of pregnancy and even decreased prescribing by health-care providers are recognized phenomena which can affect pregnant asthmatic women in numbers approaching one in three (Enriquez et al. 2006; Zetstra–van der Woude et al. 2013) and result in decreased control of asthma. The use of bronchodilators, regularly taken inhaled corticosteroids (ICS), and rescue corticosteroids was seen to drop initially (Enriquez et al. 2006), although it rebounded later on in pregnancy.

18.4.1.2 Viral Infections

Pregnant women are more susceptible to viral infections in the context of their physiologic fetal tolerance-enhancing immune status (Namazy and Schatz 2008). Pregnant women with asthma may contract more viral upper respiratory tract infections than non-asthmatic pregnant women (Murphy et al. 2013b), with the consequence of greater risk of exacerbations of asthma. Increased vulnerability to infections in pregnancy may be conferred by diminished antiviral interferon responses, epithelial cell and alveolar macrophage dysfunction, and mucus overproduction (Murphy et al. 2013b). Reduced IL-10 levels and increased IL-17 production induced by certain viral infections may potentiate asthma in pregnant women (Vanders and Murphy 2015). Proven viral respiratory infections in pregnant asthmatic patients have been associated with higher rates of preeclampsia (Murphy et al. 2013b).

18.4.1.3 Allergic Rhinitis

Allergic rhinitis, considered a risk factor for asthma, often coexists with asthma and can adversely affect asthma control (Brozek et al. 2010), including in pregnant women (Powell et al. 2015). Some data show that untreated rhinitis in patients with asthma led to increased asthma-related visits to emergency departments (Adams et al. 2002). Pregnancy-specific data from one study have not shown a significant impact of allergic rhinitis on exacerbations or perinatal outcomes but did demonstrate significant reductions in several quality of life measures, including those pertaining to asthma (Powell et al. 2015). Treatment options for

allergic rhinitis include oral and nasal antihistamines and nasal corticosteroids, many of which are classified as safe for use during pregnancy.

18.4.1.4 Cigarette Smoking

Cigarette smoking is another area that should be addressed in pregnant women. As per an extensive review of the subject (Vanders and Murphy 2015), numerous data suggest that smoking is more prevalent among asthmatic pregnant women than their non-asthmatic pregnant counterparts. This behavior can worsen asthma and has been associated with detrimental effects in the fetus, including small size for gestational age and lower mean birth weight (Newman et al. 2010). In addition, it confers increased risk for the development of asthma in offspring in their early years (Dezateux et al. 1999; Jaakkola and Gissler 2004). Health-care providers must emphasize the benefits of smoking cessation and provide support for pregnant women to encourage it.

18.4.1.5 Obesity

Obesity is another factor that can increase the risk of developing asthma exacerbations, and this has also been shown to be the case in pregnant patients with asthma (Hendler et al. 2006). More recent evidence demonstrated that pregnant women whose body mass indices (BMI) at 17 weeks of gestation were categorized as overweight (25–29.9 kg/m^2) or obese ($\geq$30 kg/m^2) had more exacerbations than pregnant women with BMI indicative of healthy weight (18.5–24.9 kg/m^2) (Murphy et al. 2017). Interestingly, in this study, excessive gestational weight gain was not associated with a higher risk of having asthma exacerbations. Thus, pre-pregnancy weight management is relevant to the care of overweight asthmatic women contemplating pregnancy.

18.5 Clinical Assessment of the Pregnant Asthmatic Patient

Pregnant patients known to have asthma should be regularly assessed at monthly intervals for the duration of the pregnancy (GINA 2018). Validated questionnaires about symptoms can be used to gauge disease activity. In addition, specific questions should be asked of pregnant patients seeking medical attention for asthma symptoms, whether of new onset, related to worsening, or for routine assessment. Responses are useful in categorizing severity and the degree of control of asthma and can lead to identification of factors that may be contributing to any worsening symptoms. Adherence to treatment should be verified, and mastery of proper inhaler device technique where relevant should be reviewed. Physical examination findings and objective testing add further useful information that can influence and support management decisions.

18.5.1 Eliciting Symptoms, Provoking Factors, and Adherence to Treatment

Dyspnea, a common symptom experienced in asthma and other pulmonary diseases, is also frequently reported in pregnancies unaffected by asthma, where it may simply be due to perception of the normal pregnancy-associated hyperventilation (LoMauro and Aliverti 2015). History-taking during patient assessment should elicit the presence or absence of other relevant symptoms, including wheezing, cough, and a sensation of chest tightness or oppression. Asthma can manifest with nocturnal awakening, which, if frequent, suggests active asthma. Exercise tolerance, particularly cardiovascular exercise, can often be limited in the setting of active asthma, and it is relevant to question pregnant patients who exercise about this, as their aerobic working capacity should be preserved in pregnancy (LoMauro and Aliverti 2015). In searching for triggers of asthma, patients should be questioned about having any recent or concomitant symptoms of respiratory viral illnesses and gastroesophageal reflux; exposures to potential or previously identified allergens such as animals, carpeting, cockroaches, seasonal pollens, and fungi; and any significant occupational exposures. Work or school absenteeism and impact on daily activities due to asthma symptoms should be noted. Validated quality of

life questionnaires can be used to obtain scores about the impact of symptoms, which can be useful in determining response to treatments over time. Vaccination status regarding influenza viruses should be ascertained, as should tobacco use and other forms of smoking. Patients already on asthma medications should be questioned about whether or not the use of rapid-acting bronchodilator medication improves symptoms and how frequent is their use. Adherence to any prescribed inhalers and/or oral medications, particularly controller medications, should be assessed.

When diagnoses other than asthma are still being entertained, in addition to questions pertinent to asthma, history-taking should elicit the presence or absence of pleuritic chest pain, tachypnea, hemoptysis, palpitations, and peripheral edema.

18.5.2 Physical Examination

18.5.2.1 Maternal Physical Examination

Physical examination includes assessment of vital signs, namely, O_2 saturation, heart rate, respiratory rate, and blood pressure. Verification of oxygenation status is of paramount importance, and in cases of exacerbations, supplementation of oxygen should be provided to maintain O_2 saturation above 95% in order to prevent maternal and fetal hypoxia (NAEPP 2007). Pulsus paradoxus, a decrease in systolic blood pressure measurement of greater than 12 mm Hg during inspiration, may be seen in severe asthma and may rarely be observed in normal pregnancy (Chatterjee 2007). Physical examination should also look for increased labor of breathing and the use of accessory respiratory muscles. Auscultation of the chest should be performed assessing for air entry and any adventitious sounds such as wheezes. Examination of the nasal passages and oropharynx can be useful to identify signs of rhinitis, such as mucosal edema, and pallor. Cardiac and peripheral examination may be indicated when pulmonary or cardiac conditions other than asthma are being considered.

18.5.2.2 Fetal Assessment

The status of the fetus must also be examined, and which method is used to do so is determined by stage of the pregnancy. Methods of fetal status assessment include measuring fetal movement frequency, ultrasound examination, electronic fetal monitoring, and/or biophysical profile (Dombrowski and Schatz 2008; Cousins 1999). First-trimester ultrasound dating can provide information that will facilitate detection of fetal growth restriction over the course of the pregnancy (Dombrowski and Schatz 2008). Serial ultrasound examinations starting around week 32 of gestation can be used to monitor fetal activity and growth, which may be relevant for patients whose asthma is moderate-to-severe or poorly controlled, and in cases of exacerbation (Dombrowski and Schatz 2008). Fetal movement frequency can be measured by patients, and counting less than 10 movements per hour toward the end of the second trimester is a signal for further investigation (Cousins 1999).

18.5.3 Objective Tests

Along with the physical examination, objective evaluation of pulmonary function via spirometry (FEV_1, FVC, $FEF_{25–75}$) or PEFR is useful diagnostically and for gauging the severity of asthma or of an exacerbation. These parameters can then be followed to assess response to treatment. Most women with asthma during pregnancy are known to have it prior to pregnancy (Schatz and Dombrowski 2009), but in a first presentation, spirometry can be used to detect airflow limitation. FEV_1 may be reported as a percent of the predicted value and/or as a proportion of the FVC. As mentioned in a previous section, demonstration of improvement of 12% in FEV_1 following bronchodilator administration, with at least a 200 mL absolute increase, confirms reversible airflow limitation, a necessary criterion for the diagnosis of asthma. PEFR measurements are reported as absolute values and can also be evaluated in comparison to a patient's own best achieved levels, with any decrease of at least 20% signaling an exacerbation.

Methacholine challenge testing, a method allowing detection of airway hyperresponsiveness when diagnosis of asthma is strongly suspected but ordinary spirometry, performed with or without application of bronchodilation, is nonconfirmatory, is avoided during pregnancy due to lack of safety data for methacholine exposure in the developing fetus (Crapo et al. 2000).

Arterial blood sampling to measure PCO_2 and PO_2 can be informative about the severity of an exacerbation, keeping in mind that pregnant women have a baseline respiratory alkalosis (Hanania and Belfort 2005).

The fraction of exhaled nitric oxide (FeNO) has also shown promise for utility in management decision-making. As mentioned previously, NO is a product made in the airways in a reaction catalyzed by inducible NO synthases, which become upregulated when airway inflammation is present (Lougheed et al. 2012), and NO can be measured in exhaled breath. Its fractional concentration has been shown to be elevated in inflammatory airway diseases, of which asthma is one (Lougheed et al. 2012), and to be closely correlated with eosinophilic airway inflammation (Lougheed et al. 2012). FeNO measurements are not included as a criterion in most guidelines for asthma management at this time, but their applicability to certain patient populations and conditions is recognized (Lougheed et al. 2012; Dweik et al. 2011). Levels of FeNO remain comparable in gravid and non-gravid states (Tamási et al. 2009), and up-titration of medications based on FeNO of greater than 29 ppb and down-titration with FeNO levels of less than 16 ppb led to fewer exacerbations when compared with treatment-related decision-making based on clinical symptoms (Powell et al. 2011).

Skin prick testing is useful to identify aeroallergen sensitizations and is very rarely associated with significant complications (Bernstein et al. 2008). However, it is generally avoided during pregnancy by many health-care practitioners (Asser and Hamburger 1984), although not universally (Harwell 1985). It may be considered to be relatively contraindicated because of the very small associated risk of anaphylaxis, with possible compromise of fetal well-being due directly to anaphylaxis and also from its treatment. However, skin testing has been done with an acceptable safety profile in pregnant women under certain circumstances, such as when assessing penicillin allergy status (Macy 2006), so the contraindication to skin testing is a relative one. An alternative method by which to detect aeroallergen sensitization during pregnancy is verification of serum aeroallergen-specific IgE levels, which poses no risk to the patient.

18.6 Treatment and Management

Comprehensive asthma management guidelines and practice parameters are useful tools for health-care providers making treatment decisions. Nevertheless, involvement of specialists in asthma care, obstetrics, perinatology, and intensive care may be warranted under certain circumstances (Hanania and Belfort 2005). Multidisciplinary approaches can also be employed to assist patients in ways that will improve their control over the disease. The following sections address treatment and management principles. Details specific to medications will be presented in a later section.

18.6.1 Asthma Management Guidelines

Asthma treatment guidelines exist in many countries and provide a clear framework for assessing the severity of asthma and for the initiation of pharmacotherapy in newly diagnosed patients. They also provide guidance for assessing the control of asthma in patients with an established diagnosis and for adjustment of medications in these patients. Tables 2 and 3 are examples of guidelines developed in the USA, showing the approach recommended by an expert panel based on accumulated evidence and experience (NAEPP 2007). All major guidelines promote the active management of asthma during pregnancy, using various medications, as dictated by the frequency and severity of symptoms, and patient education regarding appropriate use of

Table 2 Classification of asthma severity in pregnant patients not yet treated with long-term control medications

Components of severity		Classification of asthma severity			
		Intermittent	Persistent		
			Mild	Moderate	Severe
Impairment (Normal FEV_1/FVC: 8–19 yr 85% 20–39 yr 80% 40–59 yr 75% 60–80 yr 70%)	Symptoms	≤2 days/week	>2 days/week but not daily	Daily	Throughout the day
	Night-time awakenings	≤2×/month	3–4×/month	>1×/week but not nightly	Often 7×/week
	Short-acting $beta_2$ agonist use for symptom control	≤2 days/week	>2 days/week but not >1×/day	Daily	Several times per day
	Interference with normal activity	None	Minor limitation	Some limitation	Extremely limited
	Lung function	Normal FEV_1 between exacerbations; FEV_1 >80% predicted; FEV_1/FVC normal	FEV_1 ≥80% predicted; FEV_1/FVC normal	FEV_1 >60% predicted but <80% predicted; FEV_1/FVC reduced 5%	FEV_1 <60% predicted; FEV_1/FVC reduced >5%
Risk	Exacerbations requiring oral systemic corticosteroids	0–1/year	≥2/year[a]		
		Consider severity and interval since last exacerbation. Frequency and severity may fluctuate over time for patients in any severity category			
Recommended step for initiating treatment (see Fig. 1 for treatment steps)		Step 1	Step 2	Step 3 Also consider short course of oral systemic corticosteroids	Step 4 or 5 Also consider short course of oral systemic corticosteroids
		Arrange for prompt reevaluation to assess level of asthma control achieved and adjust therapy accordingly; consider specialty consultation where warranted (e.g., for persistent, moderate category and worse, and as per clinical judgment); fetal assessment should be performed as warranted throughout			

Adapted from: National Asthma Education and Prevention Program 2007
FEV1 forced expiratory volume in 1 s, *FVC* forced vital capacity
[a]For treatment purposes, patients having ≥2 exacerbations requiring oral systemic corticosteroids in the past year may be considered as having persistent asthma, even in the absence of impairment levels consistent with persistent asthma

these medications (Gold and Litonjua 2018). The principles of asthma treatment remain similar in pregnant patients to those used in nonpregnant patients, following a stepwise approach to address any worsening in clinical status. Where these principles differ is in the reduction of treatment, as a pregnant patient who is well and stable on medication(s) is generally maintained on the medication(s) for the duration of the pregnancy, rather than trying to step down, as might be attempted in a nonpregnant patient. Clinicians may choose to treat differently than as recommended by guidelines, on a case-by-case basis.

18.6.1.1 Classification of Asthma Severity

In determining the severity of asthma, the following parameters are taken into account: the spirometry measurements FEV_1 and FVC; the presence of typical symptoms, i.e., cough, wheezing, shortness of breath, and chest tightness, and of nocturnal awakenings; frequency of use of short-acting $beta_2$ adrenergic receptor agonists (SABAs); and any disruption in ability to carry out normal activities (Table 2). Asthma is classified accordingly as intermittent, or persistent, with the latter being further subdivided into mild, moderate, or severe.

Table 3 Assessment of asthma control in pregnant adults and adjustment of therapy

Indicators of control		Classification of asthma control		
		Well-controlled	Not well-controlled	Poorly controlled
Impairment	Symptoms	≤2 days/week	>2 days/week	Throughout the day
	Night-time awakenings	≤2×/month	1–3×/week	≥4×/week
	Interference with normal activity	None	Some limitation	Extremely limited
	Short-acting beta$_2$ agonist use for symptom control	≤2 days/week	>2 days/week	Several times per day
	FEV_1 or PEFR	>80% predicted/ personal best	60–80% predicted/ personal best	<60% predicted/ personal best
	Validated questionnaires ATAQ ACQ ACT	 0 ≤0.75 ≥20	 1–2 ≥1.5 16–19	 3–4 N/A ≤15
Risk	Exacerbations requiring oral systemic corticosteroids	0–1/year	≥2/year[a]	
		Consider severity and interval since last exacerbation		
	Progressive loss of lung function	Evaluation requires long-term follow-up care		
Recommended action for treatment		Maintain current step (see Fig. 1) Regular monthly follow-ups to maintain control	Step up 1 step. (see Fig. 1) Reevaluate in 2–4 weeks, or sooner, as per clinical judgment	Consider short course of oral systemic corticosteroids Step up 1–2 steps. (see Fig. 1) Reevaluate in 5 days, or as per clinical judgment

Adapted from: National Asthma Education and Prevention Program 2007

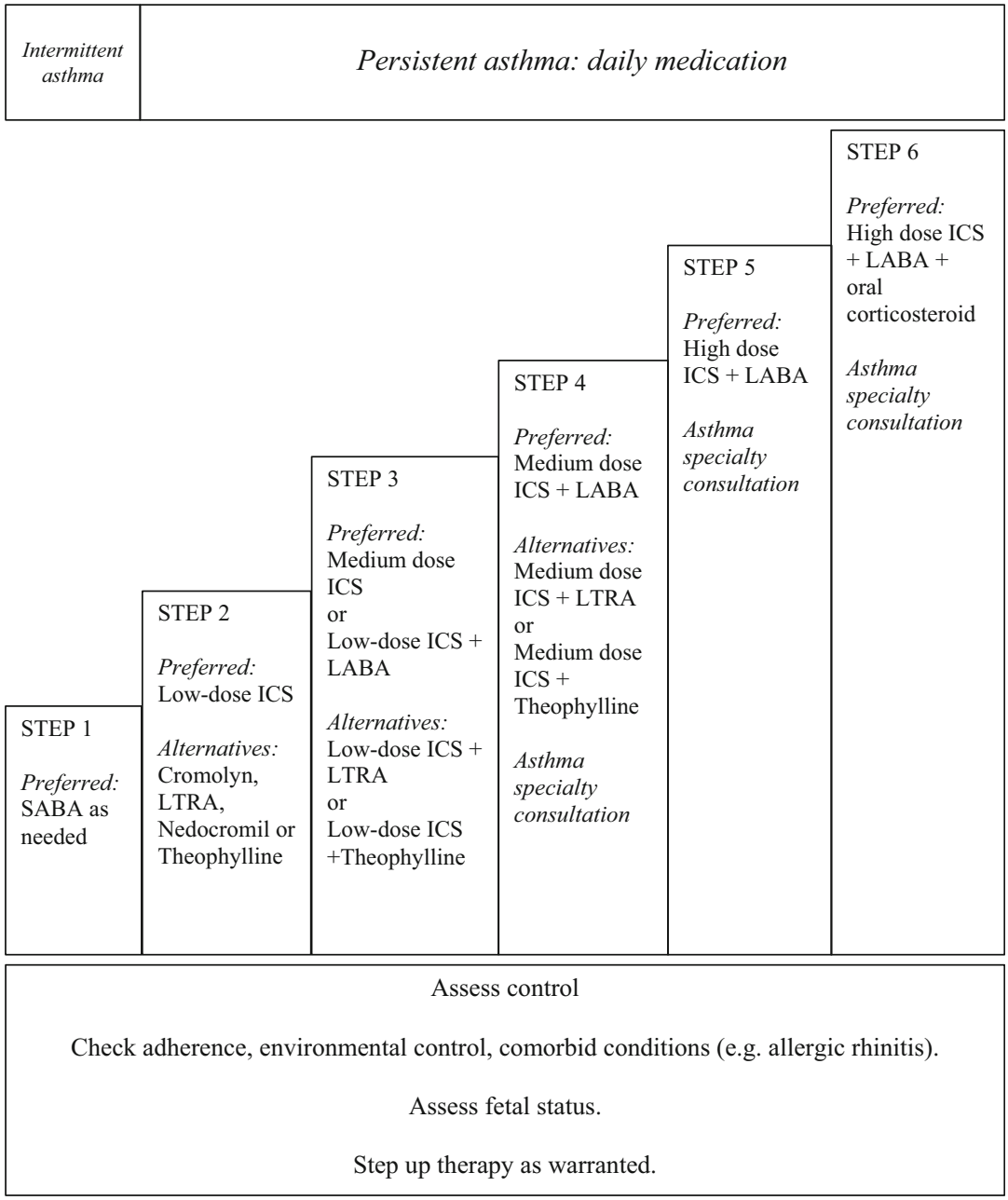
ATAQ asthma therapy assessment questionnaire, *ACQ* asthma control questionnaire, *ACT* asthma control test, *FEV1* forced expiratory volume in 1 s, *PEFR* peak expiratory flow rate

[a]For treatment purposes, patients having ≥2 exacerbations requiring oral systemic corticosteroids in the past year may be categorized as having not well-controlled asthma, even in the absence of impairment levels consistent with not-well-controlled asthma

Exacerbations requiring treatment with oral corticosteroids can influence the classification: for example, a patient with otherwise intermittent symptoms but who has experienced two such exacerbations may be classified as a patient with persistent symptoms (NAEPP 2007).

18.6.1.2 Treatment Principles

Once severity has been ascertained, treatment can be initiated for patients with a new diagnosis according to the steps outlined in the guidelines (see Table 2 and Fig. 1). Patients with intermittent asthma are usually treated with a SABA. When asthma is stratified as persistent, ICS are recommended for daily use as they reduce exacerbations during pregnancy. Patients with infrequent asthma symptoms but having one or more risk factors for exacerbations may also be treated with daily ICS. Among these risk factors is pregnancy. Others are frequent SABA use, greater bronchodilator reversibility, ongoing exposures to smoking and clinically relevant allergens, and the presence of obesity, chronic rhinosinusitis, and major psychological or socioeconomic problems (GINA 2018). Other criteria indicating a need for daily ICS are symptoms such as wheeze, chest tightness, shortness of breath, or cough occurring during the daytime more than twice per week; the use of SABA for



ICS: inhaled corticosteroid; LABA: long-acting beta2-agonist bronchodilator; LTRA: leukotriene receptor antagonist; SABA: short-acting beta2-agonist bronchodilator

Fig. 1 Stepwise approach for managing asthma in pregnant adults. (Adapted from: National Asthma Education and Prevention Program 2007)

relief of symptoms more than twice per week; any limitation in ability to conduct normal or desired activities, and/or absenteeism from the workplace or place of study due to symptoms; and experiencing awakening from sleep more than twice per month due to symptoms (NAEPP 2007).

Table 4 Examples of typical daily doses of inhaled corticosteroids used in adult pregnant patients

Drug	Low dose (mcg)	Medium dose (mcg)	High dose (mcg)
Beclomethasone HFA	80–240	>240–480	>480
Budesonide DPI	180–600	>600–1200	>1200
Fluticasone propionate HFA/MDI	88–264	>264–440	>440
Fluticasone propionate DPI	100–300	>300–500	>500
Mometasone furoate DPI	200	400	>400

Adapted from: National Asthma Education and Prevention Program 2007

In mild persistent asthma, the dose of ICS can be in the low range (see Table 4), but for asthma classified as moderate persistent, the dosage used should be within the medium range. An alternative approach to medium-dose ICS in moderate persistent asthma is to add a long-acting $beta_2$ adrenergic receptor agonist (LABA) to the low-dose ICS. Some experts recommend the former approach, i.e., medium-dose ICS alone, because although safety data for the LABAs are reassuring so far, they are less extensive than those for ICS (Schatz and Dombrowski 2009). However, for increasing severity, LABAs are considered to be the standard of care when added to medium- or high-dose ICS. Consideration of oral corticosteroids is recommended when symptoms, rescue $beta_2$-adrenergic agonist medication use, and spirometry fall in the severe category of persistent asthma.

18.6.1.3 Classification of Degree of Control of Asthma

For pregnant patients with a pre-existing asthma diagnosis, assessment of severity is nuanced by degree of control. The latter is ascertained with many of the same parameters used to determine severity (see Table 3): frequency of typical symptoms, nocturnal awakenings, interference with normal activities, and use of rescue bronchodilator medication. FEV_1 or PEFR measurements provide objective information about the degree of control of asthma, and responses to validated questionnaires pertaining to quality of life can also be helpful. The number of exacerbations of asthma requiring treatment with oral corticosteroids is also taken into consideration and, as with ascertainment of initial severity of asthma, may shift the categorization of control to one of being less well controlled, even when other parameters may be indicative of good control more often than not (NAEPP 2007).

18.6.1.4 Modification of Treatment

Once degree of control has been established, any change for the worse should be addressed with modification of medications as per the stepwise approach recommended in the guidelines. Progression is usually done one step at a time, but omitting a step to achieve more rapid improvement, with or without addition of a course of oral corticosteroid, is recommended when asthma is very poorly controlled. As mentioned previously, a pregnant patient who is well controlled on medications usually is kept on the same medications without attempting to reduce them, so as to avoid any worsening of asthma.

18.6.1.5 Alternative Drugs

Alternative pharmaceutical agents to the ones mentioned above include leukotriene receptor antagonists (LTRA), theophylline, and cromolyn. The use of these drugs is acceptable but not preferred: although theophylline was found to be as effective as ICS, it led to more side effects and required more monitoring (Dombrowski et al. 2004). Cromolyn is less effective than ICS (Guevara et al. 2006), as are LTRAs (Yang et al. 2013). Nevertheless, situations may exist where the use of these medications has advantages over ICS, such as for patients whose adherence can be improved by taking oral medications instead of using an inhaler, or who cannot master the proper technique of inhalation, thereby compromising the potential efficacy of ICS. They may also be of benefit as add-on therapies in some patients whose response to first-line therapies is suboptimal.

18.6.2 Acute Exacerbations

As previously mentioned, oxygenation status can be compromised in an asthma exacerbation, and in such circumstances, supplementing oxygen as necessary is of first importance, to minimize the risk of fetal hypoxia. Adequate hydration of the patient should be ensured (NAEPP 2007). Initial pharmacologic treatment includes bronchodilators, usually beta$_2$-agonists, and sometimes ipratropium, administered via metered dose inhalers or nebulizers, and systemic corticosteroids, whether by an oral or intravenous route. Terbutaline, another beta$_2$-agonist, can be administered subcutaneously if proper inhalation cannot be achieved. Intravenous magnesium sulfate has been shown to induce bronchodilation (Okayama et al. 1987). As with nonpregnant asthmatic patients, it can be administered to pregnant patients having severe exacerbations without significant improvement after 1 h of conventional treatment or to those having life-threatening exacerbations (NAEPP 2007).

Following stabilization of the patient, fetal assessment, and initiation of treatment, reevaluation should consist of repeated physical examination and measurement of pulmonary function. Patients seen in an emergency department setting with FEV_1 or PEFR at levels of at least 70% of predicted normal values that have been sustained for a minimum of 1 h, in addition to lack of any respiratory distress on physical examination and normal fetal status, may be discharged (Dombrowski and Schatz 2008). They should continue taking oral corticosteroids, typically in the range of 40–60 mg prednisone, or equivalent, daily for anywhere from 3 to 10 days (Dombrowski and Schatz 2008). In anticipation of the end of the oral corticosteroid course, and for the purpose of maintenance of asthma control thereafter, inhaled treatment should also be prescribed at the time of discharge. If a patient was not on such medication prior to the exacerbation, guideline classification of severity can be used to determine what this treatment should consist of, whether ICS alone or in combination with LABA, and at what doses. Stepping up of prior treatment should be considered, depending on the cause(s) of the exacerbation. Outpatient follow-up should be arranged to take place within 5 days (Dombrowski and Schatz 2008).

For patients with acute exacerbation who have not responded as well to treatment, as demonstrated by FEV_1 or PEFR measurements of at least 50%, but under 70%, of predicted normal values, and who continue to experience mild or moderate symptoms, health-care providers need to consider further treatment in the emergency department or even hospitalization (Dombrowski and Schatz 2008). Hospitalization is clearly indicated when patients have responded poorly to treatment, with measures of FEV_1 or PEFR under 50% of predicted normal values. Intensive care unit admission should be arranged for patients with poor measures of pulmonary function and severe symptoms who also have a depressed level of consciousness or altered mental status, along with pCO_2 greater than 42 mm Hg on blood gas measurement (Dombrowski and Schatz 2008). In such a context, intubation and ventilator support must be considered (Dombrowski and Schatz 2008). In some cases of life-threatening asthma that did not respond to intensive treatment and ventilation support, decisions to deliver patients in their third trimester resulted in improvement in their respiratory status (Lo et al. 2013).

18.6.3 Considerations at the Time of Labor and Delivery

All pregnant patients with asthma should continue taking their usual asthma medications throughout labor and delivery (Dombrowski and Schatz 2008). Adequate analgesia should be administered to minimize the risk of bronchospasm (Dombrowski and Schatz 2008). During labor and for the 24 h following delivery, stress doses of corticosteroids on the order of 100 mg hydrocortisone every 8 h intravenously should be administered to patients currently taking or who have had a recent course of systemic corticosteroids, in anticipation of adrenal insufficiency (Dombrowski and Schatz 2008).

Specific anesthetic agents and other agents sometimes used in the peripartum period can affect asthma. Epidural anesthesia is preferred

over general because of the intrinsic risks of atelectasis and chest infection associated with the latter (Nelson-Piercy 2001). Prostaglandin F and its derivatives, one of which is used to treat severe postpartum atony of the uterus, can cause bronchoconstriction (Cousins 1999), so its use should be avoided in asthmatics. Care should be taken if ergonovine derivatives are administered to treat postpartum hemorrhaging, as these may induce bronchospasm (Cousins 1999). On the other hand, prostaglandin E and its derivatives, one of which is used to induce labor, have bronchodilating properties and are safe (Cousins 1999).

18.7 Asthma and Perinatal Outcomes

Conflicting data have come from multiple studies regarding whether or not maternal asthma confers increased risks of perinatal complications. These have been extensively reviewed by many experts in the field, with some of the more recent reviews having been referred to here (Namazy and Schatz 2008; Murphy and Gibson 2011; Murphy et al. 2011; Ali et al. 2016).

18.7.1 Mechanisms of Adverse Effects of Asthma on the Fetus

One important mechanism by which asthma could adversely affect perinatal outcomes is fetal hypoxia caused by maternal respiratory distress (Namazy and Schatz 2008). Fetal compensatory mechanisms to counteract hypoxia include redistribution of blood flow to vital organs, reducing body movement, and increasing extraction of oxygen at the tissue level (Namazy and Schatz 2008). Chronic hypoxia may result in reduced growth and lead to small size for gestational age (Namazy and Schatz 2008). Another mechanism that could contribute to adverse effects from asthma arises from the paralleling of the smooth muscle irritability or hyper-reactivity affecting asthmatic airways in uterine smooth muscle and vasculature (Tamási et al. 2005), thereby increasing risks of preterm labor (Murphy et al. 2011). Yet another potential mechanism consists of immune dysregulation affecting the maternal immune system's perception of the fetus and ability to tolerate it (Tamási et al. 2005). Mast cell infiltration occurring in asthmatic airways may also occur in the endometrium, a potential explanation for the higher incidence of preeclampsia reported among asthmatic mothers (Murphy et al. 2011).

18.7.2 Risks of Adverse Perinatal Outcomes

Complications reported from studies of various designs have included preeclampsia, gestational diabetes, placenta previa and/or abruption, premature rupture of membranes, preterm labor and/or delivery, caesarean section, low birth weight, small size for gestational age, congenital malformations, and increased risk of perinatal mortality (Namazy and Schatz 2008; Ali et al. 2016). However, the findings are inconsistent, with some studies identifying increased risks and others not. Methodological problems identified in some of the earlier studies pertain to low power, inadequate correction or control for confounders such as smoking status and socioeconomic status, and lack of stratification of asthma severity and of consideration of which treatments patients were receiving (Murphy et al. 2011; Ali et al. 2016). Nevertheless, an understanding of the potential outcomes of concern, and the degree of risk observed, is useful for perspective about the many ways in which asthma can impact maternal and fetal health. It is also useful to appreciate how multiple variables are involved in the complexity of asthma in pregnancy and the difficulties inherent in trying to control for all of them when conducting studies. As many of these study reports note, a further challenge lies in trying to determine the contributions to risk stemming specifically from disease and those related to potential medication-related adverse events. Examples of such data are herein outlined. By and large, they show small, significant increases in risks of perinatal complications in the context of maternal asthma.

A very large study done in the UK using information extracted from a database of 37,585 pregnancies of women with asthma, and 243,434 pregnancies of non-asthmatic women over a 16 year period, showed a higher risk of miscarriage among asthmatic women (odds ratio (OR) 1.10, 95% confidence interval (CI) 1.06–1.13), and increases in the risk of antepartum hemorrhage (OR 1.20, 95% CI 1.08–1.34), postpartum hemorrhage (OR 1.38, 95% CI 1.21–1.57), anemia (OR 1.06, 95% CI 1.01–1.12), depression (OR 1.52, 95% CI 1.36–1.69), and caesarean section (OR 1.11, 95% CI 1.07–1.16) were observed (Tata et al. 2007). No elevation in risk was shown for stillbirth, placental abruption or insufficiency, placenta previa, preeclampsia, hypertension, gestational diabetes, thyroid disorders, and assisted delivery. In this study, women with more severe asthma or prior exacerbations were at greater risk of miscarriage, depression, and caesarean section (Tata et al. 2007). Limitations of this particular study were lack of data regarding premature birth and low birth weight and also a high proportion of missing data about smoking, BMI, and socioeconomic status (Tata et al. 2007).

Another large retrospective cohort study done in the USA deriving data from electronic medical records of 223,512 singleton deliveries between 2002 and 2008 showed that asthmatic women had higher odds of preeclampsia (adjusted odds ratio (aOR), 1.14, 95% CI, 1.06–1.22), gestational diabetes (aOR 1.11, 95% CI 1.03–1.19), placental abruption (aOR 1.22, 95% CI 1.09–1.36), and placenta previa (aOR 1.30, 95% CI 1.08–1.56) (Mendola et al. 2013). There were also higher odds of preterm birth (aOR 1.17, 95% CI 1.12–1.23), medically indicated preterm delivery (aOR 1.14, 95% CI 1.01–1.29), and low birth weight (aOR 1.16, 95% CI 1.10–1.23) (Mendola et al. 2013). Furthermore, risks for pulmonary embolism (aOR 1.71, 95% CI 1.05–2.79) and maternal ICU admission (aOR 1.34, 95% CI 1.04–1.72) were elevated (Mendola et al. 2013). A major limitation in this study was a lack of information on asthma control, exacerbations, and treatment, such that applicability of findings to women with well-controlled asthma remains uncertain (Mendola et al. 2013).

A meta-analysis of data obtained from cohort studies undertaken between 1975 and 2009 comparing pregnant, asthmatic women to pregnant, non-asthmatic women found greater risks of the following adverse outcomes in the setting of maternal asthma: lower birth weight (relative risk (RR) 1.46, 95% CI 1.22–1.75), of the order of 93 g less than offspring of mothers without asthma, small size for gestational age (RR 1.22, 95% CI 1.14–1.31), preterm delivery (RR 1.41, 95% CI 1.22–1.61), and preeclampsia (RR 1.54, 95% CI 1.32–1.81) (Murphy et al. 2011). Data from the meta-analysis supported the reduction in risk of preterm labor and delivery with active management of asthma. Relative risks of preterm delivery and preterm labor were reduced to non-significant levels by active asthma management ((RR) 1.07, 95% CI 0.91–1.26 for preterm delivery; RR 0.96, 95% CI 0.73–1.26 for preterm labor) (Murphy et al. 2011).

In another meta-analysis, the increased risk of low birth weight in the offspring of women with asthma exacerbated during pregnancy returned to that of non-asthmatic women when asthma was well controlled during pregnancy (Murphy et al. 2006). Data from larger, more recent studies have also shown an increased risk of lower birth weight in offspring of asthmatic women, a risk that is heightened in the context of exacerbated asthma (Enriquez et al. 2007). There is a greater risk of babies being small for gestational age among mothers who have had severe and moderate asthma during pregnancy compared to mothers with mild asthma (Firoozi et al. 2010).

18.7.3 Risks of Congenital Malformations

With regard to congenital malformations, again, conflicting conclusions are arrived at from study to study. This has been well-reviewed in multiple references, some of which are quoted here (Namazy and Schatz 2008; Murphy et al. 2011, 2013a). Congenital malformations reported

have included cleft lip and/or palate, and nervous, respiratory, cardiac, and digestive system defects including anal atresia (Murphy et al. 2013a). While some studies did not find any increased risk of birth defects (Källén et al. 2000; Enriquez et al. 2007), a meta-analysis of multiple studies looking at risks of congenital malformations and other complications in offspring of asthmatic women found that these infants are 11% more likely to manifest congenital malformations compared with infants of non-asthmatic women (RR 1.11, 95% CI 1.02–1.21, $I^2 = 59.5\%$) (Murphy et al. 2013a). Major malformations appeared not to be increased, although the analysis may not have had sufficient power to draw this conclusion with certainty. Compared with non-asthmatic pregnant women, offspring of asthmatic patients had a 30% increased risk of cleft lip and/or palate (RR 1.30, 95% CI 1.01–1.68, $I^2 = 65.6\%$). However, it is not known whether this risk is attributable to the disease itself or to the use of oral corticosteroid for asthma, particularly in the first trimester when lip and palate closure is occurring (Murphy et al. 2013a). There was an increase in the risks of neonatal hospitalization (RR 1.50, 95% CI 1.03–2.20, $I^2 = 64.5\%$) and death (RR 1.49, 95% CI 1.11–2.00, $I^2 = 0\%$), although not of stillbirth, in the context of maternal asthma (Murphy et al. 2013a). The meta-analysis did not identify any significant increase in risk of major malformations among the offspring of women who experienced asthma exacerbations during pregnancy compared with women who did not (Murphy et al. 2013a). This last finding differed from that of a retrospective cohort study of 36,587 pregnancies in asthmatic women in a data registry in Quebec, Canada, that showed that exacerbations occurring in the first trimester of severity warranting hospitalization were associated with an increased prevalence of congenital malformations (OR 1.64 for any congenital malformation, 95% CI 1.02 to 2.64; a nonsignificant OR of 1.70 for a major congenital malformation, 95% CI 0.95 to 3.02) (Blais et al. 2015). Moderate exacerbations in the first trimester, i.e., leading to emergency department visit, but not to hospitalization, were not associated with any increase in risks of birth defects (Blais et al. 2015). In this study, the prevalence of any congenital malformation was reported to be 19.1% in offspring of women with severe asthma exacerbations occurring in the first trimester versus 11.7% and 12.0% among women who had moderate exacerbations and no exacerbations during the first trimester, respectively (Blais et al. 2015). An important limitation in this study consisted of lack of medication information for a substantial number of subjects (Blais et al. 2015).

18.7.4 Longer-Term Effects of Maternal Asthma

In addition to immediate perinatal phenomena, maternal asthma may also affect the health of offspring more distantly. A recent population-based cohort study found a higher prevalence of asthma among children whose mothers had active asthma during pregnancy (Liu et al. 2017). This same study identified differences in risk and asthma phenotype depending on whether maternal asthma was mild, or moderate-to-severe, and the degree of its control. Children's asthma patterns identified were early-onset transient, early-onset persistent, and late-onset. In addition to evidence pointing to a direct effect of maternal asthma on the risk of the development of offspring asthma, the data also supported a genetic contribution (Liu et al. 2017).

18.7.5 Asthma Outcomes and Clinical Course in Subsequent Pregnancies

In the majority of women experiencing a change in their asthma during pregnancy, their condition returned to prepregnancy status during the 3 months postpartum (Schatz et al. 1988). Asthma severity during pregnancy was also observed to be similar in a subsequent pregnancy (Schatz et al. 1988).

18.8 Pharmacologic Management of Asthma and Drug Safety in Pregnant Women

In managing pregnant asthmatic patients, it is necessary to be aware of safety ratings and classifications of medications in this population. Asthma treatment frequently calls for chronic use of medication and the addition of further medications when disease control is inadequate. Thus, expectant mothers with asthma will often require medication throughout their pregnancies. Of primary concern is the potential for in utero exposure to drugs to increase risks of congenital anomalies.

As of June 30, 2015, the pregnancy letter categories A, B, C, D, and X used by the US Food and Drug Administration (FDA) have been or are being replaced by a descriptive label format (FDA 2014a). Not all medications have undergone the shift of safety labeling, so awareness of old categories is still useful. Category A implies that adequate, well-controlled human studies have not demonstrated any increased risk of adverse fetal effects and that there is no evidence of risk in the second or third trimesters (US Department of Health & Human Services 2017). No asthma medications fall under this category. A Category B rating refers to lack of risk to a fetus based on animal reproduction studies, without data from adequate and well-controlled studies in pregnant women. Several drugs used in asthma fall into this category, as well as the next, as will be discussed further on. Category C drugs have been shown to have adverse effects on the fetus via animal reproduction studies but, again, without adequate and well-controlled studies in humans. Clinicians may still choose to use them in pregnant women if potential benefits are felt to outweigh the risks. A Category D rating implies that adverse reactions have been noted to occur in the human fetus based on investigational or marketing experience. Nevertheless, as with Category C drugs, the use may be warranted after careful consideration of potential benefits versus risks. Finally, Category X drugs are proscribed in pregnant women as their use has been demonstrated in animal or human studies to result in fetal abnormalities and/or there are clear adverse reaction data from investigational or marketing experience (US Department of Health & Human Services 2017). Resources in addition to the FDA exist which provide regularly updated information on the safety of drugs in pregnant women: examples are Motherisk, MotherToBaby, and Centers for Disease Control and Prevention. Clinical practice guidelines and numerous reviews on the topic of asthma medication safety in pregnant women also detail which medications can be used in this population. Some of these have been referred to in this chapter (NAEPP 2007; Dombrowski and Schatz 2008; Namazy and Schatz 2008; GINA 2018).

18.8.1 Drugs Commonly Used in Asthma

Multiple pharmaceutical agents with different mechanisms of action are available to treat asthma. The following sections examine the roles of each class of medication in managing asthma in pregnancy and discuss safety issues.

18.8.1.1 Short-Acting Beta$_2$ Adrenergic Agonists (SABAs)

SABAs, used as rescue medication for rapid relief of asthma symptoms via their bronchodilating effects, are considered to be safe in pregnancy (Eltonsy et al. 2011; NAEPP 2007). Albuterol, also known as salbutamol, is the favored agent in this class due to more extensive experience with it or to scientific literature availability regarding its safety compared with other SABAs. Nevertheless, data exist suggesting a small increased risk of gastroschisis, a defect in the abdominal wall, in the newborn, conferred by maternal use of SABAs (Lin et al. 2008), and another study showed that among cases of newborns with cleft palate and gastroschisis, the odds of first trimester exposure to inhaled SABAs were increased (Garne et al. 2015). In their analysis of data from a large, population-based, case-control study, Lin et al. (2012) identified an association between bronchodilator use in the periconceptional period (starting 1 month prior to conception and ending after the third month of pregnancy) and isolated esophageal atresia (aOR 2.39, 95% CI 1.23, 4.66).

A similar study published later, evaluating the use of bronchodilators and anti-inflammatory medications in the same periconceptional interval, found an association between bronchodilator use and anomalous pulmonary venous return (OR 2.3, 95% CI 1.1–4.8) (Van Zutphen et al. 2015). Both studies lacked information about maternal asthma severity (Lin et al. 2012; Van Zutphen et al. 2015).

Despite these findings, SABAs are still considered safe for use in pregnancy, as the absolute risks of congenital anomalies remain very small, even in the presence of the increased risk possibly conferred by medication (Garne et al. 2015). Furthermore, causality was not established in the studies mentioned above, given that disease severity was not necessarily taken into account or that, sometimes, prescription redemption was used as a surrogate for actual intake of medication.

18.8.1.2 Long-Acting Beta$_2$ Adrenergic Agonists (LABAs)

LABAs, also used for bronchodilation, and most often in combination with ICS for synergistic/additive effects, have been in clinical use for less time than SABA. While animal studies are reassuring with regard to their safety in pregnancy, initial human data suggested that they could be associated with greater risks of cardiac malformation (Eltonsy et al. 2011). However, a strong conclusion could not be drawn based on numbers of subjects and because of the confounder of disease effect. In a later study, no difference was found in the risk of major malformations between women on a LABA plus low-dose ICS and women on a medium-dose ICS, and similarly, there was no difference for women on a LABA plus medium-dose ICS and women on a high dose of ICS (Eltonsy et al. 2015). Among the available LABAs, salmeterol has been favored for use in pregnancy over formoterol, as there is more information available about it given that it has been in use longer. However, studies have shown no difference between either in risk of low birth weight, preterm birth, and small size for gestational age (Cossette et al. 2013, 2014). Guidelines suggest using LABAs in combination with ICS in pregnant women with suboptimal control of their asthma despite medium doses of ICS. LABAs may also be continued, along with ICS, in women already taking them at the time of becoming pregnant.

18.8.1.3 Corticosteroids

Corticosteroids, also called glucocorticoids, are a mainstay in the treatment of asthma, with the inhaled route of administration being favored for chronic control and for some exacerbations, where appropriate, and oral/systemic routes for the acute management of severe exacerbations. The action of corticosteroids is largely anti-inflammatory by virtue of myriad downstream effects taking place once glucocorticoid receptors have been engaged by their corticosteroid ligands. These effects are mediated by direct and indirect modulation of transcription of genes encoding various cytokines, chemokines, receptors, enzymes, adhesion molecules, and inhibitory proteins (van der Velden 1998). Examples of cytokines which are relevant in asthma and whose transcription is decreased by corticosteroids are IL-1beta, TNF-alpha, granulocyte-monocyte-colony-stimulating factor, IL-3, IL-4, IL-5, IL-6, IL-8, IL-11, IL-12, IL-13, "regulated on activation, normal T-cell expressed, and secreted" (RANTES), eotaxin, and macrophage inhibitory protein-1alpha (van der Velden 1998). The effect achieved is a decrease in the number and activation status of cells contributing to the inflammation that occurs in the bronchi of asthmatic patients, i.e., mast cells, dendritic cells, eosinophils, and T lymphocytes (van der Velden 1998). Corticosteroids also inhibit the production of inflammatory mediators such as prostaglandins and thromboxanes while augmenting the elaboration of anti-inflammatory mediators such as IL-1 receptor antagonist (van der Velden 1998).

Corticosteroid receptors are widely expressed in many tissues, and adverse effects of corticosteroids are many, particularly when systemically administered for prolonged periods of time. In the short term, usually considered to be not more than 3–4 weeks, possible side effects of oral/systemically administered corticosteroids

include avascular necrosis, mood and sleep disturbances, psychosis, hyperglycemia, and worsening glucose control in diabetic patients (Richards 2008). Increased rates of sepsis, venous thromboembolism, and fracture have also been reported in association with courses of corticosteroid exposure lasting under 30 days (Waljee et al. 2017). Rarely, high-dose "pulse" corticosteroid treatment has been implicated in cardiovascular events such as arrhythmias and even sudden death, although mostly in the context of serious underlying comorbidities, making it difficult to ascertain causality from corticosteroids (Liu et al. 2013). Nevertheless, such risks are accepted in cases where short-term oral corticosteroids are deemed necessary, as significant adverse events are considered to be rare and also because there may be few to no alternatives. The possible side effect profile of systemic corticosteroids in the long term is extensive and includes those associated with short-term use as well as suppression of the hypothalamic-pituitary-adrenal axis, hypertension, weight gain/obesity and Cushingoid features, osteoporosis, raised intraocular pressure, cataracts, proximal muscle weakness, mood disturbances, memory deficit, psychosis, gastritis, peptic ulceration, and gastrointestinal hemorrhage (Moghadam-Kia and Werth 2010). In comparison with controls, patients with lung diseases including asthma, who were on daily doses or frequent intermittent courses of oral corticosteroid for at least 6 months, developed more osteoporotic fractures and reported more bruising, muscle weakness, oral candidiasis, use of antacids, and cataracts (Walsh et al. 2001). Hence, the use of oral corticosteroids on a chronic basis for controlling asthma is strongly discouraged and should be avoided. In addition to taking these issues into consideration when assessing the risks and benefits of treatment, attention must also be given to potential adverse effects on the fetus in pregnant patients.

Generally, when a pregnant asthmatic patient has an acute exacerbation, the benefit of treating with oral corticosteroids in order to minimize risks from uncontrolled asthma to both the mother and fetus is felt to outweigh the risks associated with these medications (NAEPP 2007; Dombrowski and Schatz 2008). However, many data point to increased risks of some maternal-fetal adverse events that health-care professionals should be aware of when counseling patients for whom oral corticosteroids are being prescribed, if only to provide reassurance, given that risks seem to be small.

Increased risks of preeclampsia and prematurity have been reported with oral corticosteroids, but it has not been possible to draw firm conclusions about causality due to the confounding effect of greater asthma severity among patients requiring oral corticosteroids (Schatz and Dombrowski 2009). In a meta-analysis of cohort studies, oral corticosteroid use was associated with an increased risk of low birth weight (RR 1.41, 95% CI 1.04–1.93) and preterm delivery (RR 1.51, 95% CI 1.15–1.98) (Namazy et al. 2013).

Findings related to congenital anomalies differ among studies. In one large study, infants with congenital anomalies had a higher odds ratio of having been exposed in utero to systemic corticosteroids than to ICS (OR 1.51, 99% CI 1.03–2.22), but specific anomalies could not be further identified due to low numbers of systemic corticosteroid exposure (Garne et al. 2016). Another study did not show higher risk of congenital anomalies (Enriquez et al. 2007) but did find a dose-response trend between lower birth weight and increasing use of oral corticosteroids during pregnancy (Enriquez et al. 2007).

In comparison to oral corticosteroids, ICS have a much better safety profile with regard to the adverse events that are not specific to pregnancy, and data support the absence of fetal adrenal suppression despite in utero exposure to ICS (Hodyl et al. 2011).

With regard to congenital malformations, there is variability in data obtained from one study to the next and in conclusions drawn. However, by and large, most data are reassuring for use of ICS in pregnancy. To illustrate the nature of the information known about risks associated with ICS in pregnancy, examples of study findings are given here, without being an exhaustive literature review.

In a cohort study of 13,280 pregnancies over a 12-year span, using information from databases, Blais et al. (2009) did not find any increased risk of congenital malformations in women using low to moderate doses of ICS. However, women who used high doses (equivalent of >1000 micrograms/day of beclomethasone dipropionate) of ICS were 63% more likely to have a baby with a malformation than women on low to moderate doses (aRR 1.63, 95% CI 1.02–2.60). In a meta-analysis of studies looking at congenital malformations and other complications arising in the offspring of women with asthma in pregnancy, the use of asthma medications including ICS was not associated with increased relative risks of major congenital malformations (Murphy et al. 2013a). In another large study, no congenital anomalies were associated with in utero exposure to ICS (Garne et al. 2015), but a later report showed significant association with anal atresia/stenosis (OR 3.40, 99% CI 1.15–10.04) (Garne et al. 2016).

In their analysis of data from a large, population-based, case-control study, Lin et al. (2012) identified associations between anti-inflammatory medication use, during the interval starting 1 month prior to conception and ending after the 3rd month of pregnancy, and isolated anorectal atresia (aOR 2.12, 95% CI 1.09, 4.12) and between bronchodilator and anti-inflammatory use and omphalocele (aOR 4.13, 95% CI 1.43, 11.95). The authors note that since the baseline prevalence of these defects is low, any absolute risks conferred by exposure to the asthma medications would be small, if indeed the associations observed were causal (Lin et al. 2012). The study was limited by lack of information on the degree of asthma severity, as well as on dose and route of administration of the medications (Lin et al. 2012).

Budesonide is the ICS molecule with the most information related to its safety in pregnancy and, for this reason, may be preferred for initiation of ICS treatment in a newly diagnosed pregnant patient (NAEPP 2007). However, data are reassuring with regard to the safety of other ICS molecules, such as fluticasone propionate, which, in one large study, was not associated with any increased risk of major congenital malformations compared with other forms of ICS (Charlton et al. 2015). Thus, a patient who becomes pregnant while on an ICS other than budesonide, and who is well controlled on that ICS, may continue to be treated with it (Cossette et al. 2014; Charlton et al. 2015).

18.8.1.4 Leukotriene Receptor Antagonists (LTRAs)

LTRAs block the actions of the inflammatory mediators known as leukotrienes C4, D4, and E4, which contribute to airway edema and smooth muscle contraction in asthma (Bakhireva et al. 2007). These drugs include montelukast and zafirlukast. Available data so far indicate that there is no increased risk of adverse perinatal outcomes or fetal malformations (Bakhireva et al. 2007). There is greatest experience with montelukast, and its use in pregnancy is acceptable.

18.8.1.5 Short-Acting Anti-muscarinic Agents

The short-acting anti-muscarinic agent ipratropium bromide, used for its bronchodilating effect, was classified as a category B drug in the former FDA classification system (FDA 2006). Its use is acceptable in treating acute asthma exacerbations, along with beta$_2$-agonists (Hanania and Belfort 2005).

18.8.1.6 Long-Acting Anti-muscarinic Agents (LAMAs)

The LAMA tiotropium, which has a bronchodilating effect, has been recently added to general asthma management guidelines (GINA 2018) for nonpregnant patients 12 years of age and older who are already taking moderate-high-dose ICS and LABA yet whose symptoms are uncontrolled and in whom there is evidence of persistent airflow limitation. However, having been labeled as a Category C drug in pregnancy as per the former classification scheme, tiotropium should be omitted during pregnancy unless its benefits are felt to outweigh its risks. Animal studies have shown toxicity to fetuses at higher doses than are used in humans, and there

are insufficient human data for further clarification (FDA 2014b).

18.8.1.7 Theophylline

Theophylline, of the methylxanthine class of drugs, functions as a bronchodilator at higher doses, via inhibition of phosphodiesterase (PDE) and has been shown in some studies to have anti-inflammatory effects at lower concentrations, postulated to be due to inhibition of PDE4 and histone deacetylase-2 activation, with subsequent reduction in expression of activated inflammatory genes (Barnes 2013). It is considered safe for use in pregnancy (Dombrowski and Schatz 2008) in a second line capacity but requires monitoring of serum levels as it can frequently cause side effects when levels are not within its narrow therapeutic window.

18.8.1.8 Cromoglycates

The cromoglycates cromolyn sodium and nedocromil sodium, also medications considered as safe in pregnancy (NAEPP 2007), act via inhibition of inflammatory mediator release from mast cells (Murphy and Kelly 1987). In general, these are not first-line drugs as they have been demonstrated to be less effective than ICS (NAEPP 2007).

18.8.1.9 Monoclonal Antibody Therapies

None of the monoclonal antibody therapies in clinical use in asthma are approved for administration to pregnant women at the present time. These consist of anti-IgE, and anti-IL-5 monoclonal antibodies, and are all of the IgG type, which signifies that they are transported across the placenta. Transport occurs increasingly as pregnancy progresses, leading to concern that the greatest potential for effects on a fetus exists in the second and third trimesters of pregnancy.

The anti-IgE antibody omalizumab inhibits the binding of IgE to the high-affinity IgE receptor (FcεRI) on the surface of mast cells and basophils (FDA 2003). It is indicated in the management of some cases of severe asthma. In the few case reports (Kupryś-Lipińska et al. 2014; Ghazanfar and Thomsen 2015; Cuervo-Pardo et al. 2016) of pregnant women exposed to the anti-IgE monoclonal antibody omalizumab in the context of either asthma or chronic spontaneous urticaria, no adverse effects on offspring were noted. Although not approved for use in pregnancy, omalizumab was classified in the B category (FDA 2003) of the former FDA drug safety scheme, based on reassuring animal data. Furthermore, a prospective, observational study of pregnant women exposed to the drug did not show any increases in major anomalies (Namazy et al. 2015). Practically, initiation of omalizumab is not recommended in pregnant women, but expert opinion favors continuation in a patient already receiving it when she becomes pregnant, as long as benefits are deemed to outweigh risks (Pongracic 2017).

Mepolizumab, reslizumab, and benralizumab all inhibit IL-5 signaling by targeting either IL-5 itself or its receptor and are indicated in the treatment of severe eosinophilic asthma. Mepolizumab is a humanized, IL-5 antagonist monoclonal antibody of the immunoglobulin G1 kappa type. Animal safety data to date regarding effects in pregnancy are reassuring, and human data are being gathered in an ongoing pregnancy exposure registry (FDA 2015; Fala 2016). Reslizumab is a humanized IgG4κ monoclonal antibody that, like mepolizumab, also binds to human IL-5, inhibiting its signaling (FDA 2016). There is insufficient human data with regard to its safety in the context of pregnancy (FDA 2016; Hom and Pisano 2017) although animal study data are reassuring. Benralizumab is an IgG1κ antibody targeting the IL-5 receptor alpha chain. It too has not been associated with any significant adverse effects in animal studies, but human data are lacking (Astra-Zeneca 2017).

Dupilumab, a human monoclonal IgG4 antibody against the interleukin-4 receptor alpha subunit (FDA 2017), inhibits signaling of IL-4 and IL-13 and is approved for use in patients with atopic dermatitis. It has shown promise in the treatment of moderate-to-severe asthma, improving lung function and reducing severe exacerbations (Wenzel et al. 2016), and evaluation of its safety for use in asthma by the FDA is slated to start in the near future

(Regeneron Pharmaceuticals Inc 2018). As with the other monoclonal antibody treatments mentioned, there are insufficient data regarding its safety in the context of human pregnancy, although animal data are reassuring to date (FDA 2017).

18.8.1.10 Medication Prescribing and Adherence

Despite evidence of the safety of multiple pharmacologic agents used in the treatment of asthma in pregnant women, particularly ICS, a significant number of patients remain wary about continuing medication for maintenance of asthma control in pregnancy, concerned about adverse fetal effects, which can affect adherence to treatment (Murphy et al. 2005). Some health-care professionals may also be reluctant to prescribe controller asthma medications during pregnancy, through inadequate knowledge or lack of confidence in managing asthma in the context of pregnancy (Lim et al. 2011). Treatment of exacerbations in emergency department settings has sometimes been suboptimal with regard to the prescribing of controller medications like corticosteroids upon discharge, with pregnant patients more likely to be discharged without them compared to nonpregnant asthmatic women, according to one study (Cydulka et al. 1999). The same study also showed that a higher proportion of pregnant women compared to nonpregnant women had symptoms of persistent exacerbation upon follow-up. Education of patients and health-care professionals will be necessary to overcome these obstacles in order to achieve optimal care of asthmatic women during pregnancy. In clinical practice, asthma management programs can be targeted to pregnant women to increase adherence with medications (Baarnes et al. 2016).

18.9 Other Treatments

Bronchial thermoplasty uses radiofrequency energy to heat the airway walls, thereby decreasing airway smooth muscle mass, and is another therapeutic option for treating severe asthma. However, its use in pregnant women has not been well-studied, such women having been largely excluded from studies (Chupp et al. 2017).

18.10 Treating Related Conditions

Allergic rhinitis often accompanies asthma and can contribute to its morbidity. Nasal corticosteroids are a mainstay of treatment for allergic rhinitis and can be used in pregnant women. Budesonide-based sprays are favored due to the molecule's long safety record in pregnancy. Loratadine and cetirizine, second-generation oral antihistamines, can also be used to provide symptom relief in pregnant patients, noting that they will have little to no effect on asthma control (NAEPP 2007).

Allergen immunotherapy, also referred to as hyposensitization and desensitization, is used to treat several conditions including allergic rhinitis and asthma (Cox et al. 2011) through modification of the immune system's response to allergens leading to tolerance. It involves administration of the allergen following specific schedules, some involving dose augmentation at regular intervals. A risk of anaphylaxis is inherent with this procedure and can lead to spontaneous abortion, premature labor, or fetal hypoxia in pregnant patients who develop systemic reactions (Cox et al. 2011). Currently, consensus is that initiation of subcutaneous immunotherapy for hyposensitization to aeroallergens is contraindicated in pregnancy but that it may be continued in those who are already receiving it at the time of conception, noting that doses should not be increased until after delivery in cases where the desired maintenance dose has not yet been achieved (Cox et al. 2011). Guidelines have refrained from making strong conclusions about sublingual immunotherapy, stating that data for pregnant patients are insufficient with regard to initiation or continuation of it during pregnancy (Greenhawt et al. 2017). Nevertheless, information available thus far is considered by some to be reassuring for being able to continue sublingual immunotherapy in those already receiving it (Oykhman et al. 2015).

18.11 Future Directions

There remains a great deal to be understood about asthma in pregnancy, particularly how physiologic changes in the immune system affect the condition and how the condition can reciprocally affect pregnancy in terms of maternal and fetal morbidity. The role that monoclonal antibody therapies targeting specific inflammatory pathways in asthma can play in the management of pregnant patients remains to be elucidated, as more safety data are gathered. Objective tests, such as FeNO measurement, which have potential in guiding treatment decisions, may facilitate personalizing asthma care as well as provide improved guidance to physicians for management decision-making. Their promise remains to be proven consistently.

Efforts to educate patients and empower them to manage their condition competently must continue to be made and may require a multidisciplinary approach to optimize outcomes.

Interventions during pregnancy aiming to reduce the occurrence of allergy and asthma in offspring are another area of interest, although not necessarily with direct impact on the patient's own asthma.

18.12 Conclusion

Asthma is common in the general population, and many pregnant women are affected by it. Since its pattern and severity can change during pregnancy in a significant number of women, close follow-up is important to adjust treatment promptly in order to prevent significant worsening and exacerbation. The goals of asthma treatment in asthmatic patients are to reduce and even eliminate symptoms, achieve optimal measures of pulmonary function, and keep exacerbations at bay. In pregnant patients with asthma, the goals are further expanded to include adequate fetal oxygenation at all times. Environmental and behavioral interventions include minimizing exposure to allergic triggers and cigarette smoking and are important features of asthma care. Many pharmacologic agents commonly used to treat asthma in the general population are safe to use in pregnant patients and include ICS and SABA. When necessary, LABA may also be used, along with several alternatives proposed in readily accessible national and societal asthma management guidelines. Patients experiencing exacerbations should be treated aggressively with adequate courses of systemic corticosteroids to minimize morbidity and risks to the fetus. In general, potential risks of adverse effects on fetal development and of perinatal complications from medications used in asthma treatment are considered to be outweighed by risks of poorly controlled asthma.

Well-controlled asthma is associated with good outcomes for pregnancy, and as asthma is a condition for which many safe treatment options exist for pregnant patients, good control is an achievable goal for every health-care provider and patient partnership. Patients should be guided and supported through any medication adjustment, with emphasis on encouraging adherence to treatment. When it is possible to do so, patients should be educated regarding the benefits that controlling asthma imparts on their health and that of their developing fetus, as well as the consequences of loss of control. Health-care providers can alleviate patient anxiety related to concerns about adverse effects of asthma medications on the developing fetus with confidence. Indeed, health-care providers can also stand to benefit from confidence-building education in order to remove hesitation about prescribing appropriate treatment to pregnant women with asthma.

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Cough and Allergic Diseases

19

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Abstract

Cough, including acute and chronic cough syndromes, is among the most common of human symptoms, heralding disease processes that range from the transient and insignificant to chronic and life-threatening. In this chapter, we consider cough that occurs in the context of allergic airway diseases including asthma, chronic rhinosinusitis, allergic rhinitis (AR) (CRS), and related allergic diseases. Acute cough lasting less than 3 weeks is usually due to respiratory tract viral or bacterial infections of the upper or lower airways. These infections usually require no specific therapy and are self-limited. In contrast, chronic cough persisting beyond 3 weeks has a broader differential diagnosis that is often related to irritating liquids arising from the upper or lower airway due to AR, CRS, or asthma. Stomach liquids refluxing into the pharynx can also produce cough and induce bronchoconstriction. Additionally, local anatomical structural and functional abnormalities, certain medications that interfere with bradykinin metabolism, and neurological issues such as vocal cord dysfunction can produce chronic cough. Central to distinguishing these conditions is evaluation for allergen sensitization and bronchial hyperresponsiveness testing in addition to obtaining a careful history and physical examination supplemented with direct laryngoscopy in selected patients. Treatment of the underlying disorder, discontinuation of offending medications, or behavioral therapy in the case of vocal cord dysfunction is usually successful in resolving the cough.

Keywords

Cough · Chronic cough · Post-infectious cough · Atopic cough · Postnasal drip · Gastroesophageal reflux · Laryngopharyngeal reflux · Asthma · Airway inflammation

19.1 Introduction

Cough is both a protective mechanism of the respiratory tract and one of the most common reasons for physician visits, especially in the context of allergic diseases such as allergic rhinitis (AR), asthma, and chronic rhinosinusitis (CRS). Effective evaluation of cough requires a thorough understanding of the contributing factors that underlie this often disabling symptom. History alone is of incomplete utility in cough evaluation; diagnostic studies and empiric therapy are essential to the workup and treatment of especially chronic cough.

19.2 Acute Cough

Cough can be classified according to its duration: a cough lasting 3 weeks is considered acute, whereas one that lasts greater than 3 weeks but less than 8 weeks is considered subacute. Cough lasting longer than 8 weeks is considered chronic. Causes of acute cough primarily involve infectious etiologies, raising the possibility that acute cough can evolve into subacute and chronic conditions depending on how successfully the underlying infection is resolved. The most common causes include upper respiratory tract infections (URI), acute viral bronchitis, and bacterial pneumonia.

URIs are most commonly caused by human rhinoviruses (HRV), adenoviruses, and enteroviruses: "the common cold" viruses. Symptoms are non-specific, usually including malaise, nasal congestion, rhinorrhea, sneezing, sore throat, and occasionally a low-grade fever that are most frequently self-limiting. Duration of symptoms can range from 3 to 10 days in healthy subjects and up to 2 weeks in smokers (Turner 1997) or longer in immunocompromised subjects. Cough can appear at any point in the evolution of URIs and is due to profound overproduction of mucoid and serous secretions from the upper respiratory tract combined with the irritant effect of viral-dependent mucosal epithelial disruption. While also usually self-limited, URI-related acute cough can evolve into chronic cough when complications such as asthma arise.

Acute viral bronchitis generally involves the lower airways, and attendant cough arises due to the same issues underlying cough in URI. Inhaled and systemic corticosteroids have not been found to be useful in the treatment of acute viral bronchitis, and antibiotics are also not indicated (De Sutter et al. 2012; Pavesi et al. 2001). If bronchitis is suspected to progress to pneumonia, a chest x-ray can be ordered to evaluate further, and antibiotics should be given in these more complex cases (Irwin et al. 2006).

A notable exception to this general rule is pertussis (whooping cough), a less common but more serious cause of acute and chronic cough. Often perceived to be an all but vanquished disease of childhood due to aggressive vaccination practices in the United States, pertussis has seen a resurgence in the United States over recent decades for reasons that are not entirely understood (Lapidot and Gill 2016). Pertussis is potentially lethal to infants but is also an important cause of disabling cough, and rarely death, in adults. As it is also highly contagious and curable with antibiotics, pertussis should remain high on the differential diagnosis of disabling acute cough in persons of all ages. Asthmatics are at particularly high risk for acquiring pertussis, perhaps due to chronic use of immunosuppressive corticosteroids (Capili et al. 2012).

19.3 Chronic Cough

A focused history and exam frequently elicit the underlying cause of cough but may mislead due to overlapping etiologies (Mello et al. 1996). In nonsmokers with a normal chest radiograph who are not on an ACE inhibitor, chronic cough is almost exclusively due to one or a combination of **"The 3 Rs"**: **R**hinitis and postnasal drip, acid **R**eflux and laryngopharyngeal reflux, and asthma-spectrum airway **R**eactivity. Allergic inflammation may play a supportive or etiologic role in these processes. URIs, including cough as a herald, are the most common cause of asthma exacerbation in children (Osur 2002; Rancière et al. 2013), and although individual exacerbations are usually short-lived, the recurrent nature of these episodes is consistent with a chronic condition.

The first widely accepted systematic approach to evaluating chronic cough was the "anatomic, diagnostic" protocol of 1981, which focused on etiologies that could activate afferent cough reflex receptors (prominently in the pharynx, larynx, trachea, and bronchi but also in the ear and thorax) – aforementioned conditions such as rhinitis, reflux, and asthma (Irwin et al. 1977, 1981; Irwin and Curley 1989; Irwin and Madison 2000). In recent years, focus has shifted to the *cough hypersensitivity syndrome*, a model that

proposes certain factors (notably rhinitis, reflux, asthma, ACE inhibitors) lead to overall hypersensitivity of the cough reflex; the result is a lowered threshold for cough (Escamilla and Roche 2014; Morice et al. 2014; Gibson et al. 2014).

Regardless of framework, the key to chronic cough evaluation involves a systematic evaluation and exploration of the triggering factors of cough and specific (often empiric) treatment for such. One framework that has been useful for our group is "LLLMN" – liquid, lung, local, medications, neurologic (Table 1):

- **Liquid** (liquid from above as postnasal drip, liquid from below as reflux or aspiration, or liquid from the lung).
- **Lung** (primary lung diseases).
- **Local** (local anatomic structural and functional issues; activation of peripheral cough receptors, such as in the ear).
- **Medications** (ACE inhibitors).
- **Neurologic** (vocal cord dysfunction, neurogenic).

Below we detail the evaluation and management of these etiologic conditions that may contribute to chronic cough.

Table 1 Causes of chronic cough

Causes of chronic cough "LLLMN"
Liquid
From above
Postnasal drip
From below
Reflux
Aspiration
From the lung
Lung
Primary lung disease
Local
Anatomic structure issues
Functional issues
Medications
ACE inhibitors
Neurologic
Vocal cord dysfunction
Neurogenic

19.4 Upper Airway Cough Syndrome (Postnasal Drip Syndrome)

Drainage of nasal secretions into the pharynx (postnasal drip, PND) is one of the most common causes of chronic cough. There are as of yet no objective tests for the diagnosis or grading of postnasal drip syndrome (PNDS), and furthermore it is unclear if PND is a direct cause of cough or acts indirectly to increase overall inflammation, irritation, and cough sensitivity. For these reasons, *upper airway cough syndrome* (UACS) has been suggested as a replacement for the term *postnasal drip syndrome* (Pratter 2006). Or perhaps PND as a symptom or syndrome is best discussed exclusively in terms of rhinitis, CRS, and the general cough hypersensitivity model.

Classically, patients with PND and UACS will describe a sensation of something draining into their throat, and a preceding viral upper respiratory illness is common. However, perhaps one-fifth of patients with UACS are unaware they have PND ("silent PND") or disease significant enough to be triggering their cough (Pratter 2006). Non-allergic rhinitis is a frequent cause of postnasal drip, although prolonged post-viral rhinitis and allergic rhinitis are not uncommon causes. Patients with CRS may also develop postnasal drip. Structural factors such as nasal septal deviation and turbinate or adenoid hypertrophy may likewise lead to postnasal drip (Irwin et al. 1977). Rhinitis medicamentosa arising from overuse of nasal vasoconstricting agents (ephedrine, oxymetazoline) may worsen postnasal drip in addition to congestion.

For patients with typical postnasal drip, improvement with an empiric trial of antihistamine and decongestant, or ipratropium bromide nasal spray particularly in non-allergic cases, would suggest PNDS/UACS might play a causative role; nasal decongestants should not be continued long term. PND symptoms without medication response should suggest additional workup with CT sinus and aeroallergen sensitivity testing if not already done so.

19.5 Lower Airway

Primary disease of the lung parenchyma and airways is a frequent cause of chronic cough, spanning the spectrum from cough-variant asthma and eosinophilic bronchitis to severe asthma with fungal sensitization (SAFS) (Denning et al. 2009). Destructive lung diseases such as chronic obstructive pulmonary disease (COPD) or interstitial lung disease (ILD) should be ruled out with non-contrast CT imaging, especially in patients with worsening symptoms and a history of smoking, occupational exposure, or autoimmune comorbidities. Smoking itself, leading to COPD, is the most common cause of chronic cough, and COPD patients are susceptible to developing concomitant asthma (Postma and Rube 2015).

Pulmonary function testing is required for the diagnosis of asthma. The hallmark of cough-variant asthma is significant reversibility of airway obstruction in response to a bronchodilator, sometimes seen in the absence of true obstruction as assessed by spirometry. Pulmonary specialist evaluation is warranted for significant lower airway symptoms.

In patients with significant lung disease, sensitization to aeroallergens including fungi, dust mites, and pollen may greatly contribute to the pathogenesis of cough, sinusitis, and chronic lung disease. Aeroallergen skin testing and evaluation for possible allergen immunotherapy, biologic immune-modulating therapy, or antifungal antibiotics are often beneficial for patients who cannot be controlled on first-line therapy.

In many patients, cough is due to factors affecting both the upper and lower airways, often in the context of more complex allergic airway disease. CRS with nasal polyposis is the primary allergic form of CRS and is often seen in the context of concomitant asthma (Bachert et al. 2010; Pakdaman et al. 2011; Porter et al. 2014; Rix et al. 2015; Langdon and Mullol 2016). Subjects with either CRS or asthma, but especially with combined moderate to severe upper and lower airway allergic disease, often suffer from a distinctive form of daily cough. This cough manifests, often exclusively, in the morning and is frequently productive of purulent sputum. Culture of this sputum using a modified technique (Mak et al. 2013) usually reveals the presence of multiple fungi, indicative of a relatively recently described type of fungal bronchitis termed airway mycosis (Pakdaman et al. 2011; Porter et al. 2014). Identification of allergic disease patients with productive cough is thus essential as part of the diagnostic workup of patients with airway mycosis who might benefit from antifungal therapy (Denning et al. 2009; Postma and Rube 2015; Li et al. 2018).

19.6 Gastrointestinal Causes of Cough

Gastroesophageal reflux disease (GERD) is defined as the retrograde movement of gastric liquids and solids from the stomach into the esophagus that results in dysfunction or damage to the esophageal mucosa. Common symptoms of GERD include heartburn, regurgitation, and a persistent sour taste. Involvement of the contiguous organs of the aerodigestive tract and occasionally the lower respiratory tract can result in a cough making GERD one of the three most common causes of chronic cough behind upper airway cough syndrome (UACS) and asthma. However, up to 75% of individuals with diagnosed GERD may have no concomitant gastrointestinal (GI) symptoms (Irwin and Madison 2000).

Of consideration, some of these patients without GI symptoms may be suffering from laryngopharyngeal reflux (LPR), a distinct but overlapping clinical syndrome caused by the reflux of gastric contents such as pepsin into the laryngopharynx. While GERD is primarily a defect in the lower esophageal sphincter, LPR is considered an upper esophageal sphincter problem (Koufman 2002).

The mechanisms for chronic cough symptoms in patients with GERD and LPR are similar and can result directly from gastric contents irritating the mucosa in the respiratory tract or indirectly via vagal reflex from acidification of the distal esophagus causing bronchoconstriction or cough.

Patients in which GERD is the suspected cause of chronic cough should be started on a proton

pump inhibitor (PPI) along with lifestyle modifications including weight loss in obese patients, avoiding oral intake 3 h prior to bedtime, and elevation of the head of the bed (Kahrilas et al. 2013). Procedures that can help diagnose GERD include 24-h esophageal pH monitoring and barium esophagography. Esophageal pH monitoring in the setting of chronic cough is best utilized by observing reflux-induced coughs rather than the usual diagnostic criteria for GERD (e.g., percentage of time where pH <4) (Irwin and Madison 2000). Barium esophagography helps determine if there is an esophageal lesion from nonacid GERD and can sometimes be the only test to reveal reflux. Treatment can be pursued empirically with a trial of PPI and lifestyle modifications with an expected response in 3 months (Kahrilas et al. 2016).

Treatment for LPR is controversial (Kahrilas et al. 2008), with some practitioners using an alginate-containing antacid, which creates a floating barrier that prevents reflux of aerosolized gastric particles into the upper airway.

19.7 Atopic Cough

Some practitioners distinguish an *atopic cough* (AC): upper airway atopy causing increased cough sensitivity in the absence of asthma. By definition, this cough is nonproductive and bronchodilator-resistant. Diagnostic criteria have been proposed (see Fujimura et al. 2003), but isolated AC is a diagnosis of exclusion, and the topic remains contentious. The prototypical AC patient would have a sensation of tickle or irritation in the throat with a nonproductive cough that does not respond to bronchodilators (in contrast to cough-variant asthma) in the setting of atopy, normal pulmonary function testing, normal bronchial responsiveness on methacholine challenge, and increased airway cough reflex sensitivity (Gibson 2004; McGarvey and Morice 2003; Fujimura et al. 1992, 2003; Magni et al. 2010).

As with other atopic conditions, immediate hypersensitivity skin testing or allergen serology is paramount for identification of offending aeroallergens. AC diagnosis requires exclusion of asthma-spectrum disease, and significantly a presumptive diagnosis of AC should prompt consideration of additional workup in the form of bronchoscopy and bronchoalveolar lavage to evaluate for peripheral airway eosinophilia and perhaps nasal endoscopy.

Treatment with histamine H1 antagonists and ICS or oral steroids should completely resolve cough in AC. Some reports further subclassify AC based on allergen, e.g., atopic fungal cough (AFC); in case reports of AFC, oral antifungal agents such as itraconazole displayed efficacy (Ogawa et al. 2014).

19.8 Throat Structural-Functional

Structural and functional pathology in the airway can cause cough: mass, foreign body, swallowing dysfunction (aspiration), and vocal cord dysfunction. Direct visualization with nasal endoscopy provides high diagnostic yield. Hypersensitivity of throat structures lowers the cough threshold, fitting into the aforementioned *cough hypersensitivity* model (Sandhu and Kuchai 2013; Gibson and Vertigan 2015; Hull and Menon 2015). Modified barium swallow is useful for evaluation of swallowing dysfunction, and speech therapy can improve vocal cord dysfunction, potentially in combination with relaxation techniques and biofeedback (Tarlo et al. 2016).

19.9 Medication-Induced Cough

19.9.1 ACE Inhibitors

A relatively common type B adverse drug reaction to angiotensin-converting enzyme (ACE) inhibitors is a chronic, nonproductive cough. The incidence of cough with ACE inhibitors likely exceeds 10% of patients treated with these agents (Sato and Fukuda 2015; Bangalore et al. 2010). Cough onset is typically days to weeks but may be protracted and misleading and should not preclude a trial off ACE inhibitor therapy. Resolution of cough typically occurs 1–4 weeks after medication cessation but may take up to 3 months (Sato

and Fukuda 2015; Humbert et al. 2017). Angiotensin II receptor blockers (ARBs) have a similar pharmacologic profile but without significant cough risk (Pinargote et al. 2014; Dicpinigaitis 2006; Caldeira et al. 2012).

The mechanism of cough with ACE inhibitors is related to interference in the metabolism of bradykinin, a type of tachykinin. ACE is one of several enzymes that function to proteolytically inactivate bradykinin. When ACE is inhibited, concentrations of bradykinin may increase, causing sensitization of airway sensory nerves and heightened cough sensitivity. The vasodilatory effect of bradykinin is responsible for ACE inhibitor-associated angioedema (Fox et al. 1996; Hewitt et al. 2016).

Although less frequently reported, ACE inhibitors may also trigger congestion, rhinitis, and postnasal drip (Pinargote et al. 2014).

19.9.2 Other Medications

Cough is a frequently reported post-marketing side effect of numerous medications, and a strong temporal history may suggest an etiology. Several cases of cough have been reported with sitagliptin, a dipeptidyl peptidase-4 inhibitor used in the treatment of diabetes; a similar link to angioedema possibly suggests a bradykinin-mediated mechanism (Gosmanov and Fontenot 2012; Baraniuk and Jamieson 2010).

19.10 Neurologic

Vocal cord dysfunction (VCD, or PVCM, paradoxical vocal cord movement) is a common asthma mimic (or co-existing condition) that may present as cough. Speech and behavioral therapy techniques usually provide benefit.

Neurogenic and irritative cough is a complex sensory condition and a true diagnosis of exclusion. As a learned process, it requires specialist and interdisciplinary evaluation (Yu et al. 2015; Gibson and Vertigan 2015). Various medications to reduce cough sensitivity have been suggested, but a full discussion of this topic is beyond the scope of this chapter (Yu et al. 2015; Gibson et al. 2016).

19.11 Miscellaneous

Cough may be a secondary result of dysfunction in other organ systems or illnesses, as seen in obstructive sleep apnea and pulmonary edema ("cardiac asthma"). Attention should be paid to comorbid medical illnesses.

19.12 Approach to General Evaluation and Diagnosis

In light of the unreliability of history and overlapping etiologies of cough, treatment is generally empiric and directed along few lines of therapy. Assessment of medication adherence is essential in judging response to any therapy.

19.13 Treatment (Table 2)

19.13.1 Liquid

- Nasal: Obvious nasal symptoms triggering cough should respond to a trial of intranasal steroids, oral or intranasal antihistamines, or intranasal ipratropium; failure warrants nasal endoscopy and sinus CT to evaluate for structural pathology or chronic rhinosinusitis. Intranasal steroids may require more than 2–4 weeks of adherent use to demonstrate full efficacy.
- Reflux: Reflux-related disease (exceedingly common and often "silent") should respond to a trial of PPI and dietary/lifestyle changes (no food 4 h prior to bed, no spicy foods, elevate head of bed 6 in. on blocks). Persistent GERD/LPR symptoms or visualization of signs on nasal endoscopy warrants referral to a gastroenterologist for EGD. Suspicion for aspiration should prompt a swallow evaluation. Proton pump inhibitors may require adherence to an 8-week trial; early cessation may not represent therapeutic failure.

Table 2 Treatment options for chronic cough

Summary of treatments
Nasal
Intranasal steroid, antihistamine, or ipratropium (counsel on technique and adherence) Second-generation oral antihistamines Failure of medications: Nasal endoscopy Sinus CT without contrast
Reflux
Proton pump inhibitor or acid suppression
Asthma spectrum
Albuterol inhaler, inhaled corticosteroids (Do not diagnose or manage asthma without spirometry) Failure of medications: Full pulmonary function tests Referral to pulmonary specialist
Vocal cord dysfunction
Speech therapy

19.13.2 Lung

Asthma-spectrum causes of cough should respond to an inhaled bronchodilator, and eosinophilic airway inflammation should respond to a trial of an inhaled corticosteroid or oral corticosteroid. Asthma-spectrum diagnosis requires spirometry and may necessitate pulmonary specialist referral for further evaluation or bronchoscopy.

19.13.3 Local

Throat or ear issues can be directly visualized with otoscopy and nasal endoscopy, perhaps in association with ENT evaluation, if needed.

19.13.4 Medications

Removal of the offending agent should produce resolution; but as noted in the section above, this may be delayed from cessation by several weeks.

19.13.5 Neurologic

Vocal training with a speech-language therapist is beneficial in vocal cord dysfunction. Various agents have been suggested for neurogenic cough with variable efficacy.

19.14 Allergy Evaluation

Atopy is a frequently comorbid factor in cough. Aeroallergen testing is useful to evaluate for underlying allergic inflammation that may be promoting the causes of cough. Testing is performed in an allergist's clinic by pricking the skin to small amounts of extracts of allergens such as dust mites, pollens, and fungi. Blood-based assays are also available but are less sensitive. Both tests may not reflect actual clinical reactivity and need to be interpreted in the light of the patient's symptoms. If sensitivities are present, allergen immunotherapy may benefit patients and their cough, especially those with rhinitis, conjunctivitis, asthma, and other atopic disorders.

19.15 Emerging Therapy

Biologic agents targeting IgE and IL-5 have anti-inflammatory effects in allergic disorders, suggesting that they may be highly effective in the context of allergy-related cough. These agents are also prohibitively expensive for the vast majority of patients who might potentially benefit from them. In patients with SAFS, antifungal therapy may play a role in reducing airway inflammation and thus cough by resolving the underlying airway mycosis.

19.16 Conclusion

Most cases of chronic cough can be traced to rhinitis, reflux, airway reactivity, and medications. Proper evaluation, empiric treatment, and managing patient expectations will produce a good outcome in most cases. Allergic inflammation probably underlies many of the causes of cough; patients with refractory symptoms should undergo aeroallergen testing and evaluation for immunomodulating therapies.

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Allergic Bronchopulmonary Aspergillosis

20

Kaley McCrary

Contents

Abstract

Allergic bronchopulmonary aspergillosis (ABPA) is an immunological lung disorder caused by a hypersensitivity to a fungal species, usually *Aspergillus fumigatus*. Although *A. fumigatus* is the most common etiologic agent, being responsible for approximately 90% of human infections, it is not the only pathogen in this genus. *A. flavus*, *A. terreus*, *A. niger*, and *A. nidulans* can also be responsible for human disease.

This disease was initially described in 1952, with the first patient to be diagnosed with ABPA in the United States reported in 1968 (Bierman et al. Allergic bronchopulmonary aspergillosis. In: Warren Bierman C, Pearlman DS, (eds) Allergy, asthma and immunology from infancy to adulthood. 1996. pp 566–571). This condition is estimated to effect more than four million patients worldwide (Agarwal et al. 2013a). It typically occurs in asthmatics and patients with cystic fibrosis (CF), manifesting with poorly controlled

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asthma, recurrent pulmonary infiltrates, and bronchiectasis. Indolent in nature, ABPA may begin in infancy or childhood but remain dormant or undiagnosed for years. Despite extensive research and over six decades of clinical experience, the pathogenesis, diagnosis, and treatment of this disease are incompletely understood. Primary therapy consists of oral corticosteroids and antifungals. Considering ABPA being a very manageable condition if treated in a timely fashion, it is becoming more imperative for clinicians to have the fundamental knowledge regarding the care of these patients in order to prevent delays in diagnosis and treatment, potentially preserving lung function.

Keywords
Aspergillus · Allergic asthma · ABPA · Hypersensitivity aspergilloses

20.1 Introduction

First described in 1952, allergic bronchopulmonary aspergillosis (ABPA) is an immunological lung disorder caused by a hypersensitivity response to *Aspergillus* antigens (Bierman et al. 1996). This condition primarily occurs in patients with asthma or cystic fibrosis and is thought to be polygenic in nature (Agarwal et al. 2013a). With ABPA, recurrent exposure to fungal spores elicits an allergic response, sending the immune system into overdrive, which facilitates an inflammatory cascade within the lung. Resulting bronchospasm and accumulation of thick mucus cause recurrent episodes of wheezing, shortness of breath, and intractable cough. Immunologically these patients exhibit peripheral blood eosinophilia; immediate cutaneous reactivity to *Aspergillus fumigatus* (*A. fumigatus*) antigen; increased specific IgE to *A. fumigatus*; elevated total levels of serum IgE, IgG, and IgM antibodies against *A. fumigatus*; and increased concentrations of IL-2 receptor (IL-2R). The significance of prompt diagnosis and treatment relates to improvement in patient symptomology and prevention of permanent lung damage. Although indolent in nature and slowly progressing, if left untreated, the chronic inflammation and subsequent tissue damage associated with ABPA may lead to central bronchiectasis, severe persistent asthma with loss of lung function, and pulmonary fibrosis (Patterson and Strek 2010). Despite extensive research of this condition and over six decades of clinical experience, the pathogenesis, diagnosis, and treatment remain incompletely understood.

20.2 Epidemiology

This disease occurs worldwide, and its true prevalence is unknown due to limited community-based data and confounding variables such as ethnicity, exposure risk, lack of uniform diagnostic criteria, and increased prevalence found in specialty clinics. Additional discrepancies include variability in laboratory reagents, expertise of personnel, and clinical under-recognition of ABPA. However, with the data available, the prevalence of ABPA is approximately 1–2% in asthmatics, 25–28% in those with asthma and a positive *Aspergillus* skin test (specific IgE), 7–14% in those with corticosteroid-dependent asthma, and 2–15% in patients with cystic fibrosis (Radojicic 2018).

20.3 Pathogenesis

Aspergillus fumigatus (*A. fumigatus*) is a spore-bearing fungus that is widely distributed in soil, air, sewage, swimming pools, basements, bedding, and decaying vegetation (Agarwal et al. 2013b). The spores of *Aspergillus* are 2–3 μm in size and able to grow in temperatures ranging from 12° C to 53° C. Its small size facilitates easy transit into the alveoli when inhaled. In the non-susceptible host, exposure to this microorganism is typically benign.

Upon inhalation, spores enter the tracheobronchial tree, activating elements of innate and adaptive immunity. In the non-susceptible host, the spores are removed by mucociliary clearance and phagocytosis without additional sequelae.

In susceptible individuals, such as those with asthma and cystic fibrosis (CF), the spores become embedded in the viscid sputum triggering a sequence of inflammatory reactions. The susceptibility of this condition is not that well understood but is thought to be mediated by genetically determined inflammatory responses in atopic patients. ABPA occurs most commonly in patients with asthma and CF, two conditions that are strongly associated with atopy. Patients with ABPA are also noted to have a higher rate of other atopic conditions (Agarwal et al. 2017).

The underlying airway disease in patients with asthma and CF results in a hypersecretion of mucous and impaired mucociliary clearance. This combination along with defects in the immune system results in persistence of *A. fumigatus* within the respiratory tract, allowing the spores to germinate into mycelia. The mycelia then release allergens provoking a robust immune response in hypersensitive individuals. The *Aspergillus* allergens induce IgE-mediated (type 1 reaction) and IgG-mediated reactions (type 3 reaction) that result in a more intense inflammatory condition in the airway than that seen with asthma alone. The proximal bronchi become dilated and filled with mucus plugs containing eosinophils and fungal hyphae (Radojicic 2018).

Fungal proteases secreted during germination of *A. fumigatus* illicit a neutrophilic inflammatory response. The proteases come in contact with the epithelial cells and macrophages of the bronchi and cause the release of IL-8, which recruit neutrophils. Neutrophils then release their granular contents, promoting further inflammation. This pro-inflammatory cascade results in airway destruction, mucus plugging, and primary central bronchiectasis (Farnell et al. 2012).

In patients with an underlying diagnosis of CF, the CFTR mutation serves as an independent risk factor for the development of ABPA. This condition develops in genetically susceptible patients due to the increased activity of Th2 CD4+ cell lymphocytes that are *A. fumigatus* specific, promoting a heightened inflammatory response. As stated previously, fungal spores are inhaled and persist within the bronchioles due to impaired mucociliary clearance and hypersecretion of mucus. Germination and mycelia formation lead to the release of antigens, which are then processed by antigen-presenting cells and presented to T cells in the bronchoalveolar lymphoid tissue. A Th2 CD4+ cell response facilitates the synthesis and secretion of pro-inflammatory cytokines IL-4, IL-5, and IL-13. Clinically, patients with dual diagnoses of CF and ABPA demonstrate severe deterioration in all lung function parameters. The development of ABPA, especially in the setting of chronic *Pseudomonas aeruginosa* infection, leads to airway narrowing, gas trapping, and small airway disease (Radojicic 2018).

20.4 Clinical Features

Patients suspected to have ABPA typically have a medical history of bronchial asthma, atopy, or CF and present with new-onset or worsening productive cough or episodic wheezing. Other symptoms include shortness of breath with or without chest tightness, fever, malaise, weight loss, hemoptysis, dyspnea, and chest pain. Thick mucus production is also common. Patients may cough up well-formed, tan to brownish-black mucus plugs (Ortega and Patterson 2017). Additional findings include digital clubbing in patients with long-standing disease and signs of hyper-aeration, including barrel chest and prolonged expiratory phase.

20.5 Diagnostic Tests

Aspergillus Skin Test: ABPA patients have a positive wheal and flare with immediate cutaneous hypersensitivity to *A. fumigatus* antigens. Positivity is indicated as anything eliciting >3 mm wheal. A wheal less than 3 mm may occur in patients who are sensitized to aspergillus or in patients with non-ABPA aspergillus diseases. Testing is performed by skin prick test or intradermal injection. If patient has a negative skin prick test and the diagnosis is highly suspected, intradermal testing should also be performed for confirmation. A positive skin test is highly sensitive for aspergillus sensitization (~94%) but not

specific for ABPA. Prior to testing it is important to make sure that the patient is not on systemic corticosteroids because this may skew the results, decreasing the degree of reactivity to the antigen placed during skin prick testing (Patterson and Strek 2010).

Elevated Eosinophil Count: Peripheral eosinophilia, or serum eosinophil counts >1,000 cells/μL, is a major diagnostic criteria in ABPA. *A. fumigatus*-specific IgE levels are also elevated. However, there is only moderate utility in the diagnostic value of eosinophilia due to its low specificity. Eosinophilia is associated with many other conditions, and levels can normalize after receiving systemic corticosteroid. During exacerbations, when oral corticosteroids have not been initiated, most patients exhibit an eosinophil count ranging from 1,000 to 3,000/μL.

Total Serum IgE Levels: This is a useful diagnostic tool in the initial diagnosis and follow-up of ABPA patients. IgE levels >1,000 ng/mL (>420 kU/L or IU/ml) are expected for a secure diagnosis. Diagnosis should be based on the serum IgE before therapy. Increases in serum IgE may be predicative of an impending exacerbation.

Examination of Sputum: A sputum culture may be performed, to evaluate for growth of aspergillus in the airway; however, this is not always reliable. Many individuals may have aspergillus growing in their airway but do not have ABPA. On the contrary, even with a negative culture, a person can still have the diagnosis of ABPA (Patterson 2010) (Fig. 1).

Radiological Manifestations: ABPA findings on chest X-ray are divided into either transient or permanent. Transient findings include pulmonary consolidations, which occur in up to 90% of patients with ABPA. Peri-hilar infiltrates occur in 40–77% of patients. Additional transient features include fleeting shadows, which are caused by mucoid impaction within the airway and indicate active disease, tramline sign (Fig. 3), V–Y-shaped or wineglass shadows (Fig. 2), toothpaste shadows, and gloved finger shadows. Irreversible manifestations include fibrotic change and central bronchiectasis with normal peripheral bronchi and pulmonary fibrosis. CT which provides an axial view of the lung is the imaging modality of choice in evaluating for bronchiectasis. Bronchiectasis tends to be localized to the upper lobes of the lung. On CT one may see the classic signet ring and string of pearls appearance (Fig. 4). Additional CT findings include pulmonary cavitation.

Bronchoscopy and Histology: Bronchoscopic evaluation, fungal culture, and histology are not required to make a diagnosis of ABPA. Bronchoscopy is usually performed in patients with ABPA when the diagnosis is unclear. Eosinophil counts and levels of IgA, IgG, IgM, and IgE are increased in bronchial lavage fluid. Given the lack of sensitivity or specificity of aspergillus culture, it is not required for diagnosis. Aspergillus detected on lung pathology, however, is diagnostically helpful. Lung biopsy like bronchoscopy is not necessary for diagnosis. If performed, findings include infiltration of airways by eosinophils and lymphocytes, goblet cell hyperplasia, bronchocentric granulomas with distal exudative bronchiolitis, mucoid impaction, and fibrotic changes in end-stage disease.

Concludingly, the sensitivity and specificity of diagnostic studies, respectively, are as follows: *Aspergillus* skin test positivity (94.7%, 79.7%); IgE levels>1000 IU/mL (97.1%, 37.7%); *A. fumigatus*-specific IgE levels >0.35 kUA/L (100%, 69.3%); *A. fumigatus* precipitins (42.7%, 97.1%); eosinophil count >1000 cells/μL (29.5%, 93.1%); chest radiographic opacities (36.1%, 92.5%); bronchiectasis (91.9%, 80.9%); and high-attenuation mucus (39.7%, 100%) (Agarwal and Maskey) (Fig. 5).

20.6 Stages of Allergic Bronchopulmonary Aspergillosis

ABPA is categorized into five stages, described as acute, remission, exacerbation, corticosteroid-dependent asthma, and end-stage fibrosis. Staging is usually performed at the time of initial diagnosis and repeated periodically. Stage 1 is characterized as the typical clinical presentation

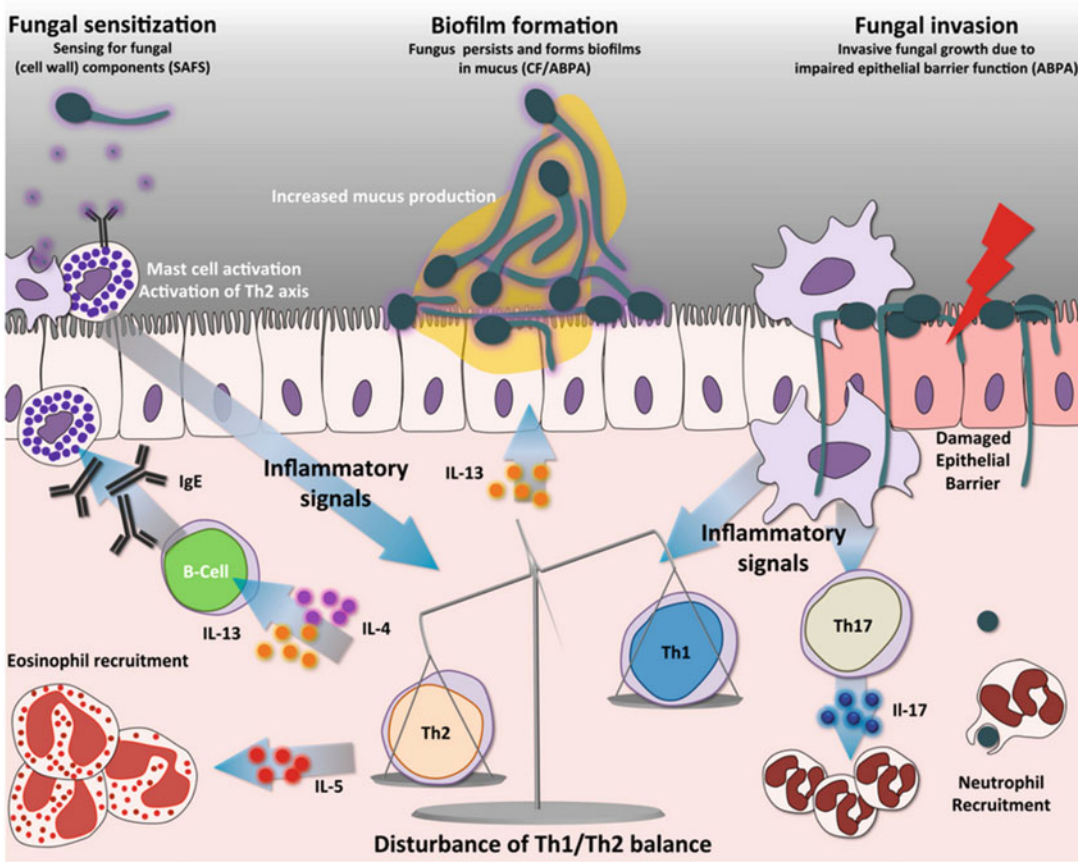

Fig. 1 During ABPA the pulmonary epithelial barrier can become compromised, allowing *A. fumigatus* to germinate and invade the tissues. A predominant non-protective Th2 response is a hallmark of this disorder. A distinct characteristic is that the high Th2 response creates an imbalance resulting in low protective Th1 responses. Th2 cells release different cytokines, among them IL-4 and IL-13, which trigger antibody class switching to IgE. In addition, these cytokines account for increased mucus production by respiratory goblet cells, and IL-5 triggers the recruitment of eosinophils. The absence of fungal clearance leads to continuous airway sensitization to fungal components, activating mast cells and the Th2 axis. Mast cell degranulation releases inflammatory mediators such as histamine and leukotriene, which also contribute to the inflammatory response. Activation of Th17 cells recruitment of neutrophils, partly contributing to the persistent immunopathology of these diseases. *EC* epithelial cell, *DC* dendritic cells, *AM* alveolar macrophages, *Th* T-helper cells, *IL* interleukin, *IFN* interferon, *TGF* transforming growth factor, *TNF* tumor necrosis factor, *AMP* antimicrobial peptide, *CTLA-4* cytotoxic T-lymphocyte antigen 4, *STAT* signal transducer and activator of transcription, *RORγt* RAR-related orphan receptor gamma t, *AHR* aryl hydrocarbon receptor, *t-Bet* T-box transcription factor 21, *GATA3* transcription factor GATA-3, *PU.1* transcription factor PU.1, *FOXP3* forkhead box P3 (Dewi et al. 2017)

for ABPA, characteristically with fever, cough, and sputum production with or without hemoptysis. In stage 2 patients demonstrate prolonged or permanent remission after treatment of stage 1 with corticosteroids. Also, radiographic findings are stable, and total serum IgE declines and remains stable for 6 months in the absence of continued systemic corticosteroid therapy. Stage 3 presents similarly to stage 1 with infiltrates on radiograph, marked elevations (>twofold increase) in serum IgE, and eosinophilia. Stage 4 is characterized by acute asthma exacerbation, return of pulmonary infiltrates on radiograph, or worsening asthma during a systemic corticosteroid taper. In stage 5 there is permanent pulmonary fibrosis demonstrated

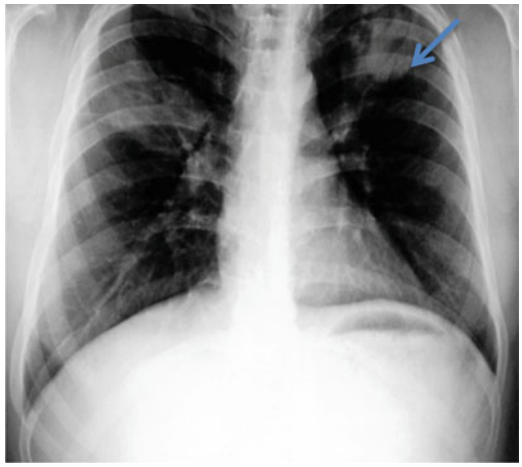

Fig. 2 Chest radiograph with characteristic wineglass opacity in the left upper zone (blue arrow). Non-homogeneous consolidation is also seen on the right side (Shah and Panjabi 2014; Reproduced with permission of the © ERS 2018: European Respiratory Review Mar 2014, 23 (131) 8–29; https://doi.org/10.1183/09059180.00007413)

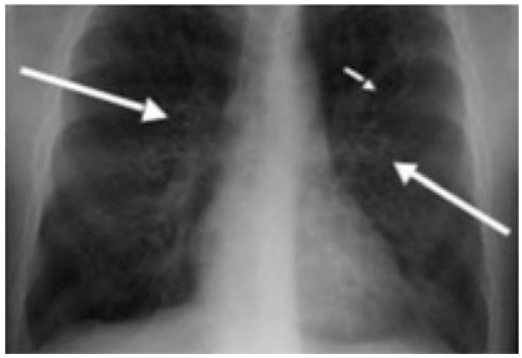

Fig. 3 Chest X-ray with ring shadows (long arrows) representing bronchiectatic airways; tram lines (short arrow) are also seen. (Reproduced with permission of the © ERS 2018: European Respiratory Review Mar 2014, 23 (131) 8–29; https://doi.org/10.1183/09059180.00007413)

with chest radiographs or CT and irreversible restrictive and obstructive pulmonary function (Shah and Panjabi 2014).

Stage 1: Acute
- Fever, cough, chest pain, hemoptysis, and sputum
- Infiltrates in the upper or middle lobe
- Serum IgE – markedly elevated

Stage 2: Remission
- Asymptomatic/stable asthma
- No infiltrate; off prednisone >6 months
- Serum IgE – elevated or normal

Stage 3: Exacerbation
- Symptoms mimicking acute stage or asymptomatic
- Infiltrates in the upper or middle lobe
- Serum IgE – markedly elevated

Stage 4: Corticosteroid-dependent asthma
- Persistent severe asthma
- Infiltrates absent of intermittent
- Serum IgE – may be normal

Stage 5: End-stage fibrosis
- Cyanosis and dyspnea
- Fibrotic, bullous, or cavitary lesions
- Serum IgE – may be normal

20.7 Screening

Screening for ABPA should not be performed in the general, asymptomatic population; however, it should be considered in high-risk patients, such as those with atopic asthma and cystic fibrosis. In asthmatics, the recommended initial screening test is skin testing for sensitivity to *A. fumigatus* antigen. If negative, diagnosis can be ruled out; a positive reaction warrants further investigation. In patients with cystic fibrosis, screening should be performed in individuals with a high level of suspicion for ABPA. Screening tests include annual specific IgE *A. fumigatus* levels and subsequent skin testing to *A. fumigatus* antigen if total serum IgE is markedly elevated (Radojicic 2018).

20.8 Diagnostic Criteria

There is currently no consensus for diagnostic criteria and standards differ among countries. In the United States, the most commonly accepted criteria required for a diagnosis of allergic bronchopulmonary aspergillosis are divided into major criteria and minor criteria (Cheezum and Lettieri 2008). The ISHAM Working Group[29] has proposed a set of revised criteria wherein the items are broadly divided into "obligatory" and "other"

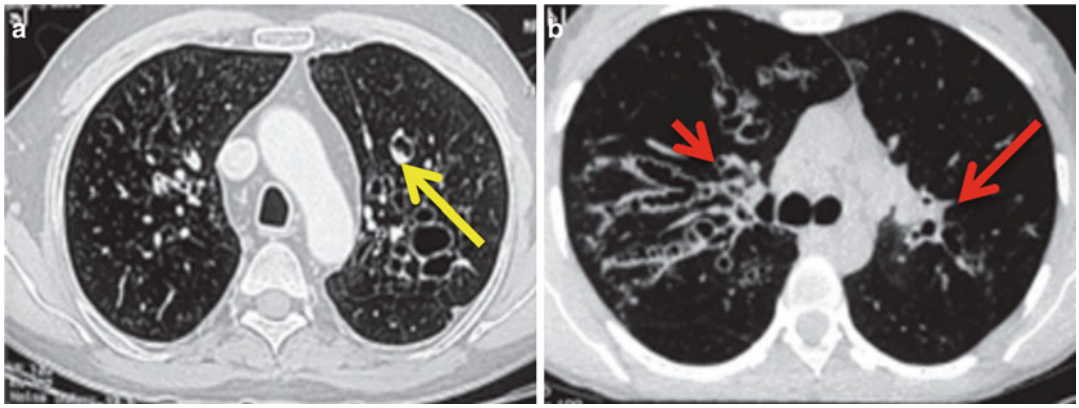

Fig. 4 (**a**) Computed tomography of the thorax with the classic signet ring appearance, indicative of central bronchiectasis (yellow arrow). (**b**) CT of the thorax with string of pearls appearance (red arrows) bilaterally also indicative of central bronchiectasis (Shah and Panjabi 2014; Reproduced with permission of the © ERS 2018: European Respiratory Review Mar 2014, 23 (131) 8–29; https://doi.org/10.1183/09059180.00007413)

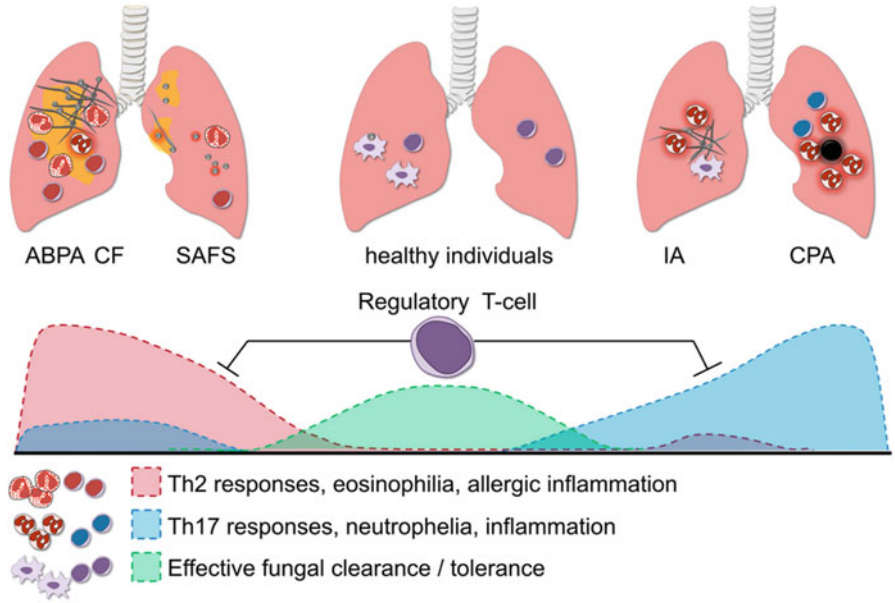

Fig. 5 Predominant Th2 response in allergic aspergilloses, such as ABPA and severe asthma with fungal sensitization, leading to persistent inflammation and fungal colonization (Dewi et al. 2017)

criteria. The two features of the obligatory criteria are as follows: (1) positive immediate (type I) cutaneous hypersensitivity to aspergillus antigen or elevated specific IgE levels against *A. fumigatus* and (2) elevated total IgE levels >1,000 IU/mL. Both of these findings must be present to establish a diagnosis of ABPA. At least two out of three other criteria should be fulfilled: (1) the presence of precipitating or IgG antibodies against *A. fumigatus* in serum, (2) radiographic pulmonary opacities consistent with ABPA, and (3) total eosinophil count >500 cells/μL in corticosteroid-naïve patients. However, these criteria need further refinement and validation (Shah and Panjabi 2016). Below lists the well recognized major and minor criteria regarding the diagnosis of ABPA.

Major Criteria

- *History of asthma or cystic fibrosis*
- *Central bronchiectasis on chest radiographs*
- *Immediate skin reactivity to Aspergillus*
- *Elevated total serum IgE (>1,000 ng/mL)*
- *Elevated IgE or IgG specific for Aspergillus*

Minor Criteria

- *Serum eosinophilia (>500/mm^3)*
- *Precipitating antibodies to A. fumigates*
- *Pulmonary opacities/infiltrates*
- *Mucous plugging*
- *Broncholiths*
- *Bronchial culture positive for Aspergillus*

20.9 Treatment

The treatment of ABPA aims to mitigate inflammation, suppress airway hypersensitivity, and/or reduce exposure to the fungal spores. Therapy is disease stage specific with the goal to prevent progressive loss of lung function. Systemic corticosteroids and antifungal agents are the two mainstays of treatment. Inhaled corticosteroids are used for asthma control but do not prevent the respiratory symptoms associated with acute ABPA exacerbation (Shah and Panjabi 2014).

Corticosteroids: Oral corticosteroid is the cornerstone and is the most effective treatment of ABPA. Dosing schedule and duration of therapy are variable and individualized. Once the diagnosis is made, therapy is initiated, usually with prednisone 0.5 mg/kg/day or equivalent as a single morning dose for 2 weeks (Greenberger 2014). Efficacy is evaluated by resolution of radiographic findings. If imaging remains stable or improved along with improvement in clinical status; corticosteroids are tapered to an alternate day schedule with the same dose for an additional 6–8 weeks. Serum total IgE should be measured monthly for the first 3 months. If levels decline by 35% with resolution of radiographic infiltrates, corticosteroid taper is continued with a decrease in the dose by 2.5–5 mg of prednisone or equivalent every 2 weeks. The patient should be monitored every 6–8 weeks to ensure remission once corticosteroid therapy is discontinued (Shah et al. 2016). Patients with stage 4 ABPA (systemic corticosteroid-dependent asthma) usually require alternate day therapy with prednisone 5–40 mg indefinitely for sustained symptom control. Patients with stage 5 ABPA usually require daily prednisone (usually 10–40 mg) or equivalent along with supplemental interventions for the management of cor pulmonale and arterial hypoxemia. In severe cases, pulse therapy with IV methylprednisolone 10–20 mg/kg/day for three consecutive days may be efficacious (Shah et al. 2016).

Antifungals: Antifungals are used as adjunctive therapy aimed to reduce the fungal burden. Azole antifungals (e.g., itraconazole, voriconazole, and ketoconazole) are effective against *A. fumigatus*. The mechanism of action of the azole class is inhibition of fungal cytochrome P450 CYP51A1, which catalyzes the conversion of lanosterol to ergosterol. Itraconazole improves clinical outcomes in some patients due to decreasing the length of therapy with oral steroids, due to the mitigation of fungal burden as described above. Recommended dosing of itraconazole is 200 mg twice daily for 4–6 months followed by a 4–6-month corticosteroid taper. Duration of therapy is contingent on response to treatment, severity of disease, and need for long-term use of corticosteroids. Some patients will require antifungal therapy indefinitely.

Itraconazole also has fewer systemic side effects than ketoconazole. Ketoconazole may cause severe liver injury and adrenal insufficiency by decreasing the body's production of corticosteroids, through the inhibition of the cytochrome P450 isoenzyme system. This drug should only be used for life-threatening fungal infections where alternative therapy is unavailable or not tolerated. If used, healthcare professionals should monitor adrenal function in patients taking ketoconazole who have existing adrenal problems or in patients who are under prolonged periods of stress such as those who have had a recent major surgery or who are receiving intensive care in the hospital (Center for Drug Evaluation and Research 2017).

Newer agents such as voriconazole have been reported to improve asthma severity by 70%.

However, skin cancer may be associated with prolonged use. Azole antifungals can have major interactions with other medicines, including increasing the systemic effects of corticosteroid therapy, and thus careful consideration should be given prior to prescribing (Radojicic 2018).

Environmental control: Patients should be counseled to avoid areas of possible exposure to *A. fumigatus*. This organism may occur in high quantities in dead and decaying organic matter, i.e., compost piles. Homes that have damp areas or have suffered from water damage, which facilitates that growth of fungi, could also be sources of exposure (Radojicic 2018).

Omalizumab: Omalizumab is a humanized monoclonal antibody against IgE that prevents binding of the IgE antibody to receptors on effector cells. Since there is a lack of randomized studies, routine use in patients with ABPA is not recommended. However, the limited data available demonstrate significant improvement in symptoms, pulmonary function tests, hospitalization episodes, and exacerbation rates. There is also a reduction in the usage of oral corticosteroids with omalizumab therapy. Recent studies in patients with ABPA with underlying asthma also demonstrate statistically significant improved symptom control, reduction in eosinophilia and total IgE levels, improved FEV_1, fewer asthma exacerbations, and decreased usage of oral corticosteroids during omalizumab therapy. Currently, omalizumab is considered in patients with corticosteroid dependence or in those with adverse reactions to corticosteroid therapy (Shah and Panjabi 2014).

20.10 Surveillance

Monitoring is recommended in patients with ABPA due to concern for asymptomatic exacerbations. After treatment with corticosteroid, total serum IgE should be checked every 2 months for 1 year. If the total serum IgE level does not decrease >35% over the first 8 weeks of therapy, this suggests possible non-compliance with medications or an alternative diagnosis. If serum IgE increases by >100% at any stage, repeat chest radiograph is indicated. Chest radiograph or CT chest should be repeated after 4–8 weeks of therapy for assessment of infiltrates. Pulmonary function testing and spirometry should be conducted yearly. A decrease in vital capacity of ≥15% may indicate an exacerbation of ABPA. Patients on long-term corticosteroids should have yearly eye exams, to check for cataracts and signs of glaucoma (Collins et al. 2012), and bone density measurement every 1–3 years along with glucose and cholesterol monitoring, at baseline, 1 month after corticosteroid initiation and then every 6–12 months thereafter (Liu et al. 2013). In patients using corticosteroids for longer than 2–3 months, physicians should consider implementing corticosteroid "prophylaxis" with vitamin D, calcium, and/or bisphosphonate supplementation, pending baseline bone mineral density analysis (Prasad 2010). Growth parameters should be followed in children on long-term corticosteroids.

20.11 Conclusion

ABPA is potentially progressive with potential permanent lung damage. The use of corticosteroid and antifungal therapy has improved the quality of life and prognosis of this disease. Although the pathophysiology and disease susceptibility of APBA is incompletely understood, disease awareness and diagnostic criteria facilitate recognition and timely therapy of affected individuals. Early recognition and therapy improve the clinical outcome in ABPA and likely prevent irreversible loss of lung function.

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Part V

Drug and Latex Allergy

Drug Allergy and Adverse Drug Reactions

21

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Abstract

Adverse reactions to drugs are common and may result in increased healthcare utilization and cost. It is important to distinguish between medication side effects and hypersensitivity, as recommendations regarding medication use and diagnostic testing depend on this classification. Hypersensitivity is driven by immune reactions to medications and can be categorized according to the Gell and Coombs classification, as discussed in this chapter. Hypersensitivity to antibiotics account for a

majority of allergic drug reactions. However, reactions can occur to almost any drug, and allergy to anesthetics, chemotherapeutic agents, NSAIDs, biologics, and radiocontrast are important considerations. This chapter will review the mechanisms and clinical features that underlie allergy to each of these classes of medications. Furthermore, approaches to diagnosis and management of drug hypersensitivity will be discussed. The chapter will also review severe drug reactions, such as Stevens-Johnson Syndrome, toxic epidermal necrolysis, acute generalized exanthematous pustulosis, and drug rash with eosinophils and systemic symptoms, as these are life threatening reactions that require immediate recognition.

Keywords
Drug allergy · Hypersensitivity · Desensitization · Mechanism

21.1 Introduction

Adverse drug reactions (ADRs) occur when a medication produces any noxious, unintended, or undesirable effects. These ADRs can be classified into two types: predictable (Type A) and unpredictable (Type B). Type A drug reactions are dose-dependent "side effects" related to the pharmacology of the drug, and account for at least 80% of ADRs. For example, an adverse reaction of urinary retention to ipratropium would be classified as "Type A," given its mechanism of action as an anti-cholinergic drug.

In contrast, Type B reactions are unpredictable and typically unrelated to the pharmacology of the drug. Type B reactions can be further subdivided into drug intolerance, idiosyncratic or pseudoallergic reactions, and drug hypersensitivity. Drug intolerances occur when an individual experiences a known adverse reaction at subtherapeutic drug dosage in the absence of abnormalities in metabolism, excretion, and bioavailability of the drug. An example is development of tinnitus with aspirin. Idiosyncratic reactions are often driven by pharmacogenomic effects, where genetic factors related to drug metabolism, drug–receptor interactions, or other effects in pathways regulated by a drug, result in ADRs. An example (as discussed later in the chapter) is aspirin exacerbated respiratory disease, as class effect of NSAIDs that lead to overactivity of the leukotriene pathway that leads to bronchospasm and airway inflammation. Along these lines, pseudoallergies occur when mast cells and basophils (or other immune cells) are directly activated by a drug mechanism that is not due to a specific antigen–receptor interaction (like specific interaction between the drug and IgE, IgG, or T-cell receptor).

True hypersensitivity reactions are immunologically-mediated reactions that are specific to a drug. Initially described in 1963, the Gell and Coombs classification of hypersensitivity reactions has become the most widely used approach for categorizing immune-mediated drug reactions (Coombs and Gell 1963). This system subdivides drug allergies into four different types: immediate hypersensitivity (Type I), cytotoxic (Type II), immune-complex reactions (type III), and delayed hypersensitivity (Type IV). Although some immunologic drug reactions may have unknown or mixed mechanisms, majority of drug allergies still fall in one of four types of Gell and Coombs classification. True hypersensitivity to drugs is an uncommon mechanism of ADR, though commonly implicated.

21.2 Importance of History and Diagnostic Testing for Drug Hypersensitivity

Because patients with drug allergies only represent a small amount of ADRs, a comprehensive history should be obtained to determine if the patient's presentation fits with an immunologic drug reaction. An accurate and exhaustive account of a patient's clinical presentation can help guide further diagnostic testing and management. These include decisions about whether or not the drug-in-question can be re-administered safely. In the case of Type A reactions, the causative drug can usually be used again in lower doses, or a different drug in the same family can be used.

When taking a history, the physician should focus on the previous and current medication use as well as the timeline of events from the initial drug introduction to the onset of symptoms. Details of such indications for taking the drug, dose, duration, and nature of symptoms should be established. Any previous exposure to the suspected offending drug or any other drug in the same structural class must be determined. Other concurrent medications must be verified as some of these drugs may be confounders, or even be the inciting trigger for the drug reaction. Specific information about the pharmacology and immunogenicity of the patient's medications can help determine which drug is the culprit.

The onset of symptoms relative to course of treatment with the suspected offending drug can ascertain if the patient's current clinical presentation is compatible with an allergic drug reaction. A thorough review of systems will help characterize the involved organ systems. Further, any underlying condition that can mimic or predispose a patient to allergic drug reactions should be determined. This information is crucial when diagnosing an allergic drug reaction. For instance, true hypersensitivity to a drug requires a previous sensitizing course, so a reaction that occurs with the very first dose should question whether it is a true allergy.

Furthermore, the types of symptoms that constitute the reaction are crucial to establish a mechanism, and physical findings during an acute reaction can be vital. Hypersensitivity reactions often present with exanthema. Urticaria and angioedema, particularly when they develop rapidly (minutes to an hour after administration of drug), are usually associated with Type I hypersensitivity reactions and can be associated with involvement of other organs (bronchospasm, gastrointestinal symptoms, hypotension). In contrast, Type IV reactions can be macular or maculopapular and usually take more than 1 week to develop. Rashes associated with bullous lesions or mucosal involvement can help to identify severe reactions like Stevens-Johnson syndrome or toxic epidermal necrolysis, where immediate discontinuation of a drug may be lifesaving. Other presenting symptoms of immunologic drug reactions including fever, arthralgia, lymphadenopathy, hepatosplenomegaly, and pleural irritation can be helpful to categorize the reaction and determine severity.

Laboratory evaluation during an acute reaction can also be crucial to establish a mechanism. Elevated liver enzymes or serum creatnine can point to severe, systemic drug reactions. When blood eosinophilia is present (particularly at levels >1000 cells/μl) in this setting, one should consider a diagnosis of drug rash with eosinophilia and systemic symptoms (DRESS) (Mckenna and Leiferman 2004). Urine eosinophils can be useful to diagnose intersititial nephritis. Furthermore, skin biopsy can be helpful to diagnose drug reactions and differentiate from other diseases. The number and types of inflammatory cell infiltrate, immunostaining, and gross histological findings can assist with establishing a diagnosis.

21.3 Mechanisms of Drug Hypersensitivity

21.3.1 Type I Drug Reactions

Type I, or immediate hypersensitivity reactions, is driven by IgE directed against a drug. As the case with all IgE-mediated reactions, an initial sensitization phase is essential to the pathophysiology. This usually occurs during the prior treatment course with the suspected offending drug. Although this phase is asymptomatic, the stage is set for an allergic reaction. Most small molecule drugs (chemicals) are too small to be immunogenic. However, some drugs can bind covalently to proteins in the blood, like albumin. The drug (acting as a hapten) and the protein (carrier) together form a "neo-antigen," which appears foreign to the immune system (Fig. 1) (Parker et al. 1962). In some cases, the metabolite of a drug acts as a hapten (sulfonamide antibiotics). The hapten–carrier complex can be taken up by antigen-presenting cells (APCs), where the complex is proteolytically degraded, and the covalently-linked drug-peptide complex is presented via MHC-II complexes. The APCs migrate to lymph nodes, where they encounter

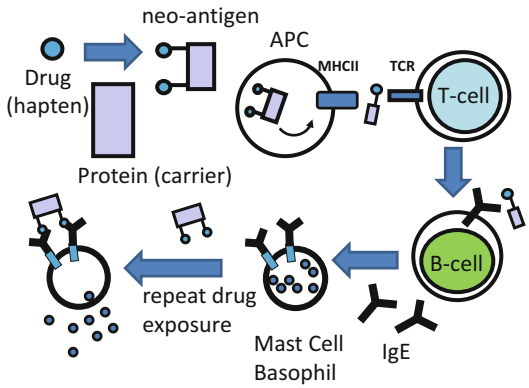

Fig. 1 Mechanism of type I drug hypersensitivity. The small molecule drug (hapten) covalently binds to a circulating protein (carrier). The complex appears foreign to the immune system (neo-antigen), is taken up by antigen presenting cells, proteolytically processed, and presented via MHCII to CD4+ T-cells. T-cells differentiate toward a Th2 phenotype, which promote class switching in B-cells towards IgE. The IgE binds to the surface of mast cells and basophils. On the next exposure to drug, the hapten–carrier complex binds to IgE and triggers degranulation

T-cells whose T-cell receptor (TCR) recognizes the drug-peptide complex, and drive differentiation of these cells down a Th2 lineage. These Th2-differentiated T-cells can promote IgE isotype switching in B-cells that produce antibodies that recognize the drug-peptide complex. These IgEs bind to mast cells and basophils, and will lead to activation of these cells on subsequent encounter of the drug. This process likely takes weeks, which explains why patients are asymptomatic during a course of therapy (like antibiotic treatment, with lasts typically for 7–14 days). Re-exposure to the drug results in activation of mast cells and basophils thereby producing the classic symptoms of allergic reactions that can include urticaria, angioedema, bronchospasm, nausea, vomiting, and hypotension. These symptoms typically have an onset of minutes to hours after re-exposure, and occur with the first dose. Furthermore, activation of mast cells and basophils require that two IgE molecules crosslink, so the hapten–carrier complex also needs to be "multivalent," or able to bind multiple molecules of IgE. Large molecular weight drugs, such as recombinant proteins or general anesthetics, can be large enough to bind to antibodies, and be multivalent. As such, these "complete" or "direct" allergens do not need to bind to a carrier. Humanized monoclonal antibodies, insulin, and vaccines are examples of direct immunogens.

The most widely-studied drug allergy is penicillin allergy. Penicillin is widely used and most of the population receives at least one course of penicillin by adulthood. The pathogenesis of penicillin allergy is drive by the classic hapten–carrier model. The beta-lactam ring of penicillin is a chemical group that makes them highly likely to covalently bind to circulating proteins (usually albumin). In normal physiologic conditions, penicillin readily forms various intermediates that can act as haptens (Parker et al. 1962). The most common is the penicilloyl moiety, also known as the major allergenic determinant of penicillin and is responsible ~60–85% of penicillin reactions. Penicillin can also isomerize to other intermediates such as penicilloate and penilloate that can also act as haptens. These minor determinant account for 10–20% of penicillin allergies.

Penicillin allergy is the most frequently reported drug allergy in the United States (Macy 2011). There are several known risk factors for developing penicillin allergies. Increased frequency of exposure to penicillin and parenteral route of administration have been hypothesized to contribute to the risk of developing a penicillin allergy (Contributors 2010). Having a personal history of atopic conditions such as allergic rhinitis or eczema and having a history of sensitivity to other drugs such as sulfonamides are also risk factors. Interestingly, children and elderly have lower rates of penicillin allergies and this may be attributed to an immature immune system in the former and a senescent immune system in the latter (Idsoe et al. 1968).

Although penicillin is the most commonly documented drug allergy, at least 90% of patients labeled with penicillin allergy are not truly allergic (Gadde et al. 1993; Blaxall et al. 2000). The true incidence of true penicillin allergy is about 1–3% (Contributors 2010). Patients labeled with penicillin allergies are often prescribed more expensive and broader spectrum antibiotics. Ultimately, this leads to higher health care costs and

has been associated with increased antibiotic resistance (Macy and Contreras 2014). In order to prevent needless avoidance of penicillin, and to identify the small number of patients who are truly allergic, it is crucial to perform allergy testing to this antibiotic.

21.3.1.1 Skin Testing to Diagnose Drug Allergy

Skin testing can be a crucial component of evaluation of Type I hypersensitivity drug reactions caused by penicillin and other drugs such as recombinant proteins, succinylcholine, and quaternary amines. For most of these drugs, skin prick testing with a full strength concentration followed by intradermal testing to 1:100 and 1:10 dilutions represents a typical protocol. However, the utility of skin testing to other small molecule drugs have poor skin test sensitivity. As skin testing to native drugs does not mimic the hapten–carrier as such, the sensitivity is usually low. In general, a negative test cannot rule out allergy but a positive test may represent a true allergy. However, this needs to be interpreted in the right context, as some drugs are irritating to the skin and cannot be tested in high concentrations. If skin testing will be performed to a drug without published irritating concentrations, it is best to perform multiple serial dilutions for prick and intradermal testing, and perform the test on a negative control subject in parallel. Another important limitation is that skin testing to drugs whose metabolites are the haptens (indirect haptens) is not useful. For instance, sulfonamide antibiotics are metabolized by the liver to a form that readily acts as a hapten, but is not present in the native drug that would be used for testing.

Penicillin testing is the most useful form of drug testing, as it is possible to use reagents that mimic the hapten–carrier complex. The major determinant can be mimicked using a poly-lysine polypeptide covalently-linked to penicillin in vitro. Furthermore, minor determinants can be produced chemically in vitro. When performed using major and minor allergic determinants, penicillin skin testing has a 99% negative predictive value (Gonzalo et al. 2007; Sogn et al. 1992). Thus, a negative result indicates no increased risk of type I hypersensitivity compared to the general population. However, the positive predictive value of penicillin skin testing has not been well studied (due to the inherent risk of challenging patients with positive skin tests), but some studies suggest it may be as low as 50% (Chandra et al. 1980; Sogn et al. 1992). Usually, patients with a positive test should avoid the medication and receive drug desensitization if penicillin is indicated. Major determinant of penicillin for skin testing is commercially available in the US, but not minor determinants. Most often, penicillin G can be substituted for the minor determinants with a slight drop in sensitivity to ~97% (Macy 2014). As a result, it is necessary to perform a challenge to penicillin in this setting to ensure that there was not a false negative skin test.

For drugs where skin testing is not available or not able to provide high sensitivity, a challenge can be considered. Usually this is performed by giving a small amount of a medication (10% dose) followed by a full dose. While this is the gold standard to determine true allergic status to a medication, it has to be weighed against risk. If a patient requires a specific medication on their allergy list, the decision whether to perform an oral challenge or drug sensitization depends on the history and clinical presentation of the suspected allergy and the clinician's index of suspicion for a true drug allergy. Oral challenge is typically performed in low risk situations where the degree of suspicion is low, while desensitization is done in moderate to high risk situations where there is a convincing history that fits with a recent allergic reaction.

Drug desensitization carries a risk of inducing an allergic reaction and requires a high amount of nursing care. The procedure must therefore be performed in a setting where the patient can be closely monitored such as the ICU. Prior to starting the desensitization, it is necessary to document that there are no other viable options as in the case of neurosyphilis. Epinephrine and oxygen must be available at bedside. The patient is initially administered a low dose, typically 1:10,000 dilution of the therapeutic dose. The dose is then increased two- to threefold every

Table 1 Sample drug desensitization table

Drug	Bag[a]	Dose #	Rounded dose (mg)	Rate (mL/h)	Infusion time (min)	Concentration (mg/mL)
Cefazolin	1	1	0.25	10	15	0.1
Cefazolin	1	2	0.5	20	15	0.1
Cefazolin	1	3	1	40	15	0.1
Cefazolin	1	4	2.5	100	15	0.1
Cefazolin	2	5	5	20	15	1
Cefazolin	2	6	10	40	15	1
Cefazolin	2	7	20	80	15	1
Cefazolin	2	8	25	100	15	1
Cefazolin	3	9	50	20	15	10
Cefazolin	3	10	200	40	30	10
Cefazolin	4	11	500	100	30	10
Cefazolin	5	12	750	100	30	15
Cefazolin	6	13	1000	100	30	20

[a]Bag concentrations: Bag 1, 5 mg/50 mL (0.1 mg/mL); Bag 2, 100 mg/100 mL (1 mg/mL); Bag 3, 500 mg/50 mL (10 mg/mL); Bag 4, 500 mg/50 mL (10 mg/mL); Bag 5, 750 mg/50 mg (15 mg/mL); Bag 6, 1000 mg/50 mL (20 mg/mL)

30 min. The cumulative dose must be kept track of especially when renal dosing. Desensitization can be maintained with once per day drug dosing. A sample protocol is shown in Table 1.

Penicillin is a member of the beta-lactam antibiotic class which includes cephalosporins, monabactams, and carbapenems. All these antibiotics contain a beta-lactam ring which is a four-member cyclic amide with three carbon atoms and one nitrogen atom. Because of their structural similarities, it was previously thought that there is a high rate of cross-reactivity among these antibiotic classes.

Studies have shown that the highest rate of cross-reactivity occurs between penicillin and first-generation cephalosporins, with a cross-reactivity rate of about 10% (Depestel et al. 2008). More recent studies have suggested that the actual cross reactivity rate may be even lower, but there is a lack of well-designed, prospective studies to address this question. Later generations of cephalosporins exhibit less cross-reactivity, which may be due to dissimilarity of the side chains between the two classes (Khan and Solensky 2010). If a penicillin-allergic patient requires a cephalosporin, a graded oral challenge with a cephalosporin containing a different side chain can be performed. Additionally, patients can also be skin tested to determine the presence of a cephalosporin allergy. Cephalosporin desensitization is also an option when indicated.

Carbapenem is another important beta-lactam antibiotic that was previously thought to have significant cross-reactivity with penicillin. In 2007, Romano et al. looked at 104 adult patients with skin testing-positive penicillin hypersensitivity (Romano et al. 2007). Of the 104 individuals, only 1 patient (0.9%) was skin test-positive for meropenem hypersensitivity. The remaining 103 were orally challenged to meropenem and were confirmed negative for meropenem allergy. A similar study involving 108 pediatric patients also reported similar findings of less than 1% cross-reactivity between penicillin and meropenem (Atanasković-Marković et al. 2008). Thus, while cross-reactivity between penicillin and carbapenem also exist, they occur at a much lower rate than previously expected.

Monobactams are beta-lactams that can be safely used in penicillin-allergic patients. The lack of a second ring structure makes monobactams unique, and may underlie the lack of cross-reactivity with penicillin.

It is also important to note that beta lactamase inhibitors (clavulante, sulbactam, tazobactam) are also beta lactams. The cross-reactivity to penicillin is low. However, allergy can occur to these agents specifically. As a result, patients that react to a penicillin–beta lactamase inhibitor combination need to be skin tested to both drugs (if available) and need to receive challenge to both.

21.3.2 Type II Hypersensitivity

Type II hypersensitivities are cytotoxic reactions mediated by IgM or IgG antibodies, and can be directed to a hapten–carrier complex. In type II reactions, the drug binds covalently to a cell surface protein on cells, which produces a neo-antigen. Typically, generation of IgG, or less commonly IgM, is responsible for hypersensitivity. The antibody then binds to the antigen on a cell surface, activates complement, and is cleared by macrophages.

The timing of the reaction may vary anywhere from 1 week to months after drug initiation. If a drug is stopped and reinitiated, symptoms can start within hours, due to presence of antibodies in circulation.

Cytolysis reactions can be serious and life threatening. Hemolytic anemias have occurred after treatment with quinidine, penicillin, and alpha methyldopa (Joint Task Force on Practice et al. 2010). A positive direct and indirect Coombs test may point to a drug specific IgG, complement, or Rh determinant autoantibody. Thrombocytopenia can occur secondary to a wide variety of medications, including heparin, vancomycin, and beta lactams. Drug–immune serum complexes mediate platelet membrane damage, which are then absorbed onto platelet membranes (Joint Task Force on Practice et al. 2010). As the case with most hypersensitivity reactions, management consists of withdrawal of the offending drug and future avoidance. Supportive care may be needed in the setting of severe anemia or thrombocytopenia.

21.3.3 Type III Hypersensitivity

Type III reactions are immune complex mediated, consisting of circulating antibody–antigen complexes. A drug carrier such as penicillin, procainamide, or a heterologous protein (e.g., animal thymoglobulin) acts as a soluble antigen and binds to IgG. Antigen–antibody equivalence leads to immune complex formation, which can deposit in tissue including blood vessels, joints, and kidney. The immune complexes activate complement or bind to Fc receptors on leukocyte cells. The resulting immune reactions can produce symptoms of vasculitis and organ-specific damage. Symptoms of serum sickness, including fever, rash, urticaria, lymphadenopathy, and arthralgias usually occur 1–3 weeks after drug exposure (Joint Task Force on Practice et al. 2010). Blood testing may show low complement levels (due to consumption) and skin biopsy can show immune complex deposition, though the sensitivity may be low. Management consists of withdrawal of the offending drug and symptomatic treatment with NSAIDs and antihistamines. Corticosteroids have not been well studied, but can be considered. In general, prognosis is excellent, but symptoms may last for weeks. It is generally recommended that patients continue to avoid the culprit drug, through it is not clear whether it can safely be used again years later.

21.3.4 Type IV Hypersensitivity

Type IV hypersensitivity, also known as delayed cell-mediated reactions are CD4+ or CD8+ T cell-mediated reactions. There are four subtypes, that are driven by the effects of T-cells on the following effector cells: monocytes (type IVa), eosinophils (type IVb), CD4/CD8 T cells (type IVc), or neutrophils (type IVd). There are two predominant mechanisms of T-cell activation. First, drugs can act as haptens, which then covalently link proteins, where are then taken up by APCs and presented to a T-cell, whose T-cell receptor (TCR) specifically recognizes the drug–peptide–MHC complex and lead to T cell activation (Fig. 2). Recently, a new concept of "p-i," or pharmacologic interaction with immune receptors has been proposed as a second model. In this concept, a drug does not act as hapten, but rather binds noncovalently to a MHC–peptide complex on the APC (without going through the typical antigen presentation pathway), facilitating interaction with a T cell receptor and leading T-cell activation (Pichler 2003; Schmid et al. 2006).

Reactions occur on a spectrum of severity, and from mild to severe. A macular drug reaction to antibiotics such as amoxicillin and sulfonomides is

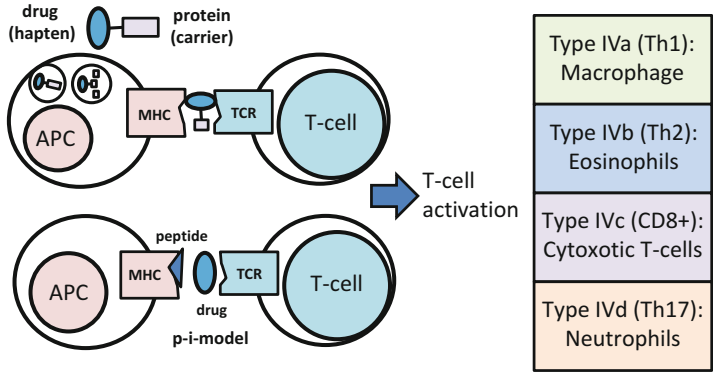

Fig. 2 Two mechanisms of T-cell activation in type IV hypersensitivity reactions. In the top model, a hapten–protein carrier is taken up by an APC undergoes proteolytic processing and is presented via MHC to a T-cell, whose T-cell receptor (TCR) recognizes the drug–peptide complex. In the bottom, "p-i" model, the drug binds noncovalantly to MHC–peptide complex, facilitating interaction with a T cell receptor (without proceeding through the antigen presentation pathway). T-cells can produced hypersensitivity via four main pathways (Type IVa–d), characterized by different effector cells and different clinical characteristics

one of the most common and mild in nature. These tend to be type IVa reactions and the drug can safely be used again. In type IVa reactions, T_H1 cells produce IFNγ and TNFα, which help to mediate macrophage activation. Patch testing may be used to verify contact dermatitis from topical medications.

Type IVb, IVc, and IVd reactions have the potential to be severe. Drug reaction with eosinophilia and systemic symptoms (DRESS syndrome) is a type IVb hypersensitivity reaction. T_H2 cells mediate secretion of IL-4, IL-5, and eotaxin, which recruit eosinophils. It has been proposed that a concomitant viral infection such as HHV6 and EBV leads to T cell activation, although it is also possible that DRESS syndrome itself, leads to viral reactivation (Shiohara et al. 2007). Aromatic anticonvulsants (phenytoin, phenobarbital, carbamazepine), dapsone, sulfonamides, allopurinol are known instigators. It can present days to months after medication initiation, with cutaneous eruptions, fever, lymphadenopathy, and eosinophilia that can then lead to liver failure, kidney failure, and death (Peyrière et al. 2006). The offending agent should be stopped immediately, and systemic steroids (usually with a long, tapering course over weeks to months) are helpful. However, resolution may still take weeks and symptoms can progress after drug discontinuation.

Once thought to be on the spectrum of severe exfoliative dermatitis, erythema multiforme is now recognized to be a distinct entity. It can present with targetoid lesions, is typically self-limited, and usually virally mediated. On biopsy, a mononuclear cell infiltration is seen. The offending agent should be withdrawn, and steroids may be needed.

In contrast, Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are examples of severe Type IVc reactions are T-cell, mediated via effects of CD8+ T-cells. The TCR-drug-specific cytotoxic T-cells induce widespread apoptosis of epithelial cells, which causes confluent purpuric macules on face and trunk, mucosal erosions, fever, and constitutional symptoms. Eventually, there is end organ damage, including eyes, liver, kidneys, and lungs. In SJS, there is detachment of $<10\%$ of the body surface; in TEN, there is detachment of $>30\%$ of the body surface (Bastuji-Garin et al. 1993a). If there is detachment of between 10% and 30% of the body surface, it is an SJS/TEN overlap. Over 100 medications have been implicated, including sulfonamides, cephalosporins, anticonvulsants, and steroids. Mortality may be as high as 50% (Bastuji-Garin et al. 1993b). Given the seriousness of these reactions, patient should be treated in an ICU setting or burn unit with attention to fluid balance, nutrition, eye

care, and pain management. Skin care consists of debridement of necrotic epidermis, artificial membranes on skin, and biologic dressings. Sepsis with *Staphylococcus aureus* and *Pseudomonas* species are frequent. Treatment with IVIG (usually at doses over 2 g/kg) may be helpful (Viard et al. 1998; Bachot et al. 2003). Glucocorticoid use is controversial, but should be avoided late in the course of TEN (Roujeau and Stern 1994; Tripathi et al. 2000).

In type IVd reactions, neutrophils are the primary effector cells, and production of cytokines like CXCL8 and GM-CSF from drug-specific T-cells are important in disease pathogenesis (Schaerli et al. 2004). Antibiotics and calcium channel blockers have been the most common drugs to be implicated in acute generalized exanthematous pustulosis (AGEP), the most common type IVd reaction. Patients develop widespread pustules on an erythematous base on the face or intertriginous areas. Biopsy shows intraepidermal pustules, marked papillary edema, and polymorphus perivascular infiltrates with neutrophils (Speeckaert et al. 2010).

21.4 Hypersensitivity to Nonantibiotic Drugs

21.4.1 Anesthetics

Reactions to local anesthetics are commonly reported, and symptoms like angiodema, flushing, hives, and tachycardia may occur. However, true allergy to local anesthetics may be extremely rare. In our clinic, for example, we have challenged over 250 patients with reported reactions to lidocaine and none have had a positive challenge. Our experience is similar to a recent publication by Kvisselgaard et al., who found no evidence of allergy to local anesthetics in 162 patients that underwent testing (Kvisselgaard et al. 2017). It may be that other agents (like narcotics) may confound the picture, or that swelling as a result of trauma (in dental procedures for example) may lead to an erroneous label of allergy. Protocols for skin testing to lidocaine and other local anesthetics are described (Berkun et al. 2003). In general, skin prick testing to full strength of the local anesthetic followed by intradermal testing to 1:100 and 1:10 dilutions can be performed, and if negative, a small volume can be injected subcutaneously as a challenge dose. In the rare event of a confirmed allergy, a different local anesthetic can be used (and skin testing/challenge can help to confirm safety). There are two major chemical classes of anesthetics that differ based on their hydrophilic amine side chains (amino amide vs. amino ester), and the typical approach would be to use a member of a different family if true allergy is established.

In contrast, hypersensitivity to other anesthetic agents is well described. Traditionally, drugs associated with general anesthesia are known to cause type I reactions. Members of the muscle relaxant families (succinylcholine, rocuronium) are multivalent compounds that can illicit drug allergy (Joint Task Force on Practice et al. 2010). These fit a classic picture of sensitizing course followed by an acute reaction, usually minutes after administration, which can produce cutaneous symptoms (hives, angioedema), bronchospasm, or hypotension. Skin testing can be very useful to confirm the presence of a type I reaction. Other agents that may be given as part of anesthesia, like antibiotics, propofol, benzodiazepines, or even skin cleansers, can cause allergic reactions; so often these may need to be considered for skin testing if a patient has an allergic reaction during surgery. In addition, latex allergy should be part of the differential, as exposure can occur with products such as gloves, catheters, or rubber components in syringes or vial stoppers.

21.4.2 Radiocontrast

Radiocontrast agents can produce reactions that can range from mild (rash) to severe (anaphylaxis). Some contrast agents, particularly those with high osmolarity, are known to trigger mast cell degranulation via non-IgE pathways. The symptoms of these reactions are indistinguishable from IgE-mediated reactions and can include urticaria, angioedema, bronchospasm, and/or hypotension. Unlike IgE-mediated reactions,

however, these reactions can occur with the first exposure to the contrast. Most of the time, premedication with oral corticosteroids (prednisone 50 mg 13 h, 7 h, and 1 h prior to procedure) and antihistamines (diphenhydramine 50 mg, 1 h prior to procedure) are effective in preventing contrast reactions. Recent publications have indicated that some patients may develop IgE-mediated reactions to contrast, and premedication may not be helpful in this group (Sese et al. 2016; Morales-Cabeza et al. 2017; Trcka et al. 2008). In these cases, choosing a different contrast agent is recommended.

21.4.3 Angiotensin-Converting Enzyme Inhibitors

Angiotensin-converting enzyme (ACE) inhibitors commonly cause cough and angioedema, and these side effects may be mediated by overabundance of bradykinin, a substrate of ACE. The cough occurs anywhere from hours to months after initiation, is dry in nature, and is possibly mediated by bradykinin, substance P, or another mechanism (Nussberger et al. 2002). ACE inhibitor related angioedema can occur hours to years after drug initiation, and accounts for around 1/3 of patients presenting to the emergency department for angioedema (Banerji et al. 2008). Swelling is most often in the head and neck, but laryngeal edema can occur as well. For these patients, they should be switched to an alternate medication, such an angiotensin II receptor blocker.

21.4.4 Biologics

The development and use of immune modulators has dramatically increased in recent years. Reactions can develop as a result of the mechanism of action of these agents, because of hypersensitivity, or because of off-target effects. Some reactions are directly related to high cytokines or from cytokine release, like in capillary leak syndrome, which can be caused by IL-2, GM-CSF, and G-CSF. Patients can develop fever, pulmonary edema, ascites, pleural effusions, pericardial effusions, hypotension, hypoalbuminemia, multiorgan failure, and death. Cytokine dysregulation also lead to immune dysregulation, like autoimmunity.

IVIG is associated with infusion reactions varying from headache, fever, chills, tachycardia, anxiety, nausea, dyspnea, arthralgia/myalgias, and more seriously, hypotension. This reaction is possibly from immunoglobulin aggregates, antigen–antibody complexes, and contaminant vasoactive proteins leading to activation of complement (Ballow 2007).

Biologics can also cause hypersensitivity reactions, through antibody or cell-mediated effects (González-López et al. 2007). Antibodies that contain foreign sequences (like mouse), as the case for the chimeric antibody infliximab, have potential to cause IgE-mediated reactions. Reactions include urticaria/angioedema, hypotension/hypertension, chest pain, fever, and dyspnea (Campi et al. 2007). In some cases of non-IgE reactions, patients can continue with reduced rate or with premedication (Cheifetz et al. 2003). In other cases, it is necessary to switch to a different agent or perform desensitization every time a patient needs the medication. Other mechanisms of hypersensitivity can occur, and patients can have delayed serum sickness like reactions with urticaria/angioedema, fevers, and myalgias. Etanercept, and less commonly adalimumab, can cause these delayed reactions, which usually happen within first 2 months of therapy, and generally does not require discontinuation.

21.4.5 NSAIDs

Reactions to NSAIDs may occur via a variety of mechanisms that ranges from idiosyncratic to hypersensitivity. Aspirin and NSAIDs can cause urticaria, angioedema, anaphylaxis, underlying respiratory disease, and sometimes pneumonitis and meningitis. In the case of IgE-mediated reactions, there is a sensitizing dose of the medication, followed by reaction with the subsequent dose. Symptoms are typical of IgE-mediated reactions, and can produce anaphylaxis. Typically, IgE is specific to a particular NSAID and the patient

can use other NSAIDs without a reaction (Joint Task Force on Practice et al. 2010).

However, the mechanism of reaction can be difficult to elicit based on history. Patients with underlying chronic urticaria/angioedema may experience worsening of symptoms with NSAIDs. NSAIDs may also provoke urticaria/angioedema via idiosyncratic effects, perhaps through its effects on COX-1 inhibition (leading to excess leukotriene production). This may be the mechanism of cutaneous effects in patients with underlying chronic urticaria/angiodema, but can occur in patients without this diagnosis.

Often, idiosyncratic effects of NSAIDs are associated with respiratory symptom. Aspirin exacerbated respiratory disease (AERD) is a condition where patients with chronic respiratory diseases (asthma, rhinitis, sinusitis, nasal polyposis) develop respiratory reactions in response to aspirin or NSAIDs. In fact, it is expected that these symptoms are 100% cross-reactive to non-selective COX inhibitor (due to inhibition of COX-1 effects). It affects up to 20% of adult asthmatics, usually starts around 30 years old, and affects women more than men (Stevenson and Szczeklik 2006). After taking aspirin/NSAIDs, patient can develop rhinoconjunctivitis and bronchospasms, which can be severe enough to require mechanical ventilation. AERD usually presents as rhinitis, and then progresses to hyperplastic sinusitis, nasal polyposis, and possibly asthma. Gastrointestinal symptoms and urticaria are possible extrapulmonary manifestations. The development of this condition involves increased cysteinyl leukotriene production, increased inflammatory cells expression of cysteinyl leukotriene 1 receptors, and increased airway responsiveness to the leukotrienes. Aspirin/NSAIDs inhibit COX-1, leading to decreased prostaglandin E2 levels, thus increasing arachidonic acid metabolism through 5-lipoxygenase pathway, leading to increased cysteinyl leukotriene production. Since the effect is mediated through COX-1, AERD is not usually associated with COX-2 inhibitors or acetaminophen (though high doses >1000 mg has been reported to trigger respiratory symptoms in some patients). Diagnosis can be confirmed with a controlled oral challenge with aspirin. Desensitization to aspirin is an effective method to reduce polyp formation, reduce need for future sinus surgeries, improve asthma control, and allow patients to take NSAIDs (for pain control or use aspirin for cardiovascular reasons) (Stevenson 2009; Macy et al. 2007).

21.4.6 Chemotherapeutic Agents

Hypersensitivity reactions are associated with most chemotherapeutic agents. Taxanes (paclitaxel, docetaxel) can cause non-IgE-related immediate anaphylactoid reactions, often with first administration. Pretreatment with steroids and antihistamines helps to prevent anaphylaxis in most cases (Eisenhauer et al. 1994). Platinum compounds (cisplatin, carboplatin, oxaliplatin) can cause hypersensitivity reactions after several treatments, and are thought to be IgE-mediated. Cetuximab is a monoclonal antibody used in colorectal cancer, and can cause IgE-mediated anaphylaxis (Chung et al. 2008). Drug desensitization procedures have been successful (Castells et al. 2008).

21.4.7 Drug Reactions in HIV

Anti-retrovirals have been associated with reactions ranging from mild rashes to SJS/TEN. Abacavir is a nucleoside reverse transcriptase inhibitor associated with a hypersensitivity reaction of fever, rash, fatigue, respiratory symptoms, and GI symptoms in 4% of treated patients (Hetherington et al. 2001). Recent studies showed an association between the HLA-B*5701 gene and hypersensitivity, and subsequent screening reduced reaction rates significantly (Young et al. 2008). Observations show that patients with HIV have an increased chance of drug-induced reactions (Davis and Shearer 2008).

In HIV positive patients, the incidence of a generalized maculopapular eruptions, fever, and pruritis a few weeks after initiation of trimethoprim/sulfamethoxazole is significantly increased (Dibbern and Montanaro 2008). Induction of drug tolerance can be performed in these patients to use trimethoprim/sulfamethoxazole in

the future. Sulfonamide antibiotics (sulfadiazine, sulfamethoxazole) are a common cause of drug induced allergic reactions (Dibbern and Montanaro 2008). They are the most common cause of SJS/TEN (Roujeau et al. 1995). Delayed reactions to sulfonamides are mediated through the N4 aromatic amine and N1 substitute ring, but since nonantibiotic sulfonamides lack these structural components, they do not cross react with sulfonamide antibiotics (Strom et al. 2003).

21.5 Conclusion

Drug hypersensitivity reactions occur via different immunological mechanisms and have different clinical presentations. It is important to perform thorough history and physical exams, as these are crucial to characterizing the mechanism of drug allergy. It is particularly important to identify severe drug allergy syndromes (e.g., SJS, TEN, DRESS, AGEP), as these can be life threatening. Skin testing can be useful for Type I hypersensitivity reactions, but there is a great need for development of diagnostic tests for other hypersensitivity reactions. Although much of the drug allergy literature has focused on antibiotic allergy, hypersensitivity/pseudoallergic reactions to anesthetics, chemotherapeutic agents, NSAIDs, biologics, and IV contrast are important considerations. Evaluation and management of these drug reactions varies by the nature and mechanism of reaction to these medications.

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Penicillin Allergy and Other Antibiotics

22

Thanai Pongdee and James T. Li

Contents

Abstract

Penicillin allergy is commonly diagnosed, reported in approximately 8% of the general population and 10–15% of hospitalized patients. Although penicillin allergy is widely reported, 80–90% of individuals with self-reported penicillin allergy are actually able to tolerate penicillins after undergoing evaluation for penicillin allergy. Since the majority of patients with self-reported penicillin allergy will have subsequent negative allergy testing and tolerate penicillins, they may be unnecessarily exposed to broader spectrum antibiotics. Use of such antibiotics leads to increased risks of developing antibiotic resistant microorganisms and incur greater health care utilization costs. Penicillin allergy evaluation and management should be a core component of antibiotic stewardship and can significantly improve health care quality and value for individual patients and health care systems as well as the public at large. Key knowledge points to effectively evaluate and manage patients with penicillin allergy discussed in this chapter include (1) clinical

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manifestations of penicillin allergy; (2) utility of clinical history; (3) methods for penicillin allergy testing; (4) management options based on testing results; and (5) penicillin allergy cross-reactivity with other beta-lactam antibiotics.

Keywords
Drug · Allergy · Penicillin · Cephalosporin · Carbapenem · Monobactam · Beta-Lactam

22.1 Introduction

Penicillins (see Table 1) represent the most common antibiotic class prescribed both in the USA and worldwide (Hicks and Taylor 2013; Van Boeckel et al. 2014). Antibiotics are indisputably one of the most successful medical therapies developed in the history of medicine, enabling the control of infectious diseases that were once lethal and facilitating other medical advances such as cancer chemotherapy and organ transplantation (Aminov 2010; CDC 2014). Although the prompt use of antibiotics to treat infections has been proven to reduce morbidity and mortality, judicious decisions for antibiotic selection and initiation must be employed.

Penicillin allergy is the most commonly reported drug-class allergy in the United States (Macy 2014). As penicillins are the treatment of choice for many types of common infections, clinical decisions regarding penicillin allergy evaluation and management significantly impact both individual patient care and public health. The prevalence of self-reported penicillin allergy is approximately 8% of the general population and 10–15% of hospitalized patients (Macy 2014; Apter et al. 2008; Lee et al. 2000). Strikingly, although penicillin allergy is commonly reported, several studies demonstrate that 80–90% of individuals with self-reported penicillin allergy are actually able to tolerate penicillins after undergoing evaluation for penicillin allergy. Thus, the vast majority of patients who report penicillin allergy are unnecessarily avoiding penicillin class antibiotics as either their penicillin allergy waned over time or prior reactions should not have been attributed to penicillin (Solensky and Khan 2010).

Currently, most health care providers avoid prescribing penicillin or related beta-lactam antibiotics in patients with self-reported penicillin allergies. However, using alternative antibiotics without further evaluation of self-reported penicillin allergy has significant ramifications, especially regarding costs and antibiotic resistance. Antibiotic costs are 63–158% higher in those with reported penicillin allergy than for those not allergic to penicillin. Moreover, patients labeled as penicillin allergic have significantly longer hospitalizations with associated increased costs (Sade et al. 2003; Picard et al. 2013; Li et al. 2014; Macy and Contreras 2014). In one specific healthcare system, evaluation of penicillin allergy with testing and consultation resulted in savings exceeding $2 million over a 3.6-year time period (Macy and Shu 2017).

Not only does self-reported penicillin allergy lead to significantly increased costs but it may also contribute to the threat of drug resistant microorganisms. Commonly used alternatives to penicillin, such as vancomycin, clindamycin, and fluoroquinolones are clearly associated with the development of resistant organisms such as vancomycin resistant Enterococcus and increased rates of Clostridium difficile. The Centers for Disease Control and Prevention recently estimated that more than two million people have

Table 1 Classification of Penicillins (Wright and Wilkowske 1991)

Natural penicillins
Penicillin G
Penicillinase, antistaphylococcal penicillins
Nafcillin
Oxacillin
Cloxacillin
Dicloxacillin
Aminopenicillins
Ampicillin
Amoxicillin
Carboxypenicillins
Carbenicillin
Ticarcillin
Ureidopenicillins
Piperacillin

infections with antibiotic-resistant microorganisms each year, resulting in 23,000 deaths annually (CDC 2014).

Since the majority of patients with self-reported penicillin allergy will have subsequent negative allergy testing and tolerate penicillins, they may be unnecessarily exposed to broader spectrum antibiotics. Use of such antibiotics leads to increased risks of developing antibiotic resistant microorganisms and incur greater health care utilization costs. Therefore, penicillin allergy evaluation and management should be a key component of antibiotic stewardship and can significantly improve health care quality and value for individual patients and health care systems as well as the public at large.

22.2 Penicillin Allergy

22.2.1 Overview of Drug Allergy

Adverse drug reactions (ADRs) are defined by the World Health Organization as any noxious, unintended, and undesired effect of a drug that occurs at doses typically used in humans for prevention, diagnosis, or treatment (World Health Organization 1969). ADRs are further categorized into Type A and Type B reactions. Type A reactions are predictable and are usually dose dependent. Type A ADRs are related to the known pharmacologic actions of the drug and occur in otherwise healthy individuals. Type A reactions account for approximately 80% of all ADRs and may be further subcategorized into side effects, overdose, secondary effects, and drug interactions (Khan and Solensky 2010). Type B reactions are generally unpredictable and may not be reliably dose dependent. Type B ADRs are mediated by mechanisms other than the pharmacologic activity of the drug. Approximately 20% or less of ADRs are Type B reactions, the majority of which are considered to be due to drug allergy (Wheatley et al. 2015).

Drug allergies encompass adverse reactions for which a definite immunological mechanism is demonstrated. Immune mechanisms in drug allergic reactions may involve drug-specific antibodies and/or activated T cells directed against the specific drugs or its metabolites (Demoly et al. 2014). The traditional Coombs and Gell classification system of hypersensitivity (see Table 2) is the most common method to describe the types of immunological mechanisms involved in drug allergies (Coombs and Gell 1975). Of these pathophysiologic mechanisms, the most common drug allergic reactions are IgE- and T-cell-mediated (Demoly et al. 2014).

22.2.2 Classifications and Clinical Manifestations of Penicillin Allergy

Penicillin and other drug allergic reactions may be classified as either immediate- or delayed-onset depending on the onset of signs and symptoms after exposure to the allergen. Immediate-onset drug allergic reactions are typically IgE-mediated and occur within minutes to hours of exposure from the last drug administration (Demoly et al. 2014). Drug exposure generates drug-specific IgE antibodies that attach to the high-affinity receptors on the surface of mast cells and basophils. Subsequent drug exposure binds IgE and cross-links these receptors, resulting in the release of preformed mediators, such as histamine and tryptase, and also triggering the production of new mediators such as leukotrienes, prostaglandins, kinins,and various cytokines (Corry and Kheradmand 1999; Demoly et al. 2014). Symptoms of immediate reactions may include urticaria, pruritus, angioedema, rhinitis, conjunctivitis, bronchospasm, gastrointestinal symptoms (nausea, vomiting, or diarrhea), or anaphylaxis and anaphylactic shock. Penicillin allergy is the best defined immediate-type drug allergic reaction (Demoly et al. 2014).

In contrast to immediate reactions, delayed-onset drug allergic reactions may occur at any time from 1 h after the initial drug administration. Delayed-onset reactions usually occur days to weeks after initial drug administration and are associated with a T-cell-dependent immune mechanism. The majority of delayed-onset reactions are uncomplicated cutaneous manifestations

Table 2 Classification and clinical symptoms of drug hypersensitivity (Coombs and Gell 1975; Pichler 2003)

Extended Coombs and Gell classification	Type of immune response	Pathologic characteristics	Clinical symptoms	Cell type
Type I	IgE	Mast cell degranulation	Urticaria, anaphylaxis	B cells/ immunoglobulin
Type II	IgG	Fc receptor dependent cell destruction	Blood cell dyscrasia	B cells/ immunoglobulin
Type III	IgG and complement	Immunocomplex deposition	Vasculitis	B cells/ immunoglobulin
Type IVa	Th1	Monocyte activation	Eczema	T cells
Type IVb	Th2	Eosinophilic inflammation	Maculopapular exanthema, bullous exanthema	T cells
Type IVc	Cytotoxic T cells	C4- or CD8-mediated killing of cells	Maculopapular exanthema, bullous exanthema, pustular exanthema	T cells
Type IVd	T cells	Neutrophil recruitment and activation	Pustular exanthema	T cells

such as maculopapular exanthemas and delayed urticaria. However, delayed-onset reactions also include severe reactions that may be life-threatening such as Stevens-Johnson syndrome, toxic epidermal necrolysis, DRESS (drug reaction with eosinophilia and systemic symptoms), and vasculitis (Wheatley et al. 2015).

22.2.3 Penicillin Structure and Immunogenicity

The penicillin molecule has a core bicyclic structure consisting of a four-member beta-lactam ring and a five-member thiazolidine ring (see Fig. 1, Levine and Ovary 1961). The allergenic components of penicillins are derived either from the beta-lactam ring core or from a specific R-side chain group. The beta-lactam ring structure is shared among penicillin-related antibiotics such as cephalosporins, carbapenems, and monobactams. R-group side chains differentiate antibiotics within these related beta-lactam classes (Zagursky and Pichichero 2017).

Penicillin's molecular structure is not sufficient in size to be immunogenic unto itself. Penicillin is chemically inert in its natural state, and the beta-lactam ring opens spontaneously under physiologic conditions to form reactive intermediates. These reactive intermediates may then bind to tissue and serum proteins, by way of the carbonyl group forming an amide linkage with lysine residue amino groups on nearby proteins. These complexes of penicillin degradation products bound covalently to proteins are then capable of eliciting an immune response (Levine and Ovary 1961; Parker et al. 1962). Approximately 95% of penicillin is tissue bound in the penicilloyl form which is known as the "major antigenic determinant." The remaining penicillin either remains in the native state or degrades to form other derivatives referred to as "minor antigenic determinants," of which penicilloate and penilloate figure prominently in inducing allergic reactions (see Fig. 1, Levine and Redmond 1969). Knowledge of this penicillin immunochemistry has allowed for the development of the skin testing reagents used in penicillin allergy evaluation.

22.2.4 Evaluation of Penicillin Allergy

22.2.4.1 Clinical History

A comprehensive history is an essential component of penicillin allergy evaluation. The clinical history provides information that may guide

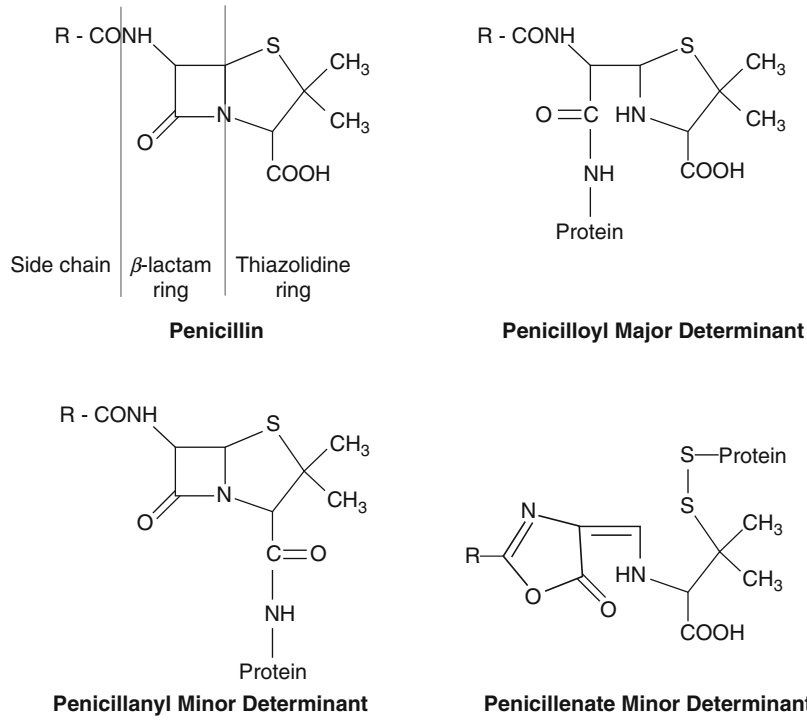

Fig. 1 General structure of penicillin and major and minor allergenic determinants. (Adapted from Gruchalla and Pirmohamed 2006)

decisions such as choice of diagnostic testing, recommendations after allergy testing is completed, and safety regarding reintroduction of penicillin or similar-type antibiotics. Specific questions that are particularly important include the following (Khan and Solensky 2010):

- *What were the signs and symptoms of the adverse drug reaction?* Signs and symptoms consistent with IgE-mediated reactions may corroborate that an allergic reaction had occurred. Symptoms more consistent with Type A ADRs such as dyspepsia, diarrhea, or headache may question whether a prior reaction should have been attributed to penicillin allergy. If blistering skin eruptions, skin desquamation, or mucous membranes were involved with the drug reaction, then a severe cutaneous reaction may have occurred. Severe non-IgE-mediated reactions such as Stevens-Johnson syndrome, toxic epidermal necrolysis, and DRESS require strict avoidance of the culprit drug.
- *When did the drug reaction occur?* Penicillin allergy tends to wane over time, so individuals experiencing reactions years ago may have a greater likelihood of being nonallergic.
- *What was the time course of the adverse drug reaction?* Symptoms occurring either during or immediately following a treatment course would be more consistent with an IgE-mediated allergic reaction. Delayed-onset reactions occurring well after a treatment course is completed would be expected to have negative penicillin allergy skin testing and may necessitate different management options from that of immediate reactions.
- *Were other medications used concurrently at the time of the adverse drug reaction?* Although penicillin and other antibiotics are frequent causes of drug reactions, other medications such as nonsteroidal anti-inflammatory drugs or opiates may cause similar symptoms.
- *Why was penicillin or related antibiotic prescribed?* Signs and symptoms that were attributed to an adverse drug reaction may have been due to the underlying condition being treated. For example, streptococcal pharyngitis or viral syndromes may cause a rash unto itself no matter that penicillin was used as therapy.

- *Had the same or a similar medication been used prior to the reported adverse drug reaction?* Classically, IgE-mediated allergic drug reactions require prior exposures during which allergic sensitization occurs. After this period of sensitization, re-exposure to the drug may elicit an allergic reaction.
- *Has the same or a similar medication been used since the previous adverse drug reaction?* If individuals have tolerated the reintroduction of penicillin or related antibiotic, their allergy may have waned over time. Repeated reactions to the same or similar medications suggests ongoing allergy.
- *Have symptoms similar to the adverse drug reaction occurred in the absence of medication therapy?* In some instances, chronic idiopathic urticaria may mimic aspects of drug allergic reactions.
- *How was the adverse drug reaction treated?* Self-discontinuation of drug and spontaneous resolution of symptoms versus reactions requiring emergent treatment and hospitalization may provide clues as to the severity of the reaction if other historical details are lacking.
- *Has the medical record been reviewed for documentation of penicillin allergy and antibiotic use?* Individuals may not recall specific details of their prior reactions or whether penicillin was actually the antibiotic used with prior reactions. They may also not realize that penicillin or a related antibiotic has been used since their initial reaction.

Although obtaining a thorough clinical history clearly aids diagnostic and management decisions, the reaction history alone cannot accurately diagnose or exclude penicillin allergy. A number of studies have demonstrated that clinical histories may not correlate well with penicillin allergy skin test results. Gadde et al. (1993) reported that a previous history of anaphylaxis or urticaria had rates of positive penicillin skin tests observed in 17.3% and 12.4% of subjects respectively. Green et al. (1977) reported somewhat better correlation between clinical history and penicillin skin test results with positive tests noted in 46% with a history of anaphylaxis, 17% with a history of urticaria or angioedema, and 7% in subjects with a history of maculopapular skin eruption. Similar to other studies, Stember (2005) reported that only 14.1% of subjects with convincing histories of penicillin allergic reactions, defined as having IgE-mediated features, had positive penicillin allergy skin tests. In contrast, patients with vague histories may have positive allergy skin testing and be allergic to penicillin. A large review demonstrated that about one-third of individuals with positive penicillin allergy skin tests had vague histories such as nonpruritic maculopapular rashes, isolated gastrointestinal symptoms, or simply unknown details of the prior reaction (Solensky et al. 2000).

Patients with histories consistent with IgE-mediated type symptoms may have subsequent negative evaluations due to multiple reasons including: (1) penicillin specific-IgE antibodies may wane over time; (2) penicillin was misidentified as the antibiotic used during the prior reaction; (3) previous symptoms were caused by an underlying illness rather than penicillin; or (4) previous reactions were the result of interactions between the underlying infectious agent and the antibiotic (Solensky and Khan 2010). Thus, individuals with either consistent or vague reaction histories should be considered for penicillin skin testing prior to the use of penicillins.

22.2.4.2 Penicillin Allergy Skin Testing

Penicillin skin testing is the preferred, optimal method for evaluation of IgE-mediated penicillin allergy. Penicillin skin testing includes prick and intradermal skin testing to both the major and minor determinants of penicillin. The major determinant used for penicillin skin testing is penicilloyl-polylysine (PPL). Minor determinants of penicillin that have been used for testing include benzylpenicillin (penicillin G) and minor determinant mixtures (MDM) including benzylpenicilloate, benzylpenilloate, or benzylpenicilloyl-*N*-propylamine (Fox and Park 2011). Testing with amoxicillin has also been recommended by the European Network for

Drug Allergy since side-chain structures have been recognized as antigenic determinants (Blanca et al. 2009). Penicillin skin testing should only be performed by personnel skilled and experienced in the administration and interpretation of such testing.

As to the skin testing procedure itself, prick skin testing with penicillin major and minor determinants along with a positive control utilizing histamine and a negative control consisting of saline is performed first. If prick skin testing is negative, then intradermal testing is performed again with penicillin major and minor determinants. A wheal 3 mm or greater than that of the negative control for either the prick or intradermal tests constitutes a positive skin test response (Solensky and Khan 2010). Penicillin skin testing is considered safe with serious reactions due to testing being extremely rare. When undergoing stepwise skin prick and intradermal testing by appropriate personnel using proper technique, the incidence of systemic reactions to penicillin skin testing is considered to be less than 1% (Gadde et al. 1993; Valyasevi and Van Dellen 2000).

Both major and minor determinants are recommended for penicillin skin testing (Solensky and Khan 2010). Up to 84% of penicillin skin test-positive patients are positive to PPL, with up to 75% reacting to PPL only (Gadde et al. 1993; Sogn et al. 1992; Green et al. 1977). Approximately 10% of penicillin skin test-positive patients are positive to MDM only (Sullivan et al. 1981; Park et al. 2007; Solensky and Macy 2015). When both major and minor determinants are used for penicillin allergy testing, the negative predictive value for serious, immediate-type reactions is 97–99% (Gadde et al. 1993; Sogn et al. 1992; Solley et al. 1982). A precise positive predictive value is unknown since penicillin is typically avoided with positive test results due to the safety and ethical concerns of administering penicillin to individuals who are skin test-positive. Based on limited penicillin challenges to skin test-positive individuals, the positive predictive value ranges between 50% and 67% (Solley et al. 1982; Green et al. 1977).

22.2.4.3 Oral Challenge

Although drug challenge is considered the gold standard for identification of a drug eliciting an allergic reaction, due to its inherent risks, a challenge procedure should only be performed at the end of a full drug allergy evaluation in which a patient is unlikely to be allergic to the given drug. In this setting, drug challenges may establish or exclude a specific drug allergy or may be performed to demonstrate tolerance to a less likely eliciting drug in order to identify safe alternatives (Demoly et al. 2014). Another approach to penicillin testing involves skin testing with only major determinant and penicillin G followed by oral challenge to amoxicillin in those with negative skin tests. Outcomes from utilizing this methodology were reported by Macy and Ngor (2013) in 500 individuals with self-reported penicillin allergy. In this study, the index allergic reaction for subjects was nonhive rash (40.8%), hives/angioedema (33.8%), unknown (14.4%), other adverse reaction (8.2%), and anaphylaxis (2.8%). The time since the index reaction and penicillin skin testing was 20.2 ± 19.7 years. There were four subjects (0.8%) with significant objective challenge reactions to amoxicillin, all consisting of urticaria that resolved with oral antihistamines. An additional 15 study subjects (3%) reported acute subjective reactions during the 1-h observation after amoxicillin challenge. None of these subjective reactions required any therapy.

Recent studies have explored the utility and safety of direct oral challenges in individuals with a more limited role for penicillin skin testing. Mill et al. (2016) performed a graded amoxicillin challenge in 818 children with a history of a suspected reaction to amoxicillin. Prior reactions were primarily cutaneous in nature, involving either hives or maculopapular rash. In this study, 94% of children tolerated the amoxicillin challenge. However, 17 (2.1%) patients did have an immediate reaction consisting of hives that resolved with oral antihistamine therapy. Tucker et al. (2017) reported on 328 military recruits with self-reported penicillin allergy who underwent amoxicillin challenge without preceding penicillin allergy testing. In this cohort, five recruits

(1.5%) had an objective challenge reaction. All reactions were cutaneous in nature with one involving globus sensation as well. The five reactors were treated with an oral antihistamine and a single dose of intramuscular epinephrine to avoid reaction progression. Confino-Cohen et al. (2017) evaluated 617 patients with a history of a delay-onset reaction to penicillins, defined as a reaction starting longer than 1 h after the last drug administration. In this study, the mean population age was 19.9 years, with 66% being younger than 18 years. The mean time elapsed from the index allergic reaction was 7.1 years (±12.4), and the most common index reaction symptom was rash (90%). Patients underwent a graded oral challenge to either penicillin or amoxicillin. Immediate reactions, all consisting of rashes, occurred in 1.5% of patients. Delayed reactions, defined as reactions on day 2–5 after the challenge day, occurred in 6.1% of patients. All delayed reactions were rashes that resolved without medical treatment.

These three recent studies (Mill et al. 2016; Tucker et al. 2017; Confino-Cohen et al. 2017) suggest a possible role for direct oral challenges without preceding penicillin skin testing in certain patient populations. However, each of these studies were single center experiences in limited numbers of patients with specific clinical characteristics, and thus these practices are not yet considered standard of care. Further research is needed to determine whether oral challenges without allergy skin testing is safe and appropriate in specific situations.

22.2.4.4 In Vitro Allergy Testing

In vitro testing for detection of specific IgE to penicilloylpolylysine, penicillin G, penicillin V, amoxicillin, and ampicillin is commercially available. However, such testing is not considered an adequate alternative to allergy skin testing due to their unknown predictive value. Although a positive in vitro specific IgE to penicillin test result in the appropriate clinical context suggests the presence of an IgE-mediated penicillin allergy, a negative in vitro test does not exclude a penicillin allergy (Solensky and Khan 2010). The sensitivity of in vitro specific IgE testing for penicillin has been reported as low as 45% when compared with skin testing, and positive in vitro tests have a high frequency of false-positive results (Johansson et al. 2013; Macy et al. 2010). Another type of in vitro test, the basophil activation test, which uses flow cytometry, has also been shown to be inferior to skin testing for penicillin allergy (Sanz et al. 2002; Torres et al. 2004). Thus, penicillin skin testing is the preferred and most reliable method for the evaluation of penicillin allergy.

22.2.5 Management of Penicillin Allergy

22.2.5.1 Penicillin Allergy Testing Results

For patients with a history of an adverse reaction to penicillin that is consistent with an IgE-mediated allergic reaction, penicillin testing to major and minor determinants is recommended. The results of penicillin skin testing are only predictive of IgE-mediated reactions to penicillin. Penicillin testing offers no predictive value for non-IgE-mediated events such as serum sickness, interstitial nephritis, drug fever, thrombocytopenia or for more severe non-IgE-mediated reactions such as Stevens-Johnson syndrome, toxic epidermal necrolysis, or DRESS. A history of severe non-IgE-mediated reactions related to penicillin use requires strict avoidance of penicillins (Solensky and Khan 2010; Fox and Park 2011).

When the penicillin skin test result is negative, a patient has low risk of having an immediate-type allergic reaction to penicillin. The negative predictive value of penicillin skin testing for serious, immediate-type reactions is 97–99% which is essentially the baseline 1–3% risk of penicillin allergy in individuals with no previous history of allergic reaction to penicillin (Gadde et al. 1993; Sogn et al. 1992; Solley et al. 1982). If a penicillin skin test result is positive, then an alternative antibiotic is recommended or a penicillin desensitization procedure may be considered (Solensky and Khan 2010).

If penicillin skin testing is not available, the approach to patients with a history of penicillin allergy is based on the reaction history and the absolute/relative need for treatment with

penicillin. As detailed previously, both convincing and vague histories do not necessarily correlate well with penicillin allergy as evidenced by positive penicillin skin testing (Gadde et al. 1993; Green et al. 1977; Stember 2005; Solensky et al. 2000). However, the time elapsed since the index reaction may be useful, as studies have demonstrated that penicillin specific IgE antibodies wane over time. After 5 years from reacting, approximately 50% of patients with penicillin IgE-mediated allergy lost their sensitivity to penicillin (Blanca et al. 1999). Furthermore, approximately 80% of patients were found to be no longer sensitive to penicillin after 10 years from their reaction (Sullivan et al. 1981). Therefore, patients with distant (greater than 10 years) reaction histories coupled with questionable reactions, such as delayed onset maculopapular rash, may be candidates to receive penicillin via graded challenge as opposed to drug desensitization. In contrast, patients with recent reactions and convincing histories, such as anaphylaxis, should be considered for drug desensitization. Both challenges and desensitization involve risks, and thus a thorough assessment of risks and benefits must be performed before proceeding with either procedure (Solensky and Khan 2010). If alternatives to penicillin may be used, then continued avoidance of penicillin would be advised until penicillin testing may be performed.

22.2.5.2 Penicillin Desensitization

Drug desensitization, also referred as temporary induction of drug tolerance, is defined as the induction of a state of unresponsiveness to the drug responsible for an allergic reaction. Unlike allergy immunotherapy with common peptide allergens, such as inhalant allergens and insect venoms, drug desensitization induces only a temporary state of tolerance. Thereby, if the drug concerned is discontinued, the induced state of tolerance is lost within a period of time varying from a few hours to a few days. Drug desensitization is not without risks and is only indicated when alternate medications cannot be used. In addition, for patients treated with beta-blockers, who have experienced severe anaphylaxis, or with hepatic, renal, or cardiac diseases with increased risks for complications, desensitization should only be considered after a careful evaluation of individual risks/benefits. Furthermore, desensitization is absolutely contraindicated in patients who have experienced severe life-threatening reactions such as Stevens-Johnson syndrome, toxic epidermal necrolysis, or DRESS (Cernadas et al. 2010).

In penicillin induction of drug tolerance, the initial dose of administered penicillin is typically 1/10,000 of the full therapeutic dose. Subsequently, increasing doses of penicillin are given at 15- to 30-min intervals with the full therapeutic dose achieved within 4–12 h. Approximately, one third of patients undergoing penicillin induction of drug tolerance experience allergic reactions. Induction of drug tolerance procedures should only be performed by experienced personnel in an appropriate setting with continual patient monitoring and the ability to readily treat any reactions, including anaphylaxis, that may occur (Solensky and Khan 2010).

22.2.6 Resensitization to Penicillin

Resensitization refers to the redevelopment of penicillin allergy after having negative penicillin skin testing and then receiving a course of penicillin. Studies have demonstrated that the rate of resensitization for both adult and pediatric patients receiving single or multiple courses of oral penicillin is rare, ranging from 0% to 3% (Mendelson et al. 1984; Solensky et al. 2002; Hershkovich et al. 2009). In contrast, one study demonstrated that the risk of resensitization may be greater for those who have received intravenous penicillins with a resensitization rate of 20% (Parker et al. 1991). Based on these studies, repeat penicillin skin testing is not recommended for those individuals who have a history of penicillin allergy and have tolerated one or more courses of oral penicillin. For individuals with a history of penicillin allergy and have tolerated intravenous penicillins, consideration may be given to perform repeat penicillin testing prior to the next course of penicillin (Solensky and Khan 2010).

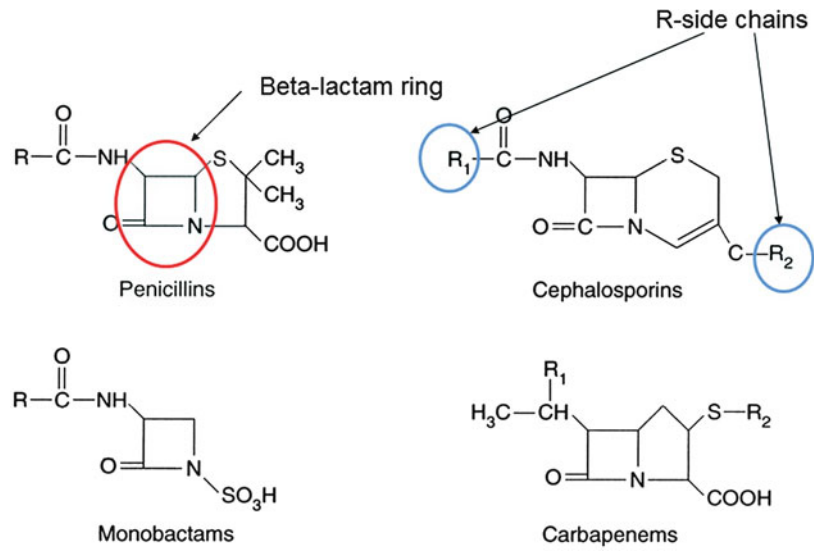

Fig. 2 Beta-lactam antibiotic structures

22.2.7 Penicillin Allergy Cross-Reactivity with Other Beta-Lactam Antibiotics

22.2.7.1 Cephalosporins

Penicillins and cephalosporins (see Fig. 2) structurally both possess a four-member beta-lactam ring and may possess identical or similar R side chains. Metabolic derivatives of these structural similarities may account for allergic cross-reactivity between penicillins and cephalosporins. Similar to penicillin, a cephalosporin determinant, cephalospoyl, is formed from the disruption of the beta-lactam ring by the amino group of plasma or cell membrane proteins. The resulting compound is unstable and undergoes multiple fragmentations of the dihydrothiazine ring. Although the cephalospoyl grouping is fragmented, the side chain structure usually remains intact and represents the major factor for cross-reactivity between penicillins and cephalosporins. Specifically, cross-reactivity between penicillins and cephalosporins mainly stems from whether their R1 side chains are structurally similar (Pichichero and Zagursky 2014).

Studies from the 1970s reported that patients with a history of penicillin allergy and who did not have penicillin skin testing had a fourfold to eightfold increased risk of cephalosporin reactions compared to those with no history of penicillin allergy (Dash 1975; Petz 1978). Additional studies from the mid-1960s through 1980 examined the cephalosporin reaction rate in patients with a history of penicillin allergy and who had positive penicillin skin testing (Girard 1968; Assem and Vickers 1974; Warrington et al. 1978). Based on this group of studies, the overall cross-reactivity rate between penicillins and cephalosporins was approximately 10–20%.

The earlier cross-reactivity rates may have been skewed higher for two reasons. First, early cephalosporins were manufactured by starting with *Penicillium* mold production of penicillin and then chemically modifying the five-member thiazolidine ring attached to the beta-lactam ring to a six-member dihydrothiazine ring. Different side chains were then added. As a result, early cephalosporins produced from the mid-1960s through the mid-1980s had minor contamination of penicillin (Pichichero and Zagursky 2014). Secondly, all reported penicillin allergic patients who reacted to a cephalosporin before 1980 had received first-generation cephalosporins that share similar R-side chains with benzylpenicillin (Dickson and Salazar 2013).

Since 1980, studies involving patients with a history of penicillin allergy and positive penicillin skin tests who subsequently received cephalosporins demonstrate an overall reaction rate between 2% and 3% (see Table 3). Although a

Table 3 Reactions to cephalosporins in patients with history of penicillin allergy and positive penicillin skin testing

Study	Number of patients challenged	Number of reactions (%)
Girard 1968	23	2 (8.7)
Assem and Vickers 1974	3	3 (100)
Warrington et al. 1978	3	0
Solley et al. 1982	27	0
Saxon et al. 1987	62	1 (1.6)
Blanca et al. 1989	19	2 (10.5)
Shepherd and Burton 1993	9	0
Audicana et al. 1994	27	1 (3.7)
Pichichero and Pichichero 1998	43	2 (4.7)
Novalbos et al. 2001	41	0
Macy and Burchette 2002	42	1 (2.4)
Romano et al. 2004	101	0
Greenberger and Klemens 2005	6	0
Park et al. 2010	85	2 (2.4)
Ahmed et al. 2012	21	0
TOTAL	512	14 (2.7)

2–3% reaction rate may be considered infrequent, anaphylactic reactions, some fatal, have occurred with cephalosporin administration in patients with penicillin allergy (Spruill et al. 1974; Pumphrey and Davis 1999). Consequently, penicillin allergy testing should be considered in patients reporting penicillin allergy prior to the administration of cephalosporins, as most patients with negative penicillin tests may receive all beta-lactams safely. Alternatively, in the absence of a severe or recent penicillin allergy reaction, cephalosporins may be given directly with a reaction rate of approximately 1% within 24 h. However, this alternative management strategy is controversial as the reactions that do occur may be anaphylactic in nature. Patients with positive penicillin test results who require cephalosporins may undergo a graded challenge or drug desensitization (Solensky and Khan 2010). Cephalosporin skin testing may be considered as another method for risk stratification. However, such testing is not standardized, and the positive and negative predictive values are not well established (Pichichero and Zagursky 2014).

Table 4 Reactions to carbapenems in patients with history of penicillin allergy and positive penicillin skin testing

Study	Number of patients	Number of reactions (%)
Romano et al. 2006	110	0
Romano et al. 2007	103	0
Atanaskovic-Markovic et al. 2008	107	0
Atanaskovic-Markovic et al. 2009	123	0
Gaeta et al. 2015	211	0
TOTAL	654	0

Limited data suggest that individuals who are selectively allergic to aminopenicillins have a higher risk of allergic cross-reactivity to cephalosporins with identical R-group side chains (Audicana et al. 1994; Miranda et al. 1996; Sastre et al. 1996). Therefore, patients selectively allergic to amoxicillin may consider avoidance of cefadroxil, cefprozil, and cefatrizine or consider desensitization. For those selectively allergic to ampicillin, avoidance may be considered for cefaclor, cephalexin, cephradine, cephaloglycin, and loracarbef or consider administration via desensitization if needed (Solensky and Khan 2010).

22.2.7.2 Carbapenems

Carbapenems are similar to penicillins (see Fig. 2) as both have a four-member beta-lactam ring core structure, but in carbapenems, the beta-lactam ring is attached to a five-member carbon-only cyclic ring and a sulfur atom is linked to C_2 (Zagursky and Pichichero 2017). When considering carbapenems, both prospective and retrospective studies have demonstrated very low cross-reactivity rates between carbapenems and penicillins, likely less than 1% (see Table 4). Current practice guidelines recommend that patients with negative penicillin skin testing may safely receive carbapenems. Patients with positive penicillin skin tests or patients with a history of penicillin allergy who do not undergo penicillin skin testing may consider administration of

carbapenems via a graded challenge procedure (Solensky and Khan 2010).

22.2.7.3 Monobactams

Monobactams are also structurally similar to penicillins (see Fig. 2) but are unique in that the beta-lactam ring is not fused to another ring structure (Zagursky and Pichichero 2017). Similarly to carbapenems, allergic reactions to the monobactam aztreonam are uncommon as aztreonam appears less immunogenic than both penicillins and cephalosporins. Previous testing and challenge studies have demonstrated no cross-reactivity between either penicillins or cephalosporins with aztreonam with the exception of ceftazidime, which shares an identical R side chain with aztreonam (Moss 1991). Thus, patients with either penicillin or cephalosporin allergy may safely receive aztreonam, with the exception of those allergic to ceftazidime (Solensky and Khan 2010).

22.3 Conclusion

Penicillin allergy is widely reported in the general population thereby significantly impacting healthcare decisions and potentially increasing morbidity and financial costs. Evaluation of penicillin allergy should include a comprehensive history as well as penicillin allergy skin testing. Individuals with a history of penicillin allergy and penicillin testing negative to both major and minor determinants have low risk of IgE-mediated, immediate-type reactions to penicillin or cephalosporins. When penicillin skin testing is positive, an alternative antibiotic is recommended or a penicillin desensitization procedure may be considered. In those with penicillin allergy, risks are generally low for allergic cross-reactivity to other beta-lactam antibiotics including cephalosporins, carbapenems, and monobactams. Strategies to incorporate penicillin allergy management into antibiotic stewardship programs would improve health care quality and value for the millions of patients labeled as allergic to penicillin and would address a significant public health problem.

22.4 Cross-References

▶ Drug Allergy and Adverse Drug Reactions

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Chemotherapy and Biologic Drug Allergy

23

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Contents

Abstract

With increased utilization of chemotherapeutic agents and monoclonal biological agents for the treatment of malignancies, autoimmune diseases, and allergic diseases, the incidence of adverse reactions secondary to the usage of the agents is expected to increase. In evaluating a patient with adverse reaction to the agents, obtaining a history is the most important step to define the mechanism. Type A adverse drug reaction is expected side effect of the drug. Type B reaction can be systemic inflammatory response syndrome or immediate hypersensitivity. If the adverse drug reaction is an

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immediate hypersensitivity reaction by history, diagnostic test like elevation of serum tryptase level within 4 h of the reaction may be important to prove that the reaction is an immediate hypersensitivity. Skin testing if positive may also help to confirm the diagnosis of type I reaction. If the reaction is immediate hypersensitivity, rapid drug desensitization can be utilized to induce a state of temporary tolerance so that the patient can continue to receive the agent which is critical for his or her survival and quality of life. Desensitization protocols have been described and are similar to penicillin desensitization protocols. If carefully implemented, the procedure is effective with reasonable benefit to risk ratios. Attachment B and Attachment D are two spread sheets for intravenous desensitization and subcutaneous desensitization, that a licensed physician, who specializes in drug desensitization, can utilize to conveniently write the order for the desensitization procedure.

Keywords

Hypersensitivity reactions · Chemotherapeutic agents · Biological agents · Monoclonal antibodies · Carboplatin · Adalimumab · Bevacizumab · Rituximab · Cetuximab · Infliximab · Trastuzumab · Anaphylaxis · Desensitization · Instruction for using intravenous desensitization spreadsheet: Attachment A · Spreadsheet for intravenous desensitization: Attachment B · Instruction for using subcutaneous desensitization spreadsheet: Attachment C · Spreadsheet for subcutaneous desensitization: Attachment D

23.1 Introduction

The field of oncology is changing rapidly due to scientific advancement that supports the care of patients with malignancy. Treatment has become more precise and more effective than that in the past. As the general population gets older, there has been an increase in malignancy. In 2014, close to 1.6 million new cases of cancer were diagnosed and close to 0.6 million people died of cancer in the United States. Cancer is the second leading cause of death in the USA, exceeded only by heart disease. One of every four deaths in the USA is due to cancer (nccd.cdc.gov). Because of increased usage of chemotherapies, the number of hypersensitivity reactions is expected to increase. Biological agents, specifically monoclonal antibodies, are also increasingly being used in the treatment of autoimmune diseases and allergic diseases (Boguniewicz 2017; Joshi and Khan 2017; Kuang and Kilon 2017; Bachert et al. 2017). Similar to chemotherapeutic agents, the incidence of adverse reaction is expected to increase because of increase in utilization. The reaction can sometimes be life-threatening. Avoiding utilization of the agents that caused the allergic reaction deprives patients for potential cure and drastically reduces their quality of life. Desensitization using the agent in question may allow patients to utilize the drug again. This chapter will focus on true immunological type I reaction for which desensitization can be utilized to induce temporary tolerance.

23.2 Classification of Adverse Drug Reaction

The majority of adverse drug reactions are type A and are dose dependent and predictable (Table 1). Type B drug reactions are restricted to a small subset of general population. They are dose independent and frequently unpredictable (Tam 2016). Detailed history during and following an adverse drug reaction is important to determine the Type of reaction. For example, nausea and vomiting following chemotherapeutic agent administration are type A reaction; drug desensitization is not necessary and will not help. For chemotherapeutic and biological drug reaction, there are mainly 2 subtypes of type B reaction: systemic inflammatory response syndrome and anaphylactic type immediate hypersensitivity (Giavina-Bianchi et al. 2017; Picard and Galvao 2017). Systemic inflammatory response syndrome or cytokine release syndrome typically occurs on the first administration and wanes rapidly with subsequent exposures. They are caused by the rapid

Table 1 Classification of adverse drug reaction

Type of adverse drug reactions	Mechanism of action	Common symptoms
Type A	Drug's side effect	E.g., nausea and vomiting
Type B:		
Systemic inflammatory response syndrome	Cytokine release due to tumor lysis	Fever, chills, fatigue
Immediate hypersensitivity	1. IgE-mediated mast cell and/or basophil degranulation 2. Direct mast cell/basophil degranulation via complement pathway	Urticaria, angioedema, wheezing, hypotension

destruction of cells targeted by the chemotherapeutic and biological agents through antibody-mediated cell death and/or complement-mediated reaction. The destruction of the target cells leads to release of proinflammatory cytokines like tumor necrosis factor and IL-6. Clinical features include chilling, shivering, pyrexia, and fatigue. These reactions can be reduced by premedication with corticosteroid, acetaminophen, and slowing the infusion rate and desensitization is not indicated (Picard and Galvao 2017). Patients with anaphylactic type immediate hypersensitivity reaction due to chemotherapeutic and monoclonal antibody can be desensitized.

23.3 Immediate Hypersensitivity

IgE-mediated reactions to chemotherapeutic and biological (monoclonal) agents typically occur after at least one uneventful administration of the drugs because the patient has to be sensitized to the specific agents initially. Symptoms range from skin reaction like urticaria to hypotension (anaphylactic shock) and usually occur within 2 h of the administration of the drug. Patient can also have respiratory symptoms like wheezing and gastrointestinal symptoms like abdominal pain and/or vomiting. A skin test using nonirritating concentration of the agent in question can confirm the diagnosis, but false negative finding can occur. Acute serum total tryptase level (measured by blood test within 4 h of reaction), which is at least 20% plus 2 ng/ml over the baseline level, is suggestive of mast cell degranulation.

Patients with immediate hypersensitivity to chemotherapeutic and biological agents can tolerate the offending drug through rapid drug desensitization. If the patient has Stevens Johnsons Syndrome, toxic epidermal necrolysis, overlap syndrome, or serum sickness secondary to the chemotherapeutic and biological agents, the agents should be avoided as desensitization will not work for these types of reaction and are dangerous if implemented.

A unique type 1 reaction is cetuximab in which the patient might have reaction to the drug the first time because he or she has a preexisting specific IgE hypersensitivity to alpha-1,3 galactose present on the Fab portion of the cetuximab heavy chain and in mammal meat like beef, pork, and lamb (Chung et al. 2008). The reaction usually occurs within the first hour of the drug infusion and can occasionally be delayed up to 6 h. Testing to mammal extract by subcutaneous route may be helpful if positive. An in vitro test is also available for IgE against alpha-1,3-galactose antigen.

23.4 Drug Allergy Secondary to Chemotherapeutic Agents

23.4.1 Diagnosis

23.4.1.1 History

Obtaining a complete history from the patient, from the health care providers taking care of the patient, and from patient's family members is the most important diagnostic step to determine whether the patient has a true IgE-mediated immediate hypersensitivity to the chemotherapeutic agent in question. The timing and the manifestation of the reaction after taking the agent are important part of the history keeping in mind the type of adverse reaction the patient might have as discussed in Sects. 2 and 3.

Table 2 Skin test for chemotherapeutic agents

Class of Agents	Specific Agents	Concentration for prick skin test	Concentration for intradermal skin test
Platinum-Base	Carboplatin	10 mg/ml	1 mg/ml
	Oxaliplatin	5 mg/ml	0.5 mg/ml
	Cisplatin	1 mg/ml	0.1 mg/ml
Taxanes	Paclitaxel	1 mg/ml	0.01 mg/ml
	Docetaxel	1 mg/ml	0.01 mg/ml
Doxorubicin		Not appropriate	Not appropriate

23.4.1.2 Biomarker

If serum tryptase is obtained within 4 h after the allergic reaction and it is elevated (Sect. 3), diagnosis is suggested given the appropriate history.

23.4.1.3 Skin Test

Skin test using nonirritating concentration of the chemotherapeutic agent can be used to confirm IgE-mediated allergic reaction, but false negative skin test response can occur (Table 2) (Giavina-Bianchi et al. 2017). Nonirritating concentration appropriate for skin test is not available or not known for all chemotherapeutic agents. Therefore, the practitioner may have to proceed with desensitization without skin test if history is suggestive to type I IgE-mediated allergic reaction.

23.4.1.4 Graded Drug Challenge (Test Dosing)

If skin test is negative or not available and the history is not consistent with an allergic reaction or systemic inflammatory response, one can perform specific drug provocation under physician observation in case of anaphylaxis. This will help to determine if the patient can safely tolerate the medication in question when diagnostic testing to determine the possibility of true drug allergic reaction is not available, the history is not definite for drug allergy, and/or the patient has to continue the medication without alternatives. The principles of incremental test dosing are to administer sufficiently small doses that would not cause a serious reaction initially and increase by safe increments, usually by tenfold, every 20–60 min over a few hours, or a few days. In situations that are unlikely to result in anaphylaxis, a 10% and 90% challenge can be done. The procedure is not a true desensitization as the dose is increased more rapidly compared to desensitization. The intent of graded drug challenge is to assure that the patient can tolerate a small dose without allergic reaction before administering a higher dose safely. Repeated drug administration is contraindicated after any life-threatening reaction that is not mediated by IgE mechanism (e.g., drug-induced hemolytic anemia, immune complex reaction, and Stevens-Johnson Syndrome).

23.4.2 Consultation with Oncologist

After determining that the patient has IgE-mediated allergic reaction to the chemotherapeutic agent, the practitioner will need to discuss the case with the attending oncologist in order to assure that an alternative agent is not available or that the alternative agent is inferior to the offending chemotherapeutic agent. If so, the practitioner will discuss the situation and recommendation with the patient before implementing specific drug desensitization.

23.4.3 Desensitization

If a patient has Type I IgE-mediated reaction to the chemotherapeutic agent, the agent can be reintroduced via desensitization, provided that the medication is the one the patient needs without good alternative. In other words, the benefit of administering the medication via desensitization is higher than the risk of complications associated with the desensitization. Protocol of chemotherapeutic agent desensitization is based on the best described desensitization protocol for penicillin (Celik et al. 2014). General desensitization

Table 3 General drug desensitization protocol

1. Baseline monitoring of a patient in a medical setting (clinic or hospital depending on severity of the reaction and route of administration of the medication).
2. Premedication may be implemented: e.g., cetirizine, ranitidine, and montelukast.
3. Start an intravenous line in case fluid resuscitation is necessary.
4. Initial dose of the medication should be between 1/1,000,000 and 1/10,000 of full therapeutic dose depending on severity of prior allergic reaction.
5. Route: oral, subcutaneous, intramuscular, or intravenous.
6. Dose interval: every 15–20 min for parenteral doses; every 20–30 min for oral dosing.
7. Dose escalation: twofold increments.
8. Repeat dose for mild to moderate systemic reactions, after treatment of the reactions.
9. Mild reaction can be treated with antihistamine and more severe reaction can be treated with intramuscular epinephrine.
10. Drop back two doses for any reaction producing hemodynamic changes.

protocol is described in Table 3 (Celik et al. 2014). Protocols of chemotherapeutic agents have been described (Castells et al. 2008). The starting dose is about 1/46,000 of the target dose and the amount is doubled every 15 min. If allergic reaction develops, the symptoms should be treated. Mild reaction can be treated with antihistamine. More severe reaction should be treated with 0.3 mg intramuscular epinephrine at the mid anterior-lateral region of the thigh (Simons et al. 2001). Once hypersensitive symptoms resolve, the desensitization can be resumed at the last tolerated step and continued with close monitoring. Table 4 below is the carboplatin desensitization protocol the author used to successfully desensitize a patient who is allergic to the agent. *Similar protocol can be used for other chemotherapeutic agents*.

Based on rapid desensitization protocol established for antibiotics like penicillin and based on success using the same principal for chemotherapeutic agents and monoclonal agents, two spread sheets for intravenous desensitization and subcutaneous desensitization, respectively, were developed by the author to assist licensed physician who specializes in drug desensitization to conveniently write the order for the desensitization procedure (Attachment A contains instruction on how to enter variables for Attachment B, which is the spreadsheet for intravenous desensitization; Attachment C contains instruction on how to enter variables for Attachment D, which is the spreadsheet for subcutaneous desensitization). Table 5 is an example of an order written for desensitizing a patient allergic to Carboplatin using spread sheet for IV desensitization. To generate the desensitization order as shown in Table 5, one just needs to enter:

- The unit of the medication in question: in this case, mg
- The top concentration of the solution: in this case, 1.2 mg/cc
- The number of solution to be used: in this case, 3
- The final desired rate of infusion: in this case, 75 ml/h
- The interval between each escalation of dose: in this case, 15 min
- Total cumulative dose desired: in this case, 300 mg.

Starting dose for the published Carboplatin desensitization is 1/50,000 of the target 300 mg dose as shown in Table 4. Starting dose using a protocol generated by author's spreadsheet is 1/30,000 of the target 300 mg dose as shown in Table 5. The spreadsheet is based on the principle of doubling up the dose every 15 min. The spreadsheet then calculates the appropriate infusion rate of the specific concentration of Carboplatin. Therefore, the spreadsheet calculation is more precise than the published protocol in that the dose is exactly doubled every 15 min. The nursing staff can simply utilize the rate of infusion to deliver the target dose within the 15 min period for each step. Cumulative dose is automatically calculated when generating the desensitization table using the spreadsheet. Estimated time to top rate and estimated time to complete the desensitization are also automatically calculated by the spreadsheet.

Table 4 Desensitization for carboplatin

Table 4a: Desensitization protocol for chemotherapy agent Carboplatin
Patient: _____Oncologists: _____PMD: _____

Type	Procedure
Premedication for allergic reaction	1. Evening before procedure, the following medications are given for an adult patient: a. 10 mg Cetirizine b. 10 mg Montelukast c. 40 mg Prednisone 2. 1-2 hours before start of procedure, the following medications are given: a. 10 mg Cetirizine b. 10 mg Montelukast c. 20 mg Prednisone d. 150 mg Ranitidine
Premedication for chemotherapy chosen by oncologist (to be administered in ICU)	1. Ondansetron 8 mg within 15 min of the start of chemotherapy 2. Dexamethasone 8 mg IV within 15 min of the start of chemotherapy
Emergency medications available at patient's room	1. Epinephrine 1:1000 1 mg vial x 5 vials with IM needle/syringe available for 0.3. – 0.5 cc increment doses 2. Benadryl for IV dosing: total of 100 mg available 3. Pepcid 20 mg IV available 4. Solumedrol 80 mg available on floor for IV dose 5. Albuterol nebulizer available: 2.5 mg/3cc vial x 5 ready to use (nebulizer machine available) 6. Oxygen available (nasal canula) 7. Usual resuscitation devices
Vital sign measurement	1. HR, bp, RR: baseline then every 10 min x 3.5 hours then every 15 min x 3 hours, then every 30 min x 3 hour, then every hour 2. Continuous oxygen saturation monitoring 3. Cardiac monitoring

Comments:
Setting: ICU with MD present
Solutions to be prepared by pharmacy: Carboplatin

Table 4b: Solutions

Carboplatin	Volume (ML or cc)	Concentration	Total amount (Mg)
Solution 3	250 cc	0.012 mg/cc	3 mg
Solution 2	250 cc	0.12 mg/cc	30 mg
Solution 1	250 cc	1.2 mg/cc	300 mg

Table 4c: Steps

Step no.	Solution no.	Rate (ml/hr)	Time (min)	Volume infused per step (ml)	Administered dose (mg)	Cumulative dose (mg)
1	3	2.0	15	0.50	0.006	0.06
2	3	5.0	15	1.25	0.015	0.075
3	3	10.0	15	2.50	0.03	0.105
4	3	20.0	15	5.00	0.06	0.165
5	2	5.0	15	1.25	0.15	0.315
6	2	10.0	15	2.50	0.30	0.615
7	2	20.0	15	5.00	0.60	1.215
8	2	40.0	15	10.00	1.20	2.415
9	1	10.0	15	2.50	3.00	5.415
10	1	20.0	15	5.00	6.00	11.415
11	1	40.0	15	10.00	12.00	23.415
12*	1	75.0	184.5	230.63	276.76	300.18

Comments:

Final cumulative dose and thus volume infused is determined by oncologist and may be different for subsequent infusions.

Total time: 349.5 min (5.825 hours) and may be longer because of modification of above procedure by allergist during the desensitization period.

Post-infusion monitoring: 6 hours for this initial desensitization and may be shortened to 1.5 hours in future if patient is doing well provided that the patient carries an Epipen to go home in case of delayed allergic reaction.

Table 5 Desensitization to Carboplatin using author's spread sheet (Attachment A & Attachment B**)**

Carboplatin	Volume (ML or cc)	Concentration	Total amount (Mg)
Solution 3	250 cc	0.012 mg/cc	3 mg
Solution 2	250 cc	0.12 mg/cc	30 mg
Solution 1	250 cc	1.2 mg/cc	300 mg

Step no.	Solution no.	Rate (ml/h)	Time (min)	Volume infused per step (ml)	Administered dose (mg)	Cumulative dose (mg)
1	3	3.7	15	0.92	0.01099	0.01099
2	3	7.3	15	1.83	0.02197	0.03296
3	3	14.6	15	3.66	0.04395	0.07690
4	3	29.3	15	7.32	0.08789	0.16479
5	2	5.9	15	1.46	0.1758	0.34058
6	2	11.7	15	2.93	0.3516	0.69214
7	2	23.4	15	5.86	0.7031	1.39526
8	2	46.9	15	11.72	1.4063	2.80151
9	1	9.4	15	2.34	2.813	5.61401
10	1	18.8	15	4.69	5.625	11.23901
11	1	37.5	15	9.38	11.250	22.48901
12	1	75.0	15	18.75	22.500	44.98901
13	1	75.0	170	212.51	255	300

Total time to top rate based on spread sheet calculation: 3 h

Total time including final step: 5.83 h

Table 6 Skin test for biological agents

Agents	Concentration for prick skin test	Top concentration for ID skin test
Adalimumab	40 mg/ml (full strength)	0.4 mg/ml (1/100 of full strength)
Bevacizumab	25 mg/ml (full strength)	2.5 mg/ml (1/10 of full strength)
Cetuximab	2 mg/ml (full strength)	0.2 mg/ml (1/10 of full strength)
Infliximab	10 mg/ml (full strength	1 mg/ml (1/10 of full strength)
Omalizumab	125 mg/ml (full strength)	0.00125 mg/ml (1/100,000 of full strength)
Rituximab	10 mg/ml (full strength)	1 mg/ml (1/10 of full strength)
Tocilizumab	20 mg/ml (full strength)	20 mg/ml (full strength)
Trastuzumab	21 mg/ml (full strength)	2.1 mg/ml (1/10 full strength)

23.5 Drug Allergy Secondary to Biological Agents

Monoclonal antibodies are a class of targeted biological agents. They are utilized to treat cancer, autoimmune diseases, and immunological induced allergic disease including asthma. With increased usages of these agents, hypersensitivity to the agents is encountered frequently.

23.5.1 Diagnosis

History of the hypersensitivity reaction is the most important step in determining whether the reaction is an IgE-mediated reaction as discussed in Sects. 4.1 and 2.

Skin test using the monoclonal antibody is helpful to confirm suspected IgE-mediated allergy. A negative skin test, however, may not reliably rule out IgE-medicated allergy especially if history indicated otherwise. To reduce the chance of false negative result, skin test should be avoided within 4 weeks after the initial anaphylactic episode. Suggested skin test concentration for monoclonal antibodies has been described (Picard and Galvao 2017). In general, full strength of the specific monoclonal antibody can be used for prick testing. Suggested concentrations for intradermal skin test are different among different agents (Table 6). A wheal reaction with a mean diameter of 3 mm greater than the negative control is considered positive. If negative, intradermal skin test is performed with a 1:1000 dilution of full strength biologic solution, followed by 1:100 and 1:10 dilutions if the result is negative. The intradermal skin test is regarded as positive if the initial wheal increased by at least 3 mm in diameter and is surrounded by erythema after 20 min.

23.5.2 Desensitization

Adalimumab. Desensitization protocol is similar to that of penicillin desensitization and that as described for Carboplatin desensitization (Table 4). Using this protocol, desensitization for Adalimumab, Bevacizumab, Cetuximab, Infliximab, Rituximab, and Trastuzumab has been described (Bavbek et al. 2016; Sloane et al. 2016). A more rapid (over 2 h) desensitization has been described for Tocilizumab (Justet et al. 2014). Table 7 is an example for an agent given subcutaneously (Bavbek et al. 2015). Table 8 is subcutaneous desensitization (3 solutions) using spreadsheet created by the author (Attachment C and Attachment D). To generate the desensitization order as shown in Table 8, one just needs to enter:

- The unit of the medication in question: in this case, mg
- The top concentration of the solution: in this case, 50 mg/cc
- The number of solution to be used: in this case, 3
- The interval between each escalation of dose: in this case, 30 min
- Total cumulative dose desired: in this case, 40 mg

Table 7 Reported subcutaneous desensitization to Adalimumab (Bavbek et al. 2015)

Solutions to be prepared: Adalimumab			
Adalimumab	**Volume (ML or cc)**	**Concentration**	**Total amount (Mg)**
Solution 3	1 cc	0.5 mg/cc	0.5 mg
Solution 2	1 cc	5 mg/cc	5 mg
Solution 1	0.8 cc	50 mg/cc	40 mg

Desensitization: protocol for administration of Adalimumab					
Step no.	**Solution no.**	**Time from start of injection (min)**	**Volume injected (ml)**	**Administered dose (mg)**	**Cumulative dose (mg)**
1	3	0	1	0.5	0.5
2	2	30	0.15	0.75	1.25
3	2	60	0.25	1.25	2.5
4	2	90	0.5	2.5	5.0
5	1	120	0.1	5.0	10
6	1	150	0.2	10	20
7	1	180	0.4	20	40

Total time: 3 h
Total dose: 40 mg subcutaneously

Table 8 Desensitization (3 solutions) to Adalimumab using author's spread sheet **(**Attachment C and Attachment D**)**

Solutions to be prepared: Adalimumab			
Adalimumab	**Volume (ML or cc)**	**Concentration**	**Total amount (Mg)**
Solution 3	1 cc	0.5 mg/cc	0.5 mg
Solution 2	1 cc	5 mg/cc	5 mg
Solution 1	0.8 cc	50 mg/cc	40 mg

Desensitization: protocol for administration of Adalimumab using author's spread sheet (Attachment C and Attachment D)					
Step no.	**Solution no.**	**Time from start of injection (min)**	**Volume injected (ml)**	**Administered dose (mg)**	**Cumulative dose (mg)**
1	3	0	0.1563	0.078	0.078
2	3	30	0.3125	0.156	0.234
3	3	60	0.625	0.313	0.547
4	2	90	0.125	0.625	1.172
5	2	120	0.25	1.25	2.422
6	2	150	0.5	2.5	4.922
7	1	180	0.1	5.0	9.922
8	1	210	0.2	10	19.922
9	1	240	0.4	20	39.9

Total time: 4 h
Total dose: 39.9 = ~40 mg

Table 9 is a more rapid subcutaneous desensitization (2 solutions) using spreadsheet created by the author (Attachment C and Attachment D). To generate the desensitization order as shown in Table 9, one just needs to enter:

- The unit of the medication in question: in this case, mg
- The top concentration of the solution: in this case, 50 mg/cc
- The number of solution to be used: in this case, 2
- The interval between each escalation of dose: in this case, 30 min
- Total cumulative dose desired: in this case, 40 mg

Table 9 Desensitization (2 solutions) to Adalimumab using author's spread sheet (Attachment C and Attachment D)

Solutions to be prepared: Adalimumab			
Adalimumab	**Volume (ML or cc)**	**Concentration**	**Total amount (Mg)**
Solution 2	1 cc	5 mg/cc	5 mg
Solution 1	0.8 cc	50 mg/cc	40 mg

Desensitization: protocol for administration of Adalimumab using author's spread sheet (Attachment C and Attachment D)					
Step no.	**Solution no.**	**Time from start of injection (min)**	**Volume injected (ml)**	**Administered dose (mg)**	**Cumulative dose (mg)**
1	2	0	0.125	0.625	0.625
2	2	30	0.25	1.25	1.875
3	2	60	0.5	2.5	4.375
4	1	90	0.1	5.0	9.375
5	1	120	0.2	10	19.375
6	1	150	0.4	20	39.3

Total time: 2.5 h
Total dose: 39.3 = ~40 mg

Protocol created by using author's spreadsheet as shown in Table 8 is more conservative than that published by Bavbek et al. (2015) by starting at a much lower dose and takes longer to finish the desensitization process. Table 9 is a more rapid desensitization created by author's spreadsheet by using 2 solutions instead of 3 solutions. As one can see, the starting dose is a little higher than that published by Bavbek. The concept for desensitization as stated by Bavbek is very similar that that generated by the author's spreadsheet. The author's spreadsheet, however, is easier to generate by entering few variables. The dose is doubled every 30 min. By using higher number of solutions, a more conservative protocol is generated with a corresponding lower starting dose and a longer time before completing the protocol.

For patient who has immediate hypersensitivity to Omalizumab, which is infused subcutaneously, desensitization can also be implemented using the same basic protocol. However, if the reaction is the type that is delayed like >24 h after injection, the usual protocols like that in Tables 7, 8, and 9 should not be utilized since the practitioner would not be able to determine if the patient could tolerate the dose within a 30-min interval before advancing to a higher dose.

Bevacizumab. Successful rapid desensitization to intravenous bevacizumab has been described (Williams et al. 2017). Table 10 shows the administered dose every 15 min and the cumulative dose reported by Williams et al. Table 11 is an example of an order written for desensitizing a patient allergic to Bevacizumab using spread sheet for IV desensitization created by author (Attachment A and Attachment B). To generate the desensitization order as shown in Table 11, one just needs to enter:

- The unit of the medication in question: in this case, mg
- The top concentration of the solution: in this case, 11 mg/cc
- The number of solution to be used: in this case, 3
- The final desired rate of infusion: in this case, 64 ml/h
- The interval between each escalation of dose: in this case, 15 min
- Total cumulative dose desired: in this case, 1100 mg

After entering the above 6 variables, Table 11 is generated indicating the number of solutions to be used including the specific concentration. The table will also indicate the desired infusion rate and the corresponding volume of the drug administered. The spreadsheet will also calculate the cumulative dose administered after each step. The spreadsheet will calculate the time required to reach to top rate of infusion and the approximate time it will take to complete the

Table 10 Published successful rapid desensitization to IV Bevacizumab (Williams et al. 2017)

Step no.	Solution concentration (mg/ml)	Rate (ml/h)	Time (min)	Administered dose (mg)	Cumulative dose (mg)
1	0.11	2	15	0.055	0.055
2	0.11	5	15	0.1375	0.1925
3	0.11	10	15	0.275	0.4675
4	0.11	20	15	0.55	1.0175
5	1.1	5.0	15	1.375	2.3925
6	1.1	10.0	15	2.75	5.1425
7	1.1	20.0	15	5.5	10.6425
8	1.1	40.0	15	11	21.6425
9	11	10.0	15	27.5	49.1425
10	11	20.0	15	55	104.1425
11	11	30.0	15	82.5	186.6425
12	11	40.0	15	110	296.6425
13	11	60.0	15	165	461.6425
14	11	60.0	58	638.3575	1100

Total time: 4.2 h
Total dose: 1100 mg

Table 11 Desensitization to Bevacizumab using author's spread sheet (Attachment A and Attachment B)

Bevacizumab	**Volume (ML or cc)**	**Concentration**	**Total amount (Mg)**
Solution 3	250 cc	0.11 mg/cc	27.5 mg
Solution 2	250 cc	1.1 mg/cc	275 mg
Solution 1	250 cc	11 mg/cc	2750 mg

Step no.	**Solution no.**	**Rate (ml/h)**	**Time (min)**	**Volume infused per step (ml)**	**Administered dose (mg)**	**Cumulative dose (mg)**
1	3	3.1	15	0.78	0.08594	0.08594
2	3	6.3	15	1.56	0.17188	0.25781
3	3	12.5	15	3.13	0.34375	0.60156
4	3	25.0	15	6.25	0.68750	1.28906
5	2	5.0	15	1.25	1.3750	2.66406
6	2	10.0	15	2.50	2.75	5.41406
7	2	20.0	15	5.00	5.5	10.91406
8	2	40.0	15	10.00	11.000	21.91406
9	1	8.0	15	2.00	22.000	43.91406
10	1	16.0	15	4.00	44.000	87.91406
11	1	32.0	15	8.00	88.000	175.91406
12	1	64.0	15	16.00	176.000	351.91406
13	1	64.0	63.8	68.01	748	1100.00

Total time: 4.1 h
Total dose: 1100 mg

desensitization. The administered dose of Bevacizumab is doubled every 15 min, which is the principal of drug desensitization.

There is not too much difference between Table 11 generated by author's spreadsheet and Table 10, reported for successful desensitization to Bevacizumab. Both protocols are based on doubling up the dose every 15 min starting from low dose. Table 11 generated by the spreadsheet is more precise in terms of doubling the dose every 15 min. Table 11 can easily be generated by entering six numerical variables as stated above.

Table 12 Published successful rapid desensitization to IV Rituximab (Wong and Long 2017)

Step no.	Solution Concentration (mg/ml)	Rate (ml/h)	Time (min)	Administered dose (mg)	Cumulative dose (mg)
1	0.02	2.5	15	0.0125	0.0125
2	0.02	5	15	0.025	0.0375
3	0.02	10	15	0.05	0.0875
4	0.02	20	15	0.1	0.1875
5	0.2	5.0	15	0.25	0.4375
6	0.2	10.0	15	0.5	0.9375
7	0.2	20.0	15	1.0	1.9375
8	0.2	40.0	15	2.0	3.9375
9	2.0	10.0	15	5.0	8.9375
10	2.0	20.0	15	10.0	18.9375
11	2.0	40.0	15	20.0	38.9375
12	2.0	60.0	15	30.0	68.9375
13	2.0	80.0	15	40.0	108.9375
14	2.0	80.0	146.6	391.0625	500

Time to complete desensitization: 5.7 h
Final dose: 500 mg

Table 13 Desensitization to Rituximab using author's spread sheet **(**Attachment A and Attachment B**)**

Step no.	Solution concentration (mg/ml)	Time (min)	Rate (ml/h)	Volume infused per step (ml)	Administered dose (mg)	Cumulative dose (mg)
1	0.02	15	3.9	0.98	0.01953	0.01953
2	0.02	15	7.8	1.95	0.03906	0.05859
3	0.02	15	15.6	3.91	0.07813	0.13672
4	0.02	15	31.3	7.81	0.15625	0.29297
5	0.2	15	6.3	1.56	0.3125	0.60547
6	0.2	15	12.5	3.13	0.6250	1.23047
7	0.2	15	25.0	6.25	1.25	2.48047
8	0.2	15	50.0	12.50	2.5	4.98047
9	2.0	15	10.0	2.50	5.0	9.98047
10	2.0	15	20.0	5.00	10.0	19.98047
11	2.0	15	40.0	10.00	20.0	39.98047
12	2.0	15	80.0	20.00	40.0	79.98047
13	2.0	157.5	80.0	210.01	420	500

Time to Top Rate: 3 h
Time to complete desensitization: 5.6 h
Final dose: 500 mg

Rituximab. Successful rapid desensitization to intravenous Rituximab has been described (Wong and Long 2017). Table 12 shows the administered dose every 15 min and the cumulative dose reported by Wong and Long. Table 13 is an example of an order written for desensitizing a patient allergic to Rituximab using spread sheet for IV desensitization created by author (Attachment A and Attachment B). To generate the desensitization order as shown in Table 13, one just needs to enter:

- The unit of the medication in question: in this case, mg
- The top concentration of the solution: in this case, 2 mg/cc
- The number of solution to be used: in this case, 3

- The final desired rate of infusion: in this case, 80 ml/h
- The interval between each escalation of dose: in this case, 15 min
- Total cumulative dose desired: in this case, 500 mg

After entering the above 6 variables, Table 13 is generated indicating the number of solutions to be used including the specific concentration. The table will also indicate the desired infusion rate and the corresponding volume of the drug administered. The spreadsheet will also calculate the cumulative dose administered after each step. The spreadsheet will calculate the time required to reach to top rate of infusion and the approximate time it will take to complete the desensitization. The administered dose of Rituximab is doubled every 15 min, which is typical of most drug desensitization protocols.

There is minimal difference between Table 13 generated by author's spreadsheet and Table 12 reported for successful Rituximab desensitization. Both protocols are based on doubling up the dose every 15 min starting from low dose. Table 13 generated by the spreadsheet is more precise in term of doubling the dose every 15 min. Table 13 can easily be generated by entering six numerical variables as stated above.

Cetuximab. Successful desensitization for Cetuximab has been described (Jerath et al. 2009). The protocol contains 5 solutions at a fixed infusion rate of 5 ml/min or 300 ml/hour (Table 14). Although the dose is doubled every step, the time required to deliver the dose can vary from 1 min to 32 min. Therefore, the patient may not have received exactly double of the dose within 15 min. Table 14 shows the dose adjustment required to complete the procedure because an allergic reaction; it also contains information on the time that will be required to complete the procedure if the patient does not experience an allergic reaction so one can compare the published protocol with that generated by the spreadsheet as stated in Table 15. Table 15 is an example of an order written for desensitizing a patient allergic to Cetuximab using spread sheet for IV desensitization created by author (Attachment A and Attachment B). To generate the desensitization order as shown in Table 15, one just needs to enter:

- The unit of the medication in question: in this case, mg
- The top concentration of the solution: in this case, 2 mg/cc
- The number of solution to be used: in this case, 5
- The final desired rate of infusion: in this case, 300 ml/h
- The interval between each escalation of dose: in this case, 15 min
- Total cumulative dose desired: in this case, 844 mg

After entering the above 6 variables, Table 15 is generated indicating the number of solutions to be used including the specific concentration. The table will also indicate the desired infusion rate and the corresponding volume of the drug administered. The spreadsheet will also calculate the cumulative dose administered after each step. The spreadsheet will calculate the time required to reach the top rate of infusion and the approximate time to complete the desensitization. The administered dose of Cetuximab is doubled every 15 min, which is the principal of drug desensitization. In this protocol, there is no waiting time between the doses as opposed to that reported by Jerath et al., which was 15 min. The time required to administer a specific dose for each step is 15 min. Therefore, the dose escalation (Table 15) is more precise within a set period of time (15 min) than the dose escalation described by Jerath et al. (Table 14). By using the spreadsheet created by the author as described in Table 15, one can finish the desensitization by 5.9 h (Table 15) instead of 7.6 h (Table 14). A more precise doubling the dose of Cetuximab as stated in Table 15 may render a better tolerated protocol to a patient than that reported by Jerath et al. The advantage of using the spreadsheet developed by the author is that the respective infusion rate for each dose escalation is calculated

Table 14 Published successful rapid desensitization to IV Cetuximab (Jerath et al. 2009)

Step no.	Solution concentration (mg/ml)	nfusion rate (ml/h)+	Time of infusion (min)	Volume of infusion (ml)	Dose of Cetuximab (mg)	Cumulative dose (mg)	Cumulative time (min)
1	0.0002	300	1	5	0.001	0.001	1
*							16
2	0.0002	300	2	10	0.002	0.003	18
*							33
3	0.0002	300	4	20	0.004	0.007	37
*							52
4	0.0002	300	8	40	0.008	0.015	60
*							75
5	0.002	300	1.5	7.5	0.015	0.03	76.5
*							91.5
6	0.002	300	3	15	0.03	0.06	94.5
*							109.5
7	0.002	300	6	30	0.06	0.12	115.5
*							130.5
8	0.002	300	13	65	0.13	0.25	143.5
*							158.5
9	0.02	300	2.5	12.5	0.25	0.5	161
*							176
10	0.02	300	5	25	0.5	1	181
*							196
11	0.02	300	10	50	1	2	206
*							221
12	0.02	300	20	100	2	4	241
*							256
13	0.2	300	4	20	4	8	260
*							275
14	0.2	300	8	40	8	16	283
*							298
15	0.2	300	16	80	16	32	314
*							329
16	0.2	300	32	160	32	64	361
*							376
17++	2	300	78	390	780	844	454 (7.6 h)
17+++	2	300	6.5	32.5	65	129	382.5
**							412.5
18	2	300	13	65	130	259	425.5
**							455.5
19++++	2	150	52*+	130	260	519	507.5
*							522.5

(*continued*)

Table 14 (continued)

Step no.	Solution concentration (mg/ml)	nfusion rate (ml/h)+	Time of infusion (min)	Volume of infusion (ml)	Dose of Cetuximab (mg)	Cumulative dose (mg)	Cumulative time (min)
20	2	150	65*++	162.5	325	844	587.5 (9.8 h)

*: Interval between doses (15 min)
+: Infusion rate (fixed at 300 ml/h unless if patient has an allergic reaction)
++: Last step of desensitization if Jerath et al. did not illicit an allergic reaction (total time to achieve target dose of 844 will be 7.6 h
+++: Patient developed rash and infusion stopped after 6.5 min of infusion (step 17)
**: Extra interval of 30 min because of allergic reaction requiring treatment with antihistamine and steroid
++++: Infusion rate was reduced by ½ as patient developed rash again at step 18
*+: Based on reported infusion time of 60 min at a rate of 150 ml/h, the total volume should be 150 ml and not 130 ml as stated by the author. Therefore, assuming the dose was 260 mg of Cetuximab, I believe the author meant the infusion time to be 52 min to deliver a dose of 260 mg Cetuximab
*++: Based on reported infusion time of 60 min at a rate of 150 ml/h, the total volume should be 150 ml. I believe the author meant 65 min of infusion and this will yield a total dose of 325 mg of Cetuximab.
Total dose: 844 mg
Total time to complete desensitization if patient did not have reaction: 7.6 h
Total time to complete actual desensitization: 9.8 h

for the practitioner. Of course, a change in protocol may be necessary if the patient experiences an allergic reaction.

Infliximab. Successful desensitization to Infliximab has been described (Mourad et al. 2015). The protocol contains 3 solutions. The top target cumulative dose was listed as 380 mg. The author chose starting dose at 0.01 mg. The dose of each administered step was not always two times higher than the prior step; the range could be as low as 1.14 or could be as high as 5x of the prior dose. In any case, the desensitization was successful in all 12 patients who underwent the desensitization procedure. The author did not specify the infusion rate for each infusion step. The protocol is summarized in Table 16. Table 17 is an example of an order written for desensitizing a patient allergic to Infliximab using spread sheet for IV desensitization created by author (Attachment A and Attachment B). To generate the desensitization order as shown in Table 17, one just needs to enter:

- The unit of the medication in question: in this case, mg.
- The top concentration of the solution: in this case, 5 mg/ml.
- The final desired rate of infusion: in this case, 125 ml/h.
- The interval between each escalation of dose: in this case, 15 min.
- Total cumulative dose desired: in this case, 380 mg.
- The number of solution to be used: in this case, 3. If one enters 3 solutions, the starting dose will be 0.08 mg, which is 1/4750 of the target dose which is the general recommended starting dose for desensitization as stated in Table 3. The dose is higher than that started by Mourad et al. stated in Table 16, which is 0.01 mg.

After entering the above 6 variables, Table 17 is generated indicating the number of solutions to be used including the specific concentration, the exact rate of infusion, volume infused for each step, dose of each step, cumulative dose, and estimated cumulative time to complete the desensitization. Escalation of dose for each step is precise: doubling the dose of the immediate prior dose. The respective infusion rate for each step to achieve the specific dose within the 15 min period is calculated for the practitioner. Although the protocol generated in Table 17 using the spreadsheet has not been validated in a patient who is allergic to Infliximab, the

Table 15 Desensitization to Cetuximab using author's spread sheet (Attachment A and Attachment B)

Step no.	Solution concentration (mg/ml)	Infusion rate (ml/h)+	Time of infusion (min)	Volume of infusion (ml)	Dose of Cetuximab (mg)	Cumulative dose (mg)	Cumulative time (min)
1	0.0002	5.7	15	1.43	0.00029	0.00029	15
*							15
2	0.0002	11.4	15	2.86	0.00057	0.00086	30
*							30
3	0.0002	22.9	15	5.72	0.00114	0.002	45
*							45
4	0.0002	45.8	15	11.44	0.00229	0.00429	60
*							60
5	0.002	9.2	15	2.29	0.0046	0.00887	75
*							75
6	0.002	18.3	15	4.58	0.0092	0.01802	90
*							90
7	0.002	36.6	15	9.16	0.0183	0.03633	105
*							105
8	0.002	73.2	15	18.31	0.0366	0.07296	120
*							120
9	0.02	14.6	15	3.66	0.073	0.14620	135
*							135
10	0.02	29.3	15	7.32	0.146	0.29268	150
*							150
11	0.02	58.6	15	14.65	0.293	0.58565	165
*							165
12	0.02	117.2	15	29.3	0.586	1.17159	180
*							180
13	0.2	23.4	15	5.86	1.2	2.34346	195
*							195
14	0.2	46.9	15	11.72	2.3	4.68721	210
*							210
15	0.2	93.8	15	23.44	4.7	9.37471	225
*							225
16	0.2	187.5	15	46.88	9.4	18.74971	240
*							240
17	2	37.5	15	9.38	18.8	37.49971	255
*							255
18	2	75	15	18.75	37.5	74.99971	270
*							270
19	2	150	15	37.5	75	149.99971	285
*							285
20	2	300	69.4	347	694	844	300 (5 h)

*: There is no waiting time between each step
Total dose: 844 mg
Total time to complete desensitization: 5 h

basic principle as stated in Table 3 is implemented. The dose escalation as stated in Table 17 is more precise than that in Table 16. Of course, deviation of the protocol may be necessary during the procedure depending on patient's allergic tolerance and the practitioner's judgment.

Table 16 Published successful rapid desensitization to IV Infliximab (Mourad et al. 2015)

Step no.	Solution concentration (mg/ml)	Infusion rate (ml/h)	Time of infusion (min)	Volume of infusion (ml)	Dose (mg)	Cumulative dose (mg)	Cumulative time (min)
1	0.1	?	?	0.1	0.01	0.01	?
2	0.1	?	?	0.2	0.02	0.03	?
3	0.1	?	?	0.5	0.05	0.08	?
4	0.1	?	?	1	0.1	0.18	?
5	0.1	?	?	5	0.5	0.68	?
6	0.1	?	?	10	1	1.68	?
7	0.1	?	?	25	2.5	4.18	?
8	1.0	?	?	5	5	9.18	?
9	1.0	?	?	10	10	19.18	?
10	1.0	?	?	12.5	12.5	31.68	?
11	1.0	?	?	17.5	17.5	49.18	?
12	1.0	?	?	20	20	69.18	?
13	1.0	?	?	30	30	99.18	?
14	5.0	?	?	8	40	139.18	?
15	5.0	?	?	18.31	0.0366	0.07296	?
16	5.0	?	?	16	80	220	?
17	5.0	?	?	32	160	380	?

?: Infusion rate and infusion time were not specified by the author. It was unknown whether the author waited for 15 min before next administration or each step took 15 min. Therefore, cumulative time to finish the desensitization was not known
Total time to complete the desensitization: unknown
Total dose: 380 mg

Table 17 Desensitization to Infliximab using author's spread sheet **(**Attachment A and Attachment B**)**

Step no.	Solution concentration (mg/ml)	Infusion rate (ml/h)	Time of infusion (min)	Volume of infusion (ml)	Dose (mg)	Cumulative dose (mg)	Cumulative time (min)
1	0.05	6.1	15	1.53	0.07629	0.07629	15
2	0.05	12.2	15	3.05	0.15259	0.22888	30
3	0.05	24.4	15	6.1	0.30518	0.53406	45
4	0.05	48.8	15	12.21	0.61035	1.14441	60
5	0.5	9.8	15	2.44	1.2207	2.36511	75
6	0.5	19.5	15	4.88	2.4414	4.80652	90
7	0.5	39.1	15	9.77	4.8828	9.68933	105
8	0.5	78.1	15	19.53	9.7656	19.45496	120
9	5.0	15.6	15	3.91	19.531	38.98621	135
10	5.0	31.3	15	7.81	39.063	78.04871	150
11	5.0	62.5	15	15.63	78.125	156.17371	165
12	5.0	125	15	31.25	156.25	312.42371	180
13	5.0	125	6.5	13.52	68	380	186.5 (3.1 h)

Total time to complete the desensitization: 3.1 h
Total dose: 380 mg

Trastuzumab. Successful desensitization to Trastuzumab has been described (Melamed and Stahlman 2002). The protocol contains 2 solutions. The top target cumulative dose was calculated as about 125 mg. The author chose starting dose at 0.02 mg. The dose of each administered step was

Table 18 Published successful rapid desensitization to IV Trastuzumab (Melamed and Stahlman 2002)

Step no.	Solution concentration (mg/ml)	Infusion rate (ml/h)	Time of infusion (min)	Volume of infusion (ml)	Dose (mg)	Cumulative dose (mg)	Cumulative time (min)
1	0.01	?	15	2	0.02	0.02	15
2	0.01	?	15	4	0.04	0.06	30
3	0.01	?	15	6	0.06	0.12	45
4	0.01	?	15	12.5	0.125	0.245	60
5	0.01	?	15	25	0.25	0.495	75
6	1.0	?	15	0.5	0.5	0.995	90
7	1.0	?	15	1	1	1.995	105
8	1.0	?	15	2.5	2.5	4.495	120
9	1.0	?	15	5	5	24.18	135
10	1.0	?	15	7.5	7.5	31.68	150
11	1.0	?	15	10	10	41.68	165
12	1.0	?	15	15	15	56.68	180
13	1.0	?	15	17.5	17.5	74.18	195
14	1.0	?	15	25	25	99.18	210
15	1.0	?	15	40	40	139	225 (3.75 h)

? Specific rate was not mentioned by author
Total time to complete the desensitization: 3.75 h
Total dose: 139 mg

not always two times higher than the prior step; the range could be as low as 1.17x or could be as high as 2.5x of the prior dose. The author did not specify the infusion rate for each infusion step but did mention that each step took about 15 min to complete. The protocol is summarized in Table 18. Table 19 is an example of an order written for desensitizing a patient allergic to Trastuzumab using spread sheet for IV desensitization created by author (Attachment A and Attachment B). To generate the desensitization order as shown in Table 19, one just needs to enter:

- The unit of the medication in question: in this case, mg.
- The top concentration of the solution: in this case, 1 mg/ml.
- The final desired rate of infusion: in this case, 93 ml/h based on manufacturer information (https://www.gene.com/download/pdf/herceptin_prescribing.pdf).
- The interval between each escalation of dose: in this case, 15 min.
- Total cumulative dose desired: in this case, 125 mg.
- The number of solution to be used: in this case, 3. If one enters 3 solutions, the starting dose will be 0.01 mg, which is 1/12,500 of the target dose which is the general recommended starting dose for desensitization as stated in Table 3. The dose is ½ of the starting dose reported by Melamed et al. as stated in Table 18.

After entering the above 6 variables, Table 19 is generated indicating the number of solutions to be used including the specific concentration, the exact rate of infusion, volume infused for each step, dose of each step, cumulative dose, and estimated cumulative time to complete the desensitization. Escalation of dose for each step is precise: doubling the dose of the immediate prior dose. The respective infusion rate for each step to achieve the specific dose within the 15 min period is calculated for the practitioner. Although the protocol generated in Table 19 using the spreadsheet has not been validated in a patient who is allergic to Trastuzumab, the basic principle as stated in Table 3 is implemented. The dose escalation as stated in Table 19 is more precise than that in Table 18. Of course, deviation of the protocol may be necessary during the procedure depending on patient's response and the practitioner's judgment.

Table 19 Desensitization to Trastuzumab using author's spread sheet (Attachment A and Attachment B)

Step no.	Solution concentration (mg/ml)	Infusion rate (ml/h)	Time of infusion (min)	Volume of infusion (ml)	Dose (mg)	Cumulative dose (mg)	Cumulative time (min)
1	0.01	4.5	15	1.14	0.01135	0.01135	15
2	0.01	9.1	15	2.27	0.02271	0.03406	30
3	0.01	18.2	15	4.54	0.04541	0.07947	45
4	0.01	36.3	15	9.08	0.09082	0.17029	60
5	0.1	7.3	15	1.82	0.1816	0.35193	75
6	0.1	14.5	15	3.63	0.3633	0.71521	90
7	0.1	29.1	15	7.27	0.7266	1.44177	105
8	0.1	58.1	15	14.53	1.4531	2.89490	120
9	1	11.6	15	2.91	2.906	5.80115	135
10	1	23.3	15	5.81	5.813	11.61365	150
11	1	46.5	15	11.63	11.625	23.23865	165
12	1	93	15	23.25	23.25	46.48865	180
13	1	93	59.7	92.51	93	139	239.7 (4 h)

Time to complete the desensitization: 4 h
Total dose: 139 mg

23.6 Designing Desensitization Protocol for Chemotherapeutic Agents and Biological Agents

The principal of drug desensitization for patient who has type I IgE-mediated allergy to the medication is to restart the medication at low dose which can be 1/1,000,000 to 1/10,000 of the normal target dose. Readers can use spreadsheets: Attachment B and Attachment D. By entering the variables including the unit of the drug, the top concentration of the drug, the final infusion rate, the target total cumulative dose of the drug, the interval between each escalation of the dose, and the number of solutions, a nursing, and a pharmacy orders can then be generated. A number of solutions correlate with the aggressiveness of the desensitization. For example, if one chooses 5 solutions, the starting dose will be much lower than if one chooses 2 solutions; the corresponding time to finish the desensitization with 5 solutions will be much longer than desensitization using 2 solutions. Therefore, spreadsheet created by choosing 5 solutions is more conservative than 2 solutions and is appropriate for a patient who is very allergic to the medication in question. Sections 4.3 and 5.2 compare the published desensitization protocols and the protocol generated by author's spreadsheet (Attachment B and Attachment D) for Carboplatin, Adalimumab, Bevacizumab, Rituximab, Cetuximab, Infliximab, and Trastuzumab. There are in general not much differences between the published protocols and those generated by the author's spreadsheet. Therefore, the reader may use the author's spreadsheet to assist him or her to create the desensitization orders. The information created will be helpful for the pharmacist and the nursing staffs in adjusting the concentration of the drug and the infusion rate. An experienced physician will also need to be present in case the patient develops an allergic reaction so that the reaction can be treated and a modified protocol can be implemented.

23.7 Conclusion

Rapid desensitization has been shown to be effective in inducing temporary tolerance so the patient can receive chemotherapeutic and biological agents. The procedure is similar to penicillin desensitization in which one will start from a very low dose such as 1/50,000 of the normal target dose of the agent. For the more sensitive patient, the starting dose can be lower such as 1/500,000. It is important to monitor the patient closely during the procedure. If a reaction

occurs, the procedure is stopped and treatment given to alleviate the reaction. Once reaction has resolved, the same dose or a slightly lower dose can be repeated and the dose is escalated every 15–30 min. In order to assure success of the procedure, correct determination of the mechanism of the initial adverse reaction is important as only immediate hypersensitivity reaction can be desensitized. If the patient has a reaction that is not IgE mediated such as Stevens Johnsons Syndrome, TENS or overlap syndrome desensitization is contraindicated and the drug should never be reintroduced. If in doubt, consultation with a specialist in allergy and immunology will be helpful. Attached to this chapter (Attachment B and Attachment D) are two spread sheets for intravenous desensitization and subcutaneous desensitization, respectively, that a licensed physician, who specializes in drug desensitization, can utilize to conveniently write the order for the desensitization procedure.

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Latex Allergy

24

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Contents

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Abstract

Natural rubber is a product most consider essential for living and is used in hundreds of commercial and household manufacturing goods. The major source of natural rubber is from a milky sap, known as latex, of various trees grown in tropical regions. The main source of latex is from a tree known as *Hevea brasiliensis*, native to the Amazon and now grown in Southeast Asia and West Africa. Two hundred and fifty types of latex protein (Heb v) have been identified, but few are known be to be allergenic. After reports of few cases of anaphylaxis, the harm of latex allergy to the users was identified and became center of attention for research. The initial step was to search for a diagnostic tool, then educate the users, and finally prevent and manage of the affected cases. The trend of our success in understanding the concept of latex allergy, diagnosis, and its management is summarized in this report.

Keywords

Latex allergy · Latex-fruit syndrome · Spina bifida · Allergic contact dermatitis

24.1 Introduction

Natural rubber is a 1:4 cis-polymer of isoprene with molecular weight 0.15–2 × 10^{-6} Da. The main source of natural rubber is from a milky sap, known as latex from a tree known as *Hevea brasiliensis*, from a family of Euphorbiacea (*spurges*). Although the trees are native of Amazon, they have been grown commercially in Southeast Asia and West Africa (Cullinan et al. 2003). The top five world's producers of natural rubber are Thailand, Indonesia, Vietnam, China, and Malaysia (MREPC 2018). Latex products are commonly used on a day-to-day basis. Most individuals use one or more types of latex products at home, work, or outdoors. Latex is frequently used in medical products. Common use of these products, specifically powdered latex gloves, has caused sensitivity and allergies in susceptible individuals. Cornstarch powder is used as a "lubricant" to facilitate glove donning. Latex proteins adhere to the powder, and individuals become sensitized by direct skin or mucous membrane contact or by inhalation.

Learning more about these products has led the investigators to identify the chemistry of latex allergens and to develop diagnostic tools. Quality assurance and safety programs combined with education increased the knowledge of medical providers and the public about the harm of latex products by implementing guides on safety precautions related to latex exposure.

24.2 First Reported Case of Latex Allergy

The first case of an allergic reaction to latex was published in German literature in 1927. The reaction, urticaria, is a result of latex exposure (Stern 1927). Over 50 years later in 1979, a second skin allergic reaction to latex was reported (Nutter 1979). This most cited reference is a case report from a British dermatologist of a 34-year-old housewife with a history of atopic dermatitis who was noted to have increased pruritus after wearing a new pair of latex gloves. Subsequent patch and prick test with pieces of the latex gloves resulted in a wheal-and-flare reaction after 15 min, confirming the diagnosis of latex allergy.

24.3 Epidemiology

The trend of increasing latex allergy reports started in 1980s and was thought to be secondary to the fact that there were many latex-containing products on the market. Certain groups of people, such as healthcare providers, who were frequently exposed to latex, were found to have a high incidence of hypersensitivity to latex. In a study of healthcare workers at Mayo Clinic in the early 1990s, a small group of employees who presented for assessment and treatment of their allergic conditions were screened for latex sensitivity by skin testing. Out of 49 patients, 34 (69%) had positive skin test to latex (Bubak et al. 1992).

In another study, a cross-sectional survey was used to assess the latex allergy among hospital staff in a tertiary care hospital in Sri Lanka. Of the 325 respondents, 53 (16.4%) reported symptoms indicative of latex allergy. Prevalence of latex allergy was highest among nurses regardless of their work units. Health providers assigned to a surgical ward had the higher prevalence of latex allergy compared to other work units (Amarasekera et al. 2010).

A study investigated the incidence of immediate allergy to latex gloves in hospital personnel by latex-gloves scratch-chamber test, prick skin test, and the use test (Turjanamaa 1987). The scratch-chamber test is a modified skin test where the skin is scratched and then a small amount of allergen is placed in an aluminum epicutaneous chamber and secured at the site and is removed after 15 min (Hannuksela and Lahti 1977). The use test is when one finger of a latex glove is worn by a subject for 15 min and is removed. A positive reaction may manifests as skin or respiratory symptoms (Kahn et al. 2015). In the study, 512 health providers (doctors and nurses) in a hospital in Finland were screened for latex allergy. All subjects (94 male and 418 female) were initially screened by latex-glove scratch-chamber test. Twenty-three (4.5%) showed positive reaction to the latex scratch-chamber test. When the same individuals were tested by prick skin test and the use test to latex, 15 showed positive reactions to prick test and 14 demonstrated positive reactions to prick test and the use test, confirming latex allergy (Turjanamaa 1987).

In a large prospective cohort study, 2053 healthcare workers with latex allergy were followed for a 10-year period (2000–2009). The study included 1040 employees who started before 2000 and 1013 who had begun employment between the 2000 and 2009. The evaluation of the subjects consisted of history, examination, prick skin testing to aeroallergens and latex allergen, and patch testing for those who had contact dermatitis symptoms. Latex sensitization was noted in 5% of the workers who had started their employment before 2000. Latex sensitization decreased in employees who had started between 2000 and 2009. There was a trend of reduction in latex sensitization form 2000 to 2005 followed by a peak in 2006. There were no sensitization documented in 2007 and 2008. The glove-related symptoms had decreased from 2004 to 2009 to approximately 10%. This reduction was thought to be due to changing to non-latex gloves, reduced previous latex exposure, and latex sensitization in new employees (Filon et al. 2014).

In a larger study that included 8580 patients, subjects were tested with several allergens including latex. The study demonstrated a trend of decreasing prevalence of sensitization to latex from 2002 to 2013. The latex sensitization declined from 6.1% in 2002–2005 to 1.9% in 2006–2009 and to 1.2% in 2010–2013. In addition to this decline in sensitization, the study noted decline in latex allergy. Latex allergy declined from 1.3% in 2002–2005 to 0.5–0.6% in 2006–2013. However, the reason for this decline was not reported in the study (Blaabjerg et al. 2015).

To assess the prevalence of latex allergy in the general population, a group of investigators screened 1000 blood samples from volunteer donors for latex IgE antibody. The researchers detected 64 (6.4%) samples with latex IgE antibodies, of which 23 samples were strongly positive (2.3% of all samples) (Ownby et al. 1996).

24.4 Importance of Latex Products in Daily Life

The most common latex product used by healthcare providers is gloves. However, latex gloves are only one of numerous latex-containing products used in hospital settings. In addition, there are hundreds of latex-containing products in household settings. It is also found in some unexpected items including children's toys, mascara, false eyelashes, and other products used in day-to-day life (Table 1).

With the HIV epidemic of the 1980s, there was an explosion of the use of condoms to prevent infection. With frequent contact, sensitization increased, and many individuals developed allergic reaction to the latex protein in condoms. In a study of 46 subjects with contact urticaria to latex gloves, 29 had history of condom use, and 7 of 29 reported

Table 1 Common products containing latex

Items in doctors' office
Gloves
Syringes
Tubing of stethoscopes
Tourniquets
Blood pressure cuffs
Rubber stoppers (injectable medications)
Items in hospitals
Gloves
Tubing of stethoscopes
Blood pressure cuffs
Rubber stoppers (injectable medications)
Catheters
Oxygen masks
Intubation devices
Household items
Dishwashing gloves
Garden hose
Mouse pad (computer)
Baby bottles, nipples, pacifiers
Shoe sole
Tires (automobiles, bicycles)
Toys
Goggles
Condoms
Bandages
Cosmetics (eyelashes, etc.)

symptoms of local swelling and pruritus during intercourse. To confirm the immunogenicity of the latex allergy, the investigators used prick skin testing and tested 16 different brands of condoms. Of the tested brands, 4 elicited positive reactions in 52–67% of the patients, one was negative, and 12 were less allergenic (Turjanmaa and Reunala 1989).

24.5 Why Are Latex Gloves Preferred by Health Care Providers

Due to its unique properties, latex gloves are the first choice of medical providers.

The following are the advantages of latex gloves properties over other gloves:

- Elasticity – This is important especially during procedures.
- Dexterity – Due the elasticity and flexibility of the product.
- Comfort.
- Barrier against blood-borne organism.
- Durability.
- Cost-effective.

24.6 Latex Protein and Allergenicity

Natural rubber latex contains 250 types of proteins designated as Hev b. However, thus far only 15 of them have been identified as allergenic to humans (Table 2). There is a variation of protein different Hev b proteins in latex gloves. In earlier studies, the investigators compared the extractable total latex proteins using solid-phase inhibition assay from13 lots of surgical gloves, 9 lots of examination gloves, and 5 lots of chemotherapy, autopsy, or utility gloves. The result showed that the content of the extracted latex protein varied from one manufacturer to another in each lot of gloves. The extracted proteins from tested examination gloves varied from <10 AU to 5500 AU, surgical gloves varied from <10 AU to 2300 AU range, and the chemotherapy, autopsy, or utility gloves showed variation of <10 AU to 1000 AU (Jones et al. 1994). In a study to further assess the allergenic potential of medical gloves, the investigators tested 208 brands of medical gloves which were available in 1991, 2001, and 2003 in Helsinki, Finland. Using capture enzyme immunoassay (EIA), they measured four specific latex allergens, Hev b1, 3, 5, and 6.02 in the gloves. The results were compared with skin tests and IgE-ELISA inhibition test. The investigators noted a correlation between the sum values of these four allergens to the IgE-ELISA inhibition. They noted that by setting the sum of these four allergens to 0.15 μg/g, they were able to differentiate the allergenicity of latex gloves. In other words, based on this cut off, they categorized the allergenicity of latex gloves to "low allergenic"(defined as 10 AU/ml) and "moderate to high allergenic" (defined as ≥10 AU/ml). If the sum of the four allergens were not detected (i.e., were less than cut off), the gloves were considered low allergenic (Palosuo et al. 2007).

Table 2 Natural rubber latex allergens

Allergen	Biochemical name	Molecular weight (KDa)	Clinical association – allergenicity
Hev b1	Rubber elongation factor	14	Spina bifida (major allergen); healthcare workers
Hev b2	Beta-1,3-glucanase	34	Minor allergen
Hev b3	Small rubber particle protein	24	Spina bifida (major allergen); healthcare workers
Hev b4	Lecithinase homologue	53–55	Minor allergen
Hev b5	Acid protein	16	Spina bifida; healthcare workers (main allergen)
Hev b6	Hevein precursor	20	Hevb 6.02 (an N-terminal fragment of Hev b 6): Cross reactivity with fruit; healthcare workers (main allergen)
Hev b7	Patatin-like protein	42	Minor allergen; cross-reactivity with fruit
Hev b8	Profilin	15	Not known
Hev b9	Enolase	51	Not known
Hev b10	Superoxide dismutase (Mn)	26	Not known
Hev b11	Class I chitinase	30	Not known
Hev b12	Non-specific lipid transfer protein type 1 (nsL TP1)	9	Not known
Hev b13	Esterase	42	Not known
Hev b14	Hevamine	30	Not known
Hev b15	Serine protease inhibitor	7.5 KDa	Not known

References: Cabañes et al. (2012), Nettis et al. (2012), Cullinan et al. (2003), WHO/IUIS (2017)

24.7 Types of Latex Allergy

There are two types of hypersensitivity reactions to latex, acute reaction mediated by IgE antibody and delayed, which is cell-mediated. An example of an IgE-mediated reaction is when a sensitized individual develops symptoms while wearing a pair of latex gloves or after inhalation of aerosolized latex allergen particles. This type of reaction referred to as a type 1 Gell and Coombs reaction and may manifest locally as contact urticaria or systemically with respiratory or cardiac compromise.

Immediate allergic reactions to latex should be considered an emergency. Although local immediate reactions may appear to be mild, some may progress to a systemic reaction involving multiple organs. Systemic reactions may occur in different hospital settings. For example, anaphylaxis during anesthesia should prompt the providers to search for possible latex allergy. A study of 15 patients with anaphylaxis during anesthesia identified several causes secondary to latex anaphylaxis. One case was unique in that it occurred during transvaginal ultrasound (Laurauri et al. 2017).

The symptoms of delayed reaction manifest two or more days post exposure. This is a cell-mediated type IV Gell and Coombs reaction. The IgE-mediated reaction noted above is due to exposure to the latex protein, whereas the delayed (Type IV) reactions are due to chemical compounds, such as accelerators, used in production of latex products. Type I and Type IV reactions may be seen in the same individuals (Mahmoudi et al. 1998).

24.8 Latex-Fruit Syndrome

One of the interesting findings about latex is that the allergens cross-react with plant-derived foods. This shared allergenicity is estimated to be present in 30–50% of patients with latex allergy (Wagner and Breiteneder 2002). A first case of such cross-reactivity was reported between latex and banana. A 44-year-old female surgical nurse with history of allergic rhinitis developed urticaria upon exposure to latex gloves. She also had developed angioedema after ingesting banana. The prick skin test and serum IgE to latex extracts demonstrated positive reactions. Prick skin tests to banana was also positive (M'Raihi et al. 1991).

The relationship of latex allergen to certain food (fruit) became known as "latex-fruit syndrome." Subsequently such relationship of latex with other fruits was also reported. One study assessed the prevalence of latex-fruit syndrome in a group of Italian children and adolescents with latex allergy. The participants, 22 subjects with mean age 15.3 years, had positive history ranging from an immediate cutaneous to anaphylactic with natural rubber latex exposure. They were divided into two groups based on their severity of symptoms. The first group (13) consisted of those with mild cutaneous symptoms. The second group (9) had moderate to severe symptoms with latex exposure. The subjects also had either positive prick skin test or positive serum IgE titer to latex allergen. The subjects were tested (serum IgE and skin prick test) with grass and fruit allergens (kiwi, peach, chestnuts, melon, cherry, and apple). The study demonstrated cross-reactivity of latex allergen with the tested fruits; reactions to kiwi were the most common followed by chestnut, peach and melon (Ricci et al. 2013).

To identify the genes that may be involved in the pathogenesis of latex-fruit syndrome, a group investigated the gene expression profiling of the affected patients. The participants, total of 17, had either fruit allergy (5), latex allergy (6), or reaction to both. (6). The diagnosis of latex allergy was based on history and testing, prick skin test, in vitro specific serum IgE test, and confirmation of the results with a provocation test. The diagnosis of food allergy was based on history, skin testing, and specific serum IgE test. The investigators identified regulator genes common in all atopic patients in the study. These findings led the authors to conclude that a similar genetic mechanism is involved with allergy to fruit, latex, or both (Saulnier et al. 2012).

Table 3 lists some common fruits in latex-fruit syndrome.

Table 3 Common fruit in latex fruit syndrome

Kiwi
Banana
Chestnuts
Melon
Passion fruit
Avocado

24.9 Latex Allergy in Children

The prevalence of latex sensitivity in the general pediatric population has always been a question. Due to limited studies, the estimation has rarely been reported in the literature. In order to answer this question, a study in the United Kingdom used the database of the Avon Longitudinal Study of Parents and Children (ALSPAC). The ALSPAC is a prospective birth cohort of babies and included those born or expected to be born between periods of April through December 1992. Those who participated were selected at 7 years of age and were subjected to prick skin tests with various allergens including pollens, cat, peanuts, and latex. Of total of 7249 (51.8%) of the cohort who were tested, 1877 were tested to latex, of whom 4 demonstrated sensitization to latex (3.5 mm diameter wheal) and 9 others had smaller wheals (1–2 mm diameter wheal). The four sensitized children represented 0.2% of the general population (Roberts et.al. 2005).

24.10 Latex Allergy and Spina Bifida

Spina bifida is a known risk factor for latex allergy in children. To help determine the risk of latex sensitization in this group, 35 patients with spina bifida (5–32 years old) were skin prick tested with seven allergens: latex, three types of dust mites, and three commonly latex cross-reacting fruits (kiwi, banana, and avocado). Of the 35 tested, 16 (46%) showed skin test sensitization to latex allergen. Of the 16, 5 (31%) also had clinical symptoms to latex. Among the subjects sensitized to latex allergens, 6 had sensitization to tested foods as well (Chua et al. 2013). In a similar study of 80 children and adults with spina bifida (1–24 years of age, 32 male and 48 female), the presence of latex sensitization and clinical symptoms were investigated. In addition, the genetic and environmental factors in this population were assessed. The assessment included a

questionnaire, prick skin test and IgE RAST CAP test to latex. Of the tested subjects, 32 (40%) showed latex sensitization, among whom 12 (40%) had history of clinical symptoms to latex. Those with latex allergy more likely had early exposure to latex, frequent surgical procedures, and a history of atopy (Ausili et al. 2007).

To investigate when latex sensitization begins in children with spina bifida, one group focused on a prenatal population. Twelve patients with spina bifida and ten healthy matched patients were recruited for the study. After delivery, the blood samples from umbilical cords were taken and tested for total IgE and latex-specific IgE by immunoCAP testing. When test results were compared between groups, the total IgE and latex-specific IgE were significantly higher in spina bifida group than the healthy group. However when the measurements were corrected for total IgE, the difference was not significantly different (Boettcher et al. 2014).

24.11 Diagnosis

In most cases, patient will present with symptoms associated with exposure. The allergist should follow a systemic approach to identify if latex is the etiology by taking a thorough history and performing physical examination and diagnostic testing. When the latex allergy is confirmed, the provider should manage the condition by educating the patient and providing management/treatment options. A guide to approach a latex allergic patient is depicted in Fig. 1.

24.11.1 History and Physical Examination

History – Inquiring about occupation, exposure, and length of exposure to rubber products are the most important aspects of the history. Healthcare providers, specifically physicians, have a high risk of developing latex allergy. Physicians who regularly perform procedures are more vulnerable than other groups of medical providers. Other healthcare providers at risk include dentists, dental hygienist, nurses, and phlebotomists. Nonmedical workers are also at risk and include cooks, janitors, researchers, and technicians (Table 4).

The next pertinent question is the type of reaction and the length of exposure to the rubber products. The expected skin reactions may include erythema, pruritus, urticaria, and angioedema. The angioedema may involve larynx (laryngoedema) causing life-threatening reaction. The respiratory reaction may include shortness of breath, wheezing, or chest tightness. And finally, the reaction may be systemic and life threatening with multi-organ involvement.

The immediate reaction is an IgE-mediated. The patients may also develop an erythematous and pruritic rash at the site of latex exposure a day or two after the exposure to latex products. This contact allergic dermatitis is not life threatening but is an inconvenience. The location of the allergic contact dermatitis is a clue to the type of the latex products involved. For example, the hand involvement suggests latex gloves, eyelid involvement may be secondary to latex-containing makeup products (eyelashes, etc.), and genitalia involvement suggests latex condoms.

Because of cross-reactivity of certain fruits with the latex allergens, history of food allergy should also be sought.

Physical examination – Since most reactions to latex are localized, the physical examination should focus on the area of contacts. Hands in particular due to exposure to gloves should be examined. Other areas such as face, lips, eyelids, oral mucosa, and pharynx should be examined. Genitalia symptoms suggest that a genital exam should be performed.

24.11.2 Diagnostic Testing

The history and physical examination should be confirmed with objective testing. Several diagnostic tests are available to confirm the diagnosis of latex allergy.

Prick (percutaneous) skin test – Neither standardized nor FDA-approved commercial latex allergens are available for skin testing. Some

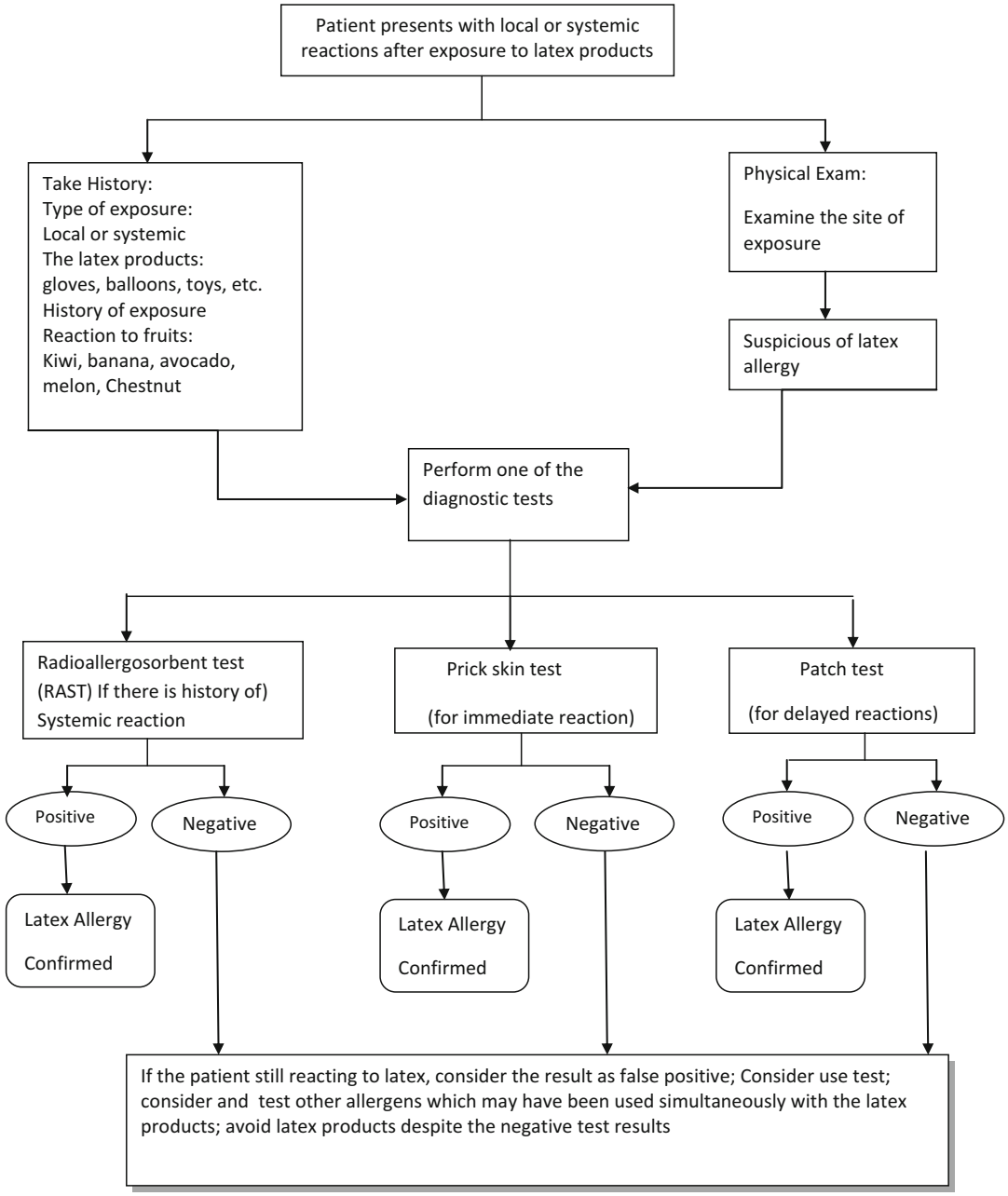

Fig. 1 Algorithm guide to diagnosis of latex allergy (adapted from Mahmoudi and Hunt 2000)

medical centers prepare their own extracts for testing; however, there is not a consensus on how best to skin test for latex allergy. Some centers extract latex protein from latex gloves and use it for skin testing, while others purchase latex used in industries to test with. A multicenter study investigated the latex skin testing efficacy among a large group of individuals with latex allergy. A total of 324 subjects with or without self-report history of latex allergy participated in the study. The subjects

Table 4 Profession at risk of latex allergy

Medical providers
Physicians (especially surgeons, anesthesiologists)
Dentists
Dental hygienists
Dental assistants
Nurses
Phlebotomists
Researchers
Research technicians
Laboratory personnel
Nonmedical providers
Cooks and cook-prep personnel
Food handlers
Janitorial
Factory workers who work with chemicals
Workers in toy manufacturing plants
Workers in tire manufacturing plants
Other groups at risk
Patients with history of multiple surgeries (spina bifida patients)

(124 adults and 10 children in the latex allergy group and 180 adults and 10 children in non-latex allergy group) received *Malaysian Hevea Brasiliensis* antigen via skin puncture in three different concentrations of 1100 and 1000 μg/ml. The investigators used a provocation test to confirm or exclude those with positive history of latex allergy with negative skin tests from individuals with negative history of latex allergy with positive skin tests. This was important to determine the sensitivity and specificity of the skin testing. The study achieved 95% sensitivity in the latex allergic subjects with 100 μg and 1000 μg/ml and 99% specificity in the same group. Therefore, the history of latex allergy should be confirmed with tests using 100 and 1000 μg to ensure high sensitivity and specificity (Hamilton et al. 1998).

In-vitro testing – Various in vitro tests have been used for detecting natural rubber latex allergens. The latex ImmunoCAP™ k82 s (supplemented with rHev b. 5), a k82 ImmunoCAP™ (without rHev b 5 supplementation, and a multi-allergen ImmunoCAP™ (contained rHevb 1. 5, 6.01, 8; Hev b mix), and another specific ImmunoCAP™ (containing horseradish peroxidase and bromelain) to detect cross-reactive carbohydrate determinants (CCDs) were used for quantitative analysis of immunoglobulin E profiles in patients allergic or sensitized to natural rubber latex. The study screened sera of 104 healthcare workers, 31 patients with spina bifida, and 10 patients with MS (multiple sclerosis) with the above-noted Latex ImmunoCAP™ tests. The results revealed that the anti-rHev b5-s IgE was the most prominent detected antibody in all groups tested. The Hev b 2, 5, 6.01, and 13 were noted to be the major allergens in healthcare workers and spina bifida patients. This study suggested that Hev b 1,2, 5, 6.01, and 13 are the major Hev b allergens and recommended that standardized latex extracts and in vitro allergosorbent tests contain these allergens (Raulf-Heimsoth et al. 2007).

Patch test – Identification of latex allergens using patch testing is based on cell-mediated mechanism. The test is valuable when the latex reactions are delayed as in allergic contact dermatitis and should not be used in those who had anaphylaxis. The affected allergic individuals react to latex allergen after 48 h or more after exposure to a latex product and may or may not develop IgE antibodies. See ▶ Chap. 10, "Allergic Contact Dermatitis" for details.

Flow cytometry – A two-color flow cytometry test has been used to diagnose IgE-mediated latex allergy. The test is based on detection of basophil activation in vitro. The whole blood is incubated with a buffer containing IL3 which activates basophiles. Then the activated blood samples are stimulated with latex. A commercially available monoclonal biotinylated human IgE is used to estimate the activated basophils. The test has been shown to have 93.1% sensitivity and 91.7% specificity (Ebo et al. 2002).

Use test – This is an older test in which a subjects wares a cut fingertip of a latex gloves. The positive results are urticaria in the area of the exposure. Since the allergen content of gloves varies from one manufacturer to another, the result of the test may not be accurate. Of importance, this should only be used in those that have limited skin symptoms and not in those with anaphylaxis.

24.12 Management and Treatment of Latex Allergy

24.12.1 Avoidance

Like all the other allergic diseases, the best way to manage latex allergy is avoidance. Avoidance is effective in reducing latex sensitization and latex allergy. In one study, 120 patients with spina bifida who were cared for in a latex-free environment were compared to a group with spina bifida who were exposed to latex on a regular basis. The former group had less evidence of latex sensitization and allergy as demonstrated by testing to various aeroallergens, foods, and latex by prick skin testing and in vitro latex-specific IgE. Of the 120 patients tested, 5% showed sensitization to latex, whereas the matched group with spina bifida and latex exposure showed 55% sensitization. This study is one example that demonstrates the avoidance of latex exposure in the spina bifida group leads to a significant reduction of latex sensitization (Blumchen et al. 2010). The following are recommended key factors in managing latex allergy. See also Fig. 1.

- Read product labels and find substitutes for latex products.
- Use latex gloves substitutes such as vinyl, nitrile, neoprene, or polyvinyl chloride gloves. Other latex products should be substituted by similar non-latex containing ones.
- Work in a non-latex environment, if possible.
- As there is homology of the latex allergen proteins with certain fruits, the latex allergic patients should avoid fruits such as banana, avocado, chestnuts, and melons.
- The co-workers of latex allergic individuals should use powder-free gloves.
- Latex allergic patient requiring surgery should be the first case of the day. This is important as there would be reduced aerosolized latex allergen in the operating environment.
- All surgical and procedural suites should be latex-free.
- Latex allergic people should carry epinephrine at all times.
- The affected individuals should inform their health providers of their conditions so they can be noted in their medical charts.
- Using a med-alert bracelet or a necklace is important identifiers for allergic patients.
- Participate in support group.
- In hospitals and clinics, latex products should be replaced with non-latex products.
- At a national level, there should be a task force to identify and educate the affected individuals as well as the public.

24.12.2 Differential Diagnosis of Latex Allergy

Local reactions:

- Irritant contact dermatitis (soap, detergents)
- Allergy to corn starch (used in some powered gloves – rare)
- Coincidental allergy to other ingredients of the latex products
- Allergy to anesthetics (usually noted in a dental office)
- Contact dermatitis secondary to rubber preservatives and stabilizers

Systemic reactions:

- Asthma due to other causes (occupational asthma)
- Anaphylaxis due to other causes (drugs, food, etc.)

24.12.3 Medications

Medications such as antihistamines are temporary means of controlling the skin/mucous membranes symptoms. Bronchodilators may be used if respiratory symptoms develop. Oral corticosteroids may also be useful in severe cases. Treatment of anaphylaxis is the same as treatment of anaphylaxis due to other allergens such as food or insect stings and is managed by using injectable epinephrine.

24.12.4 Immunotherapy

Based on results and beneficial outcome of immunotherapy for allergic rhinitis, using immunotherapy was a logical choice to treat latex allergic patients. As a result, multiple studies have investigated the effect of immunotherapy in these affected individuals. In a small study, 23 patients with latex rhinoconjunctivitis were recruited for a double-blind placebo-controlled study. They were randomized to two groups, 11 subjects in the active group and 12 in the placebo group. The participants of this study received subcutaneous injections of standardized latex extract for a two-day rush protocol and subsequent 12 months maintenance period. When the symptoms of rhinitis, asthma, conjunctivitis, skin symptoms, and the medication score compared with the baseline, no significant changes were noted between the treatment and the placebo groups (Taber et al. 2006).

A rather similar small-size study used sublingual immunotherapy to assess the effectiveness of the latex immunotherapy. Twenty-eight patients with latex allergy (5 males and 23 females) participated in the study. Of 28 subjects, 14 were in the active group and 14 in placebo group. The investigators used a commercial sublingual immunotherapy latex reagent for the treatment. The study consisted of a year of double-blind and a year of open active therapy. The participants had history of symptoms as a result of latex exposure or a positive reaction to diagnostic tests (glove use test and or conjunctival test and positive reaction to prick skin test to natural rubber latex). Of 28 patients, 19 patients completed 2 years of the study (11 from the active group and 8 from the placebo group). The study did not show significant difference between the treatment and the placebo group (Gastaminza et al. 2011).

A meta-analysis reviewed 11 clinical trials, 3 subcutaneous (SCIT), and 8 sublingual immunotherapy (SLIT) of latex allergic patients. There were some benefits of immunotherapy in two of the subcutaneous trial groups although frequent side effects were reported. Overall the sublingual immunotherapy trials were mostly effective and had a better safety profiles compared to the SLIT trials (Nettis et al. 2012).

In summary, standardized latex allergens, larger patient sample size, and standardized outcome measures are needed for better understanding latex immunotherapy effectiveness.

24.13 Conclusion

We have learned a great deal about latex allergy since its initial recognition some 40 years ago. We are now able to identify and distinguish different types of latex allergens. We are able to diagnose latex allergy and differentiate it from similar conditions. And finally, we now know how to manage the latex allergic patient. By implementing strict avoidance, we have been able to reduce the prevalence of latex allergy. The goals are to standardize prick skin testing reagents and find a safe and long-term method of treatment; however with the declining prevalence of latex allergy, neither of these two goals may be necessary.

24.14 Cross-References

▶ Allergic Contact Dermatitis
▶ Occupational Asthma

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Part VI

Food Allergy and Eosinophilic Esophagitis

IgE Food Allergy

25

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Abstract

Food allergy has become a significant public health burden over the past decades with an ever increasing prevalence. Many different pathophysiologic mechanisms have been investigated and discussed. The current consensus on development of food allergies is the alteration of clinical and immunologic tolerance to foods. Pre- and postnatal exposures and other factors both in the patient and also the environment seem to be the main drivers in this altered immune state resulting in sensitization to food proteins.

Food allergies can present as many different entities. Pure IgE-mediated allergies are IgE-mediated food allergies or pollen-food cross-reactivities, while atopic dermatitis and eosinophilic esophagitis represent a mixed IgE-/cell-mediated sensitivity to food allergens.

Symptoms of adverse reactions to food allergens manifest in most organ systems, including the lungs, gastrointestinal tract, cardiovascular system, and the skin. Often more than one organ system is affected with anaphylaxis being the most severe and potentially resulting in death.

Clinical history, specific serum IgE testing and skin prick testing are the mainstay in diagnosis of food allergies. Novel diagnostic tools utilizing advances and availability of recombinant allergens and cellular and genetic testing are being investigated.

While novel treatment approaches that are focusing on achievement of tolerance or sustained unresponsiveness are being studied on the cellular level and in clinical trials, the mainstay of management remains strict avoidance of the food allergen.

Keywords

IgE-mediated food allergy · Dual allergen exposure hypothesis · Anaphylaxis · Sustained unresponsiveness · Food challenge proven food allergy

25.1 Introduction

IgE-mediated food allergy has been increasing in the westernized world over the past decades. Symptoms of IgE-mediated food allergy can manifest in many organ systems, including the lungs, gastrointestinal tract, and skin. The most dramatic manifestation of an acute allergic reaction is anaphylaxis which can lead to hypotension and organ failure and may result in death. The cause of this significant increase is not known and various hypotheses regarding the underlying mechanism have been generated over the past years. Because of the prevalence of food allergy, the universality of food ingestion as a basic means for growth, development, and survival of human kind, and also the social aspect of food ingestion, not only patients and their families are affected by this epidemic. In an attempt to keeping patients safe and to decrease prevalence, recommendations regarding food allergy touch most areas of life, from food introduction in infancy, over guidelines for schools and camps, to food processing and labeling laws. The increased public awareness might also lead to self-imposed food avoidances for suspected reactions.

Extensive research in all aspects of food allergy is being conducted, and diagnosis, management, and treatment guidelines are being adjusted based on novel discoveries. The main focus remains on primary prevention and to establish therapies to achieve tolerance or sustained unresponsiveness in affected patients.

Solid knowledge about etiology, natural history, diagnosis, and management is crucial not only for allergists but also for other health care providers to ensure optimal patient care and selection of appropriate testing and guidance.

25.2 Epidemiology and Natural History

25.2.1 Prevalence and Incidence

Food allergies are one of the most common medical conditions in the developed world. According to some studies' metrics, the prevalence of IgE-mediated food allergy as diagnosed by oral food challenge is as high as approximately 3–8% of children and 1–3% of adults (Rona et al. 2007; Osterballe et al. 2005). Using peanut allergy as an example, epidemiologic studies reveal shared findings of high rates of allergies among developed nations. In the USA, the National Health and Nutrition Examination Survey (NHANES) showed a prevalence of peanut allergy of 1.8% of children (Liu et al. 2010). Similarly, peanut allergy affects 1.8% of children in Canada (Gupta et al. 2011), 2% of children in the United Kingdom (Nicolaou et al. 2010), and even as high as 3.0% of children in Australia (Osborne et al. 2011). While these estimates reflect a common prevalence of peanut allergy closer to 2.0%, a compilation of studies go on to reflect that a food allergy of some kind likely affects up to 8% of children and as many as 5% of adults (Sicherer and Sampson 2014). Interestingly however, according to a study investigating the prevalence of food allergies documented in electronic health records, about five times as many individuals will report having allergies than those who have actually undergone allergy testing. Furthermore, of the individuals who actually have undergone allergy testing only about half will test positive for at least an intermediate severity of IgE response (Acker et al. 2017). The increased rates of patient reported allergies indicate growing concern regarding allergic conditions in the developed world.

Allergic disease first came to the forefront as a public health issue in the mid-1900s with what has been described as the "first wave" – when a peak of almost 50% of the populations of westernized countries reported experiencing respiratory symptoms of allergic rhinitis at some stage of life (Prescott and Allen 2011). Over the past two to three decades, however, a "second wave" has since followed with food allergy becoming an important manifestation of allergic disease. Correspondingly, there has been an increase in the number of emergency room visits and hospitalizations for allergic conditions, namely, anaphylaxis, urticaria, and angioedema (Gupta et al. 2007; Lin et al. 2005; Poulos et al. 2007). In addition to the growing incidence of allergic conditions, there is also a decreased likelihood with which afflicted individuals are growing out of their allergies (Prescott and Allen 2011). For example, studies in Australia have shown there to not only be an increased prevalence of IgE-mediated allergic diseases but also a longer disease course associated with allergic conditions, which subsequently increases duration of disease burden and healthcare costs (Longo et al. 2013).

25.2.2 Risk Factors

There are numerous risk factors implicated in the development of IgE-mediated food allergy. Some of these are unmodifiable risk factors, such as gender and race, while others are modifiable risk factors such as vitamin D and dietary intake, hygiene, and certain environmental exposures. Genetic and/or endocrinologic factors may play a role in the onset of food allergy, as boys have been found to have higher rates of food allergies than girls, while women have higher rates of food allergies than men (Liu et al. 2010; Sicherer et al. 2004). Furthermore, Asian and black children in developed nations also tend to have higher rates of

food allergy as compared to white children (Sicherer and Sampson 2014). Comorbid atopic conditions, such as eczema, are associated with higher rates of food allergy as well, and there is also increased likelihood of developing food allergy if a family member also has food allergies (Sicherer and Sampson 2014). This has also been shown in sibling and twin studies. A child has a sevenfold increased risk of developing a peanut allergy if a sibling has a peanut allergy (Hourihane et al. 1996). For monozygotic twins, it has been shown that the risk of peanut allergy is 64% higher if the twin sibling also has a peanut allergy (Sicherer et al. 2000).

Certain lifestyles and dietary choices also appear to predispose to food allergy. For example, studies using NHANES data have described a higher risk of food allergy in children with low vitamin D intake in the children themselves or even in the mother during pregnancy. Similarly, individuals who live farther away from the equator and are exposed to less ambient UV radiation will have decreased endogenous vitamin D production and also have higher rates of food allergy (Osborne et al. 2012; Sheehan et al. 2009). Hygiene and germ exposure may also play a role in the development of food allergies, as children born via C-section have higher rates of food allergies. Conversely, children of lower birth order who are exposed to the infections of their older siblings as well as children who attend daycare at a young age will have lower rates of food allergy (Lack 2012). Other studies have described a higher rate of shellfish allergy among inner-city children who are more frequently exposed to the cross-reactive proteins found in cockroaches (Maloney et al. 2011; Wang et al. 2011).

The Learning Early About Peanut Allergy, or LEAP, trial has triggered a fundamental change in the concept that early food allergen exposure was a risk factor for food allergy to the opposite understanding that food allergen avoidance might actually sensitize the individual to food allergens (Fleischer 2017). In the study, infants with severe eczema, egg allergy, or both were randomized to consume or avoid peanut until the age of 60 months. It was found that early introduction of peanut resulted in a decreased frequency of peanut allergy in this high risk group (Fleischer 2017). It is clear that an understanding of the risk factors that predispose to allergic conditions can provide useful information regarding possible routes to identify and manage high risk populations, provide them with preventative measures, and reduce morbidity, mortality, and healthcare burdens and costs.

25.2.3 Prevention

The mainstay of prevention of known food allergy remains avoidance of the allergic food trigger. However, there have been recent developments in the understanding of how to possibly lower the risk of onset of food allergy in the first place. For example, while data from CoFAR, the Consortium of Food Allergy Research, have shown that maternal ingestion of peanut during pregnancy will increase infant serum peanut IgE levels, other studies have shown there to be a subsequent decrease in the development of peanut food allergy and asthma (Maslova et al. 2012).

Other data and observations have revealed mixed effects of food allergy prevention attempts. While exclusive breast-feeding continues to be recommended in infants for at least the first 4–6 months of life, certain formulas have been found to confer a protective risk against the development of atopic disease while others have not. Extensively hydrolyzed casein formula has been found to be protective against the development of eczema (but not food allergy) as compared to soy formulas or whole milk based formulas (Des Roches et al. 2012; Kelso et al. 2013).

Numerous studies have shown that avoidance of allergenic foods at a young age may actually be a risk factor in the development of food allergy and atopy in general. Conversely, food diversity at a young age has been shown to result in a decreased risk of atopic sensitization later in life. Individuals who consume more fruits, vegetables, and a variety of home-prepared meals are less likely to develop food allergy (Joseph et al. 2011).

Finally, more recent studies are also showing the protective effects of optimizing the gut flora. Prebiotics, probiotics, synbiotics, and bacterial lysates

have been increasingly studied and found to have a role in the reduction of the risk of eczema. While these studies remain inconclusive at this time, it is possible that a better understanding of bacterial diversity of the GI tract will identify another route of protection against food allergy and atopic disease (Pfefferle et al. 2013; Kuitunen 2013).

25.2.4 Natural History

The natural history of IgE-mediated food allergy diagnosed in childhood has traditionally carried a good prognosis, particularly for milk, egg, wheat, and soy allergies (Savage et al. 2010; Savage et al. 2007; Skripak et al. 2007). However recent studies have shown an increasing inability to tolerate allergenic foods even with increasing age. Previously, for example, about half of children who had a cow milk protein allergy would have resolution of their allergy by 1 year of age, about two-thirds would have resolution by 2 years of age, and as high as 90% of children would have resolution by 3 years of age (Høst 1994). However, more recent studies reveal that IgE-mediated cow milk protein allergy has been found to persist in 21% of children as old as 16 years of age (Skripak et al. 2007). Similar trends are observed with other allergenic foods, such as with egg, soy, wheat, peanut, fish, and shellfish allergy. In all cases, it appears to be the case that higher levels of IgE antibody confer an increased likelihood of persistence of an allergic condition into late childhood (Savage et al. 2010; Savage et al. 2007).

Attempts have been made to quantify the likelihood of resolution of allergic disease based on several factors, including serum IgE levels and skin prick testing results. One such resource is the Consortium of Food Allergy Research, or CoFAR, which has generated calculators predicting milk and egg allergy resolution based on data compiled from a large bank of documented food allergies (www.cofargroup.org). Similarly, resources exist to predict the likelihood of developing food allergy at all. It is worth noting that genetic factors play an important role in the natural history of allergic disease, and for this reason genetic testing has become a promising area for further exploration in an attempt to identify at-risk individuals before the onset of a severe reaction (Li et al. 2016). Moreover, advances have already been made in medicine's ability to impact the prognosis of allergic conditions and facilitate individuals' abilities to outgrow their allergies. For example, immunotherapy has yielded promising results for allergic rhinitis for years (Wood 2016). Unfortunately, the efficacy of this therapy has remained limited in regards to food allergies and for this reason allergen avoidance remains the mainstay of treatment. However, with further research and advances in immunotherapy, it is possible that over the next several years the success of immunotherapy in modulating allergic rhinitis may be able to translate to food allergies (Wood 2016).

25.3 Pathogenesis

25.3.1 Immunologic Mechanisms

All immune-mediated adverse reactions to a food are subsumed under the term food allergy. Disease entities that are included in this definition are IgE-mediated immediate hypersensitivity reactions, delayed cell-mediated reactions that are not IgE mediated, as well as a mixed presentation of both IgE and non-IgE-mediated reactions. In this chapter, we focus on IgE-mediated food allergies.

25.3.1.1 Sensitization to Foods

Experimental mouse models have significantly enhanced our understanding of mechanisms of food sensitization. In general, two routes of sensitization are used in mouse models investigating food allergies – sensitization via topical/epicutaneous exposure and sensitization via oral/intestinal exposure.

Early models mainly employed oral sensitization routes and it was noted that pure ingestion of allergens usually leads to oral tolerance in mice. To achieve sensitization via the oral route, adjuvants such as cholera toxin or staphylococcal enterotoxin B (SEB) were used (Ganeshan et al. 2009). As it became evident that topical/epicutaneous sensitization plays a major role in sensitization to food allergens, different mouse

models employing epicutaneous sensitization have been developed (Han et al. 2014; Leyva-Castillo et al. 2013; Oyoshi et al. 2010; Tordesillas et al. 2014). Tolerance is the natural response of both mice and human to exposure with harmless food proteins.

In the mouse model, it was shown that tolerance to an orally ingested antigen is mediated by presentation to $CD103^+$ Dendritic cells. Topical exposure to an antigen leads to tolerance via $CD11b^+$ and Langerhans cells.

Three different pathways leading to sensitization via the epicutaneous route (usually with breached integrity of the skin) and oral route (with exogenous adjuvants to break oral tolerance) have been described.

IL-33 expression from both keratinocytes in the skin and intestinal epithelial cells has been shown to be a central cytokine in the development of sensitization and food allergy. Allergenic triggers on intestinal epithelial cells were shown to increase OX40L expression on $CD103^+$DCs and thus causing a predominantly Th2 weighted immune response (Blázquez and Berin 2008). Similarly innate triggers on keratinocytes were shown increase IL-33 expression leading to a Th2 skewed immune response (Tordesillas et al. 2014). In addition to leading to a Th2 skewed immune response, IL-33 also stimulates group 2 innate lymphoid cells (ILC2s). The activations and proliferation of the ILC2 lead to increased production of IL-4 which results in suppressed generation of T- regulatory cells (Tregs) in the small intestine (Noval Rivas et al. 2016). IL-33 can also act directly on mast cells and augment activation in acute reactions to food allergens.

Similarly to IL-33, TSLP can increase OX40L expression on dendritic cells resulting in a Th-2 skewed immune response and recruitment of basophils (Leyva-Castillo et al. 2013). TSLP was also described to exert its effect directly on basophils (Siracusa et al. 2011) also leading to IL-4 production.

Another Th-2 inducing cytokine that plays a major role in food sensitization and allergy is IL-25 and its effect on group 2 innate lymphoid cells. IL-25 leads to release of Th-2 inducing cytokines like IL-4 from ILC2s (Lee et al. 2016).

Recently, an additional cytokine (IL-9) in the allergic response to food was described as a key player. IL-9 is a growth factor for mast cells and overexpression of IL-9 leads to intestinal mastocytosis and increased epithelial permeability (Osterfeld et al. 2010).

25.3.1.2 Dual Allergen Exposure Hypothesis

This intricate interplay of genetics and environment resulting in the immunopathogenesis of food allergy and the insight gained from murine models is also reflected in many clinical studies.

Most studies concur that the main site of food sensitization, especially in peanut allergy, is the skin. Therefore, atopic dermatitis is a major risk factor for food allergies. This has been described in very early studies investigating the relation of food protein in creams (Lack et al. 2003) and soaps (Fukutomi et al. 2014). The finding that mutations in the protein filaggrin which is essential for maintaining the skin barrier go along with higher rates of atopic dermatitis and also food allergies supports this concept (Brown et al. 2011). House dust which contained peanut protein was described as a major risk for the development of peanut sensitization in children with atopic dermatitis, especially in individuals with Filaggrin mutation.

Similarly, peanut-specific T cells from peanut allergic patients can be found in skin homing but not in gut homing compartments.

On the other hand studies have shown that early oral exposure to food proteins results in lower incidence of food sensitization and food allergies (Du Toit et al. 2008). This concept has been the basis of more recent large clinical trials and has changed recommendations regarding feeding practices and timing of food introduction (Du Toit et al. 2015; Fleischer et al. 2016). The LEAP trial, arguably one of the tide changing publications in food allergies in recent times, investigated if early introduction of peanut protein into the diet of at-risk-infants reduced the rates of peanut sensitization in these infants. This large trial showed significant reduction of peanut allergy in infants randomized into the group that started ingestion of peanut between the ages of 4 and 11 months. This effect was sustained even after peanut was avoided for up

to 1 year (Du Toit et al. 2016). A similarly designed trial investigating early introduction of egg failed to show similarly clear results (Palmer et al. 2017). It was noted that a significant proportion of the participants was already sensitized at the age of 4–6 months and egg was tolerated poorly in this cohort.

This approach is also the basis of the EAT trial. In this trial, a group of breast fed infants was introduced to six different allergenic foods to investigate the effect on tolerance. This cohort did not include specifically selected infants with eczema or prior sensitization. The adherence to the intervention was low, but a nonsignificant tendency could be shown for egg and peanut introduction (Perkin et al. 2016).

As mentioned above these trials have led to a change in recommendations. In early 2017 the American Academy of Pediatrics revised guidelines regarding introduction of peanut to advised early introduction of peanut. Infants at risk for food allergies (atopic dermatitis or other already diagnosed sensitization to other foods) are advised to consult a specialist before introduction peanut into their diet (Togias et al. 2017, Image 1).

25.3.1.3 Genetic Associations

For peanut allergy, genetic risk factors have been identified. Mutation of filaggrin, the gene that promotes barrier function of the skin, has been shown to be positively correlated with peanut allergy (Brown et al. 2011). A large US-based study performed genome wide associations on 2759 patients and reported that the variants HLA-DRB1 and HLA-DQB1 showed a statistically significant association with peanut sensitization (Hong et al. 2015). More recently a multicenter analysis pooling genome-wide association studies from multiple countries, including data from the above-mentioned study, identified c11orf30/EMSY as a gene locus linked to higher risk for both peanut allergy and food allergy in general (Asai et al. 2017).

25.3.1.4 Hygiene Hypothesis

In 1989 the hygiene hypothesis was first postulated describing an influence of family size on the development of atopic dermatitis and allergic rhinitis (Carpenter et al. 1989). This concept of environmental factors modulating the development of atopy was further supported by several European studies reporting lower rates of allergic disease in children raised in farm environments with ingestion of raw milk and close proximity to livestock (van Neerven et al. 2012; von Mutius and Radon 2008). Many additional trials have since been conducted and report lower rates of atopic disease in children exposed to more diverse environments such as larger families, livestock exposure, or daycare attendance. Savage et al. have shown that a lack of diversity in the microbiome of 3–6 months old children is associated with a higher incidence of reported IgE-mediated food allergy and sensitization at age 3 years (Savage et al. 2017).

25.3.1.5 Role of Food Processing on Allergenic Properties

The allergenic properties of food are not fixed and innate to the respective food but depend on many additional physical or chemical factors. For fruits for example, it was shown that postharvest storage and ripening can change allergenicity to more allergenic in the case of apples and to less allergenic in the case of mangoes. Thermal treatment of foods has been reported to change allergenicity as well. This has been described for fruits and vegetables in pollen food syndrome where cooking denatures the protein structure and subsequently results in better tolerance of the cooked versions of the food as compared to the raw versions. Similarly, baked milk and egg products are tolerated by a subgroup of patients with milk and egg allergy, which subsequently confers a higher probability of outgrowing food allergies. The reduced allergenicity of baked milk and egg products results from partial denaturation and mainly reaction of the food with the matrix (most commonly the grain flour). However, other foods have been reported to be resistant to thermal degradation, like the major peanut protein Ara h 1 (Koppelman et al. 1999).

Biochemical treatment of food to reduce allergenicity is used in the preparation of hypoallergenic baby formula. Milk is treated with proteolytic

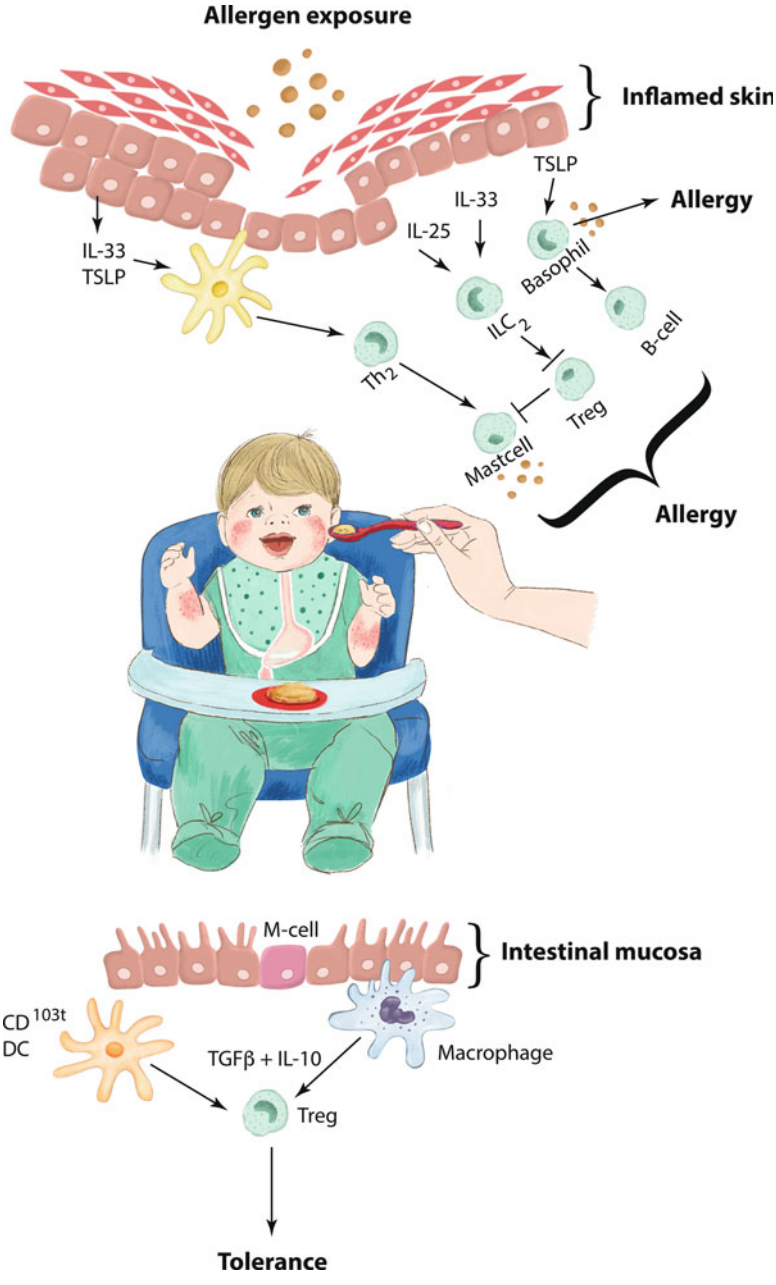

Image 1 Mechanism of sensitization (Skin vs. Gut)

enzymes resulting in degradation of the intact milk protein. Residual small protein strands are removed by hypofiltration.

Roasting of peanut on the other hand was found to increase the allergenicity (Gruber et al. 2005; Vissers et al. 2011). This at least partially explains higher rates of peanut sensitization in the United States and certain European countries as opposed to China, which has a similarly high per capita consumption of peanut, however, not roasted peanut.

To better study, the effect and allergenicity of food proteins a mouse model was developed by Ahrens et al. (2014).

Factors influencing sensitization versus tolerance are summarized in Image 2.

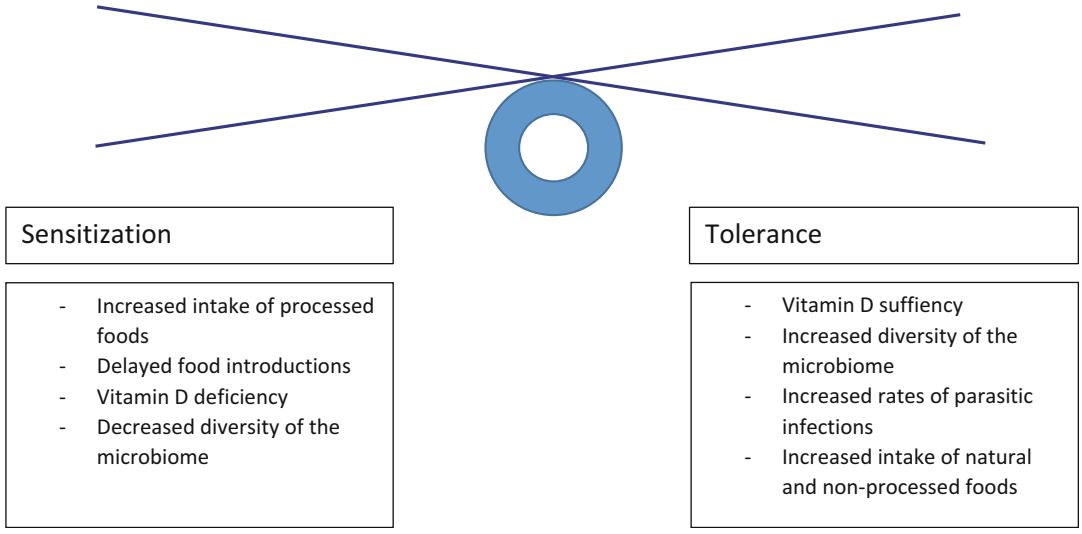

Image 2 Factors influencing sensitization versus tolerance. (Adapted from Renz, H Food Allergy Primer, Nature Reviews 2018)

25.4 IgE-Mediated Food Allergy: Subforms

The NIAID-sponsored Expert Panel Report on food allergy is defining food allergy "as an adverse health effect arising from a specific immune response that occurs reproducibly on exposure to a given food" (Boyce et al. 2011). Food allergy encompasses reactions based on IgE-mediated sensitization, non-IgE-mediated processes, cell-mediated reactions, and a mixed presentation of IgE-mediated and cell-mediated reactions. The Expert Panel Report categorized celiac disease as a non-IgE-mediated disorder and allergic contact dermatitis as a cell-mediated disorder.

This book chapter is focusing on IgE-mediated reactions. Non-IgE-mediated and cell-mediated food reactions will be discussed elsewhere.

25.4.1 IgE-Mediated Food Allergy

Reactions caused by preformed IgE antibodies to food allergens are rapid in onset (minutes to hours) and usually present as one or more of the subforms discussed below.

Eight foods have been reported as the most common food allergens in the United States (milk, egg, wheat, soy, peanut, tree nuts, fish, and shell fish).

Of these, milk, egg, wheat, and soy are food allergies that are mainly present in childhood and are usually outgrown.

Cow's milk allergy is the most common IgE-mediated food allergy affecting children. It is the third most common food involved in fatal or near fatal reactions (Bock et al. 2007). Symptoms consistent with cow's milk allergy are found in 5–15% of infants (Rona et al. 2007). Cow's milk protein is commonly the first foreign protein given to infants in developed countries. Sensitization has been reported to occur in infancy through cow's milk-based infant formula, skin contact with milk products and even transference of cow's milk proteins through maternal breast milk has also been reported. Genetic predisposition also plays a major role in the development of cow's milk allergy. When making the diagnosis of cow's milk allergy, it is important to distinguish IgE-mediated allergy from lactose intolerance, which is a completely different disease process and presents with gastrointestinal symptoms alone.

There are more than 25 different proteins in cow's milk that can all act as allergens. 80% of those proteins are caseins and 20% are whey proteins. The caseins are α_{s1}-, α_{s2}-, β-, and κ-caseins (Bos d 8). The most important whey proteins are α-lactalbumin (Bos d 4) and β-lactoglobulin (Bos d 5) (Wal 2004).

Cross-reactivity has been described between cow's milk and other mammalian milk proteins. Strong cross-reactivity has been observed between cow's milk and milk from sheep, goat, and buffalo (>90%) and a weak cross-reactivity to mare's and donkey's milk (5%). Thus, affected children may react at the first exposure to goat's or sheep's milk (Restani et al. 2002).

Interestingly, it has been found that about 13–20% kids with cow's milk allergy also react to beef. Conversely, about 92% of children with beef allergy have been found to having a concomitant cow's milk protein allergy (Martelli et al. 2002).

Based on the described cross-reactivities, other mammalian milks should not be used as substitutes in cow's milk allergic children. Soy milk can be used as a substitute but is not generally recommended as there are high rates of soy milk allergy in cow's milk allergic children as well, with up to 10–14% of infants with cow's milk allergy also having been reported sensitized to soy. Additionally many soy- or rice-based drinks do not have the nutritional value needed for optimal growth and development (Bhatia and Greer 2008; Allen et al. 2009).

In infants under 12 months of age, extensively hydrolyzed casein or whey based formulas are usually well tolerated. Occasionally the use of amino acid-based formulas is indicated.

Egg allergy is the second most common food allergy affecting children, after milk allergy. Prevalence of egg allergy has been reported in up to 2.5% of children (Rona et al. 2007). Interestingly egg allergy is the most common food allergy in children with atopic dermatitis (Caubet and Wang 2011). The major allergens in egg were found to be in egg white, ovomucoid, ovalbumin, ovotransferrin, and lysozyme (Leduc et al. 1999; Rupa and Mine 2003). Chicken egg yolk has also been reported to cause IgE-mediated reactions; however, the prevalence is much lower and it is more common in adult patients, opposite to egg white allergy in infants and children.

Milk and egg are unique among the major food allergens in that they can be consumed in both the natural form and in a baked form where heating has altered the allergenicity. The majority of young children can tolerate milk and egg in the baked (heat-denatured form), and it has been shown that children who are able to consume and tolerate milk and egg in the baked forms have higher rates of outgrowing their milk/egg allergy will eventually be able to consume the unaltered forms of milk and egg later in life, (Leonard et al. 2012). A population-based study investigating the resolution of milk allergy has reported close to 60% of children outgrowing their milk allergy by the age of 5 years. Factors that predicted persistence of the allergy beyond 5 years of age included reaction to a small amount of milk at the first exposure (less than 10 mL), having the first reaction at less than 30 days of age and having a large skin prick test size (Elizur et al. 2012).

Seafood allergy has increased following the increased ingestion of seafood over the past few decades, a spike that is thought to be likely secondary due to culinary preferences and the perceived nutritional value. Seafood allergy is typically lifelong as affected individuals generally do not outgrow their allergy. Reactions to seafood are not always IgE mediated, but can be elicited by toxins as described for scombroid poisoning or other toxins (Feng et al. 2016). An important hidden food allergen related to reactions to fish is the allergen derived from the nematode worm Anisakis simplex, which may be found in fish. The parasite was first described in the 1960s and human infestation and infection has been described under the term Anisakiasis. In the 1990s allergic and anaphylactic reactions to fish in nonfish-sensitized patients, initially mainly from Northern Spain have been reported. These reactions were caused by sensitization to Anisakis spp., though it is unclear if a previous infection with the parasite leads to sensitization (Audicana and Kennedy 2008). Contrary to what has initially been thought, cooking or heat treatment does not alter the allergenicity of the antigen.

Reactions to seafood are not only elicited by ingestion but can also be caused by handling seafood and vapor from cooking (James and Crespo 2007).

While usually combined due to origin from the water and also culinary habits, fish and shell fish are different species with unique antigens. Shell fish can be further divided into mollusks (mussels, etc.) and crustaceans (shrimp, lobster, etc.). Parvalbumin is the major food allergen in fish and has been described for Baltic cod (Gad c 1), carp (Cyp c 1), chub mackerel (Sco j 1), and Atlantic salmon (Sal s 1), (Perez-Gordo et al. 2012; Untersmayr et al. 2006). It has been described that the primary sequence of the allergens and resulting IgE binding epitopes are unique to the individual fish, while the secondary and tertiary protein structures are more comparable across different fish. That might explain the relatively low cross-reactivity to other fish species of only 50%.

Tropomyosin is the major allergen reported in shellfish (Hoffman et al. 1981). Tropomyosin is a heat stable pan allergen described in many invertebrates, including shellfish species (mollusks and crustaceans) and also dust mites and cockroaches. This explains the relatively high cross-reactivity of up to 75% or higher between different shell fish species, dust mites, and cockroaches. In fact, antigens to shrimp have been found in populations who do not consume shellfish for religious reasons (Fernandes et al. 2003). Cross-reactivity has also been reported with Anisakis spp. and fish.

Wheat allergy is the best described grain allergy and one of the seven most common food allergies. Allergy to wheat can manifest as an IgE-mediated food allergy, but wheat can also be the trigger for reactions of another underlying immune mechanism/disease entity like celiac disease, baker's asthma, FPIES to wheat and exacerbation of atopic dermatitis with wheat ingestion among others. IgE-mediated wheat allergy usually starts in infancy and early childhood and is commonly outgrown by adolescence, while some cases persist into adulthood (Keet et al. 2009). While skin prick testing and specific IgE testing are readily available for wheat, the interpretation is more challenging compared to other food allergens. Based on different studies, challenge decision points range from 20 to 100 kU/L (Sampson 2001). In addition to testing, a detailed clinical history and food challenges are crucial in the management of wheat allergy. Patients with wheat allergy are often sensitized to other grains; however, testing is not always informative or available. Food challenges are helpful in these cases.

Soy allergy is more prevalent in infants and young children. The prevalence of soy allergy is thought to be about 0.7% (Zuidmeer et al. 2008). Soy bean is a legume and among the best characterized food allergens. The allergens that are responsible for the majority of the allergic reactions in infants and children are seed storage proteins, Gly m 5, Gly m 6, and Gly m 8. In adults the majority of allergic reactions to soy bean are due to sensitization to the Bet v 1 homologue Gly m 4 (Ito 2015). For all soy components, there is a high cross-sensitivity to other legumes noted; however, cross-reactivity to other legumes is not as common. Because soy bean oils and soy lecithin are common ingredients, in many food products patients require detailed instructions regarding ingestion of these products. Processed soy bean oil and also soy lecithin contain a minimal amount of soy bean protein and are generally considered safe for patients with soy bean allergy.

Peanut allergy is the most publically discussed food allergy with a high prevalence. Investigations on early introduction of peanut into infants' diet and subsequent changes of recommendations regarding food introduction also contribute to the strong public awareness of peanut allergy (Fleischer et al. 2016; Du Toit et al. 2008, 2015, 2016).

Testing for peanut allergy is available in the form of skin prick testing and spec IgE to whole peanut and peanut components. Testing for peanut by skin prick testing and specific IgE testing has a high positive predictive value. Specific IgE levels between 13 and 15 kU/L have a 95–99 PPV for clinical reactivity in children with suggestive clinical history (Maloney et al. 2008). Similarly, wheal sizes of >8 mm were shown to have a 95–99% PPV in children with suggestive history. In children younger than 2 years, a wheal

size of <4 mm was found to be predictive of sensitization.

Tolerance of peanut in patients with test results above the described cutoffs is often due to sensitization to the Bet v 1 homologue Ara h 8. The peanut components Arah h 1, Ara h 2, and Ara h 3 are linked to systemic reactions to peanut (Flinterman et al. 2008).

Tree nut allergy is one of the most common causes for an acute IgE-mediated reaction to food. A recent metaanalysis reported a prevalence of IgE positive, challenge proven tree nut allergy of about 2%. The rate for reported, not challenge confirmed tree nut allergy, was up to 4.9% in the studies included in the analysis (McWilliam et al. 2015). Hazelnut, almond, cashew, pistachio, walnut, pecan, brazil nut, macadamia nut, and pine nut are the most frequently consumed tree nuts in the United States. Based on dietary habits and environmental factors, the prevalence of sensitization to certain tree nuts shows great regional diversity. Hazelnut is the most common tree nut allergy in Europe, while walnut and cashew are responsible for most allergic reactions to tree nuts in the United States. Almost all of the tree nuts have been reported to cause severe and possibly fatal reactions. Tree nut allergy can present both in childhood and adulthood. Both acute IgE-mediated reactions and oral symptoms due to cross-reactivity to the birch pollen component Bet v 1 can be seen in adulthood and teenagers. In children, mostly direct IgE-mediated allergy to tree nuts is being seen. Little is known about the clinical course; it was reported that children who are allergic to two or more tree nuts have a lower chance of outgrowing their tree nut allergy (Fleischer et al. 2005).

Tree nut components and cross-reactivity have been well studied, and IgE testing to tree nut components is available and offered by most major laboratories (Table 1).

25.4.2 Pollen Food Syndrome

Pollen food syndrome, also known as oral allergy syndrome or pollen associated food allergy syndrome, is a relatively common manifestation of oral allergy symptoms caused by cross-reactivity between food proteins and pollen. Foods that are not of plant origin, such as milk or egg, do not cause pollen food syndrome. Pollen food syndrome is noted in adults with pollen allergy, but it is important to note that not all patients who report symptoms of pollen food syndrome also experience symptoms of seasonal allergy or hay fever.

Pollen food syndrome is thought to be the most common food allergy in adults and likely has become more prevalent with the increase in allergic sensitization to pollen in general (Sicherer 2001).

While pollen food syndrome is more prevalent in adults, it sometimes starts in childhood. Patients usually experience symptoms of pollen allergy first and then go on to develop the oral component. It is often noted that the number of fruits and vegetables the patient reacts to increases over time, this is especially common in children. Symptoms commonly persist lifelong. While allergy immunotherapy directed against the pollen a patient is sensitized to may alleviate the symptoms of seasonal allergies, it is not guaranteed to also affect the oral manifestation of pollen food syndrome.

It is not fully understood why some patients develop pollen food syndrome while others who are also sensitized to pollen do not, though a variety of risk factors have been identified. It was noted that sensitization to tree pollen, especially birch pollen, has been more strongly associated with the development of pollen food syndrome especially if the pollen-related IgE level was significantly elevated or pollen sensitization to more than one variety of pollen was found (90, 91). Patients are more likely to develop pollen food syndrome if they also have symptomatic seasonal allergic rhinitis as opposed to sensitization to pollen alone.

The development of pollen food syndrome is also geographically associated with patients in Northern Europe and the Northern United States, with patients presenting commonly with birch pollen associated symptoms. In comparison, patients in Japan are often sensitized to cedar and present with pollen food syndrome to tomato (Inuo et al. 2015).

Table 1 Major food allergens and their components and cross-reactivities. (Adapted from Tordesillas et al. 2017)

Food	Allergic components	Family	Cross-reactivity
Cow's milk	Bos d 9	AlphaS1-casein	N/A
	Bos d 10	AlphaS2-casein	
	Bos d 11	Beta-casein	
	Bos d 12	k-casein	
	Bos d 4	Alpha-lactalbumin	
	Bos d 5	Beta-lactoglobulin	
	Bos d 6	Bovine serum albumin	
	Bos d 7	Immunoglobulin	
	Bos d 8	Caseins	
Hen's egg	Gal d 1	Ovomucoid	N/A
	Gal d 2	Ovalbumin	
	Gal d 3	Ovotransferrin/ conalbumin	
	Gal d 4	Lysozyme	
	Gal d 5	Serum albumin	
	Gal d 6	YGP42	
Fish (atlantic herring, carp, codfish, atlantic cod, tuna, etc.)	Clu h 1, Cyp c 1, Gad c 1, Gad m 1, Lat c 1, Lep w 1, Onc m 1, Rask 1, Sal s 1, Sar sa 1, Seb m 1, Thu a 1, Xip g 1	Parvalbumin	N/A
	Onc k 5	Vitellogenin	
	Sal s 2, Gad m 2, Thu a 2	Enolase	
	Sal s 3, Gad m 3, Thu a 3	Aldolase	
Crustacean shellfish (shrimp, lobster, crab)	Cha f 1, Cra c 1, Por p 1, Hom a 1, Pen s 1, Lit v 1, Pen m 1, Met e 1, Pan b 1, Pen a 1, Pen i 1, Por p 1, Pan s 1	Tropomyosin	N/A
	Cra c 2, Lit v 2, Pen m 2	Arginine kinase	
	Cra c 5, Lit v 3, Pen m 3, Hom a 3	Myosin light chain	
	Cra c 4, Lit v 4, Pen m 4	SCP	
	Cra c 6, Pen m 6, Hom a 6	Troponin C	
	Cra c 8, Arc s 8	Triose phosphate isomerase	
Tree nuts (almond, walnut, hazelnut, cashew, pecans)	Pru du 4, Cor a 2	Profilin	Components of tree nuts have been found to cross-react with certain environmental allergens such as **birch pollen** and **Alder pollen**, resulting in one of several known causes of "oral allergy syndrome." certain tree nuts also have cross-reactivity with: Peanut Aniseed Apple Apricot Caraway
	Pru du 3, Jug r 3, Cor a 8	Nonspecific lipid transfer protein	
	Pru du 5	60S acidic ribosomal protein	
	Jug r 1, Car i 1, Ana o 3, Cor a 14	2S albumin	
	Jug r 2, Jug r 6, Car i 2, Ana o 1, Cor a 11	7S globulins (vicilin-like)	
	Pru du 6, Jug r 4, Cor a 9, Car i 4,	11S globulin (legumin-like)	

(*continued*)

Table 1 (continued)

Food	Allergic components	Family	Cross-reactivity
			Carrot Celery Cherry Coriander Fennel Kiwi Nectarine Parsley Parsnip Peach Pear Pepper Plum Potato Soybean
	Jug r 5, Cor a 1	PR-10, Bet v 1 family member	
	Cor a 12, Cor a 13	Oleosin	
Peanut	Ara h 1	Cupin, vicillin-type 7S globulin	Components of peanut have been found to cross-react with certain environmental allergens such as **birch pollen**, **mugwort pollen**, and **orchard pollen**, resulting in one of several known causes of "oral allergy syndrome." Peanut also has cross-reactivity with: Tree nut Aniseed Apple Cantaloupe Caraway Carrot Celery Coriander Fennel Honeydew Kiwi Parsley Pepper Soybean Sunflower Tomato Watermelon White potato
	Ara h 2	Conglutin (2S albumin)	
	Ara h 3	Cupin (11S globulin)	
	Ara h 5	Profilin	
	Ara h 6	Conglutin (2S albumin)	
	Ara h 7	Conglutin (2S albumin)	
	Ara h 8	PR-10, Bet v 1 family member	
	Ara h 9	Lipid transfer protein type 1	
	Ara h 10	Oleosin	
	Ara h 11	Oleosin	
	Ara h 12	Defensin	
	Ara h 13	Defensin	
	Ara h 14	Oleosin	
	Ara h 15	Oleosin	
	Ara h 16	Lipid transfer protein type 2	
	Ara h 17	Lipid transfer protein type 1	
Wheat	Tri a 14	Lipid transfer protein 1	N/A
	Tri a 18	Agglutinin isolectin 1	
	Tri a 19	Omega 5-gliadin	
	Tri a 20	Gamma-gliadin	
	Tri a 25	Thioredoxin	

(*continued*)

Table 1 (continued)

Food	Allergic components	Family	Cross-reactivity
	Tri a 26	High-molecular-weight glutenin	
	Tri a 36	Low-molecular-weight glutenin	
	Tri a 37	Alpha purothionin	
	Tri a 41	Mitochondrial ubiquitin ligase activator of NFKB 1	
	Tri a 42	Hypothetical protein from cDNA	
	Tri a 43	Hypothetical protein from cDNA	
	Tri a 44	Endosperm transfer cell specific PR60	
	Tri a 45	Elongation factor 1	
Soy	Gly m 3	Profilin	N/A
	Gly m 4	PR-10, Bet v 1 family member	
	Gly m 5	Beta-conglycinin, 7S globulin	
	Gly m 6	Glycinin, 11S globulin	
	Gly m 7	Seed biotinylated protein	
	Gly m 8	2S albumin	

The most common manifestation of pollen food syndrome is urticaria of the oral mucosa with associated pruritus and mild angioedema of the lips. Systemic symptoms are rare and have been reported in less than 10% (Ortolani et al. 1993). It is important to note that a genuine food allergy should be suspected in patients with allergic reactions to fruits and vegetables with no concomitant sensitization to pollen noted.

The association of pollen sensitization to the respective fruit is detailed in Table 1.

Patients are usually instructed to avoid the food in the form that is causing symptoms. Occasionally patients report only symptoms to the peel while tolerating the pulp. Often symptoms may vary by season with more significant symptoms noted during the height of the pollen season. Heating of any form of the food commonly results in denaturation of the protein and leads to tolerance; however, heating does not lead to tolerance of the nuts that are also associated with pollen food syndrome.

In addition patients should avoid large amounts of the food, as, for example, in smoothies or other drinkable preparations, since more allergen than can be tolerated may be ingested and will pass mucous membranes more quickly, possibly leading to systemic reactions. Ingestion of

allergenic foods on an empty stomach should be avoided, as should ingestion of the food in combination with proton pump inhibitors or other medications that increase the pH of the stomach and lead to decreased destruction and digestion of the food.

Diagnosis of pollen food syndrome includes a detailed history of symptoms and past reactions. Both skin and specific IgE testing can be helpful, especially component testing to determine the degree of sensitization to pollen cross-reactive components of foods. Food challenges might be indicated on a case to case basis. Patients generally are not instructed to avoid the cross-reactive foods; however, patients should be educated about precautions and the forms of the foods that are tolerated, i.e., apple sauce or apple pie as opposed to fresh apple. An epinephrine autoinjector is prescribed for patients who are at a higher risk for systemic reactions, but it is not regularly indicated in patients with simple pollen food associated oral symptoms.

25.4.3 Association Between Aeroallergens of Animal or Fungal Origin and Food Allergens

Associations of environmental allergens to food allergens of nonplant origin have to be distinguished from pollen associated food allergy syndromes.

Allergic sensitization to indoor arthropods such as dust mites and cockroaches as well as house pets such as cats and dog and sensitization to mold and mold spores have been linked to associated allergic reaction to food allergens.

A cross-reactivity between Alternaria alternata and mushroom and spinach has been reported (Herrera et al. 2002). In addition sensitization to mold via the respiratory tract and subsequent ingestion of food containing mold spores has been reported. A notable case is the reported fatal anaphylaxis of a teenager with reported sensitization to mold and penicillin ingesting a pancake mix that was heavily contaminated by mold spores, resulting in fatal anaphylaxis (Bennett and Collins 2001). Similarly, allergic and anaphylactic reactions in mite sensitized patients who ingested mite containing foods, mainly wheat containing foods (also called Pancake syndrome), have been reported (Sánchez-Borges et al. 2009).

Sensitization to house dust mite has also been reported as the source of sensitization in the dust mite- mollusk-crustacean syndrome, a rare syndrome where sensitization to house dust mites can lead to anaphylactic reactions to shellfish even at the first ingestion (Kütting and Brehler 2001).

Furry pets are an important source of respiratory allergens in the United States and Europe. Cross-reactive serum albumins from mammals kept as pets or farm animals have been reported. Sensitization to the serum albumin occurs by inhalation or ingestion as they are present in all body fluids of the animals. The associated allergy syndrome has been termed pork-cat syndrome. Reactions to ingested pork meat in cat sensitized patients have been reported. The serum albumin is heat labile and therefore reactions are more common to smoked or dried or short cooked meats (Hilger et al. 1997). Cross-reactivity between the serum albumin as an inhalant allergen and ingested allergen is not limited to cat and pork but has been described for other mammal pairs as well as within one animal species. Bovine serum albumin is an important component of cow's milk and sensitivity to cow's milk in some cases might result in sensitivity to raw or undercooked beef. However, it is not a general recommendation that all children with cow's milk allergy also avoid raw or undercooked beef (Vicente-Serrano et al. 2007). This cross-reactivity has to be distinguished from the delayed food-induced anaphylaxis to mammalian meats as described below.

The bird-egg syndrome involves primary sensitization to bird aeroallergens with secondary reactions to egg based on cross-reactivity between the bird allergens (feathers, droppings, serum, and meat) with the egg yolk. Interestingly, the egg-bird syndrome is connected to egg yolk sensitivity that starts in infancy with subsequent bird aeroallergen sensitivity. This is due to the presence of alpha livetin, also known as chicken serum albumin in dander and the egg yolk (Popescu 2015).

25.4.4 Delayed Food-Induced Anaphylaxis to Mammalian Meats

Allergy to food proteins in the cause of most food allergies and also the forms of meat allergy discussed above.

This entity described here involves sensitization to the carbohydrate epitope galactose-alpha-1,3-galactose (alpha-gal). Alpha-gal was described to be present in the digestive tract of ticks and through a tick bite can be expressed into the human host. Alpha-gal as a carbohydrate moiety is present on cells and tissues of all mammals except the higher order primates which includes humans. Through tick bites, humans can get sensitized to alpha-gal and subsequent ingestion of meat of different species including beef, pork, and lamb leads to a delayed allergic reaction. The reaction is usually delayed by 3–6 h after ingestion. Interestingly, a cluster of reactions to cetuximab, a monoclonal chimeric mouse-human IgG1 monoclonal antibody directed against human epithelial growth factor, was reported mainly in the South Eastern United States. Alpha-gal was detected in cetuximab and patients who developed allergic reactions to cetuximab were generally sensitized to alpha-gal before cetuximab was administered (Chung et al. 2008).

Primary IgE-mediated food allergy to individual meats has to be distinguished from alpha-gal sensitization. Serum IgE to individual types of meats is available as well as IgE for alpha-gal. A detailed clinical and reaction history is also important to aid in the diagnosis and management.

25.4.5 Food-Dependent Exercise-Induced Anaphylaxis

The term food-dependent exercise-induced anaphylaxis (FDEIA) is reserved for a specific form of anaphylaxis where ingestion of a specific food leads to anaphylaxis if food ingestion is followed by exercise. Ingestion of the food without subsequent exercise does not lead to anaphylaxis, and exercise alone without prior ingestion of the food also does not result in anaphylaxis, distinguishing it from food allergy- and exercise-induced anaphylaxis. Foods commonly involved in this FDEIA are shellfish, wheat, fruits and vegetables (celery), nuts, egg, mushroom, and meats. Rare cases have been reported where any ingestion of solid foods followed by exercise can result in anaphylaxis (Morita et al. 2013). This is an IgE-mediated process and documentation of the presence of food directed IgE antibodies in combination with a convincing clinical presentation helps in making the diagnosis. Exercise challenges after ingestion of the suspected food contrasted to ingestion without subsequent exercise can be confirmatory.

25.4.6 Food Allergens in Medications

Food allergens can be present in certain medications or formulations as either a contamination of a certain lot of the medication or as a component of the medication other than the active ingredient (usually called excipients).

If a certain lot of medication is contaminated by a food protein, this poses a significant risk for a food allergic patient if the contaminant is significant enough to elicit a reaction, but the medication should not generally be avoided in patients with food allergies. The susceptibility to an allergic reaction to the food component in the medication depends on the patient's general sensitivity to the food allergen and the IgE level and also the amount of allergen present in the medication. This topic has been reviewed in detail by Kelso in 2014 (Kelso 2014).

25.5 Mixed IgE Antibody-/Cell-Mediated Allergies

25.5.1 Atopic Dermatitis

Atopic dermatitis is a chronic, pruritic, inflammatory skin condition that belongs to the family of atopic diseases such as food allergy, asthma, and allergic rhinitis. It is often associated with an increased IgE level and related atopic disorders are more common. Patients with atopic dermatitis

are at a higher risk for developing food allergies. Based on the dual allergen exposure hypothesis, patients with atopic dermatitis are at an increased risk of being exposed to the food protein via the skin before oral ingestion and thus at a higher risk of becoming sensitized rather than tolerant.

Total IgE levels are often significantly elevated in patients with atopic dermatitis. Positive testing to food allergens is also very common; however, many patients that are found to be sensitized do not show clinical allergy despite positive testing. Therefore, panels of tests for allergens that are tolerated are not generally recommended in the absence of clinical reactions. In individual patients, ingestion of certain foods can exacerbate their atopic dermatitis. Trial elimination diets and avoidance of the suspected foods for a few weeks should lead to improvement of the skin condition and reintroduction should result in an exacerbation of the skin lesions. Prolonged avoidance of foods might lead to the development of acute IgE-mediated food allergies and therefore caution is warranted when foods are being reintroduced.

25.5.2 Eosinophilic Gastroenteropathies

Eosinophilic gastroenteropathies (EGID) are characterized by chronic eosinophilic infiltration of parts of the GI tract that lead to clinical gastrointestinal dysfunction pathologic changes of the gastrointestinal tissues. The pathophysiology is poorly understood. Patients with EGID are often also diagnosed with sensitization to food or environmental allergens. Food triggers can often be identified and elimination leads to improvement of clinical, endoscopic, and histologic symptoms. However, the pathophysiologic mechanism is not completely understood.

25.6 Mimics of Food Allergy

Occasionally patients are seen in the allergy office for presentations that appear to be food allergies, but upon further investigation are found to be conditions that present with similar symptoms but a very different underlying mechanism. A classic example of a disease that presents like an acute IgE-mediated reaction is scombroid fish poisoning, a toxic reaction to histamine-like toxins in spoiled dark fish meat. Occasionally patients present with clear rhinorrhea that is usually linked to food ingestion, most commonly spicy foods. If no additional symptoms are reported, no underlying sensitization is found, and the reaction is linked to ingestion of spicy or savory foods, the diagnosis of gustatory rhinitis can be made. The auriculo-temporal syndrome is another example where a neurologic response leads to increased salivation and reflexive facial vasodilatation of the lower cheek. See also Table 2.

25.7 Diagnosis

25.7.1 Clinical/Reaction History

The clinical and reaction history is an essential part of the diagnostic work-up for a suspected food allergy. A detailed history is the initial step in the evaluation of a possible food allergy. The main goal is to distinguish a food allergy from another kind of reaction that is elicited by the food, for example, the differentiation between an acute mediated milk allergy and lactose intolerance. The clinical history also helps to differentiate between the different forms of food allergy, for example, Food Protein Induced Enterocolitis Syndrome elicited by wheat ingestion versus an acute IgE-mediated food allergy to wheat. And lastly, the clinical history often helps to identify the causing food allergen or narrow down to a few possible culprits.

A routine clinical history for the diagnosis of food allergy includes questions regarding the types of food that were ingested, type of reaction with all signs and symptoms, timing of the ingestion and subsequent reaction, treatment of the reaction, and response to that treatment. In addition it is important to document any additional allergic or atopic diseases, other food allergies, or previous reactions to the same or other foods.

When discussing possible foods that might have caused the allergic reaction, it is important

Table 2 Mimics of food allergy

Food Intolerances	Toxic reactions	Gastrointestinal disorders	Neurologic mechanisms	Psychologic factors	Contaminations	Unproven syndromes of food intolerance
Intolerance of pharmacologic components in foods	Food poisoning (Scombroid poisoning, ciguatera poisoning)	Inflammatory bowel disease (IBD)	Auriculotemporal syndrome	Food aversion (texture, smell, temperature, taste	Accidental contamination with antibiotics	Histamine intolerance
Alcohol dehydrogenase deficiency (leading to flushing after EtOH ingestion)	Other food poisoning	Irritable bowel syndrome (IBS)	Gustatory rhinitis	Bulimia nervosa and psychogenic vomiting	Accidental contamination with residues of materials used in processing or packaging	Intolerance of food additives or artificial colorings
Sulfite sensitivity (wheezing after sulfite ingestion)	Toxins (bacterial and fungal)	GERD		Functional nausea and functional vomiting	Accidental contamination with pesticides	
MSG symptom complex		Celiac disease				
		Fructose malabsorption				
		Intolerance of short chain fermentable carbohydrates				
		Bacterial or yeast overgrowth syndrome				
		Toddler's diarrhea				
		Cystic fibrosis				

to note that the seven foods discussed above are responsible for the majority of the IgE-mediated allergic reactions to food. However, food that the patient consumes on a regular basis is rarely the cause for an allergic reaction, but rather foods that are rarely eaten and are consumed knowingly or as a contaminant of the patient's food.

Contributory factors, including exercise before or after ingestion of the food, viral infections, or use of medications that might alter the gastric permeability, are important factors to note.

25.7.2 Signs and Symptoms

25.7.2.1 Urticaria/Angioedema

Localized or generalized urticaria is the most common form of an allergic reaction to a food. About 20% of cases of acute urticaria have been reported being caused by allergic reactions to food. In comparison chronic urticaria is rarely caused by food allergens. Urticaria is caused by degranulation of mast cells in the superficial dermis and also basophils resulting in mediator release leading to the characteristic symptoms. Angioedema is caused by degranulation of mast cells in deeper layers of the dermis or subcutaneous tissue. Both Urticaria and Angioedema can be the presentation of a localized reaction or be part of a systemic reaction. Generalized flushing and erythema of the skin can also be noted, often when the reaction is progressing to a more systemic form. Ocular symptoms like tearing and conjunctival injection as well as pruritus are also caused by mast cell activation and mediator release.

Acute contact urticaria can be caused by direct skin contact with the relevant food; this is commonly caused by the major allergens but can also be elicited by contact with raw meats, seafood and raw fruits and vegetables (Table 3).

25.7.2.2 Oropharyngeal Symptoms

As described above for urticaria and angioedema, oropharyngeal symptoms can represent a mild localized reaction or be a prodrome or part of a systemic reaction. Oropharyngeal symptoms as part of the oral allergy syndrome are considered a contact reaction to the profilins of the fruits and vegetables that cross-react with the pollen proteins mainly of tree, grass, and weed pollen (Refer to Sect. 4.2).

25.7.2.3 Airway Symptoms (Rhinitis/Asthma/Laryngeal Edema)

Allergic rhinitis and asthma in general are common conditions in patients with food allergy because of the shared underlying mechanism and co-presentation of atopic diseases. Additionally rhinitis, rhinorrhea, wheezing, and coughing are common presentations of acute allergic reactions to food allergens. Patients can also present with laryngeal edema and voice changes. They might report a sense of choking or difficulty swallowing their saliva. These symptoms, especially symptoms involving the lungs or larynx, are usually part of a systemic reaction and do not present as isolated symptoms of an acute allergic reaction.

Isolated asthma exacerbations by inhalation of foodstuff, especially flour in a condition called Baker's Asthma, have been described. However, this form of occupational asthma is caused by the irritation of the lungs by the food product and the food can be ingested without problems.

25.7.2.4 Gastrointestinal Symptoms

Gastrointestinal symptoms such as nausea, vomiting, abdominal pain, cramping, and diarrhea are common features in anaphylaxis. Isolated nausea can be considered a mild symptom; however, often it progresses to more significant symptoms as vomiting or abdominal cramping. The term gastrointestinal anaphylaxis can be used for severe symptoms that are limited to the GI tract. Nausea and vomiting tend to be early signs of anaphylaxis occurring within a few minutes to 1–2 h, while diarrhea might also present later in the course of the allergic reaction.

25.7.2.5 Anaphylaxis

Anaphylaxis is an acute allergic reaction that is acute in onset and can progress to death (Sampson et al. 2006). While it is the most severe and also most discussed presentation of a food allergic reaction, it is relatively uncommon with a recent meta-analysis reporting an incidence of 0.14 events per 100 patients years in patients with a

Table 3 Clinical symptoms of an acute IgE-mediated food allergy reaction

System	Symptoms
Nasopharyngeal	Rhinorrhea, nasal congestion, sneezing, pruritus and angioedema of the lips, tongue, gums, palate
Respiratory	Laryngeal edema, stridor, hoarseness, coughing, wheezing, chest tightness, dyspnea, cyanosis
Upper GI tract	Nausea, emesis
Lower GI tract	Abdominal pain, colic, diarrhea
Skin	Pruritus, erythema, flushing, urticaria, angioedema, eczema flare
Cardiovascular	Tachycardia, bradycardia, hypotension, cardiac arrest
Neurologic	Dizziness, syncope, sense of impending doom

diagnosed food allergy (Umasunthar et al. 2015). The rate of fatal anaphylaxis was reported to be 1.81 per one million patient years in patients with a diagnosed food allergy.

Anaphylaxis caused by food ingestion is often noted within minutes of ingestion and characterized by multiple, severe, progressive symptoms. All symptoms and combinations of symptoms described above can be present in anaphylaxis. Gastrointestinal symptoms are often a leading presentation. In addition the reaction can include cardiovascular collapse and may result in death. Patients sometimes describe a feeling of impending doom at the start of the allergic reaction. Cutaneous and gastrointestinal symptoms are more common in children and development of shock is more common in adult patients.

Early signs of anaphylaxis can be variable and it might not be immediately obvious that the reaction will develop into an anaphylactic reaction. The reaction can then progress in a uniphasic fashion with symptom resolution after adequate treatment or may evolve to a biphasic or protracted reaction. Biphasic reactions are characterized by recurrence of symptoms within 1–4 h after apparent resolution of symptoms. About 20% of anaphylactic reactions progress to a biphasic reaction. Protracted reactions are characterized by persistence of symptoms for hours or even days despite treatment.

Several factors influence the development of an anaphylactic reaction and also the severity of the reaction. The amount of the food that was ingested shows a positive correlation with the severity of the symptoms. Ingestion of fatty foods often results in lowered absorption of the allergen and might result in a milder reaction. Concomitant ingestion of alcohol or non-steroidal anti-inflammatory drugs can increase the gastric permeability and lead to more pronounced or rapid symptoms. Fatal anaphylaxis can occur in all ages, but young patients with food allergies are at a higher risk. Risk taking behavior, including ingestion of the food allergen, unavailability of the epinephrine autoinjector, or delayed treatment with epinephrine are risk factors for death from anaphylaxis.

Diagnosis of anaphylaxis aside from reported or observed symptoms can be difficult as no reliable laboratory testing exists. Histamine can be transiently elevated and while tryptase levels can be elevated they are often normal in food induced anaphylaxis. Therefore, negative testing does not exclude an anaphylactic reaction (Sampson et al. 2006).

Treatment of anaphylaxis is reviewed below and summarized in Table 4 (Sect. 8.2).

25.7.3 Diagnostic Tests

Diagnostic testing for patients with food allergies is a crucial step in diagnosing or confirming and documenting a sensitization and to estimate the risk for reaction.

The Updated Practice Parameters on Allergy Diagnostic Testing in detail summarizes and describes diagnostic testing for allergies.

25.7.3.1 Skin Testing

The development of skin testing in the historical context is reviewed and summarized in the Updated Practice Parameters. In brief, skin testing was first described in 1867 by Charles Blackley.

Table 4 Management of anaphylaxis. (Adapted from Boyce, JA PMID: 21310308)

Setting	First line therapy	Adjunct therapies
Outpatient	Auto-injector: 10–25 kg: 0.15 mg epinephrine autoinjector, IM (anterior-lateral thigh) >25 kg: 0.3 mg epinephrine autoinjector (anterior-lateral thigh)	Bronchodilator (b2-agonist): albuterol MDI (child: 4–8 puffs; adult: 8 puffs) Nebulized solution (child: 1.5 mL; adult: 3 mL) every 20 min or continuously as needed
	Epinephrine (1:1000 solution) (IM), 0.01 mg/kg per dose: maximum dose, 0.5 mg per dose (anterior lateral thigh)	H_1 antihistamine: diphenhydramine 1–2 mg/kg per dose Maximum dose, 50 mg IV or oral (oral liquid is more readily absorbed than tablets) Alternative dosing may be with a less-sedating second generation antihistamine
	query ID="AU5"/>Both auto-injector and 1:1000 solution are suitable options	Supplemental oxygen therapy
	Epinephrine doses may need to be repeated every 5–15 min	IV fluids in large volumes if patient presents with orthostasis, hypotension, or incomplete response to IM epinephrine
		Place the patient in recumbent position if tolerated, with the lower extremities elevated
Inpatient	Epinephrine IM as in outpatient setting. Can consider continuous epinephrine infusion for persistent hypotension (ideally with continuous noninvasive monitoring of blood pressure and heart rate). Alternatives routes include endotracheal or intraosseous epinephrine	Bronchodilator (b2-agonist): albuterol MDI (child: 4–8 puffs; adult: 8 puffs) Nebulized solution (child: 1.5 mL; adult: 3 mL) every 20 min or continuously as needed
		H_1 antihistamine: diphenhydramine 1–2 mg/kg per dose Maximum dose, 50 mg IV or oral (oral liquid is more readily absorbed than tablets) Alternative dosing may be with a less-sedating second generation antihistamine
		H_2 antihistamine: ranitidine 1–2 mg/kg per dose Maximum dose, 75–100 mg oral and IV
		Corticosteroids Prednisone at 1 mg/kg with a maximum dose of 60–80 mg oral or Methylprednisolone at 1 mg/kg with a maximum dose of 60–80 mg IV
		Vasopressors (other than epinephrine) for refractory hypotension, titrate to effect
		Glucagon for refractory hypotension, titrate to effect
Advice at time of hospital discharge	Epinephrine auto-injector prescription (2 doses) and instructions	H_1 antihistamine: diphenhydramine every 6 h for 2–3 days Alternative dosing with a nonsedating second generation antihistamine
	Education on avoidance of allergen	H_2 antihistamine: ranitidine twice daily for 2–3 days Corticosteroid: prednisone daily for 2–3 days
	Follow-up with primary care physician	
	Consider referral to an allergist	

He reported placing allergens on abraded skin to test the reactivity. This method of placing an allergen on the skin was further developed by von Pirquet who first established the tuberculosis intradermal testing. Over the following years various clinicians furthered this concept and applied this method to various disease contexts. Schloss rubbed food on a small abraded area on the

forearm of children to diagnose food allergy. Later Schick and Cooke developed an intracutaneous method to test allergens on the skin. In the 1950s, the practice of producing a skin abrasion for skin testing was changed because it produced permanent skin changes and since it is custom to prick the skin with a lancet, needle, or plastic prick.

Skin testing is based on the principle that IgE is bound to cutaneous mast cells. Allergen exposure cross-links the IgE molecules and leads to Histamine release (Sampson et al. 2014). The resulting wheal and flare reaction can be measured after approximately 15 min. The wheal and flare is documented in millimeter (wheal mm/flare mm) A positive (histamine) and negative (saline) control are applied and read at the same time as the allergen extracts too assess and account for the reactivity of the skin (Khan et al. 2012).

The size of the wheal and flare reaction depends on the location where the test is applied and is usually larger on the back versus the arm. Specific devices used are known to produce a larger reaction, and it is therefore useful to continue using the same type of prick test device to make testing comparable. Potency of skin testing extract depends on the age of the extract and also the manufacturer. In the case of fruit and vegetables, testing with the fresh fruit is usually more potent as the allergenicity is decreased during the production of the extract.

Larger wheal and flare reaction are predictive of a higher likelihood of reaction to the food tested. The severity of the allergic reaction cannot be extrapolated from the size of the skin test reaction (Sporik et al. 2000).

The positive predictive value of skin testing is variable for different foods used. One study showed an excellent positive predictive value of skin testing in children with peanut, milk, and egg allergy; 100% of children with a skin testing larger than 8 mm (>4 mm for children younger than 2 years old) had a positive food challenge to the food tested (Hill et al. 2004).

Widespread skin conditions can make the application and interpretation of skin testing difficult. In patients who have had a severe or anaphylactic reaction to the food, skin testing should only be performed with caution and assessment of risks and benefits. The same holds true for asthmatic patients, especially for patients with a current asthma flare. The skin of infants and young children might be less responsive to skin testing, on the other hand they might be at a higher risk of developing severe reactions to the testing reagents.

Several additional factors influence the responsiveness of the skin to skin testing. In general there is a variable response to skin testing in the individual patient over time. A recent anaphylactic reaction might leave the skin unresponsive for about 6 weeks after the reaction and skin testing is usually deferred during that time period. Concomitant use of H1-anthistamines, H2- receptor blockers, phenothiazine antiemetics, tricyclic antidepressants, higher doses of methotrexate, topical steroids, and also omalizumab can also render the skin less responsive or unresponsive to allergens and histamine. If patients are unsure about prior antihistamine use or there are other questions about the reactivity of the skin, it is common practice to apply only the positive (histamine) and negative (saline) control to test the responsiveness of the skin before applying all allergens that to be tested.

The practice parameters recommend skin testing to help identify foods that might be provoking an IgE-mediated allergy, but also stress that positive skin testing alone is not diagnostic of an IgE-mediated food allergy.

25.7.3.2 Serum Testing

Another widely available diagnostic test for food allergy is immunoassay testing. These tests are in vitro assays to identify IgE antibodies directed against allergens. Historically radioallergosorbent testing (RAST) was the most widely used test. Today the method for detection of the allergic antibody does not depend on marking it with radioactivity but rather fluorescent dye. The most common immunoassay testing today is Fluorescent Enzyme Immuno Assay (FEIA). However, the term RAST is still in use and often also reported by clinical laboratories even though the assay used was FEIA. The result is reported in kU/L. Most large studies in the United States use

the ImmunoCAP FEIA from Phadia. Results obtained from other Immunoassays are not fully interchangeable. The laboratories also report a class or percentage value of the test results based on a comparison to a standard curve. However, those values are commonly not taken into consideration by allergists when interpreting these results because of their larger heterogeneity.

Serum testing is significantly more expensive than skin testing for food allergies, but it has several advantages over skin testing. It is also available to physicians who do not practice as allergists. It can also be used in patients who are currently or permanently not candidates for skin testing, for either dermatologic conditions, recent anaphylaxis, or medication use that interferes with skin testing. The wide availability also poses a trap and can lead to frequent and unnecessary testing, which then can lead to unnecessary elimination diets.

Serum testing alone is not diagnostic or exclusive of a food allergy and other factors such as clinical history also have to be taken into account.

About 95% predictive values to predict the positive challenge outcome have been established for milk, egg, peanut, tree nuts, and fish. Similar studies for wheat and soy are not available (Martínez-Aranguren et al. 2014).

Technological advances in protein identification and methods have led to the development of specific IgE testing to individual protein components of the allergenic food. Component testing is available for pollen-related plant-derived foods and for animal derived foods. Two different assays exist for the measurement of component specific IgE.

Fluorescent enzyme immunoassays are available for the detection of IgE directed against individual protein components of the food. Testing can be performed to components of selected foods both plant or animal derived. This testing results quantitative levels to individual components and is used increasingly in daily practice to help distinguish between patients at a high risk for an allergic reaction and patients who are sensitized but clinically tolerant to the food tested. This test is available for protein components of most major food allergens and other food allergens. In the United States component testing for certain allergens is FDA-approved and thus usually covered by third party payers. Insurance coverage often determines if these tests are used in the diagnostic work-up of individual patients.

A broader screening method is the ImmunoCAP ISAC (Immune solid phase allergy chip). This test is a protein microarray where binding to multiple proteins is measured simultaneously (refer to Sect. 7.3.6). This test is a semiquantitative screening testing and not used in daily practice by most allergists (Martínez-Aranguren et al. 2014).

Peanut component testing is the most broadly used component test which is also FDA-approved. Interpretation of IgE binding to specific peanut components helps in the differentiation between patients with pollen allergy-induced symptoms with peanut and patients with primary peanut allergy. Peanut component testing is most helpful in certain scenarios: “Patients who have tolerated peanut earlier in life and subsequently have developed mild to moderate, mainly oral symptoms. Patients with an IgE level of 25 kU/L and below. Patients with a concomitant allergy to tree pollen, mainly birch pollen.” It is less likely to add additional essential information in younger children who have had anaphylactic reactions with peanut exposure (Martínez-Aranguren et al. 2014). Sensitization to the heat stable components Ara h1, Ara h2, and Ara h3 is associated with a more severe, systemic reaction then sensitization to the birch (Bet v1)-related component Ara h8 (Table 1).

Testing for hazelnut components is also commercially available. Testing criteria similar to peanut can be applied to hazelnut component testing. Sensitization to Cor a1, a heat labile Bet v1 analog is usually associated with mild oral symptoms. A study from the Netherlands has shown that sensitization to the components Cor a9 and Cor a14 is associated with systemic reactions (Andrews and Banks 2014). In Mediterranean patients, sensitization to the Lipid Transfer Protein (LTP) Cor a8 is associated with severe reactions (Hansen et al. 2009).

Less data are available on component testing for other allergens like soy and wheat. Component testing for most fruits and vegetables is not commercially available and limited to research settings.

25.7.3.3 Trial Elimination Diets

Elimination diets are a possible step in the diagnosis of food allergies. At least three different types of elimination diets exist.

Elimination diets are commonly used in conditions that do not cause acute anaphylaxis to the food in question but rather a more subtle, chronic reaction as can be seen in patients with atopic dermatitis or eosinophilic esophagitis.

An elimination of one or more foods from the diet for a limited time can be used to determine if the food is causing or exacerbating a chronic condition. The elimination period should not exceed more than 2–3 weeks and in small children or the elimination of multiple common foods should involve the guidance of a nutritionist. If an improvement of the condition is noted, further testing should be initiated to determine a sensitization to the food in question.

Elimination diets are one pillar in the management of Eosinophilic Esophagitis.

Milk is the most common trigger of symptoms in patients with Eosinophilic Esophagitis and a trial of milk (and wheat) avoidance is a common step in the management. These targeted elimination diets in which less than six foods are eliminated are more successful in children then in adults. Other empiric elimination diets as the elimination of the six major food allergens have been studied and shown success in up to 70% of children and adults (Straumann and Schoepfer 2014).

A second, very different elimination diet is the complete avoidance of all foods that are commonly considered antigenic and only very few "oligoantigenic" foods are allowed in the diet. This approach is used in chronic conditions as atopic dermatitis or chronic hives but very rarely (Sicherer 1999).

Diets low in histamine containing foods or other pseudoallergens are occasionally recommended in patients with chronic idiopathic urticarial. Dietary modification in the management of urticarial is controversial and not generally recommended (Bernstein et al. 2014).

Elemental diets are the third and most extreme form of elimination diets. In this form the patient avoids all proteins in the diet and receives nutrients via an aminoacid-based or extensively hydrolyzed formula. This diet is an accepted step in the management of Eosinophilic Esophagitis and has shown success in >80% of patients (Straumann and Schoepfer 2014). However, extreme caution and the guidance of a nutritionist are recommended especially in young children and infants.

In the diagnosis of food triggers in severe atopic dermatitis, elimination diets are sometimes advised for 2 weeks prior to the food challenge. This approach allows for the clearance of the suspected allergen from the system before it is reintroduced as the continued ingestion might leave the skin irritated and not allow for the evaluation of the effect of the food because of the already irritated skin condition.

25.7.3.4 Food Diary

Keeping a food diary that records all oral intake but also possible skin contact to foods or cosmetics that may contain food protein over a period of 1–2 weeks can help in the identification of potential allergens that were overlooked by the patient and not elicited during the detailed history.

25.7.3.5 Food Challenge Testing

Food challenge testing is considered the gold standard test for the diagnosis of IgE-mediated food allergy. It is mainly used in two circumstances, to confirm a diagnosis of a food allergy or to check for persistence or resolution of a known food allergy.

A food challenge is usually the gradual feeding of a food under close supervision. The challenge can be in an open fashion or single or double blinded and placebo controlled as described further below. A challenge is usually preceded by a period of abstinence of the food. The food in question is either avoided for therapeutic reasons as it had or is suspected to have had elicited an acute allergic reaction in the past or for diagnostic reasons as the food is suspected to chronically exacerbate a certain condition as detailed above in "Trial Elimination Diets." Several clinical factors have to be considered when undertaking an oral food challenge. The physician will consider the risk of a continued allergy. IgE levels or skin test sizes that

are associated with a high likelihood of reaction or a recent anaphylactic or other severe reaction to the food are strong indicators of a continued food allergy and likely positive challenge outcome and will usually preclude the challenge.

The decision to perform a food challenge should be made by the physician and the patient and/or patient's family. Several factors of patient readiness and personal preferences should be considered. A challenge could be considered unnecessary if the patient has no interest including the food into the diet or if the food is considered of low nutritional importance or rare and exotic. Again, personal preference of the patient and family on the other hand might make an indication for a challenge in this case. Foods that are considered staple foods might be challenged even if the risk of failing is higher because avoidance might have nutritional and quality of life implications. A concern that a failed challenge will result in higher IgE levels and increased skin test sizes was not found to be true when examined in a cohort of patients undergoing a food challenge to egg, milk, and peanut (Sicherer et al. 2016).

Three main categories of oral food challenges exist: open, single-blind, and double-blind placebo controlled.

The open food challenge is the most common food challenge performed in daily practice. Both the patient and the observer know which food is being tested and the food is administered in an unmasked fashion. There is little concern for bias in a negative food challenge. Symptoms noted during the challenge can be either subjective or objective and bias can be present in both the patient and the provider.

In a single-blind challenge the taste, texture and color of the food is masked. It can be combined with a placebo challenge to help investigate subjective symptoms. Single-blind challenges help to minimize the subjective patient bias but do not change the observer bias.

Double-blind placebo-controlled food challenges are considered the gold standard of the oral food challenges. It is more labor and time intensive and is usually used in research settings. The DBPCFC aims to minimize both the patient and observer bias.

Certain safety precautions have to be considered before undertaking any kind of food challenge. Challenges should be performed in an office or hospital setting depending on the anticipated risk. Adequate rescue equipment, medication, and trained personnel should be available. Patients are recommended to fast 1–2 h before the challenge and should have stopped all antihistamines, beta agonists and beta adrenergic blockers or other medication that might interfere with challenge outcome or necessary resuscitation.

The physician performing the challenge will examine the patient and consider the current state of health and also all present co-morbidities that will interfere with the challenge or treatment of a reaction or that will increase the likelihood of an acute reaction. There has been one reported fatality with an oral food challenge (http://acaai.org/allergists-respond-death-3-year-old-boy-during-oral-food-challenge).

25.7.3.6 Future Diagnostic Approaches

The main difference between current diagnostic methods for food allergy and novel diagnostic tools for food allergy is the use of more refined technology. Current methods are mainly based on the use of crude allergen extracts of the food. As described above these extracts have the potential to be cross-contaminated. The most refined and detailed form of allergy testing that is currently on the standard armamentarium of the allergist is component testing as reported above.

Novel diagnostic methods are now focusing on other sources of allergens that are sourced by identification and cloning of the allergens leading to less cross-contamination and contamination by carbohydrate epitopes. These conventional diagnostic tests often leave the patient at an equipoise with an oral food challenge being required to make the final determination of clinical reactivity to a food versus sensitization only noted in diagnostic tests.

Peptide and Protein Microarrays have been developed over the past 25 years. The microarray samples up to 5000 individual datapoints on one single chip. Protein microarrays are used to detect sensitization to multiple allergens simultaneously; peptide microarrays detect

allergen epitope recognition patterns. It has been shown that microarray assays correlate well with IgE levels but are less sensitive. Protein microarrays designed for the diagnosis of food allergies exist, but no application is FDA approved yet.

Peptide microarrays have been applied to the definition of IgE binding epitopes in food allergy (Lin et al. 2009; Lin and Sampson 2009). IgE binding epitopes of various foods have been reported (Shreffler et al. 2005; Vereda et al. 2010). However, studies investigating the correlation of clinical reactivity to binding patterns are rare. It has been shown that there is a correlation between reaction severity and epitope diversity with patients exhibiting a more diverse epitope profile also showing more severe allergic reactions to the allergen (Flinterman et al. 2008). Another major disadvantage had been the limitation to sequential linear epitopes. Recently studies have expanded the application of microarray to conformational epitopes, furthering the development of preventative and diagnostic methods based on this platform (Hochwallner et al. 2010).

Basophil activation testing is one of the novel tests that are aiming to address the diagnostic conundrum of true allergy versus sensitization. In basophil activation testing, the change in expression of basophil surface protein after activation with an allergen is measured by flow-cytometry (Knol et al. 1991). Basophil activation testing has been used in other fields of allergy but over the past years has also been applied to food allergy diagnosis and prediction of challenge outcome. Glaumann et al. investigated the basophil allergen sensitivity and antibodies to peanut components compared to challenge outcome of DBPCFC to help in the diagnosis of peanut allergy in allergic children (Glaumann et al. 2012). The authors were able to show that a negative basophil allergen threshold sensitivity excluded peanut allergy. In addition basophil activation tests have been used in the differentiation of patients with a clinical allergy to one food and a noted sensitization to a cross-reactive allergen. The basophils of the patients were activated by the allergen they had shown clinical allergy to but not by the cross-reactive allergen that was noted be positive on component testing but did not elicit a clinical reaction (Wallowitz et al. 2007). Basophil activation testing has been used to identify patients with a more sever phenotype. It has been shown that patients with a current milk allergy showed increased basophil activation compared to patients who had outgrown their milk allergy (Wanich et al. 2009).

25.8 Treatment/Management

25.8.1 Treatment of Mild Symptoms

Mild localized symptoms can be managed with a trial of oral antihistamines. Liquid diphenhydramine at a dose of 1–2 mg/kg or cetirizine 5–10 mg PO or other first or second generation antihistamines can be given orally for mild localized hives and oral pruritus. However, treatment with antihistamines should not delay administration of IM epinephrine if clinically indicated (Andreae and Andreae 2009). Steroids are often used as a conjunctive treatment but usually do not have a role in management of mild symptoms.

25.8.2 Emergency Treatment

The management of anaphylaxis has been well characterized and studied. Both in the outpatient and hospital settings, the foremost treatment for anaphylaxis following elimination of exposure to the responsible allergen is intramuscular epinephrine. IM epinephrine can either come as an autoinjector with weight-range dosing or in a 1:1000 solution that is also delivered according to weight. While epinephrine doses may need to be administered as often as every 5–15 min during an anaphylactic event given signs of shock and vital sign abnormalities, there are other adjunctive therapies that can have a role in the management of anaphylaxis as well. Albuterol, a bronchodilator, can be administered in the event of airway narrowing with or without supplemental oxygen as indicated by blood oxygen saturations.

Antihistamines, both first and second generation H1 antagonists as well as H2 antagonists, can have a role in the management of anaphylaxis as well. Similarly, additional fluid volumes can be administered if the anaphylactic patient presents with orthostasis, hypotension, or an incomplete response to IM epinephrine. To ensure adequate blood flow to the vital organs, the patient should also lie supine with legs elevated. In a hospital setting, further pharmacologic measures can be employed as well including corticosteroids, vasopressors other than epinephrine, and glucagon (Table 4).

25.8.3 Avoidance

Avoidance of allergens has been the core feature of food allergy management to date.

On a society level, food allergy has become a focus of attention and awareness of food allergies has significantly increased over the past one to two decades. In 2004 Congress mandated labeling of the eight major food allergens on all packaged food products by passing the Food Allergen Labeling and Consumer Protection Act (FALCPA). This law applies only to packaged foods and does not regulate labeling of food allergens on restaurant menus, for example. This law also only includes the eight major food allergens and other allergens like garlic or celery might be labeled just under spices. For seafood finned fish and crustaceans are labeled while squid and mollusks like clam, mussels, and oysters are not included. Other countries of the world have different regulations in their labeling laws. In addition the advisory statement "may contain. . ." has not been regulated and is often used by companies as a low cost measure against law suits following possible food allergen exposures or contaminations of the packaged food (Roses 2011).

This area of uncertainty has become an increasing concern among allergy providers and food allergic patients and their families. Studies investigating foods with advisory labeling have found detectable levels of food proteins in about 5.3% of foods that had the advisory labeling versus 1.9% of foods without advisory labeling (Ford et al. 2010). This rate was even higher (42%) in the case of milk contamination of chocolates with the advisory labeling "May contain milk" (Risks associated with foods having advisory labeling Crotty and Taylor). Until this issue is being addressed and potentially thresholds of reactivity are being defined it is considered safer for allergic patients to avoid those foods. Certain situations require a risk benefit analysis, for example, in the case of the influenza vaccine that might contain residual amounts of egg. The benefit of receiving the influenza vaccine most often outweighs the minimal risk of an allergic reaction. The most recent statement from the committee on infectious diseases states that all children with egg allergy can get the influenza vaccine without further precautions (Committee on Infectious Diseases 2016).

Patients have to be aware that also alcoholic beverages may contain common food allergens and nonfood items such as play dough may contain wheat and other arts and craft items such as finger paint may also contain egg.

The public discussion that followed the labeling laws has also brought increasing awareness of food allergies to the restaurant and hospitality industries as well as to schools.

While some schools opt to have peanut and tree nut free classrooms or cafeterias, most of the other common food allergens cannot be easily excluded from the meal plans. Therefore, education of teachers but also cafeteria personal and school bus drivers on food allergies including safe handling of food, recognition and treatment of food allergy reactions and implementation of avoidance measures.

Education of patients and their families on food allergies, emergency treatment, and avoidance practices is the most important aspect of food allergen avoidance. Young children and toddlers have to be strictly supervised. Kindergarten and school age children will have to be instructed not to share foods and about possible food allergens hidden in arts and craft projects. The older the child the more responsibility they will be able to have regarding their food allergies, starting from communicating with teachers, peers, and also restaurant staff. Teens will also be able to start carrying and administering epinephrine by themselves.

An important topic that has to be discussed with school age children and especially teenagers is bullying around the topic of food allergies. Sicherer et al. have conducted extensive research around the topic of food allergy-related quality of life issues and mental wellbeing, including bullying. It was found that children with food allergies who are being bullied in school have significantly lower quality of life compared to children with food allergies who are not being bullied. Parental awareness of the bullying does offset the decreased quality of life significantly (133–136). Teenagers should be encouraged to make their friends and teachers aware of their food allergies and signs and symptoms of possible reactions to ensure prompt recognitions and treatment of possible reactions.

Vigilance around food allergies of all parties involved in the patient's life is crucial to ensure a favorable outcome as most reactions are reported due to lack of vigilance. Wearing medical identification jewelry is helpful, also in older children who become more independent. In general avoidance and treatment plans should be in place for both home, school, restaurants, and also travel. It was found that during international travel communication of food allergies to restaurants can be difficult due to the language barrier. Carrying "chef cards" that explain the food allergy, possible cross-contamination and also methods to prepare allergen-free food in the local language are recommended. Some families prefer to rent apartments when traveling to be able to prepare their own food safely. Airlines have moved away from completely peanut free flights but might restrict peanut distribution on certain flights if a severely peanut allergic patient is traveling on a flight. For infants and toddlers, parents might want to inspect the seat for food residues in folds and crevices of the seat and wipe down the seat and tray table to clean possible contamination from previous passengers.

The role of the allergist in avoidance is first and foremost in education of the patient and family as well as making sure emergency treatment and emergency treatment plans are well understood and in place. Review of the indications and proper administration of injectable epinephrine is indicated at every return visit.

25.8.4 Emerging Therapies

While avoidance is crucial and at this time the most important step in avoiding reactions to food allergens, affected individuals are having high hopes for an eventual cure or state of less reactivity to food allergens. While some food allergies are often and others are sometimes outgrown as discussed above, there is a large percentage of food allergic individuals who do not outgrow their food allergies and depend on the combination of avoidance and treatment of accidental ingestions.

Over the past decade significant advances have been made in the investigation of treatments for food allergies. The novel treatment approaches can be broadly classified into two groups, food-allergen-specific treatments and nonfood-allergen-specific treatments. The underlying idea is to achieve a state of sustained unresponsiveness to the food allergen in question. As we will discuss below, safety, tolerability, and also side effects of the therapies have to be investigated. The duration of therapy versus the necessity of continued treatment to maintain tolerance is another topic currently being investigated.

25.8.4.1 Food-Allergen-Specific Therapies

The main goal of food-allergen-specific therapies is to achieve tolerance to the food allergen in question. This would enable patients to consume the food allergen without a reaction and also would allow for periods of avoidance without development of a reaction upon reintroduction. Not all patients are able to reach this state, and while some patients do not reach the full maintenance dose of the allergen, they are able to tolerate smaller amounts of the food allergen shielding them from reactions with accidental ingestion of small or trace amounts. However, in this case patients often have to continue ingesting the tolerated amount of the food allergen daily because reactivity after a prolonged phase of abstinence cannot be excluded.

Oral Immunotherapy has been shown to be effective in both observational studies and randomized clinical trials. It has also received press

coverage over the past years sparking more interest from the food allergy patient community. http://www.nytimes.com/2013/03/10/magazine/can-a-radical-new-treatment-save-children-with-severe-allergies.html.

The underlying concept of oral immunotherapy is that oral exposure to a food protein does elicit an immune system response but usually results in oral tolerance rather than sensitization, as described above. The induction of tolerance is thought to be mediated by upregulation of T regulatory cells in response to small amounts of the protein and T cell anergy or deletion in response to large amounts of the protein (Vickery and Burks 2009). While in the first 12 months a gradual increase in the food-specific IgE levels is seen, those levels subsequently decrease and are accompanied by a gradual increase of IgG4 and IgA (Wright et al. 2016).

Different levels of tolerance can be achieved and exact definition of those states is important for management but also continuing research efforts. While some patients do not tolerate the full maintenance dose, their reaction threshold has increased and they are now able to tolerate larger amounts of the allergen, with the main benefit of protecting them from accidental ingestion of small amounts. Up to 75% of patients receiving oral immunotherapy are reaching this state. However, maintaining desensitization is dependent on continued ingestion of the food. Prolonged intervals of abstinence might result in a return of reactivity to the food.

The main goal of the therapy is induction of tolerance meaning achieving full tolerance even after prolonged intervals of abstinence.

In oral immunotherapy, patients are receiving small increasing amounts of the food, starting with a very small dose, gradual increase until a maintenance dose is achieved. Common protocols have the initial and early step-up doses administered in the clinic with the remainder of the dose increases and the maintenance doses being taken at home. Usually the patient is restricted from ingesting the food included in the OIT during the treatment phase. However, it is unclear what treatment interval is required to maintain sustained unresponsiveness. A general recommendation is to continue ingestion of the food indefinitely about 1–2 times per week. It is not defined what period of abstinence followed by proven maintenance of tolerance defines achievement of complete tolerance. Therefore, the term "sustained unresponsiveness" has been coined to describe permanent tolerance.

Most clinical trials include a period of abstinence and it has been shown that starting OIT at a younger age is highly effective in achieving sustained unresponsiveness (Vickery et al. 2017).

In addition it was noted that lower pretreatment IgE levels and longer treatment times lead to higher rates of sustained unresponsiveness (138, 140).

Side effects from OIT are common and have been reported in all phases of build-up and maintenance. Allergic reactions have been reported in all clinical trials and anaphylactic reactions have also been described. These reactions result in some participants withdrawing from the trials. Development of Eosinophilic Esophagitis has also been reported and the rates and mechanism of that remain to be studied in more detail (141–143).

The underlying mechanism bases on the concept that food extracts applied under the tongue are taken up by dendritic cells and presented to T cells in the draining lymph nodes. Most likely this results in an upregulation and activation of T regulatory cells and a downregulation of mast cells. Sublingual immunotherapy as oral immunotherapy has a much milder side effect profile compared to subcutaneous immunotherapy (Narisety et al. 2015). Protocols are similar to OIT schedules, with SLIT having an even milder side effect profile than OIT, with mainly oropharyngeal pruritus and rare reports of anaphylaxis.

Epicutaneous Immunotherapy follows the same basic mechanism of chronic exposure to the allergen, in this case through application on the skin and subsequent dissemination into the stratum corneum. There is a concern that epicutaneous immunotherapy might lead to sensitization rather than desensitization as based on the concepts of sensitization to food allergens described above (145). Clinical trials have now established the importance of applying the epicutaneous patches to intact skin rather than eczematous skin (Mondoulet et al. 2009). In this

form of immunotherapy, no dose escalation is required and the initial dose is also the maintenance dose. The rate of allergic reactions is much lower than in other forms of immunotherapy. Side effects were mainly localized to the skin and the resulting drop-off rate was generally low with good adherence reported in most trials. Outcomes of a recently reported US multicenter clinical trial using EPIT for peanut allergy were a generally good tolerance of treatment, good adherence, and but only a modest response to treatment. Efficacy of treatment was found to be higher in younger participants (Jones et al. 2017).

Subcutaneous immunotherapy as a possible treatment for food allergies has been investigated. Clinical trials have shown efficacy, but they have also documented more severe and frequent side effects and allergic reactions to the treatment compared to oral and epicutaneous immunotherapy (Nelson et al. 1997)

Research mostly on mouse models has been conducted using either short overlapping peptides covering the sequence of the entire protein or a chemically modified peanut extract (Zuidmeer-Jongejan et al. 2015).

A more recent approach has been the development of DNA-LAMP vaccines. The allergen is presented to the immune system using lysosome associated membrane proteins (LAMP). This leads to allergen presentation and triggering not only through the MHC class I but also the MHC class II pathway resulting in a CD-8+ and CD-4+ T-cell response (Su et al. 2016).

Genetically modified proteins have been used for subcutaneous and intramuscular immunotherapy. The underlying concept is that these protein sequences are altered in a way that they are not able to trigger and cross-link IgE molecules and therefore do not stimulate mast cells while still being recognized by T cells. This should lead to more safety and a less severe side effect profile.

25.8.4.2 Therapies Not Specific for Food Allergens

Nonfood-allergen-specific therapies are mainly aimed at reducing the general reactivity of the immune system.

IgE is the main driver of allergic reactions leading to mast cell activation and subsequent release of histamine and other mediators of allergic reactions.

Anti-IgE treatment using omalizumab a humanized monoclonal antibody directed against IgE has been used as a conjunctive treatment in many clinical trials for food-allergen-specific immunotherapy. It has been shown to reduce side effects of oral immunotherapy. It has not been used as a treatment for food allergies alone.

Similarly an anti-IL-4 fully human monoclonal antibody dupilumab has been used in patients with atopic dermatitis and is also under investigation for patients with eosinophilic esophagitis and food allergies.

Li et al. have extensively investigated the effect of Chinese Herbs and mushrooms on the immune system in patients with asthma and food allergies (Srivastava et al. 2012; López-Expósito et al. 2015). The herbal formula for food allergies that was studied in murine models has been used in clinical trials. It has been shown to be safe and well tolerated with an inhibitory effect on basophil numbers. Further clinical investigation is necessary before herbal formulas can implemented as a nonfood-specific treatment for food allergies.

25.8.5 Unproven Therapies

As discussed above the rate of patient reported food allergy and physician diagnosed food allergy is discordant in the westernized world. The subjective feeling of food allergy or intolerance and the failure to prove this allergy in standardized and validated testing motivates a subgroup of patients to undergo alternative testing methods to validate their symptoms. In addition skin testing and serum IgE testing can only be used to diagnose IgE-mediated food allergy and do not aid in the diagnosis of other food intolerances or food hypersensitivities. It has been reported that about 1 in 5 patients has pursued alternative testing for food allergies for themselves or their child (Ko et al. 2006).

IgG levels to a particular food have been shown to be present if a food is ingested on a regular basis. IGG to cow's milk can be found in about 98% of children at the age of 2 years (Siroux

et al. 2017). There are no studies showing a role of IgG in food allergies. Nevertheless, there are large panels of IgG levels for food testing available to patients and physicians. While these tests are marketed as not being diagnostic for acute or anaphylactic reactions to foods but are rather advertised as supplying additional information aiding in the diagnosis of chronic fatigue or irritable bowel syndrome, many patients interpret the results as diagnostic for food allergies. Hence, positive IgG levels, as are expected if the food is ingested on a regular basis invariably, lead to unnecessary food avoidances.

Hammond and Lieberman report and summarize other unproven methods that are occasionally used in the diagnosis of food allergies (Hammond and Lieberman 2018).

Pulse testing has been reported by author Dr. Arthur Coca in 1956. The underlying concept is based on the belief that sublingual or intradermal exposure to the investigated food will lead to an increase in the pulse by 16 beats per minute if the food tests positive. It is unnecessary to stress that apart from the missing scientific basis of this test, it can put patients with a true IgE-mediated food allergy at an unnecessary risk for severe allergic reactions. Hammond and Lieberman reported that they were unable to identify any scientific reports studying this test.

Provocation and neutralization tests are also exposing the patient to the food either sublingually or intradermally. Any patient reported symptom within 10 minutes of exposure is considered a positive result. This positive test can be followed by a Neutralization phase where the food is given at a different dosage until the reaction subsides. Usually no placebo is used. Again, also this method poses a significant risk for patients with acute IgE-mediated food allergy.

Cytotoxic testing investigates the morphological change of leukocytes after exposure to an allergen. When this method was first described, changes were detected by microscopy. However, already at that time investigators proved that there was no correlation between test result and clinical presentation as well as no reproducibility of the results (Semizzi et al. 2002).

Applied Kinesiology is another unproven method used in diagnosing food allergy. In this test the patient holds a vial with the allergen that is being testing. The investigator applies light pressure to the opposite arm, if a drop in the strength of that arm is noted the test is considered positive. No studies have provided a scientific basis or validity of this method.

Patch testing is an established diagnostic tool for diagnosing contact dermatitis. At this time there is no standardized patch testing method for IgE-mediated food allergies. Patch testing for mixed IgE-/cell-mediated allergies is discussed elsewhere.

25.9 Conclusion

Food allergy is an increasingly prevalent disease that has been recognized as a significant public health problem in the past decades. While it is agreed upon that prenatal and early life exposures and interactions play a significant role in the development of food allergies, the exact mechanism and combination of factors that lead to the development of sensitization versus tolerance is not known. Different hypotheses to help understand the context that leads to the development of food allergies have been developed, most recently the dual allergen exposure hypothesis. Based on these concepts, research is being focused on primary prevention strategies to help avoid a further increase in food allergies and also immunologic mechanisms to develop treatment tools to achieve desensitization or tolerance in patients that are already affected by food allergies.

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Non-IgE Food Immunological Diseases 26

Brian Patrick Peppers, Robert Hostoffer, and Theodore Sher

Contents

Abstract

Non-IgE food immunological diseases encompass a wide range of illnesses that can involve one of more systems in the body. The gastrointestinal track is the most commonly involved system, but cutaneous and respiratory systems can also be involved. This chapter will primarily be focused on identification, diagnosis, and treatment options for non-IgE food immunological diseases involving the gastrointestinal track directly. Current difficulties in diagnosis and pathophysiology behind non-IgE food immunological diseases will be explored.

Keywords

Non-IgE · Non-IgE food allergies · Mixed IgE food triggers · Non-IgE food immunological diseases

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26.1 Introduction

Non-IgE food immunological diseases encompass a wide range of illness. Akin to IgE-mediated food allergies, clinical history is

paramount in the diagnosis. One important difference between non-IgE and IgE-mediated immunological processes is the lack of potential confirmation in vivo, or in vitro tests for non-IgE food-related diseases. Diagnosis by personal clinical history and general common food triggers for trial avoidance remain a popular strategy for initial management. When appropriate oral challenges can be used to officially diagnose certain forms of non-IgE food immunological disease. On the occasion when there is a mixed IgE and non-IgE dietary trigger, IgE in vivo and in vitro testing have been used to help diagnosis by potential association with the non-IgE component. To date there has been no successful association of IgG or immunoglobulin subclass level testing to help elucidate the dietary trigger of non-IgE-mediated food immunological disease. Screening for them by these means is not recommended (see ▶ Chap. 33, "In Vitro Allergy Testing" for more information).

Identification of food responsible for inciting the non-IgE immunological disease is important to ensure quality of life and nutrition and prevent secondary illnesses and in certain cases life-threatening sequela. Avoidance and time often alleviate the unwanted immunological response to a specific food, and eventual reintroduction is possible. Consideration for potential confounding non-immunological food triggers is important as these tend to extend from a metabolic or pharmaceutical affect, vary in sensitivity, and remain for life.

26.2 Non-IgE Food Immunological Diseases

Food immunological disease or food allergies have been defined as: "an adverse health effect arising from a specific immune response that occurs reproducibly on exposure to a given food" (Sampson et al. 2014). This definition encompasses IgE, non-IgE, and mixed food-triggered immunological diseases. Dietary triggers can come from solid foods, drinks, chewing gum, additives, and even dietary supplements. Most non-IgE-mediated food allergies are not immediate making their diagnosis based on history more complicated for patient and practitioner alike.

One of the challenges facing practicing physicians is to help discern and educate the general public on the meaning of "specific immune response" within the definition of food allergies. Adverse reactions to one's diet can also be caused by non-immunological triggers. These sources can be from metabolic (e.g., lactose intolerance), toxic (e.g., food poisoning), and pharmacological (e.g., caffeine).

When examining more classic non-IgE-mediated food allergies, it is often divided into the system that is affected. Within the gastrointestinal track, allergic proctocolitis, food protein-induced enterocolitis syndrome, dietary protein-induced enteropathy, and celiac disease are the hallmark examples. Cutaneous manifestations can be seen in systemic contact dermatitis and dermatitis herpetiformis. In rare instances the respiratory track has also been affected with pulmonary hemosiderosis (Heiner syndrome). Other forms of mixed IgE and non-IgE food immunological disease such as systemic contact dermatitis, atopic dermatitis, and eosinophilic esophagitis will be discussed in their respective chapters. There is not one particular food that is seen in all forms of non-IgE-mediated food immunodeficiency diseases. Within a particular illness, there are often more than one possible trigger. Celiac disease is a notable exception to this generality.

26.3 Gastrointestinal Non-IgE Food Immunological Disease

26.3.1 Allergic Proctocolitis

Allergic proctocolitis, also known as food protein-induced allergic proctocolitis (FPIAP) or allergic colitis, is generally considered to be a benign condition primarily affecting infants and toddlers (Nowak-Wegrzyn et al. 2015). The exact mechanism is unknown but thought to involve T-cell-mediated pathways (Morita et al. 2013). The most prominent clinical feature is gross bloody or blood-tinged (macroscopic) stools. Diarrhea and emesis are also commonly seen but are not

essential clinical features for the diagnosis of FPIAP. On rare occasions mild anemia may result from unrecognized or untreated FPIAP, but most infants do not succumb to failure to thrive or developmental sequela.

The only known treatment is removal of the offending food source. In infants, elemental formula, although very effective, is reserved for cases where no trigger can be identified and partially hydrolyzed formulas have failed to resolve the blood streaking. Once the dietary antigen(s) is removed from the diet, clinical improvement is seen in as little as 48–72 h. Complete healing of the distal and sigmoid colon has been postulated, however, to take up to 4 weeks.

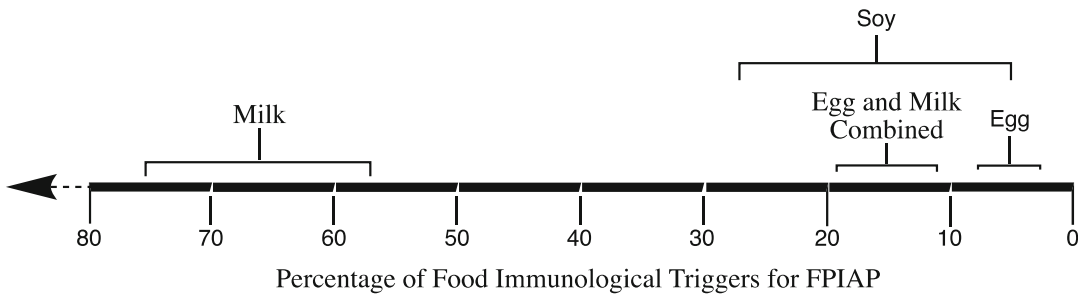
Colonoscopies have been used in studies to diagnose and monitor healing. Histological biopsies have shown the presence of eosinophil's, but not in every case, and their presence is not universally considered to be necessary for diagnosis. The number of eosinophils per high-powered field reported has been from >6 to >50 and particularly in the lamina propria (less often in muscularis mucosae) (Lake et al. 1982; Winter et al. 1990; Xanthakos et al. 2005; Yantiss 2015). Colonoscopies are not recommended in the routine clinical diagnosis or management of FPIAP (Sampson et al. 2014). In the event a trigger cannot be found and clinical symptoms persist or worsen, the use of colonoscopies has been advocated for in the literature (Erdem et al. 2017).

Maternal breast milk (MBM), unlike with IgE-mediated allergies or atopy, is not considered to help prevent FPIAP. In fact, breast milk is one of the more common dietary staples during the onset of FPIAP. Approximately 60% of babies under the age of 6 months that develop FPIAP are on MBM (Erdem et al. 2017). The first signs of FPIAP can be seen in infants that are only a few days old but more often after the age of 2 months old and under 1 year of age is typical. Children over the age of 2 and up to 14 years old have been reported to suffer from FPIAP (Ravelli et al. 2008). The true prevalence of FPIAP is not known. In adults FPIAP is poorly described, and more often eosinophilic colitis or ulcerative colitis is reported. If there is a relationship between the two latter diagnoses and FPIAP it is not well understood.

Regardless of the age of onset, the most common trigger reported is cow's milk (Sampson et al. 2014). This remains true even for infants that are exclusively breastfed. In exclusively breastfed babies, the rare recommendation that the mother ceases ingestion of dairy products is warranted and often resolves the FPIAP while still being able to breastfeed (Erdem et al. 2017). When the dietary antigens in the maternal diet cannot be identified, atopy patch testing has been reported to help identify potential triggers, but its use remains controversial (Lucarelli et al. 2011; Sampson et al. 2014). Results of atopy patch testing have shown in these severe cases of FPIAP unresponsive to maternal hypoallergenic diet which yielded up to 100% positive testing to MBM itself (Lucarelli et al. 2011).

Studies tend to differ on the exact percentage of participants with single non-IgE food immunological triggers, but cow's milk is repeatedly reported as the most common trigger followed by eggs or soy and then a mixture of other foods. Studies that include soy are far less common than those reporting on milk and eggs, with some of the original studies only containing six subjects (Lake et al. 1982). As seen in Fig. 1, the percentages for each food allergen range considerably (Erdem et al. 2017; Fiocchi et al. 2010; Lake 2000; Xanthakos et al. 2005).

Abstinence of the offending food trigger is the only known treatment. The duration of avoidance required to become tolerance of the food in question ranges from a few weeks to years. The average duration of time ranges from 8 to 15 months (Erdem et al. 2017). The initial duration for avoidance is normally recommended for 12 months. This can vary and reintroduction has been suggested in as little as 4–8 weeks. Milk and/or egg has been reported to be involved in over 90% of toddlers unable to develop tolerance by the age of 2 (Erdem et al. 2017). Unlike in IgE-mediated allergies and food protein-induced enterocolitis syndrome (FPIES), trial reintroduction or challenge can be done at home and without medical supervision. There is not a universal protocol for the challenge or reintroduction (Nowak-Wegrzyn



* All Others: Idiopathic ~10%, Corn <5-6%, <5%: Wheat, Rice, Meats, Misc.

Fig. 1 Percentage spectrum of responsible food immunological triggers

et al. 2015). Some studies have modeled the challenge after protocols similar to a FPIES challenge (Erdem et al. 2017; Nowak-Wegrzyn et al. 2009; Sampson et al. 2014). The general premise however is to reintroduce the food protein back into the regular diet gradually and to observe for return of blood streaking in the stools.

26.3.2 Food Protein-Induced Enterocolitis Syndrome

Food protein-induced enterocolitis syndrome (FPIES) can be life-threatening. The onset of symptoms is 1–4 h after ingestion of the food antigen (Sampson et al. 2014). This is a delayed reaction when comparing the onset of IgE-mediated food allergies that 97% of reactions are within an hour of ingestion (with vast majority prior to 30 min). History and oral food challenges are the only known methods of diagnosis and confirmation. Although delayed, with a predictable window of 1–4 h of symptom onset after ingestion, the identification of the offending food trigger is less complicated then with FPIAP.

The exact prevalence of FPIES, much like FPIAP, is unknown. The age of onset is normally after 2 months of age but can be sooner (Manti et al. 2017). Apposed to FPIAP, FPIES is recognized to occur in adults, albeit less frequently. Cow's milk and soy are the most common triggers prior to 4 months of age. Maternal breast milk is not thought to prevent FPIES but has been reported to delay onset to when the infant starts to ingest solid foods. As an infant starts to ingest nutrition by solid foods at ages 4 months and above, the sources of possible triggers diversify to include rice, grains, eggs, vegetables, fruits, fish, and legumes. Studies have found cow's milk to be the most common causative agent (~60–70%) with conflicting data for the percentages of soy, eggs, rice, fish, and others. The discrepancies are partially thought to be due to regionally diverse diets beyond cow's milk. Most studies have favored a singular causative antigen responsible for FPIES in an individual. However with 35–80% reports of multiple food triggers, having more than one food antigen leading to FPIES in a patient is by no means rare or uncommon.

Clinical presentation of FPIES can range from mild to severe and life threatening. The onset of symptoms normally starts from 1 to 4 h after ingestion, with ~2 h being the most common. The entire reaction from start of symptom onset to clinical resolution can last 6–8 h. Although there is room for variable presentation, there does exists a prodromal sequence of events. The initial symptoms often start with abdominal cramping and nausea and closely followed by repeated and profuse emesis. The addition of diarrhea may present a few hours after onset of emesis with that average time around 5 h, but occurrence is not necessary for diagnosis. Lethargy, pallor, and hypothermia can also be seen toward the end of the attack. The most concerning and life-threatening symptoms are hypotension and shock secondary to fluid loss particularly in infants and children. It is for this reason that oral food challenges are recommended only

Table 1 Food protein-induced enterocolitis syndrome challenge dosing protocols

Protein (g)/body weight (kg)	Body weight (kg)								Maximum patient weight for 10 g protein challenge limit (kg)
	5 kg	10 kg	15 kg	20 kg	30 kg	40 kg	50 kg	60 kg	
0.6	3	6	9						16.7
0.3	1.5	3	4.5	6	9				33
0.15	0.75	1.5	2.25	3	4.5	6	7.5	9	67
0.1	0.5	1	1.5	2	3	4	5	6	100
0.06	0.3	0.6	0.9	1.2	1.8	2.4	3	3.6	167

Total protein given over 3 equal doses, with 10 g total limit

under physician supervision and often times in a hospital setting.

Diagnosis of FPIES is often done based on history alone provided there is reliable and repeated sequence of events related to a particular food antigen. This is of particular importance when life-threatening reactions have been described in the history. Oral food challenges (OFC) under supervision may be necessary when more than one food item is suspected or the history is not as clear. Given the potential for hypotension and shock, intravenous access is often recommended prior to initiating the OFC.

In some cases a comorbid IgE sensitization may be present. Skin prick testing and serum IgE testing can be useful in the identification of potential food triggers in up to 30% of cases. This mixed IgE and non-IgE presentation is sometimes referred to as atypical FPIES and is reported to be more common in those with atopy and prolonged or chronic FPIES. It is thought that atypical FPIES represents a more severe phenotype as the addition of classic IgE-mediated allergic responses compound potential life-threatening events.

Atopy patch testing has been studied for the potential of identifying food antigens in FPIES. Initially promising reports of high sensitivity (100%) and high negative predictive values (100%) have been challenged in recent years. Validation studies have reported markedly low sensitivity of 11.8% and positive predictive value (PPV) of 40% and negative predictive value of (54.5%). Specificity has been reported up to 85.7% in the same study. Studies on atopy patch testing have been relatively small with 19–25 participants, and further investigation has been suggested before routine use can be recommended.

Oral food challenges remain the gold standard for diagnosis and verification of food allergy resolution. Depending on the patients history, the quantity of protein ingested during the OFC varies (Table 1). Regardless of the quantity of protein given during a challenge, the total dose is divided into equal thirds and given 15 min apart over a 30-min period (or three doses for ~22 min apart over a 45-min period) (Nowak-Wegrzyn et al. 2009).

Those without a history of severe past reaction of hypotension and shock are generally challenged with the higher doses. Individuals with a severe past reaction are normally started at the lower dosing range (Nowak-Wegrzyn et al. 2009). The recommended maximum amount of food protein administered during a challenge has ranged from 3 to 10 g. If considering the total weight of the food, 10–20 g has been suggested as a reasonable cutoff (Manti et al. 2017). If a single-blind oral challenge is desired, a liquid or solid vehicle may be used depending on the protein source. The vehicle should be inert and of reasonable quantity (Nowak-Wegrzyn et al. 2009).

A positive oral food challenge to FPIES would include the clinical presentation described above along with some ancillary laboratory test. The onset of symptoms although normally start after 1 h is considered positive as they start as soon as 30 min after ingestion. Recommended laboratory tests are taken prior to starting a challenge and if clinical symptoms are observed or reported are repeated 6 h after initial ingestion. Table 2 outlines the most common laboratory indicators used during a challenge.

Table 2 FPIES Confirmation Laboratory Tests

Laboratory test	Positive result
Periphereral polymorphonuclear leukocytes (neutrophils)	>3500 cells/mm^3 or Increase by 5000–16,800 cells/mm^3
Fecal studies	Occult blood Leukocytes Eosinophils

Fecal studies are only warranted if diarrhea is present

Of note, fecal tests are only ordered if diarrhea is present during the time of the challenge. Otherwise only blood and serum serology is used. Methemoglobinemia has also been reported in more severe cases along with metabolic acidosis. Management during a positive FPIES challenge centers around aggressive hydration, prevention of hypotension, and shock. Administration of epinephrine by intramuscular means has a role if IgE-mediated symptoms are present. Otherwise standard hypotension interventions are the mainstay of treatment. For those with acute FPIES, complete resolution of clinical symptoms is normally within hours of ingestion. In individuals with chronic FPIES, clinical resolution may take up to 10 days.

With strict avoidance reintroduction after a negative oral food challenge is possible. The exact timing to challenge is not well described. It is recommended to wait till after 12 months of age to challenge to see if tolerance has been reached. Tolerance also tends to depend on the allergen in question. For cow's milk tolerance for majority of patients has been reported by ages 3–5. However, for those allergic to rice, only 50% are reported to be tolerant by age 5. Challenging 12–24 months after a positive OFC has been recommended.

The pathophysiology behind FPIES is thought to involve a T-cell-mediated process but is not universally agreed upon. Proinflammatory cytokines TNF-alpha and interferon-gamma have been detected in higher quantities in those with an acute FPIES episode. These cytokines are reported to increase intestinal permeability ultimately leading to fluid shifts. Reciprocally with elevated TNF-alpha and interferon-gamma, TGF-beta has been noted to be decreased. Upon resolution of FPIES and induction of tolerance, this imbalance of TNF-alpha and TGF-beta has been reported to be resolved.

26.3.3 Dietary Protein-Induced Enteropathy

Dietary protein-induced enteropathy, also known as food protein-induced enteropathy (FPE), and malabsorption syndrome present with protracted diarrhea as opposed to FPIES that presents with protracted emesis (Kuitunen et al. 1975; Nowak-Wegrzyn 2009; Sampson et al. 2014). Similar to FPIAP and FPIES, onset of presentation is often prior to 1 year of age. Cow's milk or cow's milk-based formula is the most common causative agent followed by soy (Nowak-Wegrzyn et al. 2015). The onset of symptoms can be as early as a few weeks after initial introduction of food allergen into a regular diet. For infants starting formula right after birth or shortly after, symptoms can be seen as soon as 4–8 weeks of life (Kuitunen et al. 1975; Saarinen et al. 1999). Mixed presentation of IgE-mediated sensitization has not been reported with FPE. The insidious nature of symptoms onset makes diagnosing FPE after starting solid foods more difficult.

Joining the FPIAP and FPIES, FPE's prevalence is also unknown. The onset of protracted diarrhea is more gradual than FPIES and does not carry the risk of acute life-threatening sequela. Diarrhea also need not start within so many hours after food ingestions like FPIES. Failure to thrive (FTT) is, however, a real concern in those with undiagnosed or poorly controlled FPE (Nowak-Wegrzyn 2009). It has been reported that 50% of infants with FPE succumb to FTT. Prognosis is however good with removal of food allergen. Breastfeeding or breast milk is thought to delay onset, but not prevent FPE's in infants. Multiple food antigens are known to coexist, but not often as in FPIES and FPIAP.

Confounders that make proper diagnosis of FPE revolve around similarities that the clinical presentation has with postinfectious gastroenteritis and lactose intolerance (Nowak-Wegrzyn et al. 2015). There are no laboratory tests to help confirm FPE. Secondary to the malabsorption,

nonspecific laboratory results of anemia, hypoalbuminemia, and hypoproteinemia are commonly seen, but not required for diagnosis (Nowak-Wegrzyn et al. 2015). It is recommended to have endoscopy with biopsy to help confirm FPE. This is in contrast to recommendations against routine endoscopy/colonoscopy for acute FPIES and FPIAP. Histological findings of lymphonodular hyperplasia in the duodenal bulb and intraepithelial lymphocytes >25/100 epithelial cells are characteristic of FPEs (Fontaine and Navarro 1975). The intestinal wall may or may not have erosions as well. Positive biopsy with clinical correlation and negative celiac disease is strongly supportive of an FPE's diagnosis. Of note, transient gluten sensitivities have been described (Walker-Smith 1970, 2005).

Management of FPEs involves removal of the suspected offending agent with close follow-up for apparent resolution. Reintroduction of food antigen into the diet can be done as soon as 4 weeks and at home gradually with monitoring for return of symptoms. The majority of cases will resolve after 2–3 years of eliminating of the food allergen from the diet. Repeat biopsies 1–2 years after clinical resolution has been suggested in the literature. This is due to the potential for subclinical pathology still present after apparent reintroduction and tolerance of the food allergy trigger (Iyngkaran et al. 1988; Shiner et al. 1975).

26.4 Conclusion

Non-IgE food immunological gastrointestinal diseases can be particularly hard to diagnose compared to IgE-mediated allergies. Historically cow's milk protein is the most common antigen source. In the case of FPIAP, this can include cow's milk peptides from maternal breast milk. In all cases dietary elimination and time are the only known effective treatments. Reintroduction can be fairly soon after complete abstaining from exposure but often takes months to years before tolerance is seen. Food protein-induced enterocolitis syndrome can be life-threatening, and medical supervision is required during challenges. Food protein-induced enteropathy and FPIES have been reported in older children and adults, unlike FPIAP. Currently mixed IgE and non-IgE-mediated food immunological mechanisms are described in FPIAP and FPIES, but not FPE. Endoscopies are only recommended routinely for FPE for both diagnosing and monitoring silent disease states.

26.5 Cross-References

- ▶ Allergic Contact Dermatitis
- ▶ Allergy Skin Testing
- ▶ Atopic Dermatitis
- ▶ Eosinophilic Esophagitis
- ▶ In Vitro Allergy Testing

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Eosinophilic Esophagitis

27

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Abstract

Eosinophilic esophagitis is a chronic inflammatory disease of the esophagus which affects children and adults. It is a clinicopathological diagnosis and symptoms of esophageal dysfunction along with histological finding of at least 15 eosinophils per high power field in the biopsy specimen of the esophagus are required for diagnosis. Eosinophilic inflammation should be confined to the esophagus and other causes of esophageal eosinophilia have to be excluded. The prevalence and incidence have been increasing for the past two decades. Although the disease has been reported worldwide, it has been most commonly reported in the American continent and Europe. It affects white individuals and males more commonly than other races and female population. The disease is highly associated with atopic conditions, food, and aeroallergen hypersensitivities are common findings in patients with EoE.

T-helper lymphocyte-mediated inflammation is the basis of pathogenesis. A unique EoE transcriptome has been identified which differentiates this condition from gastroesophageal reflux disease.

The presenting symptoms vary by age, with dysphagia being the most common in adults. The most common and worrisome complication is esophageal stricture due to fibrosis induced by persistent inflammation. The disease does not resolve without treatment but has a waxing and waning nature.

Treatment modalities may include one or any combination of dietary modification, topical steroids, and treatment of comorbid conditions. Endoscopic dilatation of esophagus could be considered in patients presenting with fibrotic changes. Biological agents have been investigated but at this time not available for clinical use.

Keywords

EoE · Esophageal eosinophilia · Dysphagia · Reflux esophagitis · Definition · Epidemiology · Pathogenesis · Clinical features · Diagnosis · Management

27.1 Introduction

Eosinophilic esophagitis is a chronic inflammatory disease of the esophagus which affects children and adults. It is a clinico-pathological diagnosis and symptoms of esophageal dysfunction along with eosinophilic inflammation of the esophagus are required for diagnosis. The disease is highly associated with atopic conditions, food and aeroallergen hypersensitivities are common findings in patients with EoE. T-helper lymphocyte mediated inflammation is the basis of pathogenesis. The prevalence and incidence have been increasing for the past two decades. The amount of the literature related to EoE has also been remarkably increased. A unique EoE transcriptome has been identified which differentiates this condition from gastroesophageal reflux disease, various treatment modalities have been introduced and overall knowledge about the disease has been expanding.

In this chapter, the English literature have been extensively reviewed with the focus on landmark articles in the past few years.

27.2 Goals/Objectives

To provide relevant information for understanding of the symptoms, disease process, and management options in EoE to the general population, patients, and care givers in order to encourage adherence to management options to prevent complications.

To provide better understanding of the definition, epidemiology, clinical features in various age groups, pathogenesis, measures of diagnosing, and monitoring the symptoms of EoE to the health care providers. Additionally, encouraging proper referrals when evaluating patients with symptoms suggestive of the condition.

27.3 History

The first cases of eosinophilic esophagitis (EoE) appeared in the literature in the late 1970s; however, EoE as a disease entity was first described

in early 1990s (Attwood et al. 1993; Lucendo et al. 2017). Guidelines for the disease were originally written in 2007 (Furuta et al. 2007) and were updated in 2011, when for the first time a formal definition of the disease was described (Liacouras et al. 2011). The bulk of the literature in EoE has been significantly increased in the past two decades. Most recently, in 2017, European guidelines have been published based on the most recent advancement in knowledge and evidence-based publications. This guideline has used GRADE (Grading of Recommendations Assessment, Development, and Evaluation) as a tool for the development of practice guides (Lucendo et al. 2017).

27.4 Definition

EoE is a chronic immune-mediated inflammatory esophageal disease and a clinico-pathologic diagnosis. Clinically, EoE is characterized by symptoms secondary to esophageal dysfunction. Pathologically, one or more biopsy specimens must show eosinophil-predominant inflammation. Presence of at least 15 or greater eosinophils/high power field (hpf) as a peak value among specimens from various sites of esophagus is considered a requirement for diagnosis of EoE. The disease should be confined to the esophagus and other causes of esophageal eosinophilia should be excluded (Liacouras et al. 2011; Dellon et al. 2013a). EoE diagnosis should be made by clinicians, taking into consideration all clinical and pathologic information; neither of them should be interpreted in isolation (Lucendo et al. 2017).

27.5 Epidemiology

Various epidemiologic studies have estimated the incidence and prevalence of EoE either at individual center, or at a specific region, or at a national level. Based on those studies, both the prevalence and incidence of the disease have been increased in the past two decades (Straumann and Simon 2005; Dellon et al. 2014a). The figure most consistently reported for the prevalence of EoE has been 0.5 to 1 cases/1000 individuals. The prevalence in endoscopic units has been approximately 6–7%. When patients with dysphagia were the focus in these units, the prevalence close to 20% has been reported (Veerappan et al. 2009). The incidence of EoE has been estimated to be 10 cases/10,000 population per year (Dellon et al. 2014a; Dellon and Hirano 2017).

Investigations have been initiated to explain the reason for such a significant rise. Increased awareness of the condition could certainly be an explanation; however cannot completely explain the magnitude of rise. The proposed potential reasons include: changes in aeroallergens, foods and other environmental factors, decrease in rate of infection with Helicobacter pylori, and exposures during first years of life (Jensen et al. 2013; Dellon et al. 2014a; Dellon and Hirano 2017).

EoE has been reported to affect all age groups from infants to older individuals. Majority of patients, however have been children, adolescents, and young adults. Although majority of patients with EoE live in the American continent and Europe, cases have been reported from all over the world. The disease has a predilection for male gender and white race (Attwood et al. 1993; Noel et al. 2004; Moawad et al. 2012). Association with atopy has been consistently shown in children and adults with EoE (Noel et al. 2004; Spergel et al. 2009; Dellon et al. 2014a; Dellon and Hirano 2017). Association with atopy has been consistently shown in children and adults with EoE (Noel et al. 2004; Spergel et al. 2009; Dellon et al. 2014a; Dellon and Hirano 2017).

27.6 Natural History

EoE is a chronic and relapsing disease. Randomized controlled trials (RCT), prospective and retrospective research studies have shown that EoE does not resolve spontaneously. (Straumann et al. 2003; Dellon and Hirano 2017; Lucendo et al. 2017). The complication of chronic stricture may

happen overtime from prolonged esophageal inflammation and delay in diagnosis increases this risk (Schoepfer et al. 2013; Dellon et al. 2014a, b; Dellon and Hirano 2017).

Previous guidelines considered EoE and gastro-esophageal reflux disease (GERD) as mutually exclusive conditions. In the most recent European guidelines, however, EoE is described as a separate entity, which may coexist with GERD (Lucendo et al. 2017).

Studies thus far have not revealed any risk of metaplasiachanges consistent with barrett's esophagus or esophageal cancer. No association, but a potential overlap of hyper-eosniophilic syndrome (HES) with eosinophilic gastrointestinal disorders has been speculated (Dellon and Liacouras 2014). Leslie et al. in 2010 described a link between EoE and Celiac disease (Leslie et al. 2010). It had also been suggested that there is a link between EoE and Ehlers-Danlos, Marfan syndrome, and autoimmune disorders (Abonia et al. 2013). The latter link has not been validated by a recent review of the evidence-based publications (Lucendo et al. 2017).

27.7 Pathogenesis

27.7.1 Allergic Sensitization

Based on the high rate of association with atopy, high rate of symptomatic and histologic response to allergen avoidance, studies of genetic linkage and animal models, pathogenesis of EoE is closely linked with atopy (Liacouras et al. 2011). Food and aeroallergen hypersensitivity along with history of food and respiratory allergy has been shown in various studies (Greenhawt et al. 2013; Aceves 2014; Lin et al. 2015). The role of food antigen sensitization has been best shown by the high rate of response to dietary avoidance (Almansa et al. 2009; Dellon et al. 2013a).

In experimental EoE, epi-cutaneous sensitization to allergen has been shown to be the primary event leading to respiratory allergen sensitization (Akei et al. 2005). This may explain why large number of patients with EoE have history of atopic dermatitis. Studies have also demonstrated that patients with allergic rhinitis have increases in esophageal eosinophils seasonally; moreover, symptoms in patients with EoE show seasonal variations (Almansa et al. 2009).

27.7.2 The EoE Transcriptome

Studies have demonstrated over-expression of 1% of the human genome in the esophagus of subjects with active EoE, which is unique for the disease and is not seen in either GERD, chronic esophagitis without eosinophilia or individuals without esophageal disease (Blanchard et al. 2006; Wen et al. 2013; Rothenberg 2015). CCL26 (gene encoded for eotaxin) has been identified as the most highly induced gene regardless of age, gender or history of atopy (Blanchard et al. 2006; Bhattacharya et al. 2007; Rothenberg 2015). This EoE transcriptome has been shown to be induced by exposure of epithelial cells of esophagus to IL13. IL-13 also induces periostin, which is highly expressed in EoE. Periostin promotes eosinophil recruitment induced by eotaxin (Blanchard et al. 2007; Rothenberg 2015). Additionally, the EoE transcriptome contains non-coding ribonucleic acids (RNA) including micro-RNAs (miRs) and they regulate both transcription and translation. MiR-21 was shown to be strongly induced in human EoE samples (Lu et al. 2012).

27.7.3 Impaired Barrier Function

Esophageal biopsy specimens in patients with EoE show impaired barrier function when permeability and resistance were measured (Rothenberg 2015). This has been explained by loss of expression of the desmosomal cadherin, desmoglein 1 (DSG1). DSG1 deficiency induces transcriptional changes in esophageal epithelial cells which overlap with the EoE transcriptome (Sherrill et al. 2014); periostin is the most highly induced overlapping gene. Interestingly IL13 is able to down-regulate DSG1. Loss of DSG1 leads to impaired barrier function, propagation of local inflammatory responses and increased antigen uptake in the esophagus (Rothenberg 2015).

Role of T-helper 2 cell-mediated local immune response to food and/or environmental allergens, with involvement of interleukins (IL) such as IL-4, IL-5, and IL-13 have been long investigated in EoE. It has been shown that IL-5 promotes eosinophil differentiation and maturation, both IL-5 and IL-13 stimulate the esophageal epithelium to produce eotaxin 3, which potently recruits eosinophils into the esophagus (Blanchard et al. 2006; Bhattacharya et al. 2007; Aceves 2011). Activated eosinophils release factors such as transforming growth factor beta (TGF-β) that promote local inflammation and tissue remodeling. Sub-epithelial fibrosis and epithelial proliferation may explain dysfunction of smooth muscles in EoE (Aceves 2011). In addition to eosinophils and T- cells, mast cells, basophils, and natural killer cells are involved in this process (Abonia et al. 2010; Dellon and Liacouras 2014).

27.8 Clinical Features

27.8.1 Children

Infants and children up to toddler age group, present with food refusal, feeding difficulties, gagging, vomiting, or failure to thrive. Older children commonly present with nausea, vomiting, regurgitation, abdominal or chest pain (Attwood et al. 1993; Noel et al. 2004; Spergel et al. 2009; Liacouras et al. 2011). Other symptoms such as a water brash in mouth, globus sensation in the throat and decreased appetite have also been described in this age group. It is not until adolescence when patients present with dysphagia. Fever and weight loss are signs which should prompt investigation for other conditions (Dellon and Liacouras 2014). Higher rate of atopy including food allergy, asthma, eczema, or rhinitis are seen in children with EoE compared to those without EoE (Liacouras et al. 2011; Dellon and Liacouras 2014).

27.8.2 Adults

Dysphagia, particularly with solid foods, is the most common presentation of EoE in patients 18 years and older (Schoepfer et al. 2013; Dellon and Liacouras 2014). Table 1 describes the differential diagnosis of esophageal dysphagia. It has been reported that approximately 60–100% of adults present with dysphagia with or without odynophagia (Dellon et al. 2009). Based on the current data, EoE is the most common cause of food impaction in adults presenting to emergency departments (50%). Approximately 25% of adults with EoE have prior history of food impaction (Veerappan et al. 2009). Based on

Table 1 Differential diagnosis of esophageal dysphagia

Diagnosis	Comments
Peptic stricture	Structural. Long-standing history of GERD, results from healing process of erosive esophagitis
EoE/PPI responsive esophageal eosinophilia	Structural. Results from chronic inflammation
Esophageal rings/webs	Structural. Intermittent dysphagia with solids. Could be associated with iron deficiency anemia such as in Plummer-Winson syndrome.
Medication induced	Bisphosphonates, doxycyclines are common examples
Infectious esophagitis	Herpes, Candida, CMV, mycobacteria
Corrosive/Radiation induced	Structural. Esophageal burn particularly form alkaline chemicals/Following radiation therapy to the chest Motility disorder.
Esophageal carcinoma	Structural. Rapidly progressive dysphagia, older individuals, weight loss
Esophageal spasm	Motility disorder. Chest pain is common
Achalasia	Motility disorder. Degeneration of ganglion cells in the myenteric plexus causes failure of relaxation of lower esophageal sphincter. Primary or secondary to Chagas disease
Scleroderma	Motility disorder. Skin and other systemic features

these data, current guidelines recommend obtaining esophageal biopsies for all patients presenting with dysphagia, regardless of the endoscopic appearance (Dellon et al. 2009; Dellon and Liacouras 2014).

Taking a detailed history about eating habits is required to elucidate dysphagia, these could include: being the last person to finish a meal, trying to chew thoroughly and carefully to avoid symptoms, drinking plenty of water, avoiding foods that had been stuck in the past. Some individuals crush pills or avoid taking large pills out of concerns for medication getting stuck in throat and choking. Heartburn has been reported in 30–60% of adult patients with EoE. Although non-cardiogenic chest pain has been reported, nausea, vomiting, abdominal pain, diarrhea, weight loss are not commonly seen in adults with EoE (Dellon et al. 2009).

Food allergies, atopic dermatitis, allergic rhinosinusitis, and asthma are frequently seen in adults with EoE (Dellon et al. 2009; Dellon and Liacouras 2014).

27.9 Gross Endoscopic Findings

Structural changes in EoE, which could be appreciated during endoscopy, are shown in Fig. 1 (Dellon and Liacouras 2014). The most

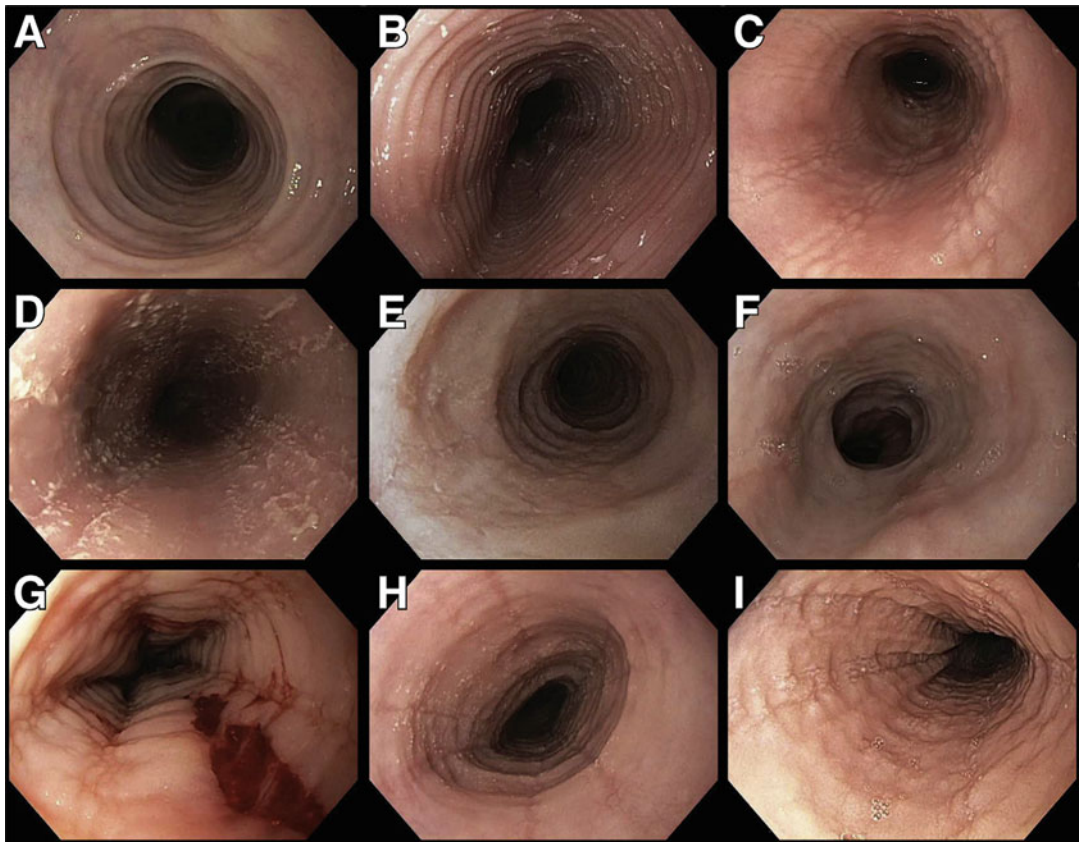

Fig. 1 Endoscopic findings in EoE. (**a**) Fixed esophageal rings (trachealization). (**b**) Transient esophageal rings (felinization). (**c**) Linear furrows (train track appearance); (**d**) White plaques/exudates (eosinophilic microabscesses). (**e**) Esophageal narrowing with mucosa edema and decreased vascularity. (**f**) Focal stricture in the distal esophagus. (**g**) Crêpe-paper mucosa, mucosal tear with passage of the endoscope in a narrowed esophagus. (**h**) Combination of findings: rings, furrows, plaques, narrowing, and decreased vascularity. (**i**) Combination of findings: rings, deep furrows, plaques, and mucosa edema

typical finding is esophageal rings. Narrowing of the esophageal lumen secondary to chronic inflammation and fibrotic changes can be seen during endoscopy which could be localized or diffuse. Other common features include: linear furrows, white plaques, or exudates. It is important to realize that up to 10% of endoscopies in patients with EoE appear normal (Dellon and Liacouras 2014).

Endoscopic findings in children tend to be more subtle and mainly consist of edema and exudates. Rings and strictures are more commonly seen in adults (Dellon et al. 2009). This could be attributed to chronic inflammation which leads to fibrosis (Dellon and Liacouras 2014).

Although endoscopic findings alone are neither sensitive nor specific to exclude or confirm a diagnosis, recently an endoscopic reference score (EREFS) has been validated to assess severity of disease. EREFS is based upon exudates, rings, edema, furrows, and strictures and hence the name (Protheroe et al. 2009).

27.10 Histological Findings

With hematoxyline and eosin staining, the histological features (Fig. 2) are the same in children and adults (Dellon and Liacouras 2014). Finding of eosinophilic infiltration of equal or greater than15 eosinophils/hpf is required for diagnosis of EoE (Liacouras et al. 2011). Other histologic findings include eosinophil micro-abscesses, basal layer hyperplasia, and lamina propria fibrosis. None of these are diagnostic by themselves (Collins 2008).

27.11 Diagnosis

In order to diagnose EoE, other causes of esophageal eosinophilia have to be excluded (Liacouras et al. 2011; Dellon and Liacouras 2014). Table 2 summarizes various causes of esophageal eosinophilia. Some of these diagnoses can be excluded based on history and routine studies. Gastric and duodenal biopsy samples should be studied to exclude eosinophilic gastroenteritis with esophageal involvement. When there is significant peripheral eosinophilia >1500/L, HES should be excluded.

The most challenging condition to exclude is GERD. Not only the symptoms of GERD and EoE overlap, but also eosinophilia can be seen in both. It has been suggested that either condition can lead to the other. GERD can cause EoE through impairing the barrier function of esophagus and EoE may lead to GERD due to esophageal malfunction. Monitoring of pH by esophageal probes is not able to differentiate the two conditions (Cheng et al. 2014).

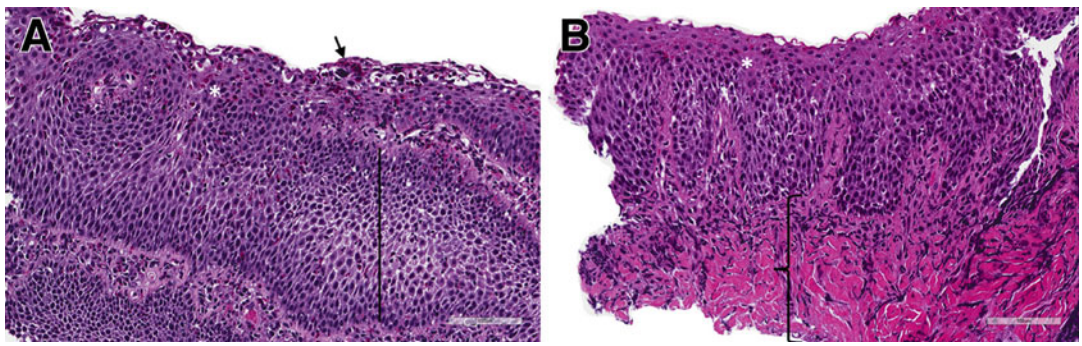

Fig. 2 Histological findings in EoE. (**a**) Marked eosinophilic infiltrate, with eosinophil degranulation (white asterisk); eosinophil microabscesses and superficial layering with sloughing of the apical epithelial cells (arrow); basal cell hyperplasia with spongiosis (black bar). (**b**) Eosinophilic infiltrate and degranulation (white asterisk), lamina propria fibrosis (black bracket)

Table 2 Differential diagnosis of esophageal eosinophilia

Disease	Comments
Gastroesophageal reflux disease	Primarily in distal esophagus
Eosinophilic esophagitis	Confined to the esophagus
PPI-responsive esophageal eosinophilia	Responds to PPI, a continuum of EoE
Celiac disease	Symptoms of malabsorption
Eosinophilic gastroenteritis	May have esophageal involvement
Inflammatory bowel diseases	Particularly Crohn's disease
Hypereosinophilic syndrome	Overlap with eosinophilic gastrointestinal disorders have been speculated
Achalasia	Decreased number of ganglion cells in the myenteric plexus, lymphocytes and eosinophils surrounding the remaining neurons
Scleroderma, pemphigoid vegetans	As part of the systemic inflammatory process
Infections	Viral, fungal, parasitic, mycobacterial in immunocompromised hosts
Graft-versus-host disease	Acute GVHD with upper GI involvement

Proton pump inhibitor responsive esophageal eosinophilia (PPI-REE) is an entity which was described in the second consensus recommendations (Liacouras et al. 2011). Patients have symptoms suggestive of EoE along with histological finding of >15 eosinophils/hpf. Following PPI treatment, both the clinical and histological findings resolve (Liacouras et al. 2011; Dellon et al. 2013a). It has been proposed that PPI has anti-inflammatory properties by reducing eotaxin 3 (CCL26) in response to T-helper 2 cytokine stimulation and appear to restore the barrier function of the esophageal mucosa (Dellon et al. 2013b). Not only clinical and histological features of EoE and PPI-REE are similar and pH monitoring does not differentiate them but also they show similar cytokine profiles and biomarkers. The most recent guideline considers PPI-REE not a separate entity but a continuum of EoE (Lucendo et al. 2017).

Another challenge in diagnosis of EoE is proper esophageal sampling for biopsy specimens. Collecting 2–4 specimens from distal and proximal or mid esophagus is currently recommended. Additionally, the peak number of eosinophils and the size of the high-power field of microscope should be reported (Liacouras et al. 2011).

A major challenge in diagnosis and monitoring response to treatment is the need for initial and further endoscopies. Other procedures have been investigated including esophageal string-test (Furuta et al. 2013). Biomarkers from the specimens which can be obtained less invasively have been vastly investigated. A promising new progress in diagnosis involves gene expression analysis in esophageal tissue of EoE patient with description of unique EoE transcriptome (Rothenberg 2015).

27.12 Management

Medical treatments constitute of dietary modifications and medications targeting the underlying inflammatory process (Reddy and Ghaffari 2013). When remodeling and fibrosis dominate the clinical picture, a surgical approach and esophageal dilatation may become necessary (Furuta et al. 2013).

Clinical presentations, severity of symptoms, impact on quality of life, presence of complications, cost and convenience of the treatment, availability of resources, patient/care giver as well as physician preference may all affect the choice of treatment (Dellon and Liacouras 2014; Molina-Infante et al. 2017).

27.12.1 Corticosteroids

Corticosteroids have been shown to improve clinical as well as histological features of EoE. They can also reduce tissue remodeling and esophageal fibrosis. Systemic steroids were one of the first medications used to treat patients with EoE. Relapse of the symptoms and esophageal eosinophilia were observed shortly after they were tapered. Due to significant and long-term adverse effects, this modality is only reserved for patients with very severe symptoms and when a rapid response is needed (Dellon and Liacouras 2014).

Topical corticosteroids have been introduced as a modality of treatment for number of years. Fluticasone, dispensed from a metered dose inhaler, and budesonide, administered as a viscous slurry or as a swallowed nebulized vapor, have been studied the most and have been shown to be effective. Patients should be instructed to take topical steroids after meals and not to eat or drink for 30–60 min after swallowing the drug (Dellon and Liacouras 2014; Lucendo et al. 2014; Molina-Infante et al. 2017).

27.12.2 Dietary Therapy

Removal of dietary allergens has been considered a mainstay of treatment for EoE in numerous studies. In contrast to steroids, food elimination may cause a prolonged remission and it can improve fibrosis (Molina-Infante et al. 2017; Konikoff et al. 2006).

Dietary modifications include elemental diets with an amino acid-based formulation, directed elimination diets based on allergy test results, and elimination diets based upon exclusion of common food antigens (Konikoff et al. 2006; Molina-Infante et al. 2017).

Elemental diets are highly effective, but high cost and lack of palatability are their main disadvantages. After 4–6 weeks, re-introduction of foods starting with the least allergenic foods could be considered. Ideally a follow up endoscopy should be performed to evaluate the response after introduction of each food group (Molina-Infante et al. 2017).

Test-directed and empiric elimination diets have been largely investigated. In both forms, once clinical and histological remission is achieved, single food groups can be reintroduced and re-evaluated by biopsy 4–6 weeks after each new food is introduced (Ruffner and Spergel 2017).

The efficacy of empiric diets requiring elimination of fewer food groups has been also investigated (Molina-Infante et al. 2017). Overall, the recommendations for dietary modifications should take in to account the age of patient, history of anaphylaxis to foods, patient's needs and preferences.

27.12.3 Biological Agents

Given the eosinophilic nature of inflammation in EoE, using monoclonal antibodies directed against IL-5 (major eosinophilo-poietic cytokine) is intuitive. Anti-IL-5 antibodies have been studied in small and large randomized trials. The results of those studies have been mixed. Symptomatic control was not consistently achieved despite histological response (Assa'ad et al. 2011; Stein et al. 2006).

Omalizumab, a monoclonal antibody against immunoglobulin E has shown a clinical response similar to placebo. Monoclonal antibodies against IL-13 has been studied but not available for clinical use. Monoclonal antibodies against IL-4, and eotaxin 3, are currently under investigation (Spergel et al. 2012; Dellon and Liacouras 2014).

27.12.4 Esophageal Dilatation

Endoscopic dilatation of esophagus as a surgical approach for EoE treatment has been investigated and could particularly be useful in patients presenting with food impaction and fibrotic changes (Furuta et al. 2007). Initial reports showed up to 8% risk of perforation, but more recent data from centers with high level of expertise has shown much lower risk of 0.3%. Although a potential safe option of symptoms control, endoscopic dilatation does not impact the chronic eosinophilic inflammation (Furuta et al. 2013).

Table 3 Treatment modalities, which have been used in EoE

Treatment	Status
Topical steroids	Effective, alone or combined with dietary modification, long-term side effects possible, stopping treatment will cause relapse
Amino-acid based formulas	Effective, potentially disease modifying, difficulty in adherence and cost are major limiting factors
Test-based elimination diets	Effective, potentially disease modifying, requires allergy testing and several endoscopies to monitor inflammatory response
Empiric elimination diets	Elimination of eight, six, four, or even two most common foods, potentially disease modifying.
Monoclonal antibodies against IL-5, IL-13	Have been investigated, not ready for clinical use
Monoclonal antibodies against IL-4, Eotaxins	Under investigation
Cromolyn, anti-leukotrienes	Not effective and not recommended
Immunosuppressive medications	Not recommended
Allergen immunotherapy	Very limited data on effectiveness
Omalizumab	Not effective in RCT
Systemic steroids	Rarely indicated, only in the acute onset of severe symptoms
Enteral feeding	In severe pediatric patients with feeding difficulties, in conjunction with elemental diet
Esophageal dilatation	Particularly when presenting with food impaction and signs of fibrosis

27.12.5 Other Treatments

Cromolyn and anti-leukotrienes have not been effective in several studies and are not recommended (Dellon and Liacouras 2014). Histologic remission of EoE after allergen immunotherapy was documented in two patients, but since the data is very limited, currently allergen immunotherapy as a therapy for EoE is not recommended (Lucendo et al. 2014).

Table 3 lists the various medical and surgical treatments, which have been used to treat symptoms and/or to control the esophageal inflammation in the EoE.

27.13 Conclusion

Eosinophilic esophagitis is a chronic inflammatory disease of the esophagus affecting children and adults. The incidence and prevalence of this clinico-pathological diagnosis are on the rise. The disease is highly associated with atopic conditions; food and aeroallergen hypersensitivities are common findings in patients with EoE.

T-helper lymphocyte-mediated inflammation is the basis of pathogenesis. A unique EoE transcriptome has been identified which differentiates this condition from gastroesophageal reflux disease.

The presenting symptoms vary by age, and dysphagia is the most common in adults. Esophageal stricture resulting in food impaction is the most concerning complication. Although EoE has a waxing and waning nature, it does not resolve without treatment.

Treatment modalities include one or any combination of dietary modifications, topical steroids, and treatment of comorbid conditions. Endoscopic dilatation of esophagus could be considered in patients presenting with fibrotic changes. Biological agents have been investigated but at this time not available for clinical use.

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Part VII

Insect Allergy and Anaphylaxis

Anaphylaxis and Systemic Allergic Reactions

28

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Contents

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Abstract

Anaphylaxis is a severe and potentially life-threatening reaction associated with massive release in the circulation of potent, vasoactive products from mast cells and basophils. Those vasoactive chemicals can profoundly impact the integrity of multiple life-sustaining organs and systems such as the cardiovascular and pulmonary systems. Anaphylaxis is most commonly due to exposure to allergens such as medications, usually antibiotics, foods, hymenoptera stings, and triatoma bites and mast cell activators such as radiocontrast media and certain medications. In some cases, anaphylaxis is labeled idiopathic when no etiology can be found.

During anaphylaxis, patients may experience hives, itching, and hypotension that may lead to dizziness, unconsciousness, and seizures as well as swelling of the upper and lower airways causing respiratory distress. One of the clinical manifestations of anaphylaxis is wheezing due to acute bronchospasm. Wheezing tends to occur particularly in patients with a history of asthma. Many of the symptoms of anaphylaxis are due to the effects

of histamine, platelet-activating factor (PAF), and proteases on the cardiovascular, respiratory, and cutaneous systems.

The diagnosis of anaphylaxis can be challenging due to its syndromic nature and the variability of its manifestations as well as its transient duration. Perioperative anaphylaxis is a case in point as the signs and symptoms may not be obvious in the anesthetized and draped patient. During childhood, anaphylaxis can be confused with irritability, foreign body aspiration, and sepsis. Anaphylaxis can be uniphasic, biphasic, or protracted. Therefore, patients should be monitored closely and treated for recurrent symptoms. Several factors can put patients at higher risk of anaphylaxis including mast cell disease, exercise, and medications such as beta-blockers.

Anaphylaxis can be fatal, especially when treatment with epinephrine is delayed or is ineffective because of concomitant use of drugs such as beta-blockers and/or ACE inhibitors. Patients with uncontrolled asthma may also be at higher risk of fatal anaphylaxis. Anaphylaxis should be addressed promptly and aggressively and almost always can be managed successfully.

Keywords

Anaphylaxis · Epinephrine · Histamine · Tryptase · Hymenoptera venom allergy · Anaphylactic shock · Hypotension · Biphasic anaphylaxis · Mastocytosis · Antihistamine · Glucagon

28.1 Introduction

Anaphylaxis is defined by the World Allergy Organization as a "severe, life-threatening, generalized or systemic hypersensitivity reaction." This is due to sudden and massive release of mast cell mediators into the systemic circulation (Pumphrey 2000). When that reaction is mediated through an immunologic mechanism involving IgE, IgG, or immune complex complement, it should be called allergic anaphylaxis. Otherwise, it is called non-allergic anaphylaxis. The old terminology "anaphylactoid" creates confusion and its use is discouraged (Simons and Sampson 2015).

The history, incidence and prevalence, signs and symptoms, causes and pathophysiology, differential diagnosis, laboratory evaluation, and treatment of anaphylaxis will be reviewed in this chapter. We will also briefly discuss anaphylaxis in special circumstances such as in pregnancy and breastfeeding, infancy, advanced age, exercise, and the perioperative period. Finally, we will comment on seminal fluid, catamenial, idiopathic, and fatal anaphylaxis.

28.2 History

Anaphylaxis was first called "aphylaxis" by Charles Richet in 1902. Richet and Poitier were trying to desensitize dogs to the sea anemone (*Physalia physalis*) venom. The dogs tolerated the initial dose of the venom. However, 3 weeks later, when they were injected again with the venom, they developed fatal anaphylaxis. Since the dogs were not protected, but died from the reaction, Richet coined the term a- (without) phylaxis (protection) to describe the phenomenon of extreme and lethal reaction instead of the expected desensitization or tolerance. Eventually, the word aphylaxis became anaphylaxis because it sounded "better." Richet was awarded the Nobel Prize for physiology and medicine in 1913 for the discovery of anaphylaxis (Boden and Wesley Burks 2011).

In 1925, Arthur Coca observed that the anaphylactic phenomenon could occur not only in laboratory animals but also in humans. Then, in 1945, Robert Cooke defined anaphylaxis as "a special or particular immunologic type of induced protein (or hapten) sensitivity in man or experimental animals and may be considered as a subdivision of Allergy." With the discovery of IgE by the Ishisakas and Johansson in the mid-1960s, it was widely believed that anaphylactic reactions were mediated primarily by IgE. However, we now know that anaphylaxis can be mediated by a number of other mechanisms. In many instances, we

still do not know what causes anaphylaxis, thus the term "idiopathic anaphylaxis" (Webb and Lieberman 2006).

28.3 Incidence and Prevalence

The incidence of anaphylaxis is underestimated and underreported. Anaphylaxis appears to be increasingly recognized, especially in industrialized countries. The lifetime prevalence is estimated to be between 0.05% and 2% based on data obtained from dispensed prescriptions for outpatient injectable epinephrine (Lieberman 2008). Anaphylaxis is mainly caused by medications, namely, antibiotics and nonsteroidal anti-inflammatory drugs (NSAIDs), and foods, such as peanuts, tree nuts, and fish. The incidence of anaphylaxis due to foods and drugs is increasing worldwide (Koplin et al. 2011). Perioperative anaphylaxis incidence is also increasing (Mertes et al. 2016).

28.4 Triggers of Anaphylaxis

Several triggers for anaphylaxis have been identified. By and large, the most common triggers in children are foods, namely, milk, egg, soy, and peanuts. Idiopathic anaphylaxis is the most common form of anaphylaxis diagnosed in adults (Webb and Lieberman 2006). In adults, the food items that are most commonly associated with anaphylaxis are tree nuts, fish, and shellfish. In hospitalized patients, the most common cause is the administration of drugs, and the most common drugs are penicillin, cephalosporins, and other beta-lactam antibiotics. Neuromuscular blocking agents along with antibiotics are the most likely cause of perioperative or intraoperative anaphylaxis.

Not all forms of anaphylaxis are increasing in prevalence and incidence. Latex and insulin are disappearing causes. The decreased incidence of latex anaphylaxis is the result of effective environmental control measures implemented in the 1990s when latex allergy reached an epidemic level. Also, recombinant technology has facilitated the use of less allergenic, humanized insulin significantly reducing the rate of allergic insulin reactions. By contrast, there are emerging causes of anaphylaxis with the increased use of monoclonal antibodies, super vital dyes, and chlorhexidine. Alpha-gal sensitivity is another emerging cause of anaphylaxis. Lone star tick bite exposes the immune system to the carbohydrate galactose-alpha-1,3 galactose. Those sensitized patients can have immediate anaphylaxis when exposed to cetuximab or delayed reaction when exposed to mammalian meat. Table 1 lists the most frequent triggers of anaphylaxis.

Table 1 Common triggers of anaphylaxis

1. Antibiotics (β-lactams account for 22% of all drug-related episodes)
2. Latex (most common in health-care workers and patients with multiple procedures/surgeries)
3. Perioperative anaphylaxis (muscle relaxants 62%, latex 16%, antibiotics and others, fatalities up to 7%)
4. Radiocontrast media (hyperosmolar agents up to 12% and low osmolar up to 3% have the same mortality rate)
5. Hymenoptera stings (incidence 0.8% of children and up to 3% of adults)
6. Food (incidence up to 6% children and 4% adults, peanuts most common in children and shellfish in adults. 1000 food anaphylactic events every year in the USA)
7. Nonsteroidal anti-inflammatory drugs (second most common after antibiotics)
8. Antisera (incidence with antilymphocyte globulin up to 2%, snake antivenom up to 10%, no anaphylaxis with new polyvalent immune fab derived from sheep serum)
9. Hemodialysis materials (ethylene oxide sterilized and complement-activating cellulose membranes, polyacrylonitrile AN69, high-flux membranes, and angiotensin-converting enzyme inhibitors)
10. Idiopathic anaphylaxis (up to 2/3 of anaphylaxis in adults remain idiopathic)
11. Biologic agents (increasing incidence)

Adapted from Middleton's Allergy Principles and Practice, 8th Ed. 2014 by Saunders, p. 1239

28.5 Factors in the Medical History That May Aid in the Diagnosis of Anaphylaxis

As it is with any medical condition, the history is very important in diagnosing and identifying the etiology of anaphylaxis. Several historical factors need to be emphasized such as the history of ingestion within 6 h of the reactions, timing of the event, and mitigating circumstances such as heat,

Table 2 Essential features of history in the evaluation of a patient who has experienced an episode of anaphylaxis

A	Detailed history of ingestants (foods/drugs) taken within 6 h before the event
B	Activity in which the patient was engaged at the time of the event
C	Location of the event (home, school, work, indoors/outdoors)
D	Exposure to heat or cold
E	Likely insect sting or bite
F	Time of day or night
G	Duration of event
H	Recurrence of symptoms after initial resolution
I	Exact nature of symptoms (e.g., if cutaneous, determine whether flush, pruritus, urticaria, or angioedema)
J	Relationship between the event and menstrual cycle in women and girls
K	Medical care given and treatments administered
L	Duration of symptoms before recovery and recurrence of symptoms after a symptom-free period

Adapted from Lieberman et al. (2015)

cold, and exercise. Also, the location, whether at school, work, or home, as well as the duration of the symptoms may help in the evaluation. In women and pubertal young girls, the threshold for anaphylaxis may be lower during the progesterone part of the menstrual cycle.

Table 2 is a list of the elements that need to be emphasized in the medical history.

28.6 Criteria for the Diagnosis of Anaphylaxis

Diagnostic criteria for systemic anaphylaxis are published and are validated as sensitive and specific in helping with the diagnosis. The diagnosis of anaphylaxis is highly probable when any of the criteria in Table 3 are met (Sampson et al. 2006).

28.7 Pathophysiology

The pathophysiological mechanisms of anaphylaxis include IgE-dependent and IgE-independent as well as non-immunologic pathways. Those biochemical pathways have been studied extensively in mouse models (Finkelman 2007). Several antigens are more likely to trigger the IgE-dependent pathway, such as foods, drugs, insect stings and bites, as well as intense exercise following the ingestion of food items such as wheat, shellfish, tomatoes, peanuts, and corn. Factors that may cause anaphylaxis through IgE-independent pathways include immune aggregates and anti-IgA-IgG complexes (Williams and Gupta 2017), disturbance of the arachidonic metabolism following ingestion of aspirin and other nonsteroidal drugs (Dona et al. 2016), activation of the kallikrein-kinin contact system by contact with dialysis membranes (Bender et al. 2017), and intravenous radiocontrast media (Hsu Blatman and Hepner 2017). Activation of complement, clotting, and clot lysis may be involved in anaphylaxis as well (Sala-Cunill et al. 2015). The nonimmunological pathway involves factors that directly provoke mediator release from mast cells and basophils, including certain drugs such as opiates and vancomycin, intravenous radiocontrast media, and physical factors such as exercise. Finally, there is a group of patients whose anaphylactic mechanism remains idiopathic despite investigation (Fenny and Grammer 2015). However, some patients labeled with "idiopathic anaphylaxis" may have an aberrant mast cell population with mutated c-kit and clonal markers or hyperactive mast cells which more readily release mediators of anaphylaxis (Akin et al. 2007) (Table 4)

A review describing the current understanding of the immunopathogenesis and pathophysiology of anaphylaxis, focusing on the roles of IgE and IgG antibodies, immune effector cells, and mediators thought to contribute to the disorder, has been published (Reber et al. 2017).

28.8 Mediators of Anaphylaxis

There is a long list of mediators involved in the pathophysiology of anaphylaxis. The most studied are histamine and the products of arachidonic acid metabolism such as leukotrienes, thromboxane, prostaglandins, and platelet-activating factor. Those factors are responsible for the smooth muscle spasm, mucus production and secretion, vasodilation, increased vascular permeability,

Table 3 Diagnostic criteria for anaphylaxis

Anaphylaxis is highly likely when any ONE of the following three criteria is fulfilled
1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips-tongue-uvula)
AND AT LEAST ONE OF THE FOLLOWING
A. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, hypoxemia)
B. Reduced BP[a] or associated symptoms of end-organ dysfunction (e.g., hypotonia, collapse, syncope, incontinence)
2. TWO OR MORE OF THE FOLLOWING that occur rapidly *after exposure to a LIKELY allergen for that patient* (minutes to several hours)
A. Involvement of the skin or mucosal tissue (e.g., generalized hives, itch-flush, swollen lips-tongue-uvula)
B. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, hypoxemia)
C. Reduced BP[a] or associated symptoms (e.g., hypotonia, collapse, syncope, incontinence)
D. Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)
3. Reduced BP[a] *after exposure to a KNOWN allergen for that patient* (minutes to several hours)
A. Infants and children – Low systolic BP (age-specific)[a] or greater than 30% decrease in systolic BP
B. Adults – Systolic BP of less than 90 mmHg or greater than 30% decrease from that person's baseline

Adapted from Sampson HA et al. J Allergy Clin Immunol 2008; 117, 391–7
BP blood pressure
[a]Low systolic blood pressure for children is defined as:
Less than 70 mmHg from 1 month to 1 year
Less than (70 mmHg + [2 × age]) from 1 to 10 years
Less than 90 mmHg from 11 to 17 years

activation of nociceptive neurons, platelet adherence, eosinophil activation, and eosinophil chemotaxis. Those changes are responsible for the clinical expression of the signs of anaphylaxis including, but not limited to, rhinorrhea, wheezing, urticaria, angioedema, flushing, itching, diarrhea, abdominal pain, hypotension, and cardiovascular collapse.

Neutral proteases, tryptase, carboxypeptidase, and cathepsin G are released and may cleave complement components causing chemoattraction of inflammatory cells and further activation and degranulation of mast cells. Also, the cleavage of neuropeptides leads to conversion of angiotensin I to angiotensin II. Although this may increase the blood pressure, it may also cause coronary artery vasoconstriction. The release of chemoattractants which summon cells to the site of inflammation may be responsible for the recrudescence of symptoms in the late phase of a biphasic or protracted anaphylactic reaction. Finally, TNF-alpha, by activating NF-kappa B, produces PAF which may be responsible for the vascular permeability and vasodilation that occur during the late-phase reaction.

28.8.1 Histamine

Most of the signs and symptoms of anaphylaxis can be reproduced experimentally by infusions of histamine and the activation of its primary receptors. The overall vascular effect is vasodilation and increased vascular permeability of the postcapillary venule. Histamine causes significant decrease of peripheral vascular resistance which contributes to the severe hypotension and fluid shift associated with anaphylaxis. Histamine through its activation of H1 and H2 receptors can increase the oxygen demand of the myocardium and cause coronary artery spasm. This may be the reason for acute cardiac events associated with anaphylaxis. The intense pruritus that can occur in anaphylaxis is thought to be due to the stimulation of H1 and H4 receptors expressed on type C unmyelinated fibers (Shim and Oh 2008).

28.8.2 Nitric Oxide (NO)

NO is a potent vasodilator and contributes to the peripheral vasodilation as well as the increase in

Table 4 Pathophysiology of anaphylaxis

I. IgE dependent, immunologic
Foods
Drugs
Insect stings and bites
Exercise (food dependent)
II. IgE independent, immunologic
IgG anti-IgA
Disturbance of arachidonic acid metabolism
Aspirin
Other NSAIDs
Activation of kallikrein-kinin contact system
Dialysis membranes
Radiocontrast media
Multimediator recruitment
Complement
Clotting
Clot lysis
Kallikrein-kinin contact
Platelet
III. Non-immunologic
Direct mediator release from mast cells and basophils
Drugs, e.g., opiates, vancomycin
Physical factors, e.g., cold and sunlight
Exercise
c-kit mutation (D816V)
IV. Idiopathic

Adapted from Middleton's Allergy Principles and Practice, 8th Ed. 2014 by Saunders, p. 1241

vascular permeability. NO is produced in anaphylaxis due to the engagement of the H1 receptors during phospholipase C-dependent calcium mobilization and the associated increase in activity of nitric oxide synthetase (NOS) (Lowenstein and Michel 2006).

28.8.3 Kallikrein-Kinin Contact System, Coagulation and Complement Cascade, Platelet Activation

The release of mast cell and basophil contents activates various inflammatory pathways during anaphylaxis in experimental models of anaphylaxis, including the kallikrein-kinin system, which correlates with angioedema after sting challenge in allergic subjects. Mast cell degranulation also increases IL-6. The elevation of IL-6 correlates with urticaria and hypotension (Lin et al. 2001). Also, peak histamine levels are associated with decreased factor V, factor VIII, fibrinogen, and high-molecular-weight kininogen. Platelet-activating factor and C3a levels correlate with the severity of anaphylaxis (Vadas et al. 2008).

Although all those factors may play a role in anaphylaxis and its severity, it is important to keep in mind that when frozen serum of patients who experienced anaphylaxis were evaluated, no direct correlation could be demonstrated between levels of NO, histamine, IL-6, and CRP (Lin et al. 2001).

28.9 Signs and Symptoms of Anaphylaxis

Anaphylaxis presentation may include atypical symptoms depending on the age, mode, and type of antigen exposure, circumstances, the presence of triggering or augmenting factors, and comorbidities. When anaphylaxis is caused by an injected antigen, symptoms usually occur within 5–30 min. However, if the antigen is ingested, symptoms usually occur within 2 h (Lieberman et al. 2015). Prototypical cutaneous symptoms include urticaria and angioedema, flushing or pruritus without rash. Patients may have dyspnea, wheeze, upper airway angioedema, and rhinitis. Dizziness, syncope, and hypotension may occur as well as nausea, vomiting, diarrhea, and cramping abdominal pain. Typically, tachycardia occurs and is used as a sign to differentiate anaphylaxis from vasovagal syncope. However, in some cases, bradycardia occurs due to the Bezold-Jarisch reflex secondary to the ischemia-mediated stimulation and activation of unmyelinated vagal C fibers located in the infero-posterior wall of the left ventricle. Coronary vasospasm associated with activation of mast cells and platelets may lead to myocardial infarction (Kounis et al. 2013). Occasionally, patients report an impending doom feeling and headache or develop seizures. Though skin manifestations are common signs of anaphylaxis, patients do not always demonstrate skin lesions but rather present with

cardiovascular collapse or less severe non-cutaneous signs and symptoms. Skin manifestations are more common in children. However, non-specific symptoms such as crying, fussing, fright, and irritability may also occur. Infants may exhibit dysphonia and hoarseness followed by somnolence and drowsiness and/or seizures. On physical exam, typical findings include a weak pulse, pallor and diaphoresis due to vasodilation and hypotension. Those signs may be confused with sepsis or meningitis. In toddlers, anaphylaxis is often confused with foreign body aspiration as the manifestations include cough and stridor, followed by unresponsiveness and lethargy (Simons and Sampson 2015). Vomiting is also common after the ingestion of an oral allergen in children (Fig. 1).

Anaphylaxis caused by IgE-mediated mechanism during anesthesia is more commonly associated with cardiovascular collapse and tends to be more severe than non-IgE-mediated anaphylaxis. Often the antigen is directly injected into the circulation, and signs and symptoms of anaphylaxis are immediate. Sudden, unexplained, decreased blood oxygen, profound hypotension, and difficulty in ventilation due to increased airway resistance suggest anaphylaxis (Savic et al. 2015). The surgical patient is usually draped and skin manifestations of anaphylaxis may be overlooked until more ominous signs of anaphylaxis occur. A high index of suspicion is required from the anesthesiologist to diagnose and intervene in a timely manner during intraoperative anaphylaxis (Jarvinen and Celestin 2014).

Symptoms and signs of food-induced anaphylaxis usually occur within 2 h, more commonly within 30 min, depending on the rate of absorption of the antigen (Sicherer and Sampson 2018). The clinical history is the single most important factor in the diagnosis of food allergy. Signs and symptoms should be viewed within an historical context. Also, food-induced allergic reactions have certain features that may aid in the diagnosis. For instance, patients sensitive to alpha-gal (galactose-alpha-1,3-galactose) usually have a delayed reaction to mammalian meats (beef, mutton, and pork). This sensitivity may be associated with tick bites and more common in specific geographic areas. Galactos-alpha-1,3-galactose allergy is also responsible for anaphylaxis with cetuximab therapy (Steinke et al. 2015). Also, the presence of augmentation factors associated

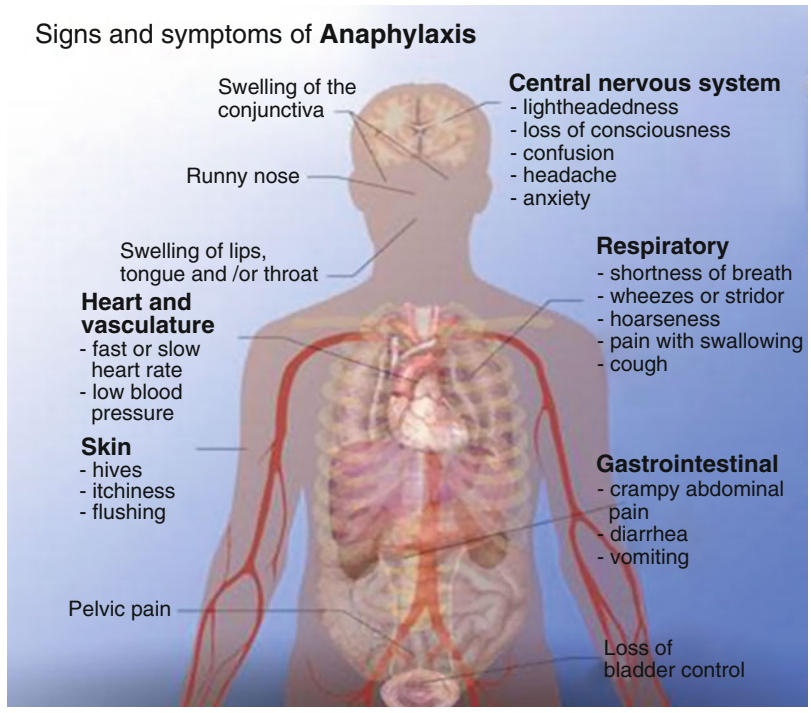

Fig. 1 Signs and symptoms of anaphylaxis

with the ingestion of a particular food can be useful in the diagnosis. Augmentation factors include ingestion of nonsteroidal drugs or alcohol, exercise, menstruation, and concomitant infectious illnesses (Feldweg 2017). In children, several conditions can be confused with food-induced anaphylaxis. One of those is food protein-induced enteropathy syndrome (FPIES) which is characterized by profuse vomiting without urticaria, followed by signs of cardiovascular collapse due to dehydration. The latter may mimic sepsis or anaphylaxis. This is a non-IgE-mediated reaction to food protein, usually cow's milk, but it may occur with other food proteins such as rice, soy, and oat (Caubet et al. 2014).

In adults, foods most commonly associated with anaphylaxis include peanuts, tree nuts, milk, egg, sesame seed, fish, and shellfish. Manifestations of food-induced anaphylaxis usually occur within 2 h after ingestion of the offending food. Cutaneous manifestations include diffuse erythema, urticaria, pruritus, and angioedema. Gastrointestinal symptoms include abdominal pain, hyperperistalsis, fecal urgency or incontinence, nausea, vomiting, or diarrhea. Upper and lower airway obstruction can involve the tongue, oropharynx, or larynx and bronchospasm associated with chest tightness, cough, wheezing, rhinitis, sneezing, nasal congestion, and rhinorrhea. Women and girls at times experience uterine cramps, urinary urgency, or incontinence. Ocular signs and symptoms include periorbital edema, conjunctival erythema, and tearing. All or any combination of these can occur (Cianferoni and Muraro 2012). Food sensitivity in some patients can be so severe that systemic reactions occur after inhalation of particles, from cooking fish or shrimp or the opening of a package of peanuts (Leonardi et al. 2014).

Stinging insect allergy is responsible for about 10% of all cases of anaphylaxis (Tankersley and Ledford 2015). Anaphylaxis triggered by venom stings can present as syncope or seizure (Worm et al. 2018). Patients with mast cell activation disorders or mastocytosis are at increased risk of anaphylaxis following insect stings (Niedoszytko et al. 2014). About one in four cases of insect sting anaphylaxis have elevated baseline serum tryptase level (Bonadonna et al. 2009). Anaphylaxis due to hymenoptera stings, such as bees, wasps, hornets, yellow jackets, or fire ants, in subjects with mast cell disorders or older adults more often results in tachyarrhythmias, coronary vasospasm with myocardial ischemia, syncope, and seizures in the absence of urticaria or angioedema (Stoevesandt et al. 2012). The absence of urticaria and angioedema during anaphylaxis is often an ominous sign associated with more severe reactions. Patients who experience profound and persistent hypotension should be evaluated for adrenal hemorrhage and/or disseminated intravascular coagulation (DIC).

Rupture of hydatid cyst may present as acute anaphylaxis in patients infected with *Echinococcus granulosus*. Patients who have lived in endemic areas may have a lifelong risk of anaphylaxis if untreated (Murali et al. 2015).

Table 5 below lists the prototypical signs and symptoms of anaphylaxis in each organ system.

Table 5 Symptoms and signs of anaphylaxis

Skin
Feeling of warmth, flushing (erythema), itching, urticaria, angioedema, and "hair standing on end" (pilor erection)
Oral
Itching or tingling of lips, tongue, or palate Edema of lips, tongue, uvula, metallic taste
Respiratory
Nose – itching, congestion, rhinorrhea, and sneezing Laryngeal – itching and "tightness" in the throat, dysphonia, hoarseness, stridor Lower airways – shortness of breath (dyspnea), chest tightness, cough, wheezing, and cyanosis
Gastrointestinal
Nausea, abdominal pain, vomiting, diarrhea, and dysphagia (difficulty swallowing)
Cardiovascular
Feeling of faintness or dizziness; syncope, altered mental status, chest pain, palpitations, tachycardia, bradycardia or other dysrhythmias, hypotension, tunnel vision, difficulty hearing, urinary or fecal incontinence, and cardiac arrest
Neurologic
Anxiety, apprehension, sense of impending doom, seizures, headache, and confusion; young children may have sudden behavioral changes (cling, cry, become irritable, cease to play)
Ocular
Periorbital itching, erythema and edema, tearing, and conjunctival erythema
Other
Uterine cramps in women and girls

Adapted from Simons FER. Anaphylaxis. J Allergy Clin Immunol 2010; 125: S161

28.10 Temporal Patterns of Anaphylaxis

Three temporal patterns of anaphylaxis occur:

28.10.1 Uniphasic

About 80% of anaphylactic reactions are uniphasic where symptoms peak in 30 min to an hour and then resolve spontaneously or with treatment within 1 h.

28.10.2 Biphasic

Biphasic anaphylaxis episodes may occur in up to 20% of cases. Patients usually present with acute signs and symptoms of anaphylaxis followed by the resolution of the symptoms for one to several hours. Then, there is a return of the symptoms and signs which can differ or be more severe than the original reaction. This delayed reaction occurs without re-exposure to the suspected allergen that caused the initial reaction (Lieberman 2005). This represents a second wave of mast cell degranulation. It is not clear what might cause the biphasic nature of the anaphylaxis. One theory is the delayed or recurrent symptoms are due to the activation of inflammatory cells including eosinophils, basophils, and lymphocytes, as well as cytokines triggered by the initial response. There was a correlation between the incidence of biphasic anaphylaxis and the serum tryptase level, histamine, IL-6, IL-10, and TNF-α, when those markers were measured during treatment or at the time of discharge of patients treated for anaphylaxis in the emergency department (Brown et al. 2013). Biphasic anaphylaxis may be due to uneven release of the allergen or could be a form of protracted anaphylaxis with waning of the initial treatment response. It is not possible to determine who will experience a biphasic reaction, although certain factors may suggest its occurrence. These include ingested antigens, severe initial symptoms, and delayed or suboptimal initial treatment. Although routinely used to prevent recurrent symptoms of anaphylaxis, there is no strong evidence that glucocorticoids reduce the occurrence of biphasic anaphylaxis (Lieberman 2005; Lee et al. 2017; Grunau et al. 2014).

28.10.3 Protracted

Protracted episodes of anaphylaxis may last for hours or days without intervening periods of resolution. Only a few cases are described in the literature. Therefore, it is difficult to determine the incidence, risk factors, and pathophysiologic mechanisms underlying this type of anaphylaxis (Limb et al. 2007).

28.11 Anaphylaxis Fatality

Anaphylactic shock is a severe and potentially fatal allergic reaction. Although the overwhelming majority of patients with anaphylaxis recover, death, when it occurs, is often due to an inability to compensate for third space fluid losses secondary to increased capillary permeability. Profound reduction of venous tone and fluid extravasation resulting in hemoconcentration and hypovolemia cause decreased venous return and cardiac output. Also, there is a reduction in myocardial function, relative bradycardia which may be neurologically mediated and increased pulmonary resistance. Coronary ischemia caused by vasospasm and plaque ulceration may further decrease myocardial function. The result is shock and hypoperfusion of the tissues (Kounis et al. 2013). In addition to anaphylactic shock, fatality may result from respiratory failure due to severe and intractable bronchospasm and rapid swelling of the airways including the tongue, vocal cords, and bronchial tubes. Subjects with asthma are particularly at risk of severe respiratory manifestations of anaphylaxis. Both intractable hypotension causing tissue hypoperfusion and ventilatory failure can lead to hypoxia to vital organs and death. The pathophysiological changes responsible for

fatality are important in prioritizing the treatment of patients: recumbent position, massive fluid infusion, up to 5 L within the first 20 min, airway management, and inhaled bronchodilators. Epinephrine, in addition to providing vasoconstriction, bronchodilation, and enhanced venous cardiac return, is important in improving myocardial contractility and cardiac output and perfusion (Wang et al. 2014). In contrast, antihistamine therapy offers little, if any, efficacy in the acute treatment of the physiologic derangements responsible for shock.

28.12 Factors That Can Increase the Risk of Anaphylaxis and Its Severity and Complicate Its Treatment

Several factors can increase the risk of anaphylaxis in infants whose initial signs and symptoms of anaphylaxis may go unrecognized. The infant's allergic status may not be known until presentation with anaphylaxis after the ingestion of an allergenic food. Efforts have been made to increase the awareness of anaphylaxis in infants (Simons and Sampson 2015) and preferably their allergic status. In teenagers, the risks of anaphylaxis increase with uncontrolled asthma, non-compliance with controller therapy, exercise, fasting, denial of symptoms, and delay in seeking help (Vazquez-Ortiz et al. 2014). During pregnancy, the consequences of anaphylaxis can be catastrophic for the mother as it might precipitate miscarriage or premature labor. Anaphylaxis in the mother is associated with increased risk of hypoxic encephalopathy in the fetus. Pregnant women also may be at greater risk due to the negative effect of the enlarged uterus on venous return to the heart. Therefore, procedures and interventions that have the potential of causing anaphylaxis, such as initiation of allergen immunotherapy, skin testing, and drug or food challenges, should be avoided during pregnancy (Simons and Sampson 2015). Patients with systemic mastocytosis or mast cell disorders are at greater risk of developing anaphylaxis (Valent 2014). Baseline elevation of serum tryptase is a good marker that predicts hymenoptera anaphylaxis (Fellinger et al. 2014). Patients on ACE inhibitors may be at risk for anaphylaxis following hymenoptera stings and venom immunotherapy (Worm et al. 2018; Rueff et al. 2009). This is controversial as there are studies that show no increased risk of anaphylaxis. Menstruating females are at higher risk of anaphylaxis during the progesterone phase of their cycle. Estrogen also increases vascular permeability intensifying the severity of anaphylaxis (Hox et al. 2015). Finally, certain factors may lower the antigen dose required for anaphylaxis. These include infections, stress, alcohol ingestion, exercise, and nonsteroidal drug ingestion (Wolbing et al. 2013).

Table 6 is a list of factors that can affect the risk of anaphylaxis or complicate its treatment.

28.13 Grading of Anaphylaxis

Brown developed a simple grading system of anaphylaxis after a retrospective review of the charts of over 1000 cases evaluated in the emergency department. The most important factors that determine the severity of anaphylaxis include older age at the time of the reaction, the type and route of allergen exposure, and pre-existing lung disease such as asthma. These prognostic indicators are listed in Table 7 (Brown 2004).

28.14 Differential Diagnosis

Several conditions should be considered in the differential diagnosis of anaphylaxis. Anaphylaxis is often due to the intentional administration of medications or food or unintentional arthropod exposure possibly combined with physical factors such as exercise, heat, cold, and sunlight. It may also be idiopathic.

Table 6 Factors that can increase the risk for an anaphylactic event, increase its severity, or complicate its treatment

Factor	Comment
Mastocytosis	Events due to mastocytosis are characterized by more frequent and more severe cardiovascular manifestations
Age	The elderly are at risk because of comorbidities and increased use of medications
	Infants are at risk because manifestations might not be detected
	Teenagers are at risk because of "risky behavior"
Asthma	Presence of asthma increases the risk of fatal events and the frequency of events
Atopy	Atopy increases risk because patients with atopy are at risk for food allergy
Drugs	Numerous drugs can increase the risk for a severe reaction and complicate therapy by interfering with or even accentuating the action of epinephrine
Alcohol	Alcohol impairs judgment and can diminish recognition of symptoms
Comorbidities	Presence of cardiovascular, renal, and pulmonary disease predisposes to fatalities

Adapted from Lieberman et al. (2015)

Table 7 Grading system for generalized hypersensitivity reactions

1. **Mild (skin and subcutaneous tissues only)**[a]
Generalized erythema, urticaria, periorbital edema, or angioedema
2. **Moderate (features suggesting respiratory, cardiovascular, or gastrointestinal involvement)**
Dyspnea, stridor, wheeze, nausea, vomiting, dizziness (presyncope), diaphoresis, chest or throat tightness, or abdominal pain
3. **Severe (hypoxia, hypotension, or neurologic compromise)**
Cyanosis or SpO2 # 92% at any stage, hypotension (SBP < 90 mmHg in adults), confusion, collapse, LOC, or incontinence

Adapted from Brown (2004)
SBP systolic blood pressure, *LOC* loss of consciousness
[a]Mild reactions can be further subclassified into those with and without

28.14.1 Monosodium Glutamate

Signs and symptoms of chest pain, facial burning, flushing, paresthesias, sweating, dizziness, headaches, palpitations, and nausea and vomiting have been attributed to monosodium glutamate ingestion. However, a multicenter, double-blind, placebo-controlled, and multiple-challenge evaluation failed to demonstrate any association between monosodium glutamate and the reactions that have been attributed to its ingestion (Geha et al. 2000).

28.14.2 Sulfites

Urticaria, angioedema, and anaphylactic-like reactions have been ascribed to sulfite sensitivity. However, a true association between sulfite ingestion and anaphylaxis is controversial. Acute bronchospasm is the most consistent event associated with sulfites in susceptible patients. Sulfites are added to foods to prevent browning and possess antioxidant and antimicrobial properties. Dried fruits and wine are most commonly associated with sulfite-related reactions. Sulfites may also be present in medications used to treat allergies and asthma such as injectable epinephrine, dexamethasone, ipratropium/albuterol MDI, and nasal corticosteroids (Vally and Misso 2012).

28.14.3 Scrombroidosis

Scrombroidosis is due to the ingestion of spoiled fish containing large amounts of histidine which is converted to histamine through the action of histidine decarboxylase produced by bacteria. Urocanic acid, also a by-product of histidine metabolism, is an imidazole with chemical similarity to histamine that can also degranulate mast cells, augmenting the histamine effect. Typical signs and symptoms attributed to scrombroidosis include urticaria, flushing, angioedema, nausea, vomiting, diarrhea, and hypotension. But, most commonly,

patients have flushing of the face and neck, accompanied by a sensation of heat and discomfort. Symptoms may last several days. Isoniazid increases the susceptibility to scrombroidosis (Hungerford 2010).

28.14.4 Histamine Excess Production

Several syndromes of increased histamine production may cause anaphylaxis-like reactions. These include systemic mastocytosis, urticaria pigmentosa, basophilic leukemia, acute promyelocytic leukemia, and hydatid cyst.

28.14.5 Nonorganic Conditions

Very commonly, nonorganic conditions can be confused with anaphylaxis. These include panic attacks, Munchausen stridor, vocal cord dysfunction, globus hystericus, hyperventilation syndrome, anxiety disorders, and undifferentiated somatoform anaphylaxis.

28.14.6 Other Conditions

Anaphylaxis presentations may resemble vasodepressor reactions such as flush syndromes, for example, carcinoid syndrome, medullary carcinoma of the thyroid, autonomic epilepsy, menopause, chlorpropamide or alcohol ingestion, vasovagal syncope, and idiopathic flushing. Finally, other medical conditions which may be confused with anaphylaxis are hereditary angioedema, urticarial vasculitis, pheochromocytoma, hyper-IgE syndrome, idiopathic urticaria and angioedema, hypoglycemia, pulmonary embolus, myocardial infarction, seizure, stroke, pseudoanaphylaxis, autonomic dysfunction, vancomycin-induced red man/person syndrome, and capillary leak syndrome.

Table 8 provides a list of the clinical entities that should be considered in the differential diagnosis of anaphylaxis.

Table 8 Differential diagnosis of anaphylaxis

Anaphylaxis	
A	Anaphylaxis from foods, drugs, and insect stings
B	Anaphylaxis from physical factors (exercise, cold, heat)
C	Idiopathic (cause undetermined) anaphylaxis
Vasodepressor reactions (vasovagal reactions)	
Flushing syndromes	
A	Carcinoid
B	Vaso-intestinal polypeptide tumors
C	Mastocytosis and mast cell activating syndrome
D	Medullary carcinoma of the thyroid
Restaurant syndromes	
A	Monosodium glutamate
B	Scombroidosis
Nonorganic disease	
A	Panic attacks
B	Munchausen stridor (factitious anaphylaxis)
C	Vocal cord dysfunction syndrome
D	Undifferentiated somatoform anaphylaxis
E	Prevarication anaphylaxis
Miscellaneous	
A	Hereditary angioedema accompanied by rash
B	Paradoxical pheochromocytoma
C	Red man syndrome (vancomycin)
D	Capillary leak syndrome

Adapted from Lieberman et al. (2015)

28.15 Laboratory Evaluation

Although anaphylaxis is a syndrome that no test can prove or disprove, certain laboratory tests can be helpful in supporting the diagnosis. Table 9 is a list of the chemical abnormalities that may indicate anaphylaxis has occurred or that the patient is at higher risk of anaphylaxis. In situations where anaphylaxis is suspected as the cause of death, blood samples from the femoral vein have shown elevation of serum tryptase presumably from mast cell degranulation. In the absence of hematologic disorders such as hypereosinophilia syndrome, polycythemia, mast cell disorders or certain forms of leukemia, elevation of serum tryptase, a marker of mast cell degranulation, indicates anaphylaxis.

Table 9 Laboratory evaluation of anaphylaxis

1	**Supporting anaphylaxis as a cause**
a	During an event obtain
i	Serum tryptase
ii	Plasma histamine
iii	24-h urinary *N*-Methylhistamine
iv	Urinary prostaglandin D_2
2	**Using the laboratory to establish a diagnosis of a condition mimicking anaphylaxis**
a	Serum serotonin
b	Urinary 5-hydroxyindoleacetic acid
c	Chromogranin A
d	Vaso-intestinal polypeptide
i	Substance P, vaso-intestinal polypeptide hormone, urokinase A, pancreastatin
ii	Computed tomography, magnetic resonance imaging, single-photon emission computed tomography (octreotide or pentetreotide assisted)
e	24-h urinary catecholamines
f	Serum catechols
3	**Tests that may suggest the etiology of anaphylactic events**
a	Skin tests to foods and drugs when indicated
i	Skin tests using standard commercially available extracts
ii	Prick skin tests using fresh food
b	Serum-specific IgE or RAST if indicated and available
c	Oral challenge
d	Galactose-1,3-α-galactose
e	Baseline serum tryptase
f	Baseline 24-h urinary histamine metabolites
g	Prostaglandin D_2
h	Blood determination for 816 V mutation
i	Bone marrow

Adapted from Lieberman et al. (2015)

Serum tryptase and both serum and urine histamine levels have been used to retrospectively diagnose anaphylaxis.

28.15.1 Tryptase

Serum tryptase is a serine peptidase contained in large amounts within mast cells, much less in basophils. It exists in two forms, alpha and beta, as well as a protryptase. The commercial serum tryptase assay measures protryptase and alpha- and beta-tryptase. While alpha- or immature tryptase is constitutively released, the elevation of serum tryptase during an anaphylactic reaction is mainly due to mature beta-tryptase. The pharmacokinetics of serum tryptase are that it peaks within 60–90 min after the onset of anaphylaxis and remains elevated up to 5 h, sometimes longer. When patients are evaluated in the emergency department for suspected anaphylaxis, a serum tryptase level should be considered to document whether anaphylaxis has occurred. In cases of anaphylaxis, the magnitude of serum tryptase elevation correlates with the severity of the reaction. Although serum tryptase can be normal, especially during food-induced reactions, serum levels greater than 11.5 ng/ml are suggestive of mast cell degranulation in anaphylaxis or mastocytosis. Serial serum tryptase levels may be more helpful than a single measurement (Schwartz 2006). An increase of the basal serum tryptase by 20% plus 2 ng/ml is statically associated with mast cell activation. However, anaphylaxis may occur without significant change in serum tryptase so the diagnosis cannot be excluded solely with this laboratory test. Particularly it has been noted that food challenges resulting in systemic symptoms do not increase serum tryptase. Some would argue that these reactions are not sufficiently severe to be labeled as anaphylaxis. The clinical challenge is that an increase in tryptase is typical of anaphylaxis but is neither sufficient nor necessary for the diagnosis.

28.15.2 Histamine

At baseline, histamine is usually undetectable in peripheral blood as its level is usually less than 1 ng/ml. The normal urinary histamine level is between 5 and 24 μg/24 h (Horakova et al. 1977). Histamine and its urinary metabolites are also elevated during acute anaphylaxis. In contrast to serum tryptase, histamine increases within 5–10 min and remains elevated only for 30–60 min. Therefore, by the time the patient arrives to the ER, the level of serum histamine may have already normalized. Histamine is produced in mast cells and basophils from histidine

by the action of histidine decarboxylase and stored in secretory granules. Mast cells and basophils produce approximately the same amount of histamine, which is constitutively released in small quantities. Although blood histamine increases correlate well with anaphylaxis, its elimination as previously stated is rapid. Consequently, the sample should be obtained in a timely fashion. Histamine is very unstable at room temperature, and the serum specimen needs to be frozen. Also, the diagnostic utility of histamine quantification is limited by the fact that other conditions or pretesting ingestion of various drinks and foods increases its blood concentration. Histamine can be elevated due to gut and urogenital bacteria or the ingestion of food items such as fish, aged cheeses, chocolate, red wine, and certain vegetables, including eggplant, tomato, and spinach. Assays of urinary histamine metabolites, such as *N*-methylhistamine, are more useful and are elevated up to 6 h after anaphylaxis.

28.15.3 Platelet-Activating Factor

Platelet-activating factor (PAF) is a potent proinflammatory phospholipid produced by mast cells and other immune cells. It is implicated in platelet aggregation and activation through the production of vasoactive amines during the inflammatory response. Once released, it is rapidly hydrolyzed by PAF acethylhydrolase to lysoPAF, an inactive metabolite. It plays an important role in manifestations of anaphylaxis, such as bronchoconstriction, hypotension, and decreased cardiac output in experimental animal models (Gill et al. 2015). The severity of anaphylaxis is directly associated with the elevated levels of PAF and inversely related with the activity of PAF acethylhydrolase. The correlation between increased levels of PAF and the severity of anaphylaxis was stronger than serum tryptase and histamine (Vadas et al. 2013). The level of PAF acethylhydrolase was significantly lower in fatal anaphylaxis suggesting that PAF may play a role in the severity of anaphylaxis (Vadas et al. 2008).

28.15.4 Other Mediators of Anaphylaxis

Elevated serum levels of prostaglandin D2 and carboxypeptidase have also been used to diagnose anaphylaxis, particularly in mastocytosis (Levy 2009). A test of beta-tryptase, which is a better marker of mast cell activation than total tryptase, has been described. However, it is not available for general use and application is limited to specialized laboratories.

28.15.5 Inflammatory Gene Expression

Upregulation of innate inflammatory genes of peripheral blood leukocytes has been used in the emergency room setting as a marker of anaphylaxis. This microarray gene analysis method if validated may become another tool that can be used to confirm the diagnosis of anaphylaxis (Stone et al. 2014).

The evaluation of the patient with anaphylaxis should include the drawing of blood for the current or subsequent analysis of specific-IgE against suspected antigens. If possible, serum should be frozen to be available to the allergist who will subsequently evaluate the patient. Sometimes, after a detailed history, the culprit antigen may be suspected and confirmed by testing. However, in many cases, the etiology of anaphylaxis, especially in adults, will remain elusive.

28.16 Prevention and Management

Often anaphylaxis is preventable by properly educating the allergic patient about avoidance measures once the antigen is known. A complete drug allergy history is essential as well as a knowledge of the immunological mechanisms and cross-reactivities among drugs. Whenever possible, drugs should be administered orally as anaphylaxis is less severe with that route. A medic alert bracelet or necklace should be considered. Patients should also carry an epinephrine

autoinjector with them and be knowledgeable in its indications and proficient in the techniques of administration. Patients at risk for anaphylaxis ideally should avoid beta-blockers, angiotensin-converting enzyme inhibitors (ACEIs), inhibitors of monoamine oxidase (MAOIs), angiotensin receptors blockers (ARBs), and some tricyclic antidepressants (TCAs) as these drugs may reduce the efficacy of epinephrine treatment, the best physiological antagonist of anaphylaxis, and impair the adaptive responses of the affected individual. These responses include adrenal release of epinephrine, stress release of corticosteroids, and generation of angiotensin II.

Patients known to be at risk of anaphylaxis may benefit from premedication with antihistamines and oral corticosteroids before undergoing potential risk procedures such as the injection of radiocontrast media, desensitization, and provocative challenges. In patients with a history of contrast media reaction, several protocols are available including the widely used 13-h protocol (Greenberger and Patterson 1991). This is proven effective in preventing anaphylaxis in susceptible patients.

28.17 Management of Acute Anaphylaxis

There is a paucity of clinical trials that evaluate the management of anaphylaxis due to the ethical challenges of double-blind studies in a life-threatening condition. However, there are position or consensus statements from the American Academy of Pediatrics (AAP), committee on drugs of the American Academy of Allergy, Asthma and Immunology (AAAAI), Joint Task Force on Practice Parameters of both the American College of Allergy, Asthma and Immunology (ACAAI) and the American Academy of Allergy Asthma and Immunology, and recommendations from the World Health Organization (WHO) and World Allergy Organization that provide assistance in the recognition and management of anaphylaxis.

28.17.1 Recognition

The first step in the management of anaphylaxis is to recognize the early signs and symptoms. Patients at risk and medical staff should be instructed in recognizing the first signs and symptoms. Patient education starts at the first visit for all patients who have had anaphylaxis. Also, patients who are undergoing procedures that may potentially cause acute or delayed anaphylaxis in at risk individuals, such as the administration of omalizumab, should be instructed about the indications and techniques of administration of epinephrine. Patients receiving allergen immunotherapy should be informed about anaphylaxis, and the education should be documented, for example, by retaining a signed consent form in the medical record. The staff should be appraised about any change in clinical status that may make the patient more susceptible to anaphylaxis. Ideally periodic drills should be carried out, and clinic staff should be "anaphylaxis ready" with a written emergency protocol and flow chart.

28.17.2 Positioning

All patients suspected of having anaphylaxis should be placed in supine position. They should remain in the supine position during their treatment and should not be allowed to stand or sit. Deaths from cardiovascular collapse have occurred in patients being treated for anaphylaxis when changing position from supine to erect (Pumphrey 2003). In the past, positioning the patient in a Trendelenburg position has been advocated. However, there is no evidence that this position helps prevent or improve hypotension more than being supine (Ostrow et al. 1994).

28.17.3 Treatment

Three primary treatments are recommended for acute anaphylaxis management. First, epinephrine should be administered intramuscularly (IM) as early as possible in the lateral thigh, ideally before hypotension develops. Second, if shock occurs,

then medication absorption may be poor, necessitating the more risky IV slow infusion of epinephrine. So, early administration of intramuscular epinephrine is preferred. Third, because of vascular dilatation and fluid extravasation, severely reduced cardiac venous return is a major component of anaphylaxis. Therefore, patients should remain in supine position, as stated previously, while aggressive fluid resuscitation is being implemented to control hypotension.

28.17.3.1 Epinephrine

Epinephrine is the most important medication in the treatment of anaphylaxis and should be the first drug administered. Because epinephrine antagonizes the physiological effects of mediators such as histamine and PAF, it has the potential of preventing or reversing the most important and serious manifestations of anaphylaxis including bronchospasm and hypotension. Epinephrine is best administered in the lateral thigh as soon as possible. The maximum initial dose of epinephrine in adults varies from 0.3 to 0.5 mg which corresponds to 0.3 or 0.5 ml of the 1:1000 dilution of epinephrine. In children 0.01 mg/kg should be used up to the maximum adult dose. The initial epinephrine dose can be repeated every 5–15 min or earlier depending on the patient's response. In an outpatient setting, if the patient has an epinephrine autoinjector, it should be used even if it is expired (Rachid et al. 2015) (Fig. 2). However, if the patient is not responding to IM doses of epinephrine, then the slow infusion of a dilution of 1:10,000 is a consideration. This can be prepared by adding 1 ml of the 1:1000 dilution of epinephrine to 10 ml of normal saline or 0.1 ml of 1:1000 epinephrine in 1 ml of normal saline. Slow push of IV epinephrine is a consideration only in patients with unresponsive hypotension or cardiac arrest due to the risk of ventricular arrhythmia. In certain circumstances and when available, epinephrine may be administered sublingually. Epinephrine can also be administered in a nebulized form at the dosage of 5 mg, which is 5 ml of 1:1000 concentration, in patients with airway compromise. In intubated subjects, similar doses of epinephrine can also be administered intratracheally for mucosal absorption and systemic effects.

28.17.3.2 Oxygen

Oxygen is a very important, low-risk therapeutic intervention in the management of anaphylaxis. Patients with anaphylaxis benefit from supplemental oxygen up to 100% through face mask at a flow rate up to 10 L/min if needed to keep the oxygen saturation at least between 94% and 96%.

28.17.3.3 Fluids

Profound and protracted hypotension is one of the most important and challenging manifestations of anaphylaxis. Up to a third of the patient's total blood volume may be shifted to the extravascular space within the first 10 min. Therefore, up to 50 ml/kg of crystalloids may be necessary during initial resuscitation. Up to 1–2 L of normal saline should be infused rapidly within the first 5 min or up to 30 ml/kg in children IV or intraosseous via a large bore needle in the proximal tibial area.

28.17.3.4 Other Vasopressors

The usefulness of vasopressors in the treatment of cardiovascular collapse associated with anaphylaxis has not been substantiated, as is true of almost all of the recommendations. Current recommendations are to start an infusion of epinephrine, norepinephrine, dobutamine, or dopamine. This can be done by mixing 1 ml of epinephrine 1:1000 in 250 ml of D5W yielding a concentration of 4.0 μg/ml infused at 1–4 μg/min (16–60 drops/min). This is best done in a hospital setting as cardiac monitoring and continuous blood pressure assessment are necessary. Intravenous infusion of dopamine or dobutamine is another option. These are administered at 1–50 μg/kg/min or 2–20 μg/kg/min, respectively, and may have less risk of arrhythmia than IV epinephrine. Vasopressin also has been suggested as a treatment.

28.17.3.5 Beta-2 Agonists

If wheezing, coughing, and shortness of breath are not improved with epinephrine, then albuterol nebulization should be administered via mask (adult dose 2.5–5.0 mg/3 ml of saline; pediatric dose 2.5 mg/3 ml). This, however, will not treat upper airway obstruction or laryngeal edema. When administered by inhaler, up to 12 puffs

Fig. 2 Technique of administration of epinephrine

(90 mcg per puff) may be administered via spacer every 20 min in adults and 5–10 puffs in children (Cheng 2011).

28.17.3.6 Atropine

In patients with bradycardia, the use of atropine at the dosage of 0.3–0.5 mg IV, repeated every 10 min, may be useful. This should be combined with aggressive volume resuscitation and administration of epinephrine.

28.17.3.7 Glucagon

Glucagon is a polypeptide hormone produced by the alpha cells of the islets of Langerhans in the pancreas. It has inotropic and chronotropic effects on the heart independent of adrenergic receptors. Therefore, this drug is ideal in patients treated with current beta-blocker therapy and who have failed or not responded to epinephrine. It is used as a bolus of 1–5 mg IV, followed by an infusion of 5–15 μg/min. Patients may experience nausea and vomiting as a side effect; therefore, their airway should be protected if they are unconscious.

28.17.3.8 Corticosteroids

Although a role for corticosteroids in the prevention of biphasic anaphylaxis has been postulated, there is no evidence of benefit. However, because of its broad anti-inflammatory role and importance in the stress response, corticosteroids are routinely used in the treatment of anaphylaxis. In adults, the usual dose ranges from 100 mg to 1000 mg of hydrocortisone or equivalent. In children, the dose varies from 10 to 100 mg or 1–5 mg/kg.

28.17.3.9 Antihistamines

Antihistamines, both H1 and H2 blockers, are more useful in treating urticaria and itching, which frequently occur in anaphylaxis, than respiratory or cardiovascular manifestations. Antihistamines cannot be substituted for epinephrine in treating acute

anaphylaxis. Indeed, they may cause hypotension if given in the absence of epinephrine due to their vasodilating effects through alpha-blocking effects.

28.17.3.10 Methylene Blue

Methylene Blue is an inhibitor of nitric oxide synthetase and guanylate cyclase. In a small clinical series, this dye was useful in the treatment of vasoplegia, a condition characterized by profound vasodilation in the setting of perioperative anaphylactic shock. It may be used as a single dose of 1–2 mg/kg IV over 20–60 min (Hosseinian et al. 2016). This agent should not be used in patients with pulmonary hypertension, glucose-6-phospate dehydrogenase (G6PD), and acute lung injury.

28.17.4 Extracorporeal Membrane Oxygenation (ECMO)

ECMO is a consideration in hospitalized patients who are refractory to advanced treatment of protracted anaphylaxis. ECMO may prevent irreversible ischemic tissue damage (Lafforgue et al. 2005).

28.17.5 Period of Observation

Patients who have been treated for anaphylaxis should be observed after the stabilization of symptoms. The duration of the observation period depends on the severity of the reaction, presence of wheezing, possibility of continued absorption of the antigen that may have caused the reaction, or a history of biphasic reaction. Most authors agree that the ideal observation period should be between 8 and 24 h for severe episodes.

28.17.6 Discharge

Patients who have been successfully treated for anaphylaxis should be given a personalized written anaphylaxis emergency action plan, an epinephrine autoinjector, and written information about anaphylaxis and its treatment. A consultation with an allergist/immunologist should be arranged. The allergist will evaluate the patient to seek a cause for the anaphylactic episode, so avoidance measures when appropriate can be implemented to prevent recurrence.

An outline of the emergency management of anaphylaxis in adults is given in Table 10, and Table 11 is for infants and children.

28.18 Fatalities

Death from anaphylaxis is fortunately rare (see Sect. 27). Anaphylaxis triggers most commonly associated with death include drugs, radiocontrast media, hymenoptera stings, and foods. Elderly patients with comorbid conditions are at higher risk of fatal anaphylaxis. The most common causes of death were airway obstruction, cardiovascular collapse, and disseminated intravascular coagulation. Perioperative anaphylaxis also has a greater risk of fatality. Asthma is a general risk factor for anaphylaxis death. Generally, anaphylactic cardiac arrest due to injected antigens occurs more rapidly, while it takes longer for hymenoptera stings and slowest for ingested allergens (Pumphrey 2000). Usually, the more rapid the onset of anaphylaxis, the more severe. Also, death is more likely when patients assume upright or sitting position during treatment as previously discussed.

28.19 Anaphylaxis in Pregnancy

Anaphylaxis during pregnancy can be very serious for the developing fetus due to the potential of severe hypoxia. Hypoxia in the mother places the fetus at risk since at baseline fetal oxygenation can be compared figuratively with someone sitting on top of Mount Everest (Eastman 1954). Specific symptoms of anaphylaxis in pregnancy include vulvar and vaginal itching, back pain, uterine cramps, preterm labor, and fetal distress. Although the etiologies of anaphylaxis in the first two trimesters are the same as for non-pregnant women, during labor and delivery, common etiologies of anaphylaxis are beta-lactam

Table 10 Rapid overview: emergency management of anaphylaxis in adults

Diagnosis is made clinically
The most common signs and symptoms are cutaneous (e.g., sudden onset of generalized urticaria, angioedema, flushing, pruritus). However, 10–20% of patients have no skin findings
Danger signs: rapid progression of symptoms, respiratory distress (e.g., stridor, wheezing, dyspnea, increased work of breathing, persistent cough, cyanosis), vomiting, abdominal pain, hypotension, dysrhythmia, chest pain, collapse
Acute management
The first and most important treatment in anaphylaxis is epinephrine. There are **NO absolute contraindications to epinephrine** in the setting of anaphylaxis
Airway: immediate intubation if evidence of impending airway obstruction from angioedema. Delay may lead to complete obstruction. Intubation can be difficult and should be performed by the most experienced clinician available. Cricothyrotomy may be necessary
Promptly and simultaneously, give
IM epinephrine (1 mg/mL preparation): give epinephrine 0.3–0.5 mg intramuscularly, preferably in the mid-outer thigh. Can repeat every 5–15 min (or more frequently), as needed. If epinephrine is injected promptly IM, most patients respond to one, two, or, at most, three doses. If symptoms are not responding to epinephrine injections, prepare IV epinephrine for infusion (see below)
Place patient in recumbent position, if tolerated, and elevate lower extremities
Oxygen: give 8–10 L/min via face mask or up to 100% oxygen, as needed
Normal saline rapid bolus: treat hypotension with rapid infusion of 1–2 L IV. Repeat, as needed. Massive fluid shifts with severe loss of intravascular volume can occur
Albuterol (salbutamol): for bronchospasm resistant to IM epinephrine, give 2.5–5 mg in 3 mL saline via nebulizer. Repeat, as needed
Adjunctive therapies
H1 antihistamine: consider giving diphenhydramine 25–50 mg IV (for relief of urticaria and itching only)
H2 antihistamine: consider giving ranitidine 50 mg IV
Glucocorticoid: consider giving methylprednisolone 125 mg IV
Monitoring: continuous noninvasive hemodynamic monitoring and pulse oximetry monitoring should be performed. Urine output should be monitored in patients receiving IV fluid resuscitation for severe hypotension or shock
Treatment of refractory symptoms
Epinephrine infusion: for patients with inadequate response to IM epinephrine and IV saline, give epinephrine continuous infusion, beginning at **0.1 mcg/kg/min** by infusion pump$^{\Delta}$. Titrate the dose continuously according to blood pressure, cardiac rate and function, and oxygenation
Vasopressors: some patients may require a second vasopressor (in addition to epinephrine). All vasopressors should be given by infusion pump, with the doses titrated continuously according to blood pressure and cardiac rate/function and oxygenation monitored by pulse oximetry
Glucagon: patients on beta-blockers may not respond to epinephrine and can be given glucagon 1–5 mg IV over 5 min, followed by infusion of 5–15 mcg/min. Rapid administration of glucagon can cause vomiting

Adapted from Campbell HL and Kelso JM UpToDate 2018

antibiotics, natural latex rubber allergy, and exposure to other preparatory items such as cleaning agents used during delivery. Avoidance of procedures such as skin testing, allergen immunotherapy buildup, food or drug challenges, and interventions that could increase the risk of anaphylaxis should be avoided during pregnancy.

Intramuscular epinephrine should be promptly used as for anaphylaxis without pregnancy. However, the caveats are that epinephrine has been associated with infant deaths, neurological abnormalities, and inguinal hernia (Chaudhuri et al. 2008). Since there are no substitutes for epinephrine, this life-saving drug should be used in the treatment of maternal anaphylaxis. In one case report, the continuous infusion for 3.5 h of epinephrine in a pregnant patient with refractory anaphylactic hypotension was not associated with any adverse effects in the fetus (Gei et al. 2003). However, because of potential fetal complications, the best treatment for pregnancy associated anaphylaxis is prevention as illustrated in Fig. 3 (Simons and Schatz 2012).

Anaphylaxis in pregnant women during labor and delivery should be treated aggressively as to minimize hypoxia to both the mother and the baby. Positioning the patient on her left side, providing high flow of supplemental oxygen, and maintaining systolic blood pressure over 90 mmHg are keys in the management. Continuous fetal monitoring is also important.

Table 11 Rapid overview: emergent management of anaphylaxis in infants and children[a]

Diagnosis is made clinically
The most common signs and symptoms are cutaneous (e.g., sudden onset of generalized urticaria, angioedema, flushing, pruritus). However, 10–20% of patients have no skin findings
Danger signs: rapid progression of symptoms, evidence of respiratory distress (e.g., stridor, wheezing, dyspnea, increased work of breathing, retractions, persistent cough, cyanosis), signs of poor perfusion, abdominal pain, vomiting, dysrhythmia, hypotension, collapse
Acute management
The first and most important therapy in anaphylaxis is epinephrine. There are **NO absolute contraindications to epinephrine** in the setting of anaphylaxis
Airway: immediate intubation if evidence of impending airway obstruction from angioedema. Delay may lead to complete obstruction. Intubation can be difficult and should be performed by the most experienced clinician available. Cricothyrotomy may be necessary
IM epinephrine (1 mg/mL preparation): epinephrine 0.01 mg/kg should be injected intramuscularly in the mid-outer thigh. For large children (>50 kg), the maximum is 0.5 mg per dose. If there is no response or the response is inadequate, the injection can be repeated in 5–15 min (or more frequently). If epinephrine is injected promptly IM, patients respond to one, two, or, at most, three injections. If signs of poor perfusion are present or symptoms are not responding to epinephrine injections, prepare IV epinephrine for infusion (see below)
Place patient in recumbent position, if tolerated, and elevate lower extremities
Oxygen: give 8–10 L/min via face mask or up to 100% oxygen, as needed
Normal saline rapid bolus: treat poor perfusion with rapid infusion of 20 mL/kg. Re-evaluate and repeat fluid boluses (20 mL/kg), as needed. Massive fluid shifts with severe loss of intravascular volume can occur. Monitor urine output
Albuterol: for bronchospasm resistant to IM epinephrine, give albuterol 0.15 mg/kg (minimum dose, 2.5 mg) in 3 mL saline inhaled via nebulizer. Repeat, as needed
H1 antihistamine: consider giving diphenhydramine 1 mg/kg (max 40 mg) IV
H2 antihistamine: consider giving ranitidine 1 mg/kg (max 50 mg) IV
Glucocorticoid: consider giving methylprednisolone 1 mg/kg (max 125 mg) IV
Monitoring: continuous noninvasive hemodynamic monitoring and pulse oximetry monitoring should be performed. Urine output should be monitored in patients receiving IV fluid resuscitation for severe hypotension or shock
Treatment of refractory symptoms
Epinephrine infusion: in patients with inadequate response to IM epinephrine and IV saline, give epinephrine continuous infusion at 0.1–1 mcg/kg/min, titrated to effect
Vasopressors: patients may require large amounts of IV crystalloid to maintain blood pressure. Some patients may require a second vasopressor (in addition to epinephrine). All vasopressors should be given by infusion pump, with the doses titrated continuously according to blood pressure and cardiac rate/function monitored continuously and oxygenation monitored by pulse oximetry

Adapted from Campbell HL and Kelso JM UpToDate 2018

All patients receiving an infusion of epinephrine and/or another vasopressor require continuous noninvasive monitoring of blood pressure, heart rate and function, and oxygen saturation. We suggest that pediatric centers provide instructions for preparation of standard concentrations and also provide charts for established infusion rate for epinephrine and other vasopressors in infants and children

IM intramuscular, *IV* intravenous

[a]A child is defined as a prepubertal patient weighing less than 40 kg

28.20 Anaphylaxis in Infants and Children

The most common cause of anaphylaxis in infants is ingestion of an allergenic food such as egg, milk, or peanut to which the child has been sensitized. However, the sensitization is often not known by the caregiver, and therefore anaphylaxis may not be recognized because the signs and symptoms associated with anaphylaxis can be non-specific. The difficulty in making the diagnosis and the lack of known allergy prior to the event often reduce suspicion and delay treatment. Infants and children, depending on their age, may not be able to express or describe symptoms such as throat

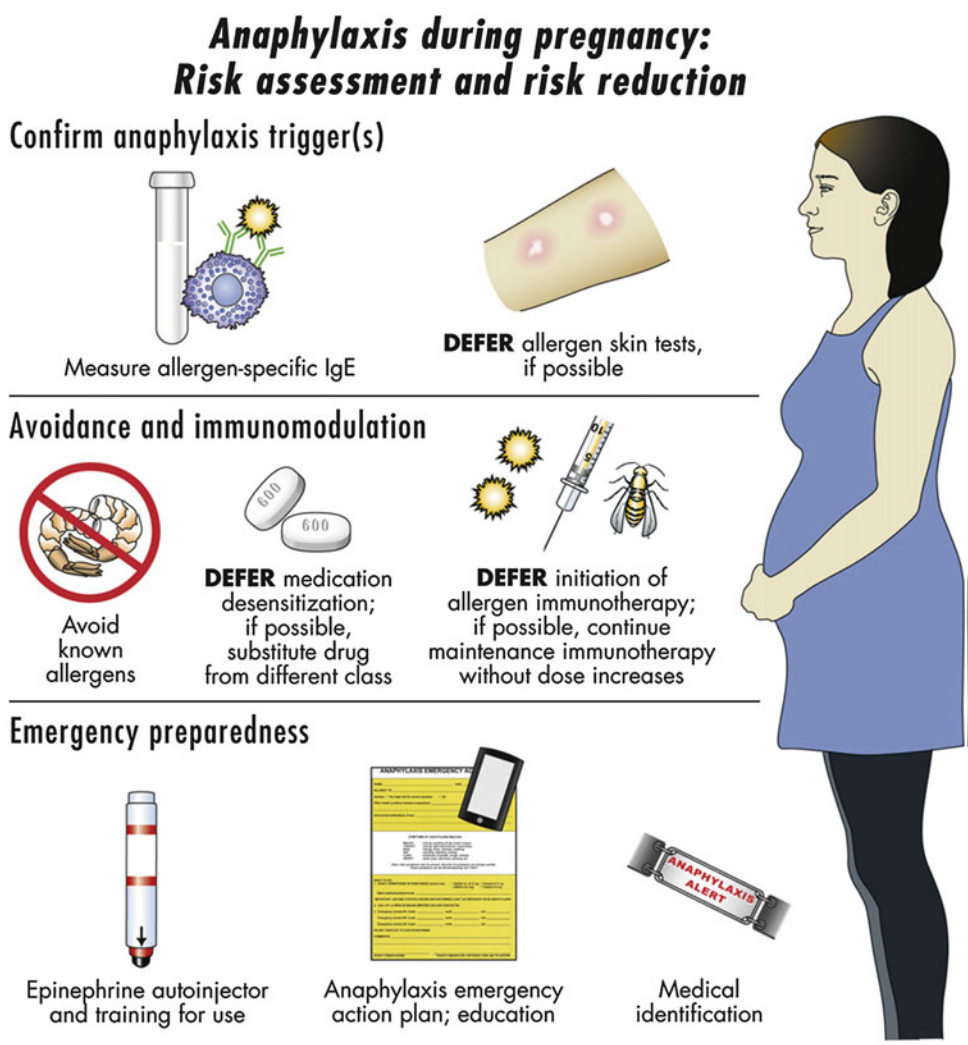

Fig. 3 Anaphylaxis prevention and treatment in pregnancy

itching, tightness of the throat or chest, and generalized itching. Also, the signs can be misattributed to other common situations such as spitting up due to esophageal regurgitation, irritability from lack of sleep, and hoarseness associated with crying spells.

Epinephrine should be used promptly in infants suspected of anaphylaxis at the dosage of 0.01 mg/kg. The epinephrine is administered IM in the lateral portion of the thigh and may be repeated every 5–15 min. Excessive dosing may be associated with cardiovascular events such as ventricular tachyarrhythmias and pulmonary edema, especially if epinephrine is used intravenously.

28.21 Anaphylaxis in the Elderly

Anaphylaxis in the elderly differs from other populations in terms of risk factors, comorbidities, causative agents, and compensatory or pathophysiological mechanisms. Polypharmacy and specific medications taken for comorbid conditions such as beta-blockers, angiotensin-converting enzyme inhibitors (ACEIs), and nonsteroidal anti-

inflammatory drugs (NSAIDs) contribute to the cause or interfere with the treatment and prognosis of anaphylaxis in the elderly. Cardiovascular symptoms are more prominent in the 65 years or older group, perhaps because of underlying cardiovascular disease or decreased cardiac reserve. Elderly patients are less able to tolerate or compensate for hypoxia, hypovolemia, and arrhythmia. Although it is true in all age groups, anaphylaxis results in cyanosis, dizziness, and syncope more often in the elderly. Coronary vasospasm secondary to mast cell mediators may cause fatal dysrhythmias and death (Ventura et al. 2015). There are no absolute contraindications for the use of epinephrine in anaphylaxis; however, its use in the elderly should be carefully evaluated in light of the myocardial oxygen demand that it causes, particularly in patients with a history of coronary vascular disease. For these reasons, some advocate for using lower doses, such as 0.005 mg/kg, and repeating the dosing more often if no adverse effects occur and treatment response is inadequate. Epinephrine preferably should be used intramuscularly as in younger subjects. If administered IV, epinephrine should be administered cautiously at a very slow continuous and titrated infusion, ideally with an infusion pump and continuous monitoring. Patients on beta-blockers may be less responsive to epinephrine. In those cases, glucagon is a consideration (Gonzalez-de-Olano et al. 2016).

28.22 Perioperative Anaphylaxis

Anaphylaxis during general anesthesia most commonly occurs in adult women. However, there is wide variability in the incidence and prevalence. The variability may be due to inaccurate recognition due to the difficulty of making the diagnosis or misattribution of the manifestations to physiologic effects of surgery and anesthesia. The most common causes of perioperative anaphylaxis are antibiotics, neuromuscular blocking agents (NMBAs), blood products, chlorhexidine, and latex. Less common agents include hypnotics, opioids, and colloids. Antibiotics, especially penicillins and cephalosporins, are the most common causes of perioperative anaphylaxis in the USA, while NMBAs are most common in Europe. The latter include rocuronium, succinylcholine, atracurium, pancuronium, and vecuronium. The high incidence of perioperative anaphylaxis in adult women may be the result of cross reactivity between highly reactive ammonium groups in NMBAs and tertiary and quaternary ammonium groups contained in topical cosmetics, over-the-counter cough remedies, and personal products. There is also a receptor on mast cells that may be specific for NMBAs designated MRGPRX2 (mas-related G protein-coupled receptor-X2). This receptor may also be activated by substance P and peptidergic agents, such as the hereditary angioedema drug icatibant. Latex is no longer a common cause of anaphylaxis as in the mid-1990s because latex is used less routinely in operative suites in the USA. Chlorhexidine, which is used as an antiseptic, may cause perioperative anaphylaxis as patients may have been sensitized through the use of toothpastes, antiseptic mouthwashes, bathing products, and lozenges.

Certain specific factors put people at risk of developing perioperative anaphylaxis such as female gender, allergic history, a diagnosis of mast cell activation syndrome or mastocytosis, and the history of multiple previous surgical procedures.

Early and mild signs of anaphylaxis may be missed in an intubated, sedated, and surgically draped patient. Anaphylaxis may not be recognized until severe respiratory and cardiovascular changes occur. These include bronchospasm with unexpected difficulty in ventilating the intubated patient, oxygen desaturation, or cardiovascular compromise ranging from tachycardia and hypotension to cardiac arrest. Laryngeal edema may manifest as difficulty to intubate or post-extubation stridor.

Severity and mortality of perioperative anaphylaxis are likely increased due to the IV route of culprit drug administration, simultaneous use of multiple agents, and the inability to quickly recognize the signs and symptoms of anaphylaxis. Estimates of mortality vary from 1.4% to 6% with another 2% of patients surviving with anoxic brain injury.

The treatment of perioperative anaphylaxis, as with all anaphylaxis, is the prompt administration of epinephrine, preferably IV, and fluid resuscitation. Intravenous administration is preferred by anesthesiologists as the response is more rapid, efficacy can be titrated, and subjects are optimally monitored. Usually the initial dose is 0.005 mg/kg or 0.1 mg. Elevated blood levels of tryptase and histamine may help confirm the diagnosis in a situation with multiple physiologic stressors.

28.23 Idiopathic Anaphylaxis

Idiopathic anaphylaxis is clinically identical to anaphylaxis following an identified trigger. This diagnosis is the most common explanation of adult anaphylaxis in several cohorts or case series. However, it is a diagnosis of exclusion, requiring a thorough evaluation for other explanations before accepting the diagnosis. Mast cell disorders should always be considered in this circumstance. Idiopathic anaphylaxis is classified as frequent or infrequent depending on whether more or less than 6 episodes occur in 12 months, respectively. Patients with idiopathic anaphylaxis should be educated and provided an autoinjector epinephrine. Potential preventive treatment includes oral corticosteroids which may be administered on an alternate-day schedule to reduce side effect and daily H1-blocking antihistamines. Montelukast, oral cromolyn, and ketotifen (not available in the USA) can be added. Patients who are resistant to those agents or experience the inevitable side effects of corticosteroid may benefit from the unapproved use of omalizumab, monoclonal antibody specific for IgE, or rituximab, monoclonal antibody specific for B lymphocytes. Fortunately, most patients experience remission after a few years, and the severity of this form of anaphylaxis is generally less with reduced mortality compared to other forms.

28.24 Exercise-Induced Anaphylaxis

Exercise-induced anaphylaxis occurs in the context of exercise and can be food dependent or independent. Symptoms include the typical anaphylaxis manifestations such as fatigue, flushing, generalized pruritus or urticaria, angioedema, wheezing, and cardiovascular collapse. The only unique feature is the condition only occurs during or following exercise. Foods implicated in food-dependent, exercise-induced anaphylaxis include wheat, nuts, celery, shrimp, and grains. The amount of food ingested, the processing and preparation of the food, concomitant NSAIDs or ethanol ingestion, and the timing and intensity of the exercise may affect the development of the syndrome (Celestin and Heiner 1993). The result of all of these mitigating factors is the possible inconsistent occurrence of anaphylaxis with exposure to the triggers. This entity could be a form of food anaphylaxis triggered by exercise. Exercise induced anaphylaxis unrelated to foods is probably due to undefined, physiologic triggers affecting mast cells during exercise. These potential triggers include endogenic substances such as endorphins and gastrin. Several cofactors in association with exercise may modulate this syndrome, including pre-exercise ingestion of NSAIDs and/or alcoholic beverages. Other factors may include high pollen counts in allergic subjects, infections, extreme heat and humidity, and menses in women. Patients with exercise-induced anaphylaxis should avoid eating at least 2 h before exercise, consider a medical alert bracelet, never exercise alone, and always carry epinephrine.

28.25 Seminal Fluid Anaphylaxis

Anaphylaxis to seminal fluid is very rare. Clinical manifestations of seminal fluid anaphylaxis include vaginal and generalized pruritus, urticaria, angioedema, wheezing, chest tightness, shortness of breath, dizziness, and loss of consciousness, occurring during or following unprotected sexual intercourse. Those reactions are not limited to one sexual partner but typically occur in the female during heterosexual intercourse. Diagnosis is by history and skin testing with fresh whole human seminal fluid or its fractions. Patients with seminal fluid anaphylaxis are generally older and have a protracted history of event occurrence. Some

affected subjects may be selectively sensitive to dog dander (Sublett and Bernstein 2011). Affected women have been successfully desensitized by the graded intravaginal administration of dilutions of seminal fluid or its extract (Friedman et al. 1984; Mittman et al. 1990). In some cases of seminal anaphylaxis that result in infertility, pregnancy has been achieved with intravaginal insemination using washed sperm (Frapsauce et al. 2010).

28.26 Catamenial Anaphylaxis

Catamenial anaphylaxis, also called progesterone-related anaphylaxis, is a syndrome that occurs in menstruating females. It is associated with the formation of specific IgE to progesterone. However, some patients with this condition may have negative skin testing or in vitro specific IgE for progesterone. This disease is characterized by recurrent premenstrual episodes of signs and symptoms of anaphylaxis. The diagnosis is established by the disappearance of the syndrome after chemical suppression of the premenstrual progesterone surge with leuprolide (Snyder and Krishnaswamy 2003). Leuprolide is a synthetic gonadotropin-releasing agonist that can suppress the production of both progesterone and estrogen from the ovaries. Affected women have been successfully desensitized to progesterone (Itsekson et al. 2011)

28.27 Fatal Anaphylaxis

Anaphylaxis can be fatal in up to 2% of the cases, up to 6% in perioperative anaphylaxis. In the largest series of fatalities associated with anaphylaxis in the UK (Pumphrey 2003), the causes of anaphylaxis were insect stings, allergic food ingestion, and administration of drugs, anesthetic agents, and radiocontrast materials. Patients with asthma were particularly at risk. The most common causes of death were airway obstruction, cardiovascular collapse, and disseminated intravascular coagulation (DIC). While most fatalities were the results of respiratory arrest due to upper airway obstruction during food anaphylaxis, the cause of death in most drug-induced or venom anaphylaxis was cardiovascular collapse and cardiac arrest. Some fatalities occurred when the patient changed position from supine to standing or sitting during treatment. The change in posture may have caused the empty ventricle syndrome characterized by pulseless electrical activity of the heart and subsequent cardiac arrest. This is attributed to the significant loss of intravascular volume and adequate venous return to the heart. For that reason, it is recommended that patients being treated for anaphylaxis remain in a supine position during the duration of the treatment. In that large series of 214 anaphylactic deaths, the median time for cardiac arrest was about 5 min for iatrogenic injections of medication or radiocontrast material, 15 min for venom and 30 min for food. Patients who died from anaphylaxis usually did not have the epinephrine autoinjector with them or experienced delay in the administration of epinephrine. Antihistamines and corticosteroids do not prevent cardiorespiratory arrest, take too long (between 50 and 100 min) to exert their effects, and do not interfere with the primary mediators of fatal anaphylaxis such as PAF and kinins (Vadas et al. 2013; Sala-Cunill et al. 2015). Therefore, those drugs should not be used in lieu of epinephrine even when treating presumably mild anaphylaxis or suspected anaphylaxis. Foods most commonly associated with fatal anaphylaxis were peanuts and tree nuts. In another series (Greenberger et al. 2007) of 25 anaphylaxis cases, identified causes of fatal anaphylaxis were medications, radiocontrast material, hymenoptera stings, and foods, in that order. Risk factors for fatal venom anaphylaxis include middle age, white race, cardiovascular disease, male gender, and possibly mastocytosis (Turner et al. 2017). Distinguishing post-mortem findings are minimal. However, blood can be obtained in the femoral vein for determination of serum tryptase and specific IgE to facilitate formulating an etiologic diagnosis. Tryptase may be nonspecifically increased by ischemia.

28.28 Conclusion

Anaphylaxis is a severe systemic reaction caused by the release of mast cell mediators. Histamine is probably the most commonly recognized mediator, and its injection can reproduce in animal models most of the signs and symptoms of anaphylaxis observed in humans. However, there are multiple other mediators that play significant roles, including several products of the metabolism of arachidonic acid. The incidence of anaphylaxis is increasing. Fortunately, its mortality has remained low.

The pathophysiology of anaphylaxis is complex. However, significant progress has been made in identifying the multiple cellular and biochemical players. Some cases that have been labeled idiopathic can now be shown to have a precise etiology, for example, in cases of c-kit mutation V816D associated with mast cell disorders.

Although there are criteria for the diagnosis of anaphylaxis, patients suspected of anaphylaxis should be treated even when all the criteria are not met, as delay in the administration of epinephrine could have life-threatening consequences and there are minimal side effects of low-dose, IM epinephrine.

Most commonly, anaphylaxis is due to the ingestion or administration of an antigen or mast cell activator such as a medication, food, radiocontrast material, and Hymenoptera venom. When the allergen is injected, symptoms are more likely immediate. However, for ingested offending agents, it may take up to 2 h or more for symptoms to appear. A range of signs and symptoms involving multiple systems typically occur. However, acute respiratory obstruction and cardiovascular collapse are the most serious and can develop in the absence of common signs such as urticaria, angioedema, and pruritus.

There are a number of factors that can predispose patients to anaphylaxis or complicate its severity and treatment. These include, but are not limited to, atopy, uncontrolled asthma, allergen immunotherapy, and concurrent medications such as beta-blockers and ACEIs. Patients with diagnosed or unrecognized mastocytosis and other mast cell disorders are particularly at risk of anaphylaxis.

The differential diagnosis is very extensive as several clinical entities can mimic anaphylaxis. Therefore, a high index of suspicion is required to differentiate anaphylaxis from other conditions. Clinical perspective will reduce the unnecessary use of epinephrine which, although very safe, is not without complications. However, when in doubt, epinephrine should be used. Antihistamine and corticosteroid therapies should not be substitutes for epinephrine.

Epinephrine should be used early in anaphylaxis to prevent cardiovascular collapse and airway obstruction which may be life-threatening. In patients who do not respond to repeated administration of parenteral epinephrine, IV fluids and inhaled beta-2 agonists should be administered early; the affected subject may need to be admitted to an intensive care unit to receive intravenous, diluted solution of epinephrine or other vasopressors and other advanced treatment and monitoring.

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Mast Cell Disorders and Anaphylaxis

29

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Contents

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Abstract

Mast cells arise from pluripotent stem cells. From the original identification of mast cells in the late 1800s, our understanding of these cells' normal function and role in pathologic disease has expanded greatly; and the understanding of mastocytosis has led to advances in classification and treatment of these diseases. The term mastocytosis describes a group of disorders characterized by abnormal proliferation of mast cells. Mast cell numbers are increased and pathologically infiltrate various organ systems, resulting in a spectrum of disorders from cutaneous mastocytosis (more common in children) to multiple subvariants of systemic mastocytosis, mast cell leukemia, and mastocytomas. Diagnostic criteria have been modified recently to aid in classifying the type of disease, which allows for better determination of both the prognosis and treatment. While treatment is largely symptomatic, with important focus on the management of anaphylaxis, several promising therapeutic targets and agents have recently been identified which may lead to improved survival in more advanced subtypes of disease. These therapies include several tyrosine kinase inhibitors which combat the activating KIT mutations present in most patients with aggressive mastocytosis.

Keywords

Mastocytosis · Mast cell · Diagnostic criteria · Tryptase · KIT D816V

29.1 Introduction

The term mastocytosis describes a group of disorders characterized by abnormal proliferation of mast cells. Mast cell numbers are increased and pathologically infiltrate the skin and other organs including the liver, spleen, bone marrow, and lymph nodes. In general, cutaneous mastocytosis (CM) refers to disease limited to the skin, and systemic mastocytosis (SM) refers to disease extending beyond the skin. In children, disease is typically restricted to the skin (CM), with low risk of progression to SM. Additionally, CM tends to regress over time in children.

In adults, disease can range from isolated skin involvement to a rare form of leukemia called mast cell leukemia. In adults, SM is characterized by symptoms of mast cell mediator release including pruritus, flushing, bronchospasm, abdominal discomfort, diarrhea, musculoskeletal pain, and episodic hypotension (Carter et al. 2014).

Indolent systemic mastocytosis (ISM) is the most common subtype of systemic disease and carries a good prognosis with similar survival to healthy individuals. Other subtypes of disease are more aggressive and thus often have a poorer 5-year survival rate; these include aggressive SM (ASM), SM with associated hematologic disease (SM-AHD), and mast cell leukemia (MCL) (Onnes et al. 2016). In these more severe subtypes, organ infiltration can also lead to hepatomegaly, cytopenias, and pathologic fractures. Different subtypes are characterized by B findings which describe an extensive degree of organ infiltration without organ dysfunction and C findings which describe resulting organ dysfunction (International Agency for Research on Cancer and World Health Organization 2008). Patients can also present with a solitary mastocytoma or mast cell sarcoma (MCS), the latter of which has a high rate of transformation to MCL (Valent et al. 2017a).

The diagnosis of SM depends on history and physical examination as well as biopsy results and examination for organ involvement and dysfunction. Accurate diagnosis of the subtype of disease is crucial as it provides important prognostic information and determines appropriate treatment, which can range from symptomatic management to systemic chemotherapy. Mast cell activation syndrome is also a disease of inappropriate mast cell activation, with less defined diagnostic criteria than CM and SM, whose treatment is primarily aimed at symptom control (Akin 2017). This chapter will review presentations, diagnosis, and treatment of these complex disorders.

29.2 Historical Perspective

The history of mastocytosis dates to 1869, when Nettleship and Tay describe a "rare form of urticaria that results in a brownish discoloration" (Nettleship 1876), a skin lesion that would later be known as urticaria pigmentosa (UP), as termed by Sangster in 1878 (Thompson 1893). In 1879, Paul Ehrlich identified and described the mast cell (Beaven 2009). Over time, the classification of mastocytosis evolved into two major variant forms, CM and SM. The distinction is based on discoveries associating mast cell hyperplasia with cutaneous and systemic pathologic conditions. In 1894, Unna would demonstrate mast cells in UP skin lesions (later classified as CM), and, in 1949, Ellis would perform an autopsy of a child with a fatal case of UP and recognize multi-organ infiltration of mast cells (later classified as SM) (Lehner 1926; Ellis 1949; Gülen et al. 2016).

As understanding of the complexity of the disease process improved, researchers would further divide cutaneous and systemic mastocytosis into subvariant categories. Classification schemes would evolve with Metcalfe providing the first proposal in 1991 (Metcalfe 1991a). This would later be adopted into our current guidelines in the World Health Organization diagnostic criteria in 2001 (Valent et al. 2001), which have been slightly modified in a subsequent update (Arber et al. 2016).

The confirmation of the diagnosis and management of mastocytosis is still reserved to a few medical specialties that have experience with the disease. The expanded clinical availability of testing, such as mutational analysis for the most common mutation responsible for mast cell disorders, a substitution of valine for aspartic acid (ASP 816 VAL, or D816V), as well as serum tryptase levels, has increased the recognition and diagnosis of mastocytosis. In this chapter, we hope to bridge the educational gap that still remains.

29.3 Epidemiology

Mastocytosis is a rare disorder and thus there are very few epidemiologic studies to estimate the incidence and prevalence of this disease, and no studies have examined this in the United States. Additionally, standardized criteria for the diagnosis of mastocytosis have only been in existence since 2001 (Valent et al. 2001). Specific criteria

coupled with improved laboratory detection methods have led to increasingly frequent diagnosis and consideration of the disorder (Brockow 2014). In a Dutch study, the prevalence of ISM among adults was estimated to be 13 cases per 100,000 inhabitants (van Doormaal et al. 2013). The experience of other centers reported at a meeting of mastocytosis experts in Boston in 2010 was similar to this number with an estimated cumulative prevalence of 1 in 10,000 people (Brockow 2014). In a 2014 Danish study which reviewed the period from 1997 to 2010, the nationwide incidence and prevalence were 0.89 per 100,000 persons per year and 9.59 per 100,000 persons in patients aged 15 years or older, respectively. In this cohort, 82% of patients were diagnosed with indolent systemic mastocytosis (ISM), 11% had SM of unknown subtype, 4% were classified as mastocytosis with an associated hematologic non-mast cell disorder (SM-AHN), 2% had aggressive SM (ASM), and 1% had a diagnosis of mast cell leukemia (MCL) (Cohen et al. 2014).

In childhood, the vast majority of cases involve only the skin, with 90% being diagnosed before age 2 years, and skin lesions tend to regress overtime (Méni et al. 2015). In adults, disease restricted to the skin is less common. In the Danish study above, most adult patients were diagnosed with systemic mastocytosis in middle age (mean age 46–61 years) with patients with MCL presenting later in life (mean age 75.4 years) (Cohen et al. 2014). Females and males are similarly affected although predominance is slightly higher in males in childhood with this trend reversing in adulthood (Méni et al. 2015). In the previously mentioned Danish study, ISM was substantially more common in females than males (62% vs. 38%), with a slight female predominance in all other subtypes except MCL which was more common in males (Cohen et al. 2014). The diagnosis of associated disorders including monoclonal mast cell activation syndrome (MMAS) and idiopathic mast cell activation syndrome (IMCAS) is less standardized and this, in combination with the presumed rarity of these disorders, makes their incidence and prevalence difficult to estimate (Brockow 2014).

29.4 Mast Cell Biology and Mastocytosis Pathogenesis

29.4.1 Mast Cell Biology Overview

Mast cells (MCs) are important effector cells of the immune system (Table 1) (Abbas et al. 2017). Normally, mature MCs are not found in circulation but can be located throughout connective tissues and mucosal surfaces. MCs are stimulated to migrate to tissues and grow by means of a growth factor called stem cell factor (SCF), which works on the MCs via signals through the tyrosine kinase KIT (CD117) receptor on the mast cell. MCs differentiate (mature) in various tissues and will express another important cell surface receptor, the high-affinity Fc epsilon receptor for IgE (FcεRI), which, when engaged, transmits signals to activate the mast cell. The primary mast cell function is to initiate inflammation and repair in response to tissue damage initiated by diverse stimuli. Upon activation, MCs release various mediators (such as proteases, cytokines, histamine, and heparin). Human MCs vary and their heterogeneity in phenotype allows for functional versatility. Understanding mast cell biology has clinical implications in host protection, disease progression, allergy development, and mastocytosis.

MCs play a protective role in wound repair, angiogenesis, immune tolerance, and defense against pathogens. However, in the setting of ongoing tissue insult, MCs can have sustained release of numerous proinflammatory mediators that damage these tissues and contribute to the pathophysiology of chronic disease states such as pulmonary fibrosis, rheumatoid arthritis, and atherosclerosis. MC activation by allergens contributes to the development of allergic diseases including asthma, rhinitis, conjunctivitis,

Table 1 Properties of mast cells

Characteristics	
Major site of maturation	Bone marrow precursors mature in connective tissue and mucosal tissue
Location of cells	Connective tissue and mucosal tissues
Life span	Weeks to months
Major growth and differentiation factor (cytokines)	Stem cell factor (SCF), IL-3
Expression of FcεRI	High
Major granule contents	Histamine, heparin, and/or chondroitin sulfate, proteases
Biologic effects of mediators	
Major granule contents (Histamine, tryptase and/or chymase, acid hydroxylases, heparin, cathepsin G, carboxypeptidase)	Tissue damage, vasodilation, vascular leak, degradation of microbial structures
Lipid mediators produced on activation (PGD_2, Leukotrienes C_4, D_4,E_4, PAF)	Bronchoconstriction, vasodilation, vascular leak, inflammation, intestinal hypermotility, mucus secretion
Cytokines produced on activation TNF, IL-3, MIP-1α IL-4, IL-13, IL-5	Mast cell proliferation, inflammation IgE production, mucus secretion eosinophil production, and activation

Reference: Abbas et al. (2017)
FcεRI Fcε receptor type I, *IL* interleukin

atopic dermatitis, urticaria, and anaphylaxis (Onnes et al. 2016). Inappropriate MC activation caused by genetic mutations, particularly by gain-of-function mutations in the mast cell's stem cell factor receptor KIT (CD117), is crucial in the development of mastocytosis (Onnes et al. 2016).

29.4.2 Mast Cell Development and Survival

MCs are derived from pluripotent hematopoietic precursor cells ($CD34^{+/}CD117^{+}$ (KIT)) of the bone marrow. Immature MCs leave the bone marrow and are recruited to tissues that mainly separate the outside world from the internal milieu, such as the skin, lung, and gastrointestinal tract. Stromal cells within these tissues produce stem cell factor (SCF), a chemotactic cytokine involved in migration of MC. In addition to SCF, there are other mast cell chemoattractants involved in recruiting (homing) MCs to specific tissues. It is in these peripheral tissues that MCs reside, and it is under the influence of SCF and the particular local cytokine milieu (IL-3, IL-4, IL-5, IL-6, IL-9, IL-15) that MCs develop and complete their maturation (Ribatti 2016; Kovalszki and Weller 2014). MC migration, growth, and survival are made possible by SCF binding with KIT (CD117), which is highly expressed on hematopoietic stem cells from the bone marrow (Onnes et al. 2016). MC differentiation occurs under the control of local cytokines, the tissue matrix, and resident cells, such as fibroblasts. These factors, as well as the MCs' particular receptor expression, cytokine content, and immunologic and nonimmunologic activation will have profound influence over the MC phenotype and, in turn, allows for versatility in MC function.

MCs secrete a plethora of autacoids, proteases, and cytokines that are relevant to the pathophysiology of allergy. Depending on the site of mediator release, acute signs and symptoms manifest clinically as rhinitis, conjunctivitis, urticaria, angioedema, erythema, bronchospasm, diarrhea, vomiting, and/or hypotension, all which can be fatal in severe reactions (such as anaphylactic shock).

29.4.3 Mechanism of Mast Cell Activation

MC activation occurs by both immunogenic, predominantly immunoglobulin E (IgE)-mediated, as well as nonimmunologic pathways. In allergic reactions, MC activation occurs primarily through an IgE-mediated immunologic mechanism. IgE, like other antibodies, is made exclusively by B

cells (specifically the plasma cells derived from B cells). IgE selectively binds to MCs via the high-affinity FcεRI expressed on the cell membrane. In individuals allergic to a particular antigen/allergen, exposure to that allergen can cause a large proportion of specific IgE to be made to that antigen. Subsequent cross-linking of the antigen to the IgE prebound to the FcεRI mast cell surface receptor can then trigger MC activation. Upon MC activation, pro-inflammatory mediators stored in MC granules are secreted by degranulation or mediators are synthesized de novo, resulting in an immediate hypersensitivity allergic reaction. MCs are also activated by a plethora of non-IgE-dependent stimuli that are relevant to many disease processes such as asthma.

29.5 Mastocytosis Pathogenesis

29.5.1 D816V KIT Mutation

The one obligatory growth factor for human MC proliferation and survival is SCF, which acts by means of signaling through KIT (CD 117). Although other hematopoietic precursor cells also signal through the KIT receptor, expression of KIT is generally lost during the differentiation process of most hematopoietic cells. MCs, however, retain KIT throughout their lifespan. It is from the work of Nagata et al. in 1995 that the D816V mutation was identified in patients with mastocytosis and associated hematologic conditions. Subsequently, the same mutation was identified in adult patients with different forms of mastocytosis in tissues where mast cells are abundant, such as bone marrow, skin, and spleen (Brockow and Metcalfe 2010). In 2012, Kristensen et al. reported that circulating D816V mutation-positive, non-mast cells could be detected in peripheral blood samples in 25 of 25 patients with indolent systemic mastocytosis, demonstrating for the first time that detectable D816V mutation in peripheral blood was a marker of SM with high specificity and sensitivity compared to healthy subjects (Brockow and Metcalfe 2010).

It is now believed that the basis of mastocytosis is predominantly due to this activating D816V mutation, but this mutation is not specific to mastocytosis, as it is also identified in other myeloid neoplasms, including myelodysplastic syndromes (MDS), myeloproliferative neoplasms (MPN), or MDS/MPN overlap syndromes (Schwaab et al. 2013). There is no convincing evidence that the D816V mutation is inherited but is a spontaneous genetic variation (Schwaab et al. 2013; Schuch and Brockow 2017).

In adults with SM, the estimated frequency of the D816V mutation is >80% with the remainder involving other genetic polymorphisms, including RAS, CBL, and TET2 gene mutations. Ras is a family of related proteins belonging to a small guanine nucleotide–binding protein (G protein) class that is involved in the activation response for T-cells and a variety of other cell types. CBL is an ubiquitin ligase involved in terminating T-cell responses. TET2 is a gene that encodes a protein that catalyzes the conversion of the modified DNA-base methylcytosine to 5-hydroxymethylcytosine. In children with CM, the D816V mutation occurs in 15–20%, with the remainder involving other KIT (CD 117) molecular abnormalities (KIT D816Y, KIT D816F, KIT E839K, KIT K509I) (Valent 2015).

29.5.2 Other Molecular Lesions

While "overactive" KIT (CD 117) mutations are present in most patients with mastocytosis, secondary or coexisting molecular events are thought to give rise to mastocytosis disease variants. Such secondary or coexisting events, including the presence of additional mutations in genes that encode signaling molecules (CBL, JAK2, KRAS, NRAS), transcription factors (RUNX1), epigenetic regulators (ASXL1, DNMT3A, EZH2, TET2), or splicing factors (SRSF2, SF3B1, U2AF1), have been reported in KIT D816V^{+} SM patients with advanced disease (Schwaab et al. 2013; Pardanani 2016; Theoharides et al. 2015; Cruse et al. 2014).

For patients with SM, the type and number of lesions (mutations) detectable correlates with prognosis, drug response, and survival (Schwaab et al. 2013). Pro-oncogenic kinases can be detected in neoplastic cells and may be responsive to tyrosine kinase inhibitors (TKIs) (Theoharides et al. 2015).

29.6 Classification of Disease and Diagnosis

The World Health Organization (WHO) classifies mastocytosis into cutaneous mastocytosis (CM), systemic mastocytosis (SM), mast cell leukemia (MCL), and mast cell sarcoma (MCS) (Table 2). This classification system provides not only a framework to characterize the subsets of mastocytosis, but, more crucially, it is of prognostic value in the initial stages of patient evaluation (Valent et al. 2017a). It is further divided into subgroups that vary tremendously in prognosis, from benign courses seen in subvariants of CM to widely divergent outcomes in the SM subvariants. The disease course seen in SM subvariants ranges from indolent with normal life expectancy in the ISM subvariant to life-threatening with rapid deterioration in the MCL subvariant. The prognostic variation of the SM subsets is laid out in the framework of the WHO classification as a benign subvariant (indolent systemic mastocytosis, ISM), a progressive subvariant (smoldering systemic mastocytosis, SSM), as well as leukemic and other aggressive subvariants (SM-AHN; MCL; MCS).

29.6.1 Cutaneous Mastocytosis (CM) Classification

CM, a common presentation of mastocytosis in children, means there is generally no evidence of pathologic mast cell accumulation in tissues other than the skin. CM is divided into three major variants – urticaria pigmentosa (UP) which is also termed maculopapular cutaneous mastocytoma (MPCM), cutaneous mastocytoma, and, less commonly, diffuse cutaneous mastocytosis (DCM). A subsequent consensus report from a task force (Hartmann et al. 2016) provides further refinements to criteria for cutaneous involvement in patients with mastocytosis. This task force has not replaced

Table 2 Classification of mastocytosis

Categories of mast cell disorders (Bold)	Abbreviations	Subvariants
Cutaneous mastocytosis	CM	
Urticaria Pigmentosa=Maculopapular CM	UP/MPCM	Variants: monomorphic versus polymorphic
Cutaneous mastocytoma		
Diffuse cutaneous mastocytosis	DCM	
Systemic Mastocytosis	SM	
Indolent systemic mastocytosis	ISM	
Smoldering systemic mastocytosis	SSM	
Aggressive systemic mastocytosis	ASM	
Mastocytosis with an associated hematologic non-mast cell disorder	SM-AHN	SM-acute myeloid leukemia (AML) SM-myelodysplastic syndrome (MDS) SM-MPN SM-chronic myelomonocytic leukemia (CMML) SM-chronic eosinophilic leukemia (CEL) SM-non-Hodgkin lymphoma (NHL) SM-myeloma
Mast cell leukemia	MCL	
Mast cell sarcoma	MCS	

References: Valent et al. (2017a), Arber et al. (2016), Weiler and Butterfield (2014), Hartmann et al. (2016)
SM with clonal hematologic non–mast cell-lineage disease (SM-AHN)

the classification developed in 2007 by the European Union-US consensus group (Valent et al. 2007), but it has suggested several modifications, including the removal of telangiectasia mascularis eruptiva perstans (TMEP) from the current classification of CM and removal of the term "solitary" from the diagnosis of solitary mastocytoma. The prognosis for childhood-onset CM is favorable as the disease typically occurs in the first year of life with resolution or fading of skin lesions by puberty. The prognosis for adult-onset CM is less favorable as it is marked by a chronic course with progression to systemic involvement (Hartmann et al. 2016).

29.6.2 Cutaneous Mastocytosis (CM) Diagnosis

The diagnosis of CM is established when 1 major criteria and at least one minor "skin-criteria" are fulfilled (Box 1) (Valent et al. 2007). The major criteria, as recommended by Valent et al. (2007), includes (I) the presence of a typical skin rash that is maculopapular and intensifies upon rubbing (Darier's sign) or (II) an atypical rash with Darier's sign demonstrated and other skin diseases excluded by laboratory studies as well as by histological examination. The minor CM criteria include (I) histology demonstrating mast cell (MC) infiltrate consisting of either large aggregates of tryptase-positive mast cells ($\geq$15 cells/cluster) or scattered mast cells exceeding 20 cells per microscopic high-power field ($\times$40) (Valent et al. 2007); (II) D816V mutation at codon 816 in RNA extracted from a lesional skin biopsy specimen.

Patients with mastocytosis in the skin can qualify as having CM (predominant in children) or more extensive SM including cutaneous involvement (predominant in adults). Therefore, for CM subvariants, the evaluation for SM should be considered in all adult patients and also in all children with following: (I) the serum tryptase is high and/or constantly increasing and/or (II) other signs of a systemic disease (e.g., cytopenia, leukocytosis, abnormal differential count, hepatomegaly, splenomegaly, and/or lymphadenopathy) occur.

Box 1 Diagnostic algorithm for cutaneous mastocytosis

Major criterion	Typical skin rash associated with Darier's sign
Minor criteria	Lesional skin biopsy: Mast cell aggregates (>15 MC/cluster) **or** monomorphic infiltrate (>20 MC/HPF) **or** KIT D816V

29.6.3 Systemic Mastocytosis (SM) Classification

SM is the most common presentation of mastocytosis in adults and is defined by multifocal infiltration of mast cells in various internal organs, including the bone marrow, spleen, liver, and gastrointestinal tract.

The subclassification of SM into its subvariants, Table 2, is decided once a diagnosis of SM is established by major and minor criteria. The SM variants include: ISM, SSM, ASM, and SM-AHN. Other mast cell neoplasms that can be associated with systemic mastocytosis include MCL and MCS. Due to its infrequent presentation, Extracutaneous Mastocytoma (ECM) has been removed from the updated classification (Valent et al. 2017a).

ISM, the most common SM, means the bone marrow examination shows abnormal mast cell collections but the mast cell infiltration causes no end-organ damage or hematologic disease. The prognosis is favorable usually with normal lifespan (Pardanani 2016).

SSM, previously categorized as a subvariant of ISM, is now provisionally a separate SM category in the 2016 updated WHO classification. The prognosis is less favorable compared with ISM but favorable compared with ASM or MCL (Valent et al. 2017a).

ASM, a less frequent (approximately 5%) subset of SM, is characterized by MC propagated end-organ damage. It is classified as either

"untransformed ASM" or "ASM in transition to MCL" (ASM-t), the latter being more severe. The prognosis is poor as there is a markedly accelerated course resembling malignancy (Valent et al. 2017a).

SM-AHN, often a progression of SM seen in up to 20% of patients with SM, is defined by the presence of a second bone marrow disease. The second hematologic abnormality is usually characterized by myeloproliferative or myelodysplastic features. The prognosis depends on the course of the second hematologic disease (Pardanani 2016).

29.6.4 Systemic Mastocytosis (SM) Diagnosis

SM diagnosis is established when the major and at least one minor criterion are established. Alternatively, SM can be diagnosed if three minor criteria are detected. The major and minor criteria for SM are shown in Box 2 (Pardanani 2016). Diagnosis based on major and minor criteria necessitate the expertise of a hematopathologist. The major criterion in the diagnosis of SM involves demonstration of compact mast cell infiltrates (at least 15 mast cells in aggregates) in sections of bone marrow or in other extracutaneous organ(s) detected by tryptase-immunohistochemistry (IHC).

The minor SM criteria include examination of extracutaneous tissues (with bone marrow as the recommended organ for screening) for (I) biopsies showing clusters of >25% of mast cells demonstrating an atypical morphology (immature forms, spindling, decentralized oval nuclei or bi- or poly-lobed nuclei, hypogranulated cytoplasm), (II) detection of a D816V mutation in bone marrow, (III) an aberrant immunophenotype MC expression of CD2 and/or CD25 in addition to normal mast cell markers, and (IV) persistent serum tryptase of >20 ng/mL (noted, this parameter is not valid for SM-AHN) (Valent et al. 2007, 2017a; Pardanani 2016).

Systemic mastocytosis subvariant (ISM, SSM, ASM, SM-AHN) diagnoses are based on criteria defining the spread of disease such as mast cell-burden and involvement of non-mast cell-lineages (B-Findings), as well as aggressiveness of disease (C-Findings). In addition, a thorough hematological evaluation is necessary to reveal or exclude the potential of an associated hematologic disorder (Valent et al. 2007). B findings include: >30% bone marrow (BM) mast cells on biopsy and/or serum tryptase levels >200 ng/mL; increased marrow cellularity/dysplasia without meeting diagnostic criteria for another myeloid neoplasm; or enlargement of liver, spleen, or lymph nodes without evidence of organ damage (Valent et al. 2017a). C findings include: evidence of organ damage caused by a local mast cell infiltrate, such as abnormal liver function and/or ascites, hypersplenism, cytopenias, large osteolytic lesions/fractures, and malabsorption with weight loss caused by mast cell infiltration in the gastrointestinal tract (Valent et al. 2017a).

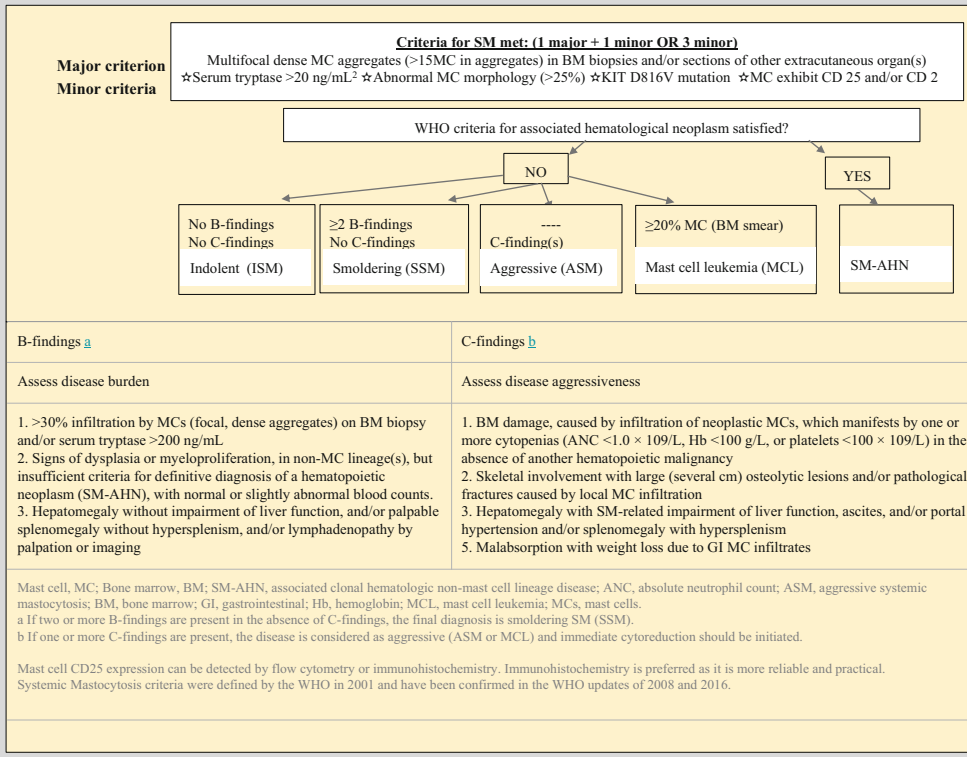
ISM, the most common SM, is defined by abnormal mast cell collections on BM examination but no other hematologic disease (no AHNMD), and absence of end-organ damage attributable to mast cell infiltration (no C-findings) (Pardanani 2016).

SSM has the same features of ISM (no AHNMD, no C-findings) and has ≥2 B-findings (Valent et al. 2017a).

ASM is defined by end-organ damage caused by a mast cell infiltration (C-findings) and no evidence of MCL. Once ASM is diagnosed, it is further classified based on BM smear mast cell percentage into (I) untransformed ASM (<5% Mast cells in BM smears) or (II) ASM-t (≥5% but less than 20% mast cells in BM smears) (Valent et al. 2017a). Relevant findings include mutation analysis almost always showing the D816V mutation. When the percentage of mast cells in the BM smear reaches 20%, the diagnosis changes from ASM-t to MCL per definition (Valent et al. 2017a).

SM-AHN is associated with a second BM disease that is usually with myeloproliferative or myelodysplastic features.

Box 2 Diagnostic Algorithm for Systemic Mastocytosis



B-findings a	C-findings b
Assess disease burden	Assess disease aggressiveness
1. >30% infiltration by MCs (focal, dense aggregates) on BM biopsy and/or serum tryptase >200 ng/mL 2. Signs of dysplasia or myeloproliferation, in non-MC lineage(s), but insufficient criteria for definitive diagnosis of a hematopoietic neoplasm (SM-AHN), with normal or slightly abnormal blood counts. 3. Hepatomegaly without impairment of liver function, and/or palpable splenomegaly without hypersplenism, and/or lymphadenopathy by palpation or imaging	1. BM damage, caused by infiltration of neoplastic MCs, which manifests by one or more cytopenias (ANC <1.0 × 109/L, Hb <100 g/L, or platelets <100 × 109/L) in the absence of another hematopoietic malignancy 2. Skeletal involvement with large (several cm) osteolytic lesions and/or pathological fractures caused by local MC infiltration 3. Hepatomegaly with SM-related impairment of liver function, ascites, and/or portal hypertension and/or splenomegaly with hypersplenism 5. Malabsorption with weight loss due to GI MC infiltrates

Mast cell, MC; Bone marrow, BM; SM-AHN, associated clonal hematologic non-mast cell lineage disease; ANC, absolute neutrophil count; ASM, aggressive systemic mastocytosis; BM, bone marrow; GI, gastrointestinal; Hb, hemoglobin; MCL, mast cell leukemia; MCs, mast cells.
a If two or more B-findings are present in the absence of C-findings, the final diagnosis is smoldering SM (SSM).
b If one or more C-findings are present, the disease is considered as aggressive (ASM or MCL) and immediate cytoreduction should be initiated.

Mast cell CD25 expression can be detected by flow cytometry or immunohistochemistry. Immunohistochemistry is preferred as it is more reliable and practical.
Systemic Mastocytosis criteria were defined by the WHO in 2001 and have been confirmed in the WHO updates of 2008 and 2016.

29.6.5 Mast Cell Leukemia (MCL) Classification

MCL, a rare subset of SM, can result from progression of ASM and MC sarcoma. The classification of MCL into subvariants is complex. It is classified as classical MCL or aleukemic MCL. It is also classified into an acute (aggressive) form or a chronic form. The acute form includes organ damage, termed C-findings, whereas the chronic form does not. In several of these cases, circulating mast cells are found. Prognosis is grave, with most MCL patients having primary drug resistance and median survival time <1 year (Valent et al. 2017a).

29.6.6 Mast Cell Leukemia (MCL) Diagnosis

ASM-t and mast cell sarcoma can progress into MCL. Note that the primary criterion to-diagnose MCL in the updated WHO classification is a percentage count of >20% mast cells in bone marrow aspirate smears. Once MCL is diagnosed, it is further classified based on peripheral blood mast cell percentage into the (I) classical MCL (mast cells compose >10% of all circulating white blood cells) or the more frequent form of (II) aleukemic MCL (mast cells compose <10%). MCL is also classified based on acute and chronic forms. The chronic form is without organ damage (no C-findings present) and a more aggressive

(acute) variant, termed acute MCL with organ damage (C-findings) (Valent et al. 2017a).

Other relevant findings include peripheral blood eosinophilia, basophilia, or an increase in blasts (see also SM-AHNMD). A proportion of MCL cases may not exhibit the D816V mutation. If dysplasia is prominent, the patient should be examined for additional signs of smoldering SM (SSM) or an associated myelodysplastic syndrome (MDS).

29.6.7 Mast Cell Sarcoma (MCS) Classification

MCS is an extremely rare variant of solid mast cell tumors. MCS is a local tumor that consists of immature mast cells and has sarcoma-like growth into adjacent tissues (Valent et al. 2017a). The prognosis of MCS is grave with median survival of less than 18 months and potential to progress to mast cell leukemia (Monnier et al. 2016).

29.6.8 Mast Cell Sarcoma (MCS) Diagnosis

MCS is diagnosed based on the clinical presentation of a tumor invading nearby tissue, with tumor cells staining positive for KIT (CD 117). MCS shows high grade cytology and has metastatic potential (Monnier et al. 2016).

29.7 Clinical Features and Patient Evaluation

29.7.1 General Clinical Features

The variable clinical presentations of mastocytosis can often be attributed to the location of pathologic MC accumulation, which is most commonly in the skin, gastrointestinal tract, and bone marrow, followed by liver, spleen, and lymph nodes, and can be associated with hematologic disorders. In Fig. 1 we discuss the clinical features of mastocytosis.

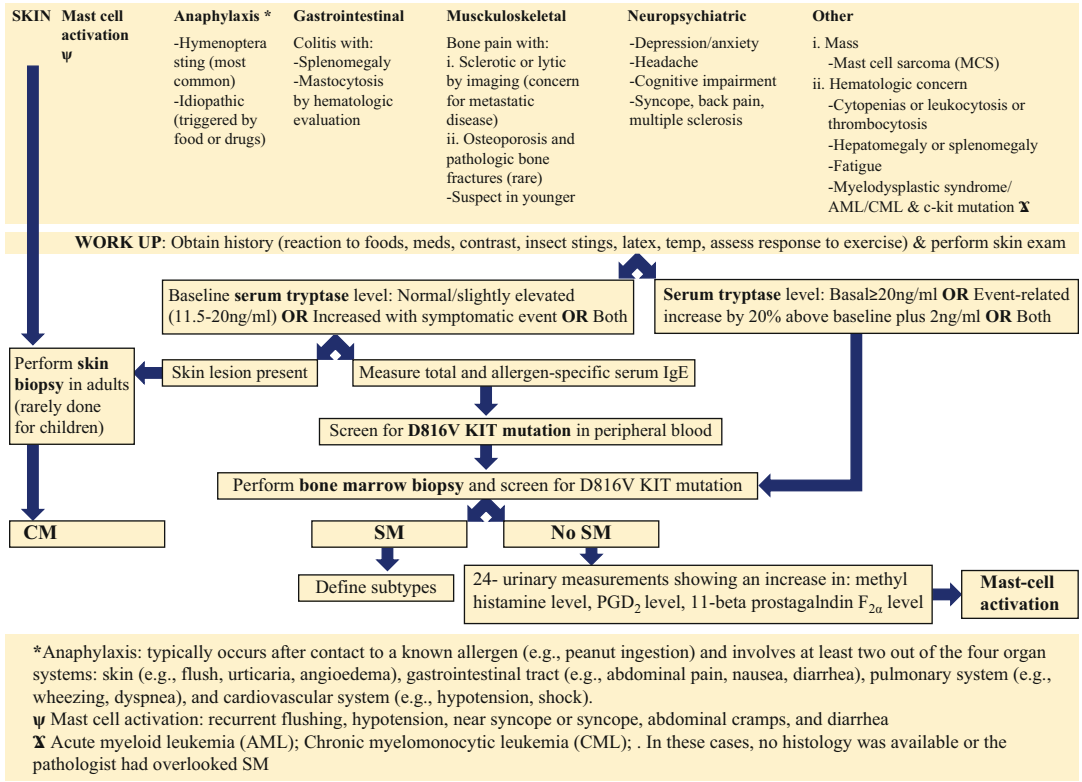
Note that the diagnosis of SM in the absence of skin involvement is considerably more challenging, especially in cases of an ISM variant with low mast cell burden. Therefore, a high index of suspicion is required in the setting of recurrent unexplained anaphylaxis, gastrointestinal (e.g., colitis), musculoskeletal (e.g., bone pain, back pain), neuropsychiatric symptoms (e.g., depression, anxiety, headache, cognitive impairment, syncope), mass (e.g., mast cell sarcoma can affect any part of the body but has been reported to affect the larynx, colon, small bowel, tibia and temporal bones, buccal mucosa), or hematologic concern (e.g., cytopenias or leukocytosis, or thrombocytosis, hepatosplenomegaly, fatigue) Fig. 1 (Pardanani 2016; Rossini et al. 2014).

The text will navigate the particular clinical manifestations of mastocytosis outlined in this figure. Note that in SM, tryptase levels reflect MC burden.

29.7.2 General Patient Evaluation

The general SM evaluation usually includes: (I) skin biopsy if skin lesions (including tan maculopaupular lesions that urticate on rubbing, nodules, or telangiectatic lesions) are present, (II) serum tryptase level, (III) serum and bone marrow evaluation for D816V KIT mutation. While serum tryptase levels are elevated in the vast majority of SM patients across all WHO subgroups, cases of AML, CML, and MDS may exhibit elevation in serum tryptase. Therefore, serum tryptase has limited diagnostic utility when a patient has a concomitant SM-associated myeloid neoplasm.

Bone marrow biopsy is part of the initial diagnostic workup of SM as the bone marrow is almost always involved in SM, and, importantly, the histopathologic aspects of mast cell disease are not well characterized in other tissues (Pardanani 2016; Akin and Valent 2014).



*Anaphylaxis: typically occurs after contact to a known allergen (e.g., peanut ingestion) and involves at least two out of the four organ systems: skin (e.g., flush, urticaria, angioedema), gastrointestinal tract (e.g., abdominal pain, nausea, diarrhea), pulmonary system (e.g., wheezing, dyspnea), and cardiovascular system (e.g., hypotension, shock).
ψ Mast cell activation: recurrent flushing, hypotension, near syncope or syncope, abdominal cramps, and diarrhea
ϫ Acute myeloid leukemia (AML); Chronic myelomonocytic leukemia (CML); . In these cases, no histology was available or the pathologist had overlooked SM

Fig. 1 Clinical manifestations of mastocytosis

29.7.3 Specific Clinical Features

29.7.3.1 Skin Lesions

The skin lesions of mast cell disease vary considerably, depending on the subform of cutaneous involvement, discussed above. Symptoms and signs of mastocytosis in the skin are related to mast cell degranulation, which can occur spontaneously or in response to physical stimuli, fever, some medications, vaccines, surgery, stress, and anxiety, among other triggers (Table 3).

A thorough skin examination is the first step in determining the subform of CM (MPCM, DCM, mastocytoma) (Fig. 2) (Hartmann et al. 2016). Cutaneous manifestations include Darier's sign, blistering, itch, dermatographism, erythema, and edema (Hartmann et al. 2016). Darier's sign is best elicited by stroking the lesion about five times with a tongue spatula, applying moderate pressure. Within a few minutes, a wheal of the lesion only, not surrounding skin, will occur. H1 antihistamines may blunt this response. Due to the high density of skin MCs in DCM, nodular form of MPCM, or mastocytoma, elicitation of Darier's sign can result in potentially massive MC degranulation that could result in severe symptoms such as flushing and hypotension and, as such, should be performed gently with close monitoring or should not be done at all (Hartmann et al. 2016).

29.7.3.2 Maculopapular Cutaneous Mastocytosis (MPCM)

MPCM, also called UP, is the most common subtype of CM in both adults and children. In adulthood, the lesions tend to be monomorphic (same size) small brown macules and papules (Fig. 2) (Rothe et al. 2016). In infancy and early childhood, they tend to be polymorphic (different size) (Hartmann et al. 2016) tan-orange plaques, often several centimeters in diameter, as well as nodular and blistering lesions (Fig. 2) (Hartmann et al.

Table 3 Potential triggers of mastocytosis resulting in symptoms as severe as anaphylaxis

Medications		
General anesthesia (succinylcholine, atracurium, rocuronium) Local anesthetics Nonsteroidal anti-inflammatory drugs (NSAIDs)	Acetylsalicylic acid Opiates Dextromethorphan Contrast media	β-lactam antibiotics Vancomycin Amphotericin B Polymyxin B Thiamine
Foods		
Food allergy (galactose-α-1,3-galactose, fish, shellfish)	Spicy foods	Alcohol
Bites/stings		
Hymenoptera venom	Jellyfish stings	Snake bites
Physical stimuli		
Rapid changes in temperature Stroking or rubbing of skin lesions	Exposure to heat/cold	Fever Sun exposure
Other		
Psychological stress, anxiety Idiopathic (often in children)	Infections Surgery	Strenuous exercise

2016; Akin and Valent 2014). MPCM lesions are located at irritation-prone sites such as the thighs and axillae (in children and adults) and spare the palms and sun exposed areas such as face (in adults). MPCM lesions are nonpruritic at baseline; however, they may itch with the triggers of mast cell degranulation mentioned above. Unlike urticaria, MPCM lesions do not migrate.

29.7.3.3 Diffuse Cutaneous Mastocytosis (DCM)

Diffuse cutaneous mastocytosis (DCM), a rare form of CM occurring at birth or early infancy, usually presents with more severe symptoms, often with extensive skin involvement in which torso and scalp are mostly affected. DCM may show a "peau d'orange," "crocodile-like pachydermia," or "elephant skin" appearance (Fig. 3). Blistering and hemorrhagic bullae also may occur. Children with bullous DCM may have a greater risk of anaphylactic shock and fatality than children with other subtypes (Hartmann et al. 2016; Matito et al. 2018).

29.7.3.4 Mastocytoma

Mastocytomas are now more appropriately called cutaneous mastocytomas (Fig. 2). Histologically, mastocytomas are indistinguishable from DCM in that both demonstrate massive MC infiltration occupying the whole dermis. Clinically mastocytomas present as one to three brown to yellowish nodular lesions that frequently involve the trunk or extremities and can be associated with blistering (Fig. 4). Patients exhibiting four or more lesions are categorized as MPCM. Although MPCM and DCM occur in adults, mastocytoma occurs at birth or develops within the first months of life (Hartmann et al. 2016).

29.7.4 Specific Patient Evaluation

29.7.4.1 Cutaneous Mastocytosis (CM) Evaluation

Due to the generally low risk of systemic involvement in children, the approach to diagnosis is different than in adults and depends largely on the index of clinical suspicion of heavy mast cell burden plus the presence of symptoms that suggest systemic disease. CM is often a clinical diagnosis marked by visualization of UP-like skin lesions and elicitation of Darier's sign, as discussed above (Fig. 2) (Rothe et al. 2016). Once CM is suspected or diagnosed, the next step is to decide whether the patient needs laboratory testing (with complete blood cell count with differential, serum tryptase, and liver function tests) and/or bone marrow (BM) biopsy to evaluate for systemic involvement (SM). Invasive testing (bone marrow biopsy) to confirm the diagnosis is rarely needed for children and should be considered in children demonstrating systemic symptoms (e.g., flushing, diarrhea, or abdominal pain), persistently elevated serum tryptase level of >20 μg/L (or an increasing trend in serial measurements), abnormal complete blood count or liver or spleen enlargement, skin lesions persisting after puberty, or bone pain (Fig. 1)

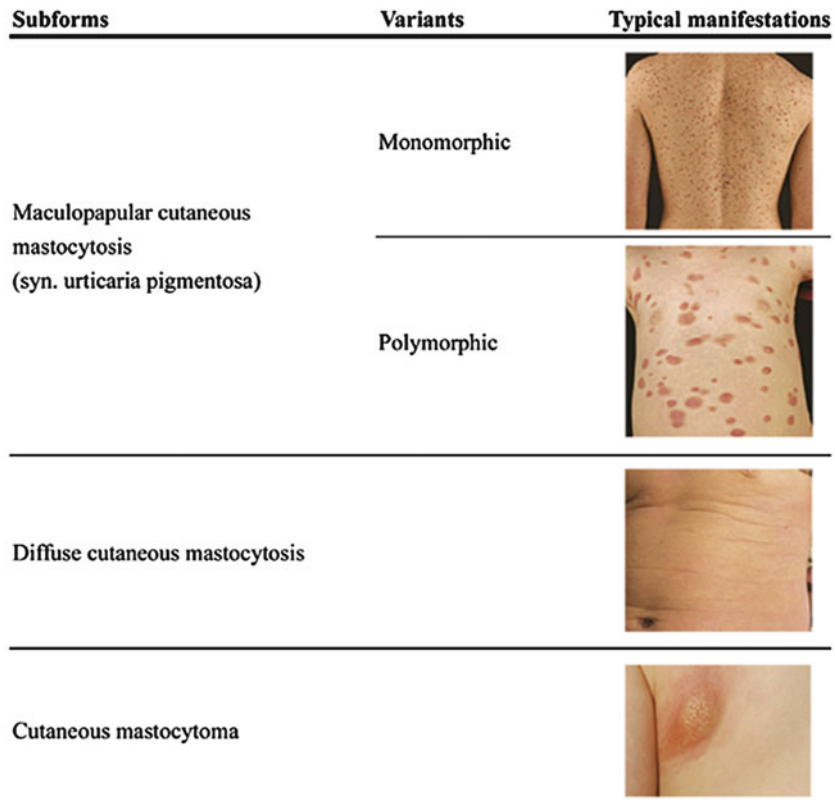


Fig. 2 Clinical manifestations of cutaneous mastocytosis. Subforms of CM. Cutaneous manifestations in mastocytosis are categorized into (i) Maculopapular cutaneous mastocytosis (MPCM), presenting with disseminated brown lesions, (ii) Diffuse cutaneous mastocytosis (DCM), presenting with generalized erythema and thickened skin, and, (iii) Mastocytoma, presenting with a brown or red elevated lesion. Note that the image of the Mastocytoma demonstrates Darier's sign, a wheal-and-flare reaction that developed upon stroking of the lesion with a tongue spatula. Also note that although Darier's sign is a highly specific diagnostic feature of cutaneous mastocytosis, it is not recommended in the evaluation of DCM, nodular form of MPCM, or mastocytoma due to the potential for inciting severe symptoms. (Used with permission from Hartmann et al. 2016)

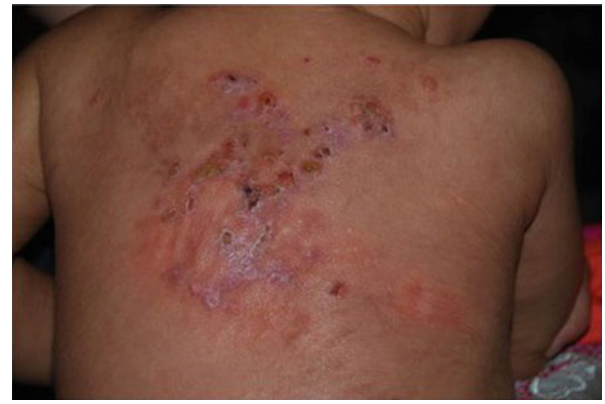


Fig. 3 Diffuse plaques with peau d'orange appearance in DCM, with associated bullae. (Used with permission from Rothe et al. 2016)

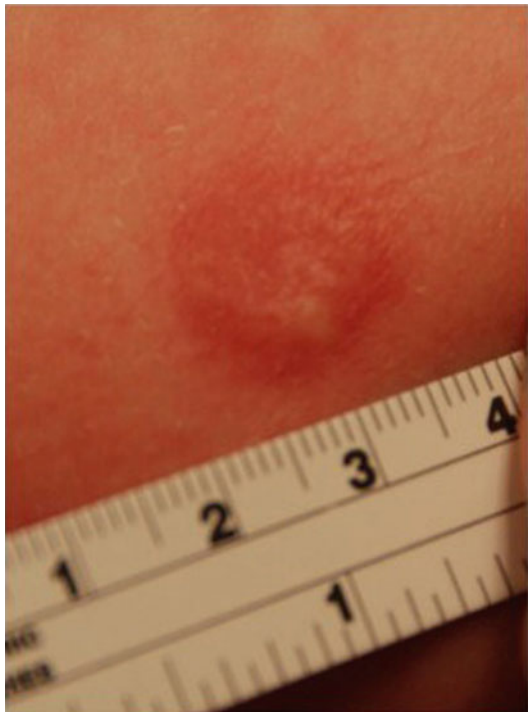


Fig. 4 Solitary mastocytoma with bulla formation. (Used with permission from Rothe et al. 2016)

(Rothe et al. 2016). In contrast, most adults meeting criteria for cutaneous mastocytosis will also exhibit SM, usually with bone marrow involvement. Therefore, it is recommended to offer all adult patients a complete staging, including a bone marrow biopsy (Valent et al. 2007).

29.7.4.2 Anaphylaxis Symptoms and Evaluation

Anaphylaxis is a systemic life-threatening and potentially fatal reaction. Adults with systemic mastocytosis have a 20%–50% risk for anaphylaxis, with the majority of episodes occurring in ISM. Anaphylaxis can occur in such patients after relevant stimuli, such as ingestion of opiates (Franklin Adkinson et al. 2013). Hymenoptera stings are the most common triggers for these reactions; however, idiopathic anaphylaxis and reactions to food or drugs occur. Anaphylaxis typically occurs after contact to a known allergen (e.g., ingestion of allergenic food) and involves at least two out of the four organ systems: skin (e.g., flush, urticaria, angioedema), gastrointestinal tract (e.g., abdominal pain, nausea, diarrhea), pulmonary system (e.g., wheezing, dyspnea), and cardiovascular system (e.g., hypotension, shock, tachycardia) (Fig. 1) (Schuch and Brockow 2017; Simons et al. 2015).

When examining a patient during an acute anaphylactic episode, a thorough physical examination should be conducted quickly, in a manner that allows quick intervention with intramuscular epinephrine (at a dose of 0.01 mg/kg at 1:1000 concentration). More commonly, the evaluation is based on a past incident, in which history of each organ system symptom and review of the medical record, if available, are combined. It is helpful if the patient's recollection of urticaria, chest tightness and wheeze, and/or dizziness or near-syncope is confirmed by supporting documentation (Simons et al. 2015).

Patients with mastocytosis should be informed about risk of anaphylaxis and prescribed emergency, self-administered medication including an epinephrine auto-injector. Ideally, the medical record should document instruction in the use of medications, specific findings that warrant medications, development of an emergency action plan, and discussion of need to share information with other health professionals. Medical bracelets may be a consideration. The risks of anaphylaxis during anesthesia should also be discussed.

29.7.4.3 Mast Cell Activation Symptoms and Evaluation

Affected subjects experience episodic, multisystem symptoms as the result of mast cell mediator release. Symptoms of mast cell activation are recurrent flushes, hypotension, tachycardia, near syncope or syncope, abdominal cramps, and diarrhea (Fig. 1). Although these symptoms may resemble anaphylaxis, an allergy evaluation (with thorough food and insect allergy history) often does not identify a culprit.

Bone marrow biopsy is recommended for the above-mentioned symptoms of mast cell activation, as evaluation for systemic mastocytosis is warranted. A search for causes of anaphylaxis, including both appropriate food allergy testing

and also testing for insect (particularly Hymenoptera) reactions in those who experience anaphylaxis to stings, should be considered. A clinical pearl is that chronic urticaria, angioedema, and upper airway swelling are rarely seen in the mast cell activation episodes, making invasive (e.g., bone marrow biopsy) workup of mastocytosis in these presentations unnecessary (Akin 2017).

29.7.4.4 Gastrointestinal (GI) Symptoms and Evaluation

Typical GI symptoms may be the first presentation of systemic disease and symptoms include nausea, vomiting, and abdominal pain, which may be suggestive of colitis or splenomegaly (Fig. 1). Colon and terminal ileum are most commonly involved. Endoscopic evaluation and multiple biopsies (as the disease is non-focal) are needed. Histology typically demonstrates aggregates of spindle-shaped mast cells with limited cytoplasm, localized beneath the surface epithelium. The mast cells are positive for tryptase and KIT (CD117) and show aberrant membranous expression of CD25 by immunostaining. CD25 is not expressed by normal or reactive mast cells; CD25 is expressed by transformed mast cells and has been found to be the most reliable immunohistochemical marker for diagnosis of mastocytosis (Doyle and Hornick 2014). In general, it is the presence of discrete aggregates or confluent sheets of mast cells, along with coexpression of CD25 that allow for a diagnosis of mastocytosis (Akin 2017). The pathology section (Sect. 8) provides further discussion of useful immunohistochemical markers. Note that there are no specific diagnostic criteria for defining the number of GI mast cells for a diagnosis of MC disease. The presence of mast cells in the GI tract is nonspecific, as they can, for example, can be found in irritable bowel syndrome and parasitic infections (Akin and Valent 2014; Doyle and Hornick 2014; Akin 2017; Akin and Valent 2014).

29.7.4.5 Musculoskeletal Symptoms and Evaluation

Bone involvement usually occurs in systemic mastocytosis and may present as generalized bone pain (54% of SM) (Hermine et al. 2008), fragility fracture (predominantly vertebral body fracture), osteoporosis (9% women, 28% of men with SM) (Rossini et al. 2011), and less frequently osteosclerosis and osteolytic lesions (Fig. 1). Although osteoporosis is common in older, frail women, the osteoporosis associated with systemic mastocytosis is more common in young males and in the spine rather than in the hip (Rossini et al. 2014). Osteoporosis in SM has been attributed to either neoplastic infiltration of the bone or marrow or the local release of mediators (histamine, heparin, tryptase, lipid mediators, and the cytokines TNF-α, IL-1, and IL-6). Mast cell stimulation of osteoclastic activity in the bone may also contribute to the osteoporosis and pathologic fractures in SM (Rossini et al. 2014). Systemic mastocytosis should be suspected if a patient (particularly a male patient) presents with these features or if a young patient (under 50 years old) presents with idiopathic osteoporosis, which is commonly a disease of the elderly. Mast cell disease limited to the skin does not affect bone physiology (Rossini et al. 2016). The absence of an increased serum tryptase should not dissuade the clinician from considering spine radiography and DEXA in all patients with SM (Rossini et al. 2016).

29.7.4.6 Neuropsychiatric Symptoms and Evaluation

In 1986, Rogers published a seminal study on psychiatric manifestations of mastocytosis (Rogers et al. 1986). Subsequent studies show neuropsychiatric symptoms to be frequently associated with mastocytosis. In particular, the various clinical features include depression and anxiety (4–60%), headache (35–56%), cognitive impairment (39%), as well as syncope and multiple sclerosis (all <5%) (Fig. 1) (Moura et al. 2014). Cognitive impairment manifests as memory trouble or fluctuations in attention or ability to concentrate. Neurologic symptoms can be related to mast cell mediator release, particularly headache and syncope. Depression is a prevalent finding in this disease, and failure to diagnose depression will complicate management. Depression may be difficult to diagnose as depression rating scales may over-represent somatic items

that overlap with symptoms of mast cell disorder itself, thus further psychiatric evaluation may be necessary (Moura et al. 2014).

29.7.4.7 Mass and Hematologic Abnormalities Signs and Evaluation

Mast cell sarcoma, the rarest and most difficult to treat mast cell neoplasm, occurs in any age group and has various presentations depending on the location of the mass (most commonly occurs in bone but also occurs in larynx, colon, small bowel, and buccal mucosa). Mast cell sarcoma is composed of cytologically malignant mast cells presenting as a solitary mass with relatively rapid growth and metastasis. It can be associated with SM and MCL (Fig. 1) (Monnier et al. 2016).

The diagnosis of MCS is based on biopsy. Diagnosis of MCS is difficult to make for two reasons: (I) Mast cells in the tumor can be highly atypical. (II) Mast cells lose some of their diagnostic surface markers, making them resemble other tumors. Furthermore, KIT D816V mutation is found in only 21% of MCS, making complete KIT gene sequencing necessary (Weiler and Butterfield 2014).

Patients with SM not infrequently present with symptoms or lab findings that require further hematologic evaluation. These manifestations include fatigue, weight loss, liver or spleen enlargement, cytopenias, leukocytosis, thrombocytosis, or unexplained eosinophilia. In patients with suspected myelodysplastic syndrome, acute myeloid leukemia (AML), or chronic myelomonocytic leukemia (CML), positive genetic testing for the KIT (CD 117) mutation may be the clue to evaluate for SM (Fig. 1) (Kovalszki and Weller 2014; Akin and Valent 2014).

29.8 Differential Diagnosis

The differential diagnosis for mast cell disorders is broad. It is determined both by the affected body systems and the degree of mast cell burden. One approach in developing the appropriate differential diagnosis is to consider whether the mast cells are limited to the skin or if additional symptoms suggest systemic involvement.

29.8.1 Differential for CM

Disorders limited to the skin, which may mimic CM are listed in Table 4. Bullae are more likely to be present in pediatric cases with DCM (Fig. 3), and these children may have a greater risk of anaphylaxis than other subgroups (Rothe et al. 2016; Lange et al. 2012). These polymorphic skin lesions in children can be distinguished from other bullous diseases by the propensity for skin irritation, from rubbing or scratching, to cause blistering (Hartmann et al. 2016). In an analysis of 10 cases by Lange et al., DCM with blistering was initially misclassified in six of the ten cases as staphylococcal scalded skin syndrome, epidermolysis bullosa acquista, impetigo bullosa, and atopic dermatitis (Lange et al. 2012).

Another bullous disease, which can affect both children and adults, is linear IgA bullous dermatosis. Juvenile xanthogranuloma, postinflammatory hyperpigmentation, café-au-lait macules (associated with neurofibromatosis type 1, with six or more lesions), congenital smooth muscle hamartoma, leiomyoma, and congenital melanocytic nevus are also in the differential diagnosis of cutaneous mastocytosis in children (Rothe et al. 2016).

Finally, diseases that are associated with secondary mast cell activation can mimic mast cell disorders. An example of a cutaneous disease that is associated with mast cell activation is psoriasis, which is an interferon-gamma (IFN-γ)-rich disease that can result in mast cell degranulation via upregulation of MC high-affinity IgG receptors (Akin et al. 2010).

Table 4 Differential diagnosis of cutaneous mastocytosis

Bullous diseases:	Postinflammatory hyperpigmentation
Staphylococcus scalded skin syndrome	Café-au-lait macules
Epidermolysis bullosa	Congenital smooth muscle hamartoma
Impetigo bullosa	Leiomyoma
Linear IgA bullous dermatosis	Congenital melanocytic nevus
Atopic dermatitis	Dermatofibromas
Juvenile xanthogranuloma	Psoriasis

References: Rothe et al. (2016), Lange et al. (2012), Hartmann et al. (2016), Valent et al. (2017a)

29.8.2 Differential for SM

Because systemic symptoms of mast cell disorders are variable, a large number of other conditions must be considered. The differential diagnosis and the evaluation for co-existing conditions should be based on the individual's clinical presentation.

There are many ways to group the diseases considered in the evaluation of SM. Table 5 represents one approach (Arber et al. 2016; Theoharides et al. 2015; Akin et al. 2010; Parker 2000; Sperr et al. 2009; Franklin Adkinson et al. 2013). While numerous examples are provided in Table 5, several are worth highlighting in more detail in the text.

Monoclonal mast cell activation syndrome (MMAS) was recognized as a distinct, primary mast cell disorder by an international consensus conference in 2007 (Valent et al. 2007). MMAS is the appropriate diagnosis when a patient has mast-cell mediated symptoms combined with only one or two of the minor diagnostic criteria for SM. These patients to do meet full diagnostic criteria for SM, and their baseline serum tryptase levels may not be elevated (Akin et al. 2010). They should be monitored yearly for changes in physical examination (such as development of organomegaly) and laboratory assessment (rise in serum tryptase level or abnormal CBC) to ensure that there is not development of mast cell expansion or evolution of a hematologic condition (Hartmann et al. 2016; Franklin Adkinson et al. 2013).

Idiopathic mast cell activation syndrome (IMCAS, which was formerly called MCAS) was proposed as a distinct disorder in 2010. These patients have recurrent mast cell-mediated symptoms affecting at least two organs yet not qualifying as anaphylaxis, a scenario in which idiopathic anaphylaxis would be a more appropriate diagnosis. These patients may have an elevation in their serum tryptase level (baseline + 0.2 × baseline + 2 ng/mL) within 4 h of onset of symptoms, but a normal serum tryptase otherwise (<20 ng/ml). They may also demonstrate an elevation in 24-h urine.

N-methylhistamine or prostaglandin D2. They tend to respond well to mast cell inhibition or

Table 5 Differential diagnosis and mimickers of systemic mastocytosis

Diseases associated with primary MC activation
Monoclonal MC activation syndrome (MMAS)
Diseases associated with secondary MC activation
Allergic disorders
MC activation associated with chronic inflammation or neoplastic disorders
Physical urticarias
Chronic autoimmune urticaria
Diseases that activate MC but cause is idiopathic
Idiopathic MC activation syndrome (IMCAS)
Anaphylaxis
Hereditary/acquired angioedema
Urticaria
Diseases that mimic MC disorders
Postural orthostatic tachycardia syndrome
Coronary hypersensitivity (Kounis syndrome)
Fibromyalgia
Parathyroid tumor
Carcinoid syndrome
Pheochromocytoma
Bony metastases
Adverse reaction to food
Eosinophilic esophagitis
Eosinophilic gastritis
Gastroesophageal reflux disease
Gluten enteropathy
Irritable bowel syndrome
Vasoactive intestinal peptide-secreting tumors
Zollinger-Ellison syndrome
Medullary thyroid cancer
Autoinflammatory conditions involving deficiency
Of interleukin-1-receptor antagonist
Familial hyper-IgE syndrome
Vasculitis
Disorders with similar bone marrow examination
Chronic eosinophilic leukemia
Myeloid and lymphoid neoplasms associated
with eosinophilia
Primary myelofibrosis
Granulomas
Hodgkin disease
Metastatic carcinoma
Kaposi sarcoma
Histiocytosis X
Reactive mastocytosis
Disorders with elevated tryptase
Myeloproliferative or myelodysplastic disease
Chronic eosinophilic leukemia
End stage kidney disease
Untreated filiriasis infection
Familial hypertryptasemia

References: Arber et al. (2016), Theoharides et al. (2015), Akin et al. (2010), Parker (2000), Sperr et al. (2009), Franklin Adkinson et al. (2013)
MC mast cell

blocking mediators with antihistamines (H1 and H2), antileukotriene modifiers, and oral cromolyn sodium. To be classified as IMCAS, primary and secondary causes of mast cell activation must be ruled out. These patients should be monitored to ensure that one of the eliminated diagnoses does not ultimately manifest, as IMCAS is an idiopathic syndrome without a definitive diagnostic test (Akin et al. 2010; Franklin Adkinson et al. 2013).

Patients who experience recurrent anaphylaxis should be considered for evaluation of mastocytosis, particularly if a trigger is not identified. Additionally, patients who have severe anaphylaxis to Hymenoptera stings should be screened with a baseline serum tryptase, and, if greater than 11.4 ng/mL, they should be evaluated further (Bonadonna et al. 2013).

The bone marrow histology examination may be similar to mastocytosis in several other diseases, all listed in Table 5 and discussed here. In chronic eosinophilic leukemia (CEL) and other myeloid and lymphoid neoplasms associated with eosinophilia, a slight increase in serum tryptase can occur (Arber et al. 2016; Parker 2000; Sperr et al. 2009). Additionally, mast cells may be spindle-shaped in appearance and may express CD25 in CEL, similar to mastocytosis, but the mast cells usually do not demonstrate CD2 or the D816V mutation typical of mastocytosis (Kovalszki and Weller 2014). These patients may have abnormalities in the genes encoding Fip1-like-1 and platelet-derived growth factor receptor alpha (*FIP1L1-PDGFRα*) or beta (*FIP1L1-PDGFRβ*), the latter of which does not occur with mastocytosis (Arber et al. 2016).

In primary myelofibrosis, the bone marrow may have spindle-shaped mast cells. Because of the extensive mast cell infiltration, fibrosis is seen in primary in myelofibrosis, but the MC pattern is usually interstitial rather than in clusters. There is no expression of CD25 or the presence of the D816V mutation, as in mastocytosis. Other conditions listed in Table 5 have cells resembling fibroblasts and histiocytes on bone marrow evaluation (Hartmann et al. 2016; Franklin Adkinson et al. 2013). As mastocytosis progresses, the marrow may appear similarly fibrotic (Parker 2000; Franklin Adkinson et al. 2013).

Several solid tumor malignancies can result in reactive mastocytosis because of tumor burden. These mast cells, however, are not spindle-shaped and do not have aberrant expression of CD2 or CD25 and lack the D816V mutation.

There are several additional disorders which can result in an elevated tryptase. Myeloproliferative or myelodysplastic disease can coexist with systemic mastocytosis, resulting in a worse prognosis (Parker 2000). End-stage renal disease, hemodialysis dependent with creatinine >5 mg/dL, and untreated helminth infections, such as filiriasis, can demonstrate elevated serum tryptase levels. A three-generational familial hypertryptasemia has been described in a 2018 abstract, in which all three generations of family members had elevated serum tryptase levels accompanied by mast-cell mediated symptoms (Alandijani et al. 2017). Familial hypertryptasemia as reported shows an autosomal dominant inheritance pattern. Patients with this disorder usually have elevated tryptase levels linked to inheritance of multiple copies of the *TPSAB1* gene which encodes α-tryptase. These patients tend to have increased rates of connective tissue disorders such as joint hypermobility, functional GI disorders including irritable bowel syndrome, skeletal abnormalities, and symptoms suggestive of autonomic dysfunction. They do not always manifest symptoms related to mast cell activation although many will suffer from recurrent flushing or urticaria. Meteroism, excessive bowel gas accumulation with abdominal distension, is a more unique characteristic. The role of tryptase in this disorder is unclear, but mast cells do not appear to be abnormally activated. No specific treatment of this disorder is currently advocated (Akin 2017; Lyons et al. 2016).

29.9 Pathology

29.9.1 Cell Markers

Non-neoplastic mast cells are round with small, centrally located nuclei, and they are typically filled with cytoplasmic granules that stain metachromatically with toluidine blue and Giemsa

stains (Markey et al. 1989). They also stain with chloroacetate esterase and aminocaproate esterase (Parker 2000). Neoplastic mast cells contain far fewer cytoplasmic granules than normal mast cells, and thus, these stains are less effective at identifying mast cells in patients with mastocytosis (Doyle and Hornick 2014). The most important mast cell-related antigens used for diagnosis in histologic sections are KIT (CD117) and tryptase.

KIT (CD117), as previously discussed, is a sensitive marker for mast cells and is present on the mast cell membrane so it is not affected by degranulation (Maeda et al. 1992). Cells not expressing KIT are not mast cells. Mutations in KIT are present in most cases of adult-onset mastocytosis and can be identified in blood, bone marrow, and other tissues; the mutation fulfills minor criteria for the diagnosis of systemic mastocytosis (Doyle and Hornick 2014). The reliability of testing for KIT is greater in tissues with greater mast cell number, making the bone marrow much more useful than peripheral blood. Thus, the diagnosis is not excluded with a negative KIT using peripheral blood.

Tryptase is a cytoplasmic serine protease that is specific for mast cells (Doyle and Hornick 2014; Markey et al. 1989; Castells et al. 1987). Tryptase can be used to reliably identify mast cells in both systemic and cutaneous mastocytosis although neoplastic mast cells tend to have less cytoplasm which can limit the marker's utility in more advanced forms of the disease (Horny et al. 1998). In rare cases of mastocytosis, tryptase levels can be decreased. Therefore, in addition to KIT and blood tryptase concentration, the expression of the antigens CD2, CD25, and CD30 (all defined below) are also used in the routine diagnostic work-up of mastocytosis (Akin 2017).

CD25 (IL-2Rα) is normally expressed on helper T cells but is aberrantly expressed on neoplastic mast cells and is thus a most reliable immunohistochemical marker for diagnosis of mastocytosis (Akin 2017; Sotlar et al. 2004). In normal mast cells, CD25 is not expressed (Escribano et al. 1998).

CD2, the lymphocyte functional antigen generally found on T cells and natural killer T cells, is aberrantly expressed in neoplastic mast cells (Doyle and Hornick 2014), and the presence of CD25 "and/or" CD2 on mast cells is a minor criterion for the diagnosis of systemic mastocytosis. However, CD2 is less sensitive and specific than other markers, making it less useful in diagnosing SM (Escribano et al. 1998; Morgado et al. 2012). CD2 may play a role in the clustering of mast cells (Doyle and Hornick 2014).

CD30 is a marker typically restricted to a group of activated lymphocytes but which is aberrantly expressed on neoplastic mast cells (Doyle and Hornick 2014). Its expression has been associated with mast cell leukemia, with more aggressive forms of SM, and occasionally with ISM as well (Akin 2017; Sotlar et al. 2011).

29.9.2 Skin Findings

Cutaneous mastocytosis is characterized on biopsy by increased numbers of mast cells infiltrating the dermis. A 15- to 20-fold increase in the number of mast cells is typical of lesions of Maculopapular cutaneous mastocytosis (MPCM). Mast cell numbers can be increased in other conditions but are not typically increased to the same extent (Garriga et al. 1988).

Four characteristic patterns of mast cell infiltration are seen in cutaneous mastocytosis (CM). These patterns are a perivascular pattern in the papillary body and upper dermis, sheet-like infiltrates of mast cells in the upper dermis, nodular infiltrates, and interstitial infiltrates. The latter two patterns typically involve the entire dermis. The pattern identified on biopsy does not reliably correspond to a specific clinical pattern of skin involvement or predict the likelihood of systemic mastocytosis, so physical examination and other appropriate evaluation are vital to accurate subtype diagnosis. Mastocytomas typically display the nodular pattern on histology (Garriga et al. 1988; Wolff et al. 2001).

Mast cell sarcoma is distinct from cutaneous mastocytosis and typically presents as a single, locally invasive mass. Histologically, tumor cells are present in sheets of medium to large,

pleomorphic, epithelioid cells which stain positively for KIT (CD 117). The histology can also show multinucleated giant cells, often accompanied by eosinophilic infiltrates. Tumor cells have abundant cytoplasm and well-defined cell borders but lack the D816V mutation (Doyle and Hornick 2014).

29.9.3 Bone Marrow

The diagnosis of systemic mastocytosis relies heavily on bone marrow biopsy findings, and the bone marrow is the most common site of mast cell infiltration in SM (Garriga et al. 1988; Wolff et al. 2001; Travis et al. 1988). As previously discussed, the major criterion for diagnosing SM is the finding of multifocal aggregates of mast cells in bone marrow or another extracutaneous tissue with at least 15 mast cells in each aggregate. The minor criteria largely describe the identified mast cells, including the presence of atypical morphology, especially spindle-shaped in more than 25% of detected mast cells, and the expression of KIT (CD 117) with CD25 and/or CD2 (Franklin Adkinson et al. 2013).

The fixation techniques used for bone marrow biopsies interfere with Giemsa and toluidine blue stains, making them less useful for identifying mast cells than they are in other tissues (Parker 1991). As discussed earlier, neoplastic mast cells in the bone marrow typically can be identified by antibodies to tryptase and KIT (CD 117). Additionally, flow cytometry should routinely be performed and can identify KIT and CD25 which are present in 90% or more of mast cells in systemic mastocytosis, making these three cell markers very useful in diagnosis, especially in subjects without the major criteria. CD2, while listed as a component of one of the minor criteria for diagnosis, is an inferior marker as mentioned above (Horny et al. 2014).

Neoplastic mast cells typically have an oval or bilobed nucleus which is located eccentrically and fine eosinophilic granules. They also tend to have less cytoplasm than non-neoplastic mast cells. Eosinophils and lymphocytes typically surround the mast cells in a perivascular, peritrabecular, or intratrabecular distribution. Mast cells are often found in clusters in which individual cells cannot be identified. This finding is specific but not sensitive for the disease. More typically, foci of spindle-shaped mast cells occur in a background of fibrosis (Parker 1991).

The bone marrow can be normocellular to hypercellular with hypercellularity often correlating with a myeloproliferative variant and a poorer prognosis. The significance of mast cell burden in the marrow is unknown, but more advanced forms of the disease often show extensive bone marrow infiltration (Parker 2000). Mast cell leukemia is characterized by immature, atypical mast cells which make up at least 20% of all cells in the bone marrow aspirate; alternatively, these cells can represent at least 10% of peripheral blood cells (Franklin Adkinson et al. 2013).

Mutational analysis should routinely be performed to assess for the D816V and other mutations in KIT (CD 117), the former of which is a minor criteria for diagnosis and is present in 80% or more of patients with SM. Traditional polymerase chain reaction (PCR) assays have fairly low sensitivity, and, over time, techniques have improved detection. Currently, the assay of choice is an allele-specific PCR assay which identifies this mutation in bone marrow or peripheral blood with excellent sensitivity, detecting 0.01–0.1% of mutated cells compared to Real-Time PCR. This PCR is specific for the traditional D816V mutation, however (Arock et al. 2015). In patients with bone marrow findings such as eosinophilia or leukocytosis which suggest another type of hematologic malignancy, other molecular testing should be performed for mutations such as *BCR/ABL* and *FIP1L1-PDGFRα* (Valent et al. 2004). Other myeloid variants of hypereosinophlia occur with rearrangements in *FIP1L1-PDGFRβ.*

29.9.4 Other Tissues

Gastrointestinal (GI) symptoms are common in SM, but the frequency of GI involvement by neoplastic mast cells is unknown. Although the major criterion for the diagnosis of mastocytosis can be fulfilled by biopsy of any extracutaneous

tissue, involvement of mucosal tissues can be patchy and subtle, making it difficult to recognize an infiltrate and limiting the utility of these biopsies (Doyle and Hornick 2014). In a case series of 24 patients with GI involvement, biopsies revealed infiltrates of ovoid to spindle-shaped mast cells in aggregates or sheets in the lamina propria. These sheets sometimes formed a band beneath the surface epithelium. In a minority of cases, biopsies had focal involvement with a single aggregate of mast cells. The colon was the most commonly involved site, followed by the ileum and duodenum (Doyle and Hornick 2014). KIT (CD 117) and CD25 are reliable markers for mast cells in the GI tract regardless of morphology, but tryptase is an inferior marker in the GI tract. As above, the mucosa can be variably involved, from sheets of mast cells under the surface epithelium to multifocal clusters of mast cells, often surrounded by eosinophils (Shih et al. 2016). In contrast to this finding in bone marrow, the presence of CD30 on mast cells in the GI tract does not seem to predict a more aggressive course, as opposed to aberrant expression of CD30 on mast cells in the bone marrow where it is often associated with more aggressive disease (Doyle and Hornick 2014).

Biopsies of other tissues are not routinely performed unless pathologic increases in size of organs or organ dysfunction prompt further investigation. Liver biopsies typically show hepatic fibrosis with mast cell infiltrates in a portal and sinusoidal distribution. Splenic involvement is characterized by focal infiltrates in parafollicular areas, intrafollicular aggregates, or diffuse red pulp infiltration. Lymph node involvement is rare, but, when it occurs, paracortical involvement is common. In all these tissues, eosinophilic infiltrates and fibrosis are typical (Shih et al. 2016; Metcalfe 1991b).

Mast cells can also infiltrate almost any other tissue. A case report of a patient presenting with cardiac tamponade showed CD25+ mast cells in the pericardium. In this case, pericardiocentesis was suspected to cause mast cell degranulation which precipitated cardiovascular collapse (Sukrithan et al. 2016).

29.10 Treatment

Treatment varies by subtype and is aimed at control of mast cell-mediator induced symptoms and treatment of the underlying mechanism of disease when possible, also referred to as cytoreductive therapy. The latter is reserved for more aggressive subtypes of disease. Currently, no curative therapy exists for mastocytosis. As mastocytosis is a rare disease, randomized trials of treatments are lacking, and most recommendations are based on expert opinion.

29.10.1 General Care

Given the rare nature of this disease, patient education is important and individualized counseling will benefit all patients. In general, adult patients should be prescribed an epinephrine auto-injector in case of episodes of anaphylaxis. Pediatric patients generally have disease limited to the skin and are at lower risk of anaphylaxis, so epinephrine can be prescribed at the discretion of the clinician. Many patients are subject to mast cell degranulation when exposed to certain triggers, as previously mentioned (Table 3), but despite many known triggers, different patients may have symptoms with specific but not all known triggers, so avoidance should be tailored to each patient's past experiences. Information should be provided about common scenarios such as risks associated with general anesthesia or exposure to radiocontrast media (Siebenhaar et al. 2014). Other triggers include exposure to extremes of temperature, stress or anxiety, consumption of alcohol or spicy foods, insect stings, and certain medications including aspirin and select antibiotics, such as vancomycin, beta-lactam antibiotics, polymyxin B, and amphotericin B (Schuch and Brockow 2017). In one large retrospective study, patients with mastocytosis more frequently experienced anaphylaxis with exposure to general anesthesia (Matito et al. 2015). Many medications may cause histamine release from mast cells by

non-immunologic mechanisms, including opiates (codeine, morphine), certain anesthesia induction agents (atracurium), and various antibiotics as mentioned above (Schuch and Brockow 2017; Veien et al. 2000). These agents should be avoided when possible in mast cell disease. Based on expert opinion, preoperative prophylaxis may reduce the risk of anaphylaxis although no consensus guidelines exist, and the efficacy of treatment is unknown. One proposed perioperative management strategy includes administering corticosteroids and antihistamines at specified intervals prior to surgery with close observation perioperatively and with avoidance of physical triggers and medications which have caused anaphylaxis in the past. Benzodiazepines may be helpful to manage associated anxiety (Hermans et al. 2017).

29.10.2 Symptomatic Treatment

29.10.2.1 Anaphylaxis

Anaphylaxis is common in adult patients with mastocytosis with a cumulative prevalence of 49% in one series and may occur in children with extensive cutaneous disease and elevated baseline, serum tryptase levels (Brockow et al. 2008). Treatment of anaphylaxis consists of prompt use of IM epinephrine (0.01 mg/kg) as first-line therapy. Antihistamines and corticosteroids may help with some symptoms but do not have a role in the initial treatment of anaphylaxis. Corticosteroids have a theoretical but unproven value in reducing protracted or biphasic anaphylaxis. Crystalloid fluid resuscitation should be administered in severe hypotension (Brockow et al. 2008; Simons et al. 2013).

29.10.2.2 Skin

Cutaneous Mastocytosis in Children

Systemic therapies for symptom control are indicated in children with extensive cutaneous disease and may be prudent as prophylaxis for mediator inhibition following unexpected mast cell degranulation in patients with elevated baseline tryptase levels. Second-generation H1 antihistamines are recommended to help control flushing and pruritus and can be increased up to four times the normal, recommended dose. H2 antihistamines may help if symptoms are not adequately controlled with H1 blockade alone and sometimes help to control gastrointestinal (GI) symptoms. Cromolyn used topically, as well as orally, in both children and adults is variably effective in relieving cutaneous symptoms (Klaiber et al. 2017; Soter et al. 1979). In children 2 years or older, topical corticosteroids may temporarily decrease the number of cutaneous mast cells. If less than 10% of the body surface is involved, a corticosteroid cream can be applied under an occlusive dressing. If more than 10% of the skin is involved, a 25% diluted preparation of fluticasone propionate 0.05% cream, applied under wet wraps, was shown to be effective in one case-controlled pilot study of 5 adults and 6 children. This therapy can be continued for 3–6 weeks (Klaiber et al. 2017; Heide et al. 2008). Topical pimecrolimus has also been used in a few cases (Correia et al. 2010). In refractory disease, psoralen-ultraviolet A (PUVA) or ultraviolet B (UVB) light can be used to control pruritus, although lesions typically recur after stopping this therapy. Long-term therapy is associated with skin cancers, although UVB therapy resulted in a lower total dose of irradiation than PUVA therapy in one study (Godt et al. 1997; Brazzelli et al. 2016). Montelukast has been used to successfully treat flushing and angioedema in one pediatric patient (Turner et al. 2011). In patients with solitary mastocytomas, surgical excision is a consideration (Ashinoff et al. 1993).

Skin Lesions in Adults

The majority of patients with adult-onset indolent systemic mastocytosis will have skin lesions, and treatment of these is similar to that in children, except that they do not tend to spontaneously resolve (Siebenhaar et al. 2013). PUVA and UVB phototherapy can be helpful for short-term reduction in skin lesions although the benefit of the therapy must be weighed against the long-term risk of developing skin cancers (Lim and Stern 2005). As in children, use of antihistamines

is recommended to control itching with doses extrapolated from guidelines for treatment of chronic urticaria (Zuberbier et al. 2014). A recent study of 178 patients suggested that even higher doses may be helpful with sedation occurring as a side effect in only 10% of patients at doses greater than fourfold the normal dose, but this practice is not currently supported by the USA or European guidelines (van den Elzen et al. 2017). A randomized trial of 30 patients with mastocytosis showed a significant improvement in quality of life related to itching in patients who received rupatadine versus placebo. Rupatadine is a second-generation antihistamine which also has some anti-platelet activating factor effects, but this medication is not available in the US (Siebenhaar et al. 2013). Topical cromoglycate may reduce itching, although the mechanism by which it does so may not be related to mast cell stabilization (Vieira dos Santos et al. 2010). As in children, topical corticosteroids may be considered although they are not suitable for long-term use. Other medications which target specific mast cell mediators, including leukotriene and prostaglandin inhibitors, may help treat refractory symptoms. Montelukast was discussed above, and aspirin may be used to treat flushing in adult patients with systemic mastocytosis who are not sensitive to aspirin or NSAIDs (Theoharides et al. 2015). This treatment decreases urinary secretion of a prostaglandin D2 metabolite suggesting a modulation of mast cell biology (Butterfield et al. 1995).

29.10.2.3 Gastrointestinal

Gastrointestinal symptoms in patients with mastocytosis are common and can be disabling. A higher incidence of duodenal ulcers occurs compared with healthy patients (Sokol et al. 2013). In addition to antihistamine therapy, oral cromolyn sodium improves gastrointestinal symptoms in patients with systemic mastocytosis but requires frequent dosing (Horan et al. 1990). In patients with a history of duodenal ulcers or with symptoms refractory to H2-blockade, proton-pump inhibitors may be helpful (Arock et al. 2015; Siebenhaar et al. 2013). In more advanced cases of systemic mastocytosis in which malabsorption and ascites develop, oral corticosteroids may provide temporary improvement in abdominal complications (Hauswirth et al. 2004). Oral prednisone is typically initiated at a dose of 40–60 mg per day and maintained for 2–3 weeks before being tapered gradually to every other day dosing (Arock et al. 2015; Hauswirth et al. 2004). Alternatively, 9 mg daily of oral budesonide can be used as an alternative treatment (Sokol et al. 2010). In a case report of a patient diagnosed with SM-AHN, octreotide in combination with total parenteral nutrition (TPN) reduced diarrhea and improved the quality of life (Sadashiv et al. 2013).

29.10.2.4 Musculoskeletal

Bone Disease

Patients with systemic mastocytosis should undergo screening for osteoporosis (Rossini et al. 2014). Osteoporosis is thought to be a product of mast cell infiltration of bone marrow as well as increased bone turnover related to several mast cell mediators (histamine, heparin, tryptase, lipid mediators, and cytokines). Histamine is the most abundant product and acts directly on osteoclasts (Dobigny and Saffar 1997; Biosse-Duplan et al. 2009). Patients with idiopathic osteoporosis without other risk factors also have an increased probability of mast cell disease and should be screened at least with a baseline serum tryptase, as mentioned earlier (Rossini et al. 2011, 2014). In one cohort of patients with systemic mastocytosis, about half had bone disease with osteoporosis being the most common diagnosis. In these patients, oral bisphosphonate therapy resulted in increased bone mineral densitometry scores, and patients with prior fractures did not suffer repeat fracture (Barete et al. 2010). Other therapies have been proposed including low-dose interferon-alpha (Laroche et al. 2011) and denosumab, a monoclonal antibody which binds receptor activator of nuclear factor kappa-B ligand (RANKL), a ligand involved in osteoclast activation (Zaheer et al. 2015). As with most therapies of SM, controlled trials are lacking (Siebenhaar et al. 2014).

Joint and Soft Tissue Pain

Bone and soft tissue pain are frequently reported symptoms in patients with systemic mastocytosis, and rheumatologic diseases should be excluded before treating with analgesics and nonpharmacologic measures such as exercise (Arock et al. 2015; Siebenhaar et al. 2014). Opioids and nonsteroidal anti-inflammatory drugs should be avoided as they can precipitate mast cell mediator release. In one retrospective analysis of patients with osteoporosis, treatment with bisphosphonate therapy also reduced bone pain (Lim et al. 2005).

29.10.2.5 Neuropsychiatric

Neuropsychiatric symptoms in patients with systemic mastocytosis are heterogeneous and include a mixed organic brain syndrome with symptoms ranging from decreased ability to concentrate to depression and chronic headaches (Escribano et al. 2006). Some patients improve with histamine antagonists (Moura et al. 2014). In general, treatment of these symptoms includes therapies for other symptoms of mast cell mediator release including leukotriene antagonists as well as antidepressants and referral for psychiatric support when indicated (Siebenhaar et al. 2014; Nicoloro-SantaBarbara et al. 2017). Cromolyn sodium may have some efficacy in treatment of these symptoms but is inconsistently absorbed with oral dosing (Horan et al. 1990).

29.10.3 Cytoreductive Therapies

In patients with more advanced forms of mastocytosis in whom mast cell burden is high, cytoreductive therapy may be indicated. Few approved therapies exist, but many agents have been used with some success.

29.10.3.1 Tyrosine Kinase Inhibitors

Imatinib is a tyrosine kinase inhibitor (TKI) which is approved for treatment of SM, but the typical D816V mutation confers resistance to this therapy, limiting its utility (Vega-Ruiz et al. 2009; Valent et al. 2017b). One study looking at subjects without this mutation showed response to therapy in patients with a mutation in the extracellular portion of KIT (CD 117) and suggested, along with other studies, that subjects with mutations in certain exons of the gene for KIT, representing transmembrane and extracellular portions of the enzyme, may be sensitive to imatinib (Zhang et al. 2006; de Melo Campos et al. 2014). In this study, subjects with wild-type KIT did not respond to treatment with imatinib in contrast to prior case reports, and patients who did respond tended to have well-differentiated SM. Dose reduction was required in a few subjects due to GI symptoms and hematologic complications (anemia and neutropenia). The most common side effects include muscle cramps, nausea, and edema (Alvarez-Twose et al. 2016). Dasatinib has in vitro activity against certain KIT mutants (de Melo Campos et al. 2014), but success has been limited in vivo (Gotlib 2017). Another TKI, nilotinib, was evaluated in a phase II trial and showed limited efficacy (Hochhaus et al. 2015). Masitinib was recently evaluated in patients with severely symptomatic, indolent SM and resulted in mild reductions in serum tryptase, decrease in body surface area affected by urticaria pigmentosa, and improvement in baseline symptoms of pruritus, flushing, depression, and/or asthenia (Lortholary et al. 2017).

29.10.3.2 Midostaurin

In April 2017, midostaurin received FDA-approval as a treatment for advanced SM including MCL (Valent et al. 2017c). Midostaurin is an inhibitor of protein kinase C which also interacts with a variety of other kinases (Fabbro et al. 2000), leading to suppression of mast cell growth (Fabbro et al. 2000; Growney et al. 2005), and activation (Krauth et al. 2009). This therapy has efficacy in patients with SM and is an option for first-line therapy for advanced disease (Gotlib et al. 2016; Chandesris et al. 2016). A recent follow-up to a phase II trial of midostaurin in 26 subjects reported that the most common side effects were GI complaints (nausea, vomiting, diarrhea, or constipation), headaches, and fatigue. Anemia and

thrombocytopenia occurred in about a quarter of subjects. Dose reduction was required in 6 (23%) subjects chiefly due to GI side effects (Chandesris et al. 2016; DeAngelo et al. 2018).

29.10.3.3 Interferon-Alpha

Interferon-alpha improves urticaria pigmentosa in case reports and in one series. In addition, mast cell burden in the bone marrow, ascites, levels of mast cell mediators and osteoporosis has improved in interferon-treated subjects with ASM (Kluin-Nelemans et al. 1992; Butterfield 1998; Butterfield et al. 2005; Lehmann et al. 1996). Major response rates (defined as resolution of at least one "C" finding) to this therapy are low but may be improved by the addition of oral corticosteroids (Pardanani 2016; Hauswirth et al. 2004; Delaporte et al. 1995). Side effects are frequent and include flu-like symptoms, fatigue, thrombocytopenia, depression, and hypothyroidism (Hauswirth et al. 2004; Butterfield 1998; Lim et al. 2009). SM usually relapses upon cessation of therapy (Simon et al. 2004).

29.10.3.4 Hydroxyurea

Hydroxyurea has been used primarily in SM-AHNMD. Hydroxyurea can improve the associated hematologic malignancy through myelosuppression without significant effect on mast cell number (Pardanani 2016; Lim et al. 2009).

29.10.3.5 Cladribine

Cladribine (2-chlorodeoxyadenosine) is a synthetic purine analog which decreases symptoms of mast cell mediator release, improves urticaria pigmentosa, and decreases serum tryptase levels in patients with SM, although relapse rate after treatment was as high as 60% in one series (Lim et al. 2009; Lock et al. 2014; Barete et al. 2015). Cladribine may have some activity in all subtypes of SM and has been suggested as a first-line treatment option in patients with symptoms refractory to interferon alpha or in those who would benefit from rapid mast cell debulking (Pardanani 2016). In 26 patients treated with this therapy at the Mayo Clinic, major side effects included myelosuppression and infection (Lim et al. 2009).

29.10.4 Anti-IgE Therapy

Omalizumab, a monoclonal antibody against IgE which leads to the downregulation of the IgE receptor on mast cells, may improve symptoms related to mast cell-mediator release in patients with disease refractory to other therapies (Carter et al. 2007; Siebenhaar et al. 2007). One study of 14 subjects with SM showed greatly decreased incidence of anaphylaxis as well as more modest improvements in GI, musculoskeletal, and neuropsychiatric symptoms (Broesby-Olsen et al. 2017). In a report of two adult patients with cutaneous lesions of mastocytosis, omalizumab reduced itching and GI symptoms in both. In one of these patients, musculoskeletal pain was not improved (Lieberoth and Thomsen 2015). In a pediatric patient with mast cell activation syndrome, treatment with omalizumab resolved recurrent episodes of anaphylaxis (Bell and Jackson 2012). Omalizumab has also been used as an adjunctive therapy in patients requiring venom immunotherapy to reduce the risk of anaphylaxis for the immunotherapy (Sokol et al. 2014).

29.10.5 Hematopoietic Stem Cell Transplant

In patients with ASM, hematopoietic stem cell transplantation can be considered if patients are otherwise healthy enough to undergo transplant (Valent et al. 2017c). In one series of 57 patients with ASM, 70% responded after HSCT with improved rates of 3-year survival in patients with most subcategories of disease; survival remained poor in patients with mast cell leukemia (Sokol et al. 2014; Ustun et al. 2014).

29.10.6 Treatment of Coexisting Allergic Disease

Patients with systemic mastocytosis are at increased risk of anaphylaxis to Hymenoptera stings (Ruëff et al. 2006). In patients with identified venom allergy, lifelong venom immunotherapy (VIT) is typically recommended

(González de Olano et al. 2008). As above, some patients may benefit from adjunctive omalizumab to help reduce reactions to VIT (Sokol et al. 2014). Allergic rhinitis, asthma, and food allergy should be treated according to normal practice. Subcutaneous immunotherapy to environmental allergens is generally avoided due to the risk of anaphylaxis associated with this therapy, although some experts support consideration of this therapy on a case-by-case basis (Akin 2017).

29.10.7 Other Syndromes

Patients with monoclonal mast cell activation syndrome should be treated symptomatically as in patients with ISM. In proposed criteria for diagnosis and treatment, patients with MCAS should also respond to treatment with medications which oppose mast cell mediators; no other standard treatments exist for this disorder (Akin 2017). In patients with familial hypertryptasemia, the role of tryptase is not clear, but mast cells do not appear to be abnormally activated, and no specific treatment of this disorder is currently advocated (Akin 2017; Lyons et al. 2016).

29.10.8 Areas of Research

Many other cell surface markers have been identified on mast cells, and monoclonal antibodies targeted against these may prove to have some efficacy in the treatment of mast cell-mediated disease in the future (Valent et al. 2017c). A promising target is CD30 which is a cell surface marker associated with poor prognosis when found on mast cells in the bone marrow. Brentuximab is a monoclonal antibody to CD30 and has activity in CD30-expressing lymphomas. In a recent phase II trial which looked at four patients with SM, this therapy was beneficial in two subjects with one experiencing major regression and another showing stable disease for 44 months (Borate et al. 2016). Another tyrosine kinase inhibitor also is currently under research. Avapritinib inhibits mutant KIT (CD 117), including the most typical D816V mutation. In a phase I study which included 32 patients with advanced systemic mastocytosis, avapritinib had an overall response rate of 72% of the 18 patients who were able to be evaluated; 56% of patients had complete or partial disease response, and 100% experienced disease control (Rose 2018). Systemic mastocytosis is a complex disease with often difficult-to-treat symptoms and historically poor response to cytoreductive therapies in more advanced forms; but with increased understanding of mast cell biology and disease pathogenesis, there may be improved therapeutic options in the future.

29.11 Prognosis

29.11.1 Cutaneous Mastocytosis

Prognosis of CM in children correlates with lesional size with larger lesions corresponding to earlier onset disease and resolution generally by late childhood or puberty. This subtype of disease often has onset within the first 6 months of life. The monomorphic variant of disease is more likely to persist to adulthood (Fig. 2) (Valent et al. 2017c; Wiechers et al. 2015). The monomorphic variant also develops in adults and, similarly, tends to persist (Onnes et al. 2016). In one study conducted as a 20-year follow-up to initial findings in 15 pediatric patients, 10 had complete resolution of skin lesions with major regression in three others. The remaining two patients had partial resolution of skin lesions with one of the two subsequently identified as having ISM and the other with the diffuse cutaneous mastocytosis subtype (Uzzaman et al. 2009). A systematic review of 1747 pediatric cases of mastocytosis showed resolution or stabilization of disease in 94% of patients with progression to more aggressive forms of the disease in 3%; although rare, the aggressive forms were fatal in this review. Half of these aggressive forms occurred in children greater than 2 years with 90% of cases of cutaneous mastocytosis developing prior to age 2 years,

suggesting a more benign course with early disease onset (Méni et al. 2015; Brockow et al. 2002).

In a 10-year cohort study of 106 adult patients with urticaria pigmentosa (UP or MPCM), only 12 experienced regression of skin lesions. Regression was not associated with resolution of underlying systemic disease and was accompanied by progression of underlying hematologic disorders in two patients with SM-AHD. The only factor which correlated with disease resolution was older age, with no patients younger than 40 years experiencing regression of skin lesions (Brockow et al. 2002).

29.11.2 Systemic Mastocytosis

Prognosis for patients with SM depends on the subtype of disease. Indolent systemic mastocytosis (ISM) tends to have a good prognosis while more aggressive forms portend poorer outcomes (Onnes et al. 2016). In a Spanish cohort of 145 patients with ISM, only 3% progressed to a more advanced subtype of disease after a median follow-up of 147 months. In these patients, age at diagnosis greater than 60 years and presence of one or more cytopenias, elevated β2-microglobulin, or D816V mutation in all hematopoietic lines were associated with increased risk of progression. In another cohort of 342 SM patients followed at the Mayo Clinic, patients with ISM tended to have better outcomes compared to patients with more advanced forms of the disease. The life expectancy of patients with ISM was similar to that of the US general population, and leukemic transformation was rare. In patients with ASM or SM-AHD, survival was considerably shorter at 3.5 and 2 years from diagnosis respectively. Patients with MCL had a median life expectancy of only 2 months. In this cohort, advanced age (>65 years), anemia, thrombocytopenia, weight loss, hypoalbuminemia, and increased bone marrow blasts (>5%) were all independently associated with shorter survival (Lim et al. 2009).

In general, prognosis becomes less favorable as disease classification progresses, with ISM being most favorable followed by SSM, ASM, and then MCL. MCL tends to be a fulminant disease with survival on the order of months, but rare patients with chronic MCL may have a slightly better prognosis. Patients with mast cell sarcoma have a similarly poor prognosis as they tend to rapidly progress to MCL (Valent et al. 2017c).

In the above cohort of 342 patients, patients with SM-AHN were examined in a subsequent analysis. These patients were further distinguished into subtypes of hematologic disease. Of 138 patients with SM-AHD, the majority (123) had an associated myeloid neoplasia and were further stratified into those with SM-myeloproliferative neoplasm (SM-MPN), SM with chronic monomyelocytic leukemia (SM-CMML), SM-myelodysplastic syndrome (SM-MDS), and SM-acute leukemia (SM-AL). These patients were followed for a median of 15 months, and 73% of patients had died by the end of follow-up. Patients with SM-MPN had a greater median survival of 31 months compared with SM-CMML (~15 months), SM-MDS (~13 months), and SM-AL (~11 months). Patients with SM-MDS were significantly more likely to undergo leukemic transformation than those with SM-MPN or SM-CMML. The presence of eosinophilia in these patients did not affect prognosis (Pardanani et al. 2009).

Another factor shown in one study to predict poorer survival in both indolent and aggressive forms of mastocytosis was elevated plasma levels of IL-2Rα/CD25 (a marker of mast cell burden) (Pardanani 2016; Pardanani et al. 2013). Assessing for the presence of other mutations often found in other myeloid malignancies may be useful in predicting prognosis in patients with SM. Mutations of *ASXL1*, *RUNX1*, and *SRSF2* genes correspond to a poor prognosis in patients with D816V + SM (Jawhar et al. 2015), and a prognostic scoring system has been proposed which includes the presence of an *ASXL1* mutation to help stratify advanced SM patients into low, intermediate, and high-risk groups (Pardanani 2016). More recently, Naumann et al. advocated that a cytogenetic profile of patients with SM-AHN should also be

obtained as karyotype analysis may also have important implications on prognosis (Naumann et al. 2018).

29.12 Conclusion

From the original identification of mast cells in the late 1800s, our understanding of these cells' normal function and role in pathologic disease has expanded greatly, and the understanding of mastocytosis has led to advances in classification, pathogenesis, and treatment of these diseases. Among these advances, identification of novel mutations helps clinicians to understand the biology of disease, assess prognosis, and select potential specific therapies.

Additional groups of patients in whom mast cell activation contributes to pathology include those with venom-induced anaphylaxis and mast cell activation who do not meet WHO criteria for SM (e.g., MMAS, IMCAS) (Schuch and Brockow 2017; Pardanani 2016). While treatment remains symptomatic in many patients, several promising therapeutic targets and agents have recently been identified. These therapies may lead to improved survival in more advanced subtypes of disease. Newer therapeutics include several tyrosine kinase inhibitors which combat the activating KIT (CD 117) mutations present in most patients, midostaurin which targets multiple kinases involved in mast cell development and activation, and brentuximab which is a monoclonal antibody against CD30, a cell surface marker associated with poor prognosis. New treatments aim to improve survival while optimizing quality of life, but life expectancy in patients with advanced forms of SM remains poor. Hematopoietic stem cell transplant is consideration in patients who have aggressive forms of the disease and who are healthy enough to tolerate this therapy (Valent et al. 2017c).

29.13 Cross-References

► Anaphylaxis and Systemic Allergic Reactions

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Insect Allergy: A Review of Diagnosis and Treatment

30

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Abstract

Insect allergy is the third most common cause of the life-threatening condition anaphylaxis, following food and medications. Insect allergy anaphylaxis poses risk of considerable morbidity and mortality. Avoidance of the offending agent is the cornerstone to the management anaphylaxis regardless of the cause. However, unlike food and medication allergy, insect allergy has been effectively treated, using well-established protocols for many years. Hymenoptera are the insects most associated with allergy and anaphylaxis with at least 40 deaths per year attributed to

insect stings in the United States. It is critical that healthcare professionals and the public understand the proper diagnosis as well as the long-term treatment of this potentially life-threatening allergy. Insect allergy from Hymenoptera, managed *prospectively* using venom immunotherapy, conveys up to 98% protection of anaphylaxis with future stings. Insects of the order Hymenoptera include bees, wasps, hornets, yellow jackets, and stinging ants. Stinging ant allergy will not be reviewed in this chapter. An understanding of the biology and habitat of the various Hymenoptera species is helpful in recommending insect avoidance strategies. The diagnosis of insect allergy relies on a history of a systemic allergic reaction followed by appropriate testing for venom-specific IgE. If the history of a generalized anaphylactic reaction to an insect sting and the presence of venom-specific IgE are confirmed, venom immunotherapy is indicated. It is venom immunotherapy, a disease modifying therapy, that provides the most effective protection against future sting reactions. Ultimately, recognition and lifesaving management is critical. Subsequently, evaluation and potentially long-term management of insect allergy include appropriate referral to an allergist familiar with insect allergy and, if indicated, venom immunotherapy.

Keywords
Insect · Hymenoptera · Anaphylaxis · Epinephrine

Insects are one of the three most common allergic triggers for anaphylaxis, the others being foods and medications (Simons 2008; Simons et al. 2007; Sampson et al. 1992; Simons and Sampson 2008). Insect allergy results in significant morbidity and mortality, with potentially life-threatening systemic reactions occurring in 0.4% to 0.8% of children and up to 3% of adults, and accounts for at least 40 deaths annually in the United States (Graft 2006; Schwartz et al. 1995). Under recognition and treatment may actually underestimate the true mortality from insect anaphylaxis (Graft 2006; Schwartz et al. 1995; Golden et al. 2011). With proper evaluation and treatment, the risk of a severe event with a subsequent sting can be dramatically diminished. Venom immunotherapy (VIT) can provide up to a 98% level of protection from future insect-related anaphylactic events (Golden et al. 2011; Valentine 1984; Hunt et al. 1978; Reisman and Livingston 1992). This chapter will address the current state of knowledge about insect allergy, including insect identification, diagnosis, and evaluation, as well as long- and short-term evaluation and treatment.

30.1 Introduction: Terminology, Types of Reactions, and History

Insects belonging to the order Hymenoptera account for the majority of serious sting-related reactions. Within this order, three families are medically relevant. These include the Apidae, Vespidae, and Formicidae families. The Apidae family includes honeybees and bumblebees; the Vespidae family includes yellow jackets, white-faced hornets, yellow hornets, and wasps; the Formicidae family includes primarily imported fire ants and harvester ants (Gurlanick and Benton 2003; Goddard 2003). The family Vespidae includes the genus *Polistes* or wasps. In North America *P. annularis*, *P. fuscatus*, *P. metricus*, and *P. exclamans* are the predominant species. In Europe *P. dominulus*, *P. gallicus*, and *P. nimphus* are widespread. Although there is some cross-reactivity between American and European *Polistes* species, there are significant differences to warrant different testing and treatment venoms (Severino et al. 2006).

Anaphylaxis to stings of the imported fire ant and to bites from reduviids and mosquitos is reviewed in a separate chapter. Non-Hymenoptera stinging and biting arthropods, such as scorpions and spiders, are more extensively reviewed elsewhere and will not be the focus of this work (Demain 2003; More et al. 2004).

30.2 Insect Biology, Terminology, and Identification

Knowledge of these Hymenoptera insects, their biology, habits, and dwellings, can assist in recognition of the insect and circumstance of sting,

though this information should not be relied upon solely in identification of the offending insect. This knowledge of the circumstance and the suspect insect can be helpful for the diagnosis and treatment of insect allergy (Gurlanick and Benton 2003; Goddard 2003).

Yellow jackets can be either ground dwelling or in nests above ground. *Vespula vulgaris* are generally ground-dwelling yellow jackets, commonly encountered during outdoor activities. *V. vulgaris* can be very aggressive after even minimal provocation, particularly with vibration, such as a leaf blower or weed whacker (Fig. 1). A second species of yellow jacket (*Dolichovespula arenaria*) nests above ground, usually in shrubs and trees. Yellow jackets are carnivorous, have smooth bodies with straight barbless stingers, and can sting multiple times.

Wasps (*Polistes*) are also carnivorous and smooth bodied. The nests of wasps can be distinguished from yellow jackets by the triangular, open-celled configuration without the outer paper encasement typical of other vespids (Fig. 2). Wasp nets are frequently found under the eaves of houses and barns.

Domestic or European honeybees are herbivorous with hairy bodies and have a barbed stinger that results in evisceration and their death after the sting. Typically, they are nonaggressive unless protecting their hives; as a result, honeybee stings are often accidental and occur in children and adults who, while barefoot, inadvertently step on them in the grass (Fig. 3). Africanized honeybees were imported to South America from Africa and have been migrating north to the United States. Unlike their domestic counterparts, they are very aggressive. The venom from Africanized honeybees is identical to their domestic cousins, and the venom volume per sting is similar. However, unlike the single sting of a domestic honeybee, Africanized honeybees often sting in large numbers and will pursue their victim for much longer distances. The domain of the Africanized honeybee is currently limited in the United States to Texas, New Mexico, Arizona, Nevada, and California (Golden et al. 2011) (Fig. 4). Imported fire ants (Formicidae), which are discussed in other chapters, also have limited, but similar domains in the Southern United States (Golden et al. 2011) (Fig. 5).

Fig. 1 Yellow jacket (Photograph courtesy of Dr. Jeffrey G. Demain)

Fig. 2 Wasp (Photograph courtesy of Dr. Jeffrey G. Demain)

Fig. 3 Honeybee (Photograph courtesy of Dr. Jeffrey G. Demain)

Unfortunately, the absolute identification of the culprit insect usually cannot be confirmed, so testing with each of the common venoms is

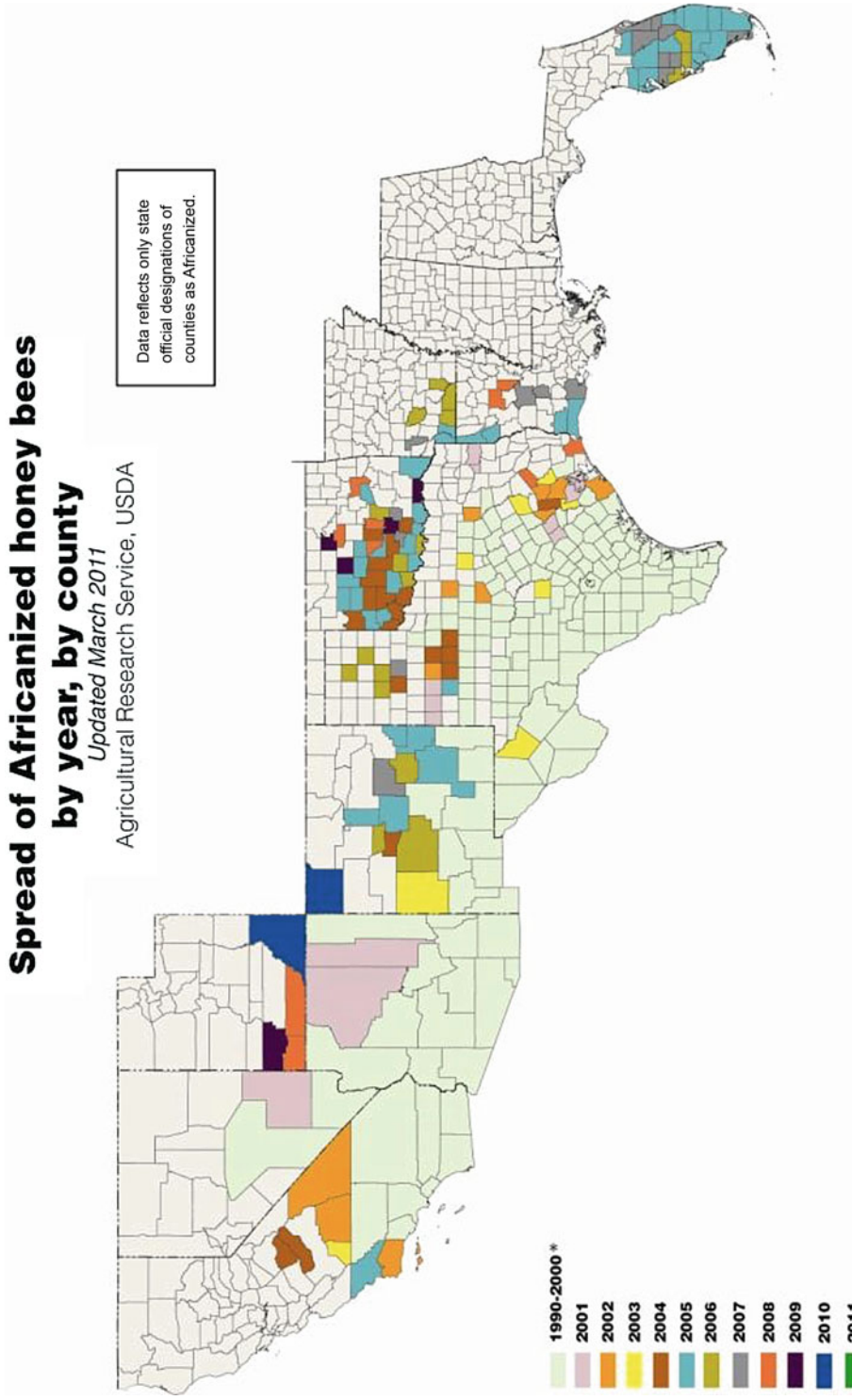

Fig. 4 Spread of Africanized honeybees (www.ars.usda.gov/SP2UserFiles/Place/53420300/New Bee Map09 compressed.jpg)

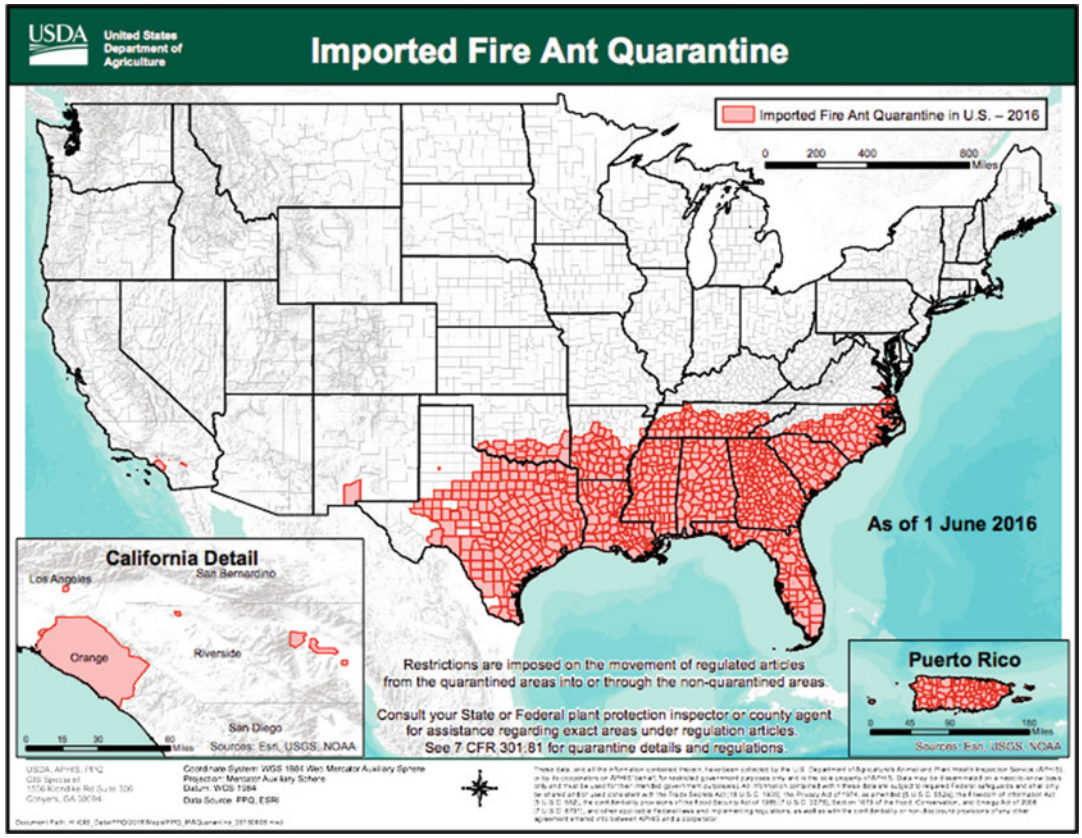

Fig. 5 Imported fire ant quarantine. (Regularly updated maps of the fire ant range and agriculture quarantine areas within the United States (Golden et al. 1989))

warranted in almost all cases, which will be discussed later. There are some circumstances where the offending insect is more obvious. As mentioned, honeybees have barbed stingers, and usually their venom sac can become lodged in the skin following a sting event. While this can be helpful in identification, it is important to note that yellow jackets may also leave the stinger embedded in the skin. In the case of imported fire ants, the presence of a pseudo-pustule up to 24 h later is virtually diagnostic of a fire ant sting (Golden et al. 2011; Moffitt 2003). When taking a history, it is important to take into account historical elements such as the person's activity at the time of the sting, insect activity in the area where the patient was stung, time of the year, and/or geographical considerations (Moffitt 2003).

The amount of venom delivered with a single sting varies between species. A single imported fire ant sting may contain up to 100 ng of venom, while in the case of honeybees, yellow jackets, hornets, and wasps, each sting can range from 20 to 50 mcg (Hoffman and Jacobson 1984). Hymenoptera venoms contain a variety of peptide and protein components. It is these components that cause the characteristic local reactions consisting of redness, swelling, and pain. Individuals having been previously stung may have generated venom-specific IgE antibodies, placing that individual at risk for a potential life-threatening anaphylaxis with subsequent stings. Individual Hymenoptera species contain some shared venom antigenic components. There is considerable immunologic cross-reactivity and sensitization between hornet and yellow jacket venoms, though there is much less between yellow jacket and hornet with wasp venoms. The immunogenic cross-reactivity and sensitization are even less

common between honeybee and the other venoms (Hoffman 1993; King et al. 1985; Reisman et al. 1982). Bumblebee (*Bombus terrestris*) venom has variable cross-reactivity and sensitization with honeybee venom, though at least two antigens are unique. Because bumblebees are non-aggressive, allergic reactions to bumblebee field stings are rare in the United States compared to other Hymenoptera stings. In Europe, bumblebees are used for pollination in greenhouses; therefore more frequent allergic reactions have been reported, particularly among greenhouse workers. Specific venom to bumblebee would be optimal for skin testing and immunotherapy but is currently not available in the United States (Franken et al. 1994; Hoffman et al. 2001; Freeman 2004; De Root 2006) (Table 1).

30.3 Diagnosis

Diagnosis of Hymenoptera allergy is based upon a comprehensive clinical history, the presence of allergic symptoms consistent with anaphylaxis, and objective evidence of venom-specific IgE antibodies. Accurate diagnosis is critical as once the thorough history supports that a generalized systemic reaction to a sting occurred, and the presence of venom-specific IgE is confirmed, the patient becomes a candidate for venom-specific immunotherapy (VIT) (Franken et al. 1994; Hoffman et al. 2001; Freeman 2004; De Root 2006). Proper treatment with VIT can result in up to 98% protection from future life-threatening sting events.

In the majority of cases, the insect sting is reported by the patient; however, it is important to know that there are reports of systemic events occurring without the patient realizing they have been stung. Following an insect sting, the initial diagnostic question is to determine whether the sting reaction is localized, cutaneous such as hives or angioedema, or a more severe systemic reaction (Golden et al. 2006). After a sting, most people develop only minor local symptoms, limited to local pain, tenderness, and swelling; these reactions are self-limited, lasting between 48 and 72 h. A local reaction is defined as a reaction in which the swelling and redness are confined to the tissues contiguous to the sting site. Large local reactions are based on size and vary from 5 to 8 cm to greater than10–16 cm. It is estimated that large local reactions make up 5–15% of sting events

Table 1 Hymenoptera biology and habitat

Common names	Taxonomic classification	Nesting habits	Feeding habit	Avoidance strategies
Honeybee[a]	Family Apidae	Commercial hives	Herbivorous. Nectar and pollen flowering trees and plants	Avoid dark or flower-print clothing and wearing floral scents; wear shoes and socks
Yellow jacket	Family Vespidae *Vespula* species	Multilayered, usually underground; although there is also an aerial yellow jacket: *Dolichovespula arenaria*[b]	Scavengers, aggressive Carnivorous	Avoid open food sources, picnic areas, garbage; destroy in-ground nests
Paper wasp	Family Vespidae *Polistes* species	Hangs from eaves and porches	Nectar and arthropods	Avoid flower-print clothing and wearing floral scents; remove nests when possible
White-faced hornet	Family Vespidae *Dolichovespula* species	Multilayered, open areas	Nectar and arthropods	Avoid flower-print clothing and wearing floral scents; remove nests when possible
Fire ant	Family Formicidae	Earthen mounds in Southern United States	Omnivorous	Avoid mounds; wear shoes, sock, and gloves

[a]A subspecies of honeybee exists in South Texas, Central and South America called "Africanized." It is more aggressive than local species and is clinically relevant in regions of infestation
[b]European species include *P. dominulus*, *P. gallicus*, and *P. nimphus*

(Golden et al. 2011). By contrast, systemic reactions, though occasionally delayed, are generally immediate-type hypersensitivity, mediated by venom-specific IgE. Systemic reactions involve signs and symptoms distant from the immediate sting site; the symptoms may range from mild to life-threatening. Mild systemic reactions, also termed cutaneous reactions, are typically limited to minimal flushing, urticaria, or angioedema. While some serious reactions may begin 15–30 min or longer after the sting, most serious reactions occur within minutes of the sting event. Generalized systemic reactions may include bronchospasm, gastrointestinal symptoms, hypotension, diaphoresis, shock, and – the most common cause of fatalities – laryngeal edema.

30.4 Diagnostic Testing

Once the history of a systemic reaction to an insect sting has been established, the next step is to discern the presence of venom-specific IgE. It is important to note that up to 27% of the general population may have detectable levels of venom-specific IgE, so the presence of venom-specific IgE *without* a history of a systemic reaction may not be predictive of a future insect-related anaphylactic event (Golden et al. 1989). As a result, skin testing is not indicated unless the patient has a history of a systemic allergic reaction other than hives to an insect sting. All individuals, regardless of age, with a history of a systemic or anaphylactic reaction, beyond hives and/or angioedema, following an insect sting should be tested (Golden et al. 2006, 2011; Light et al. 1977; Reisman 2005). Recently new guidance has emerged regarding testing and VIT in individuals with systemic anaphylactic reactions limited to cutaneous involvement (Golden et al. 2011). In the 2017, Golden et al. outlined changes for individuals with limited cutaneous systemic reactions to stinging insects and who required testing and ultimately therapy. Adults and children who have reactions limited to the skin, such as hives and angioedema, appear not to have a significant risk for more severe reactions in the future, and therefore testing is not warranted (Georgitis and Reisman 1985; Golden et al. 2017). This is a change from the previous recommendations, where adults, but not children younger than 16 years, warranted testing for hives and/or angioedema (Golden et al. 1997, 2011, 2017; Georgitis and Reisman 1985). Sensitivity can persist for many years, even in cases of an intervening sting without a reaction; as a result, testing should be performed regardless of when the systemic sting event occurred.

30.4.1 Methods

The next consideration is the selection of the method for allergy testing. Skin testing to specific venom is the gold standard for identifying venom-specific IgE. In general, skin testing is preferred over in vitro methods for initial assessment because skin testing is more sensitive and usually less costly (Hamilton 2001, 2004) and should be performed by an allergist/immunologist who has training and experience in the diagnosis and treatment of insect allergy (Golden et al. 2011). Skin testing for Hymenoptera venom is most commonly performed using a combination of epicutaneous (prick/puncture) and intracutaneous (intradermal) methods accompanied by appropriate positive and negative controls. Testing for Hymenoptera venoms usually begins with skin prick testing at 100mcg/ml concentrations and if negative followed by intracutaneous testing starting at venom concentration of between 0.001 and 0.01 mcg/ml. At intervals of 20–30 min, the skin tests are preformed using tenfold increase in concentration until a positive skin test response occurs – or a maximum concentration of 1.0 mcg/ml is administered. Venom concentrations greater than 1.0 mcg/ml are associated with an increase in irritant skin reactions or falsely positive results. A positive skin test reaction at a concentration $\leq$1.0 mcg/ml confirms the presence of venom-specific IgE antibodies (Georgitis and Reisman 1985; Golden et al. 2017). Whole-body extract is the only reagent available for testing in imported fire ant patients suspected of having fire ant hypersensitivity and is discussed in later chapters. Venom skin testing is

positive in 70–90% of patients with a significant history of a systemic reaction (Valentine 1984; Hunt et al. 1978; Reisman 2005; Golden et al. 1997; Parker et al. 1982). Since the stinging insect cannot always be reliably identified, physicians should test all relevant insects for the geographic area in question. For most areas in the United States, skin testing should include testing for honeybee, yellow jacket, yellow hornet, white-faced hornet, and wasp. Discussed in detail elsewhere, in areas of the Southern United States, testing for venomous ants including the imported fire ants should be considered. Many individuals experience reduced sensitivity to venom testing in the first few weeks after a systemic sting reaction; therefore testing should be deferred for 4 to 6 weeks, as the potential of a false-negative reaction may be greater within 4–6 weeks of anaphylaxis (Goldberg and Confino-Cohen 1997).

A negative skin test result with a convincing history of sting reaction should be interpreted with caution (Golden et al. 2001; Reisman 2001). If the initial percutaneous and intradermal tests are negative, an in vitro test, measuring sIgE for venoms, such as Immunocap Assay®, is indicated. A serum basal tryptase level should also be ordered to assess for possible underlying mast cell disease (discussed later) (Georgitis and Reisman 1985; Golden et al. 2017). If both initial skin testing and in vitro testing are negative, then the testing should be repeated in 6–12 weeks (Georgitis and Reisman 1985; Golden et al. 2017).

As previously noted, there is some antigen cross-reactivity between the various Hymenoptera species. This could be secondary to cross-reacting carbohydrate determinants, which not thought to be clinically relevant (Hoffman 1993; King et al. 1985; Reisman et al. 1982). Neither the size of the skin test reaction nor the measured level of venom-specific IgE antibodies is reliable indicators of future sting reaction severity (Hoffman 1993; Golden et al. 2001; Reisman 2001).

Periodically, falsely positive and falsely negative reactions may occur. False-positive reactions are usually caused by the inherent, nonspecific irritant effect of the venom, usually at concentrations above 1 mcg/ml (Hoffman 1993). The combination of venom skin testing and complementary in vitro testing detects 98% of sensitized individuals (Hamilton 2001, 2004). However, occasionally, an individual with a convincing history of a systemic Hymenoptera sting reaction has both negative skin and in vitro testing (Golden et al. 2001, 2003; Reisman 2001). Again, a negative venom test should be interpreted with caution. Occurrences of anaphylaxis have been reported in individuals who tested negative to both venom skin testing and in vitro methods (Hamilton 2004; Golden et al. 2001; Reisman 2001). In such cases, mast cell disorders, such as occult or indolent mastocytosis or mast cell activation syndromes, should be considered. A basal serum tryptase level is recommended in subjects with negative testing and convincing history. The role and utility of serum tryptase in the evaluation of Hymenoptera allergy and occult or indolent mast cell disorders is evolving. A baseline serum tryptase level of >11.4 ng/ml after a fully subsided reaction suggests an underlying mast cell disorder (Bonadonna et al. 2010). Serum tryptase levels of greater than 20 ng/ml would warrant consideration of additional testing, including bone marrow biopsy (González de Olano et al. 2008; Brockow et al. 2008; Rueff et al. 2009; Bonadonna et al. 2010). Individuals with underlying or occult mast cell disorders are at greater risk for anaphylaxis, particularly insect anaphylaxis (Rueff et al. 2009; Bonadonna et al. 2009, 2010). The protective level of VIT may be lower than that in the general population, and the safety of VIT may also be lower in individuals with mast cell disorders (Oude Elberink et al. 1997; Niedoszytko et al. 2009). However, VIT is recommended as affected subjects are at greater risk without treatment.

30.5 Treatment

Hymenoptera stings are usually acutely painful and the event is obvious. Local reactions – those that are limited to the area contiguous to the sting site – are treated symptomatically. If a stinger is embedded, it should be removed by flicking it out and not squeezing the attached venom sac. The rate of venom delivery can be very rapid. In honeybees 90% of the venom is delivered in 20 s, and by 1 min nearly the entire venom sac has been

emptied suggesting that the removal of the venom sac must occur within seconds to reduce the potential of anaphylaxis. Otherwise, icing the affected area, using age-appropriate analgesia and oral antihistamines, is the mainstay of treatment. Although considerable pain, erythema, and swelling may exist, even in the case of large local reactions, secondary infection is rare (Schumacher et al. 1994a).

Anaphylaxis due to insect venom is managed the same as anaphylaxis caused by any other allergen (Kosnik and Korosec 2011). Initial treatment of choice is an intramuscular injection of epinephrine, preferably into the anterior, upper, and outer aspect of the thigh. Other medications, such as oral or intravenous corticosteroids and/or H-1 and H-2 histamine receptor blockers, are secondary medications that do not substitute for epinephrine. These are secondary therapies and should be administered only after epinephrine. This is regardless of the patients' age, health status, or comorbid medical conditions (Golden et al. 2011). The time interval between the onset of anaphylactic symptoms and the first dose of epinephrine is the best indicator of a successful outcome, and delayed use is a risk factor for death. Regrettably, underuse of epinephrine in the outpatient and emergency department settings remains problematic (Simons 2008; Manivannan et al. 2009; Bilò and Bonifazi 2008; Demain et al. 2010).

Once the patient is stabilized and the effects of the initial sting event are addressed, further intervention may be necessary. If the reaction is limited to a local reaction, regardless of how large, the patient should be reassured that the risk of a more severe future reaction is small (5–10%) (Graft et al. 1984; Mauriello et al. 1984). Generally, in cases where the sting event reaction was limited to local signs and symptoms, an epinephrine auto-injector is not warranted. In rare cases, where the patient has significant anxiety about a future sting event, an epinephrine auto-injector may contribute to an improved quality of life. This requires careful consideration and should be evaluated on a case-by-case basis. If the reaction included more generalized symptoms, such as bronchospasm, gastrointestinal symptoms, hypotension, or laryngeal edema, provision of and detailed training on the utilization of an epinephrine auto-injector is recommended. The patient and/or family should be able to demonstrate understanding of appropriate utilization. Avoidance is the mainstay of the management of all allergic diseases. This is certainly true of Hymenoptera allergy, regardless whether the reaction was local or systemic. The individual or family should be counseled on the insect-appropriate avoidance strategies and the benefits of following these strategies. If the sting event resulted in systemic signs and symptoms, the appropriate next step is to refer the patient to an allergy specialist for further evaluation, where the insect allergy will be evaluated and VIT considered (Golden et al. 2011).

VIT should be considered and offered to any patient with a history of a systemic allergic reaction to a Hymenoptera sting and evidence by skin test or in vitro methods of venom-specific IgE antibodies. VIT can provide an up to 98% protection against future sting events. VIT consists of gradually increasing doses of venom, usually beginning at 0.1 to 1.0 mcg/ml. Using current guidelines, the venom for winged Hymenoptera is given subcutaneously until a total dose of 100 mcg is achieved for each of the venoms being treated (Bonifazi et al. 2005; Reisman and Livingston 1992; Golden et al. 1981). The usual venom exposure from most Hymenoptera stings is 20–50 mcg; therefore, a treatment dose of 100 mcg for each venom would represent a protective dose approximating two to five stings (Schumacher et al. 1994b). This maintenance dose was based upon published protocols and is the manufacturers' recommended dosing per the FDA-approved package inserts. A maintenance VIT dose of 100 mcg provides a protection from anaphylaxis in up to 98%, whereas a maintenance VIT dose of 50 mcg/ml, recommended by a single investigator, can provide protection in approximately 80–90% of stings (Bonifazi et al. 2005; Graft et al. 1998). In few cases, the patient experiences local and/or systemic reactions during treatment, resulting in difficulty achieving a full maintenance dose of 100 mcg. In such cases, a maintenance dose of 50 mcg, though suboptimal, may provide adequate protection. In most cases, local reactions should not prevent the achievement

of a full 100 mcg dose, and every effort should be made to achieve this dose. There have been no long-term safety or toxicity issues associated with VIT, including in young children and pregnancy.

The physician should monitor VIT patients at regular intervals of 6 to 12 months. During treatment with VIT, between 3% and 12% of patients will experience a systemic reaction, mostly during the early build-up phase (Golden et al. 2011). These reactions are usually mild. Honeybee-allergic patents and those patients with elevated baseline serum tryptase seem to be at a somewhat higher risk of a systemic reaction during VIT. In addition, patients on beta-blockers or ACE inhibitors have a somewhat higher risk (Rueff et al. 2009). Local reactions to VIT present an important, frequent but generally less serious problem than systemic reaction during VIT. Approximately one-third of venom-allergic patients on VIT will experience local reactions during treatment. Although troublesome to the patient, these local reactions for VIT do not predict an increased risk for future, systemic reactions to VIT. These reactions can be uncomfortable, and as a result, the physician may make adjustments in dosing. It is important to recognize that these adjustments in VIT are primarily made for comfort, not for safety.

30.6 Large Local Reactions and VIT

Large local reactions to Hymenoptera stings are often caused by an IgE-mediated late-phase response. These reactions are not considered life-threatening and are associated with no more than a 5–10% risk of a future sting, systemic allergic reaction. Venom allergy testing is generally not indicated (Bilò and Bonifazi 2008). However, there are data to suggest that in some patients where the reactions are debilitating, or progressively worsening, VIT may be a consideration to reduce the severity of the local reactions (Demain et al. 2010). An example would be severe facial swelling in a mailman following wasp stings. So, in special circumstances, venom testing and VIT are indicated in patients with large local sting reactions.

30.7 Duration of VIT

The duration of VIT for venom-allergic patients is unclear (Bonifazi et al. 2005; Graft et al. 1998; Golden et al. 1996, 2000; Muller et al. 1991). The majority of patients are sufficiently protected after completing a 5-year treatment plan; however some authors suggest that lifetime therapy may be warranted. Some experts suggest that repeat venom skin testing can be helpful for determining who may discontinue VIT (Forester et al. 2007; Muller et al. 1992). Although this information may be helpful, the loss of skin test reactivity is not a guarantee of an absence of risk to venom-induced anaphylaxis. Lifelong VIT should be considered in individuals who have experienced a previous life-threatening event; have honeybee allergy, mast cell disease, and comorbid conditions; or have had a systemic reaction during VIT (Georgitis and Reisman 1985; Golden et al. 1998, 2017; Lerch and Muller 1998). Those patients requiring a higher than usual venom dose, having severe anxiety concerning future stings, or having high risk for recurrent stings should also consider lifelong VIT.

30.8 Recent Developments in Insect Allergy

Advances in our understanding of the role of clonal mast cell disorders, basophil biology, and utility of serum tryptase have enhanced the evaluation of Hymenoptera sting allergy. Many of these advances will contribute to improved diagnosis and management of insect-allergic individuals. For example, the effective management of patients with a compelling history of insect-induced anaphylaxis, yet are skin and blood test negative for venom-specific IgE, has been a challenge. Occult mastocytosis or other mast cell disorders are now recognized as a potential explanation. A multicenter study of predictors of severe anaphylaxis reported elevated serum tryptase is one of the predictors (Bonadonna et al. 2010; Oude Elberink et al. 1997; Álvarez-Twose et al. 2010). Hymenoptera allergy is a frequent finding in individuals with mastocytosis. The effectiveness

of VIT is less in subjects with mastocytosis or clonal mast cell disorders (Rueff et al. 2010). The 2017 insect allergy practice parameter more thoroughly addresses the role for obtaining tryptase levels in the evaluation of insect allergy and supports the role of VIT in patients with clonal mast cell disease (Georgitis and Reisman 1985; Golden et al. 2017). Finally, several recent cases have reported the usefulness of the immunomodulatory effects of omalizumab, a monoclonal antibody specific for IgE antibody, in the management of difficult to treat insect anaphylaxis in subjects with indolent or occult mastocytosis (Galera et al. 2009; Kontou-Fill et al. 2010). Though not an FDA-approved indication, in special circumstances, omalizumab may be a consideration (Georgitis and Reisman 1985; Golden et al. 2017).

In addition to the evolving understanding of clonal mast cell disorders and Hymenoptera allergy, the role of basophils in the diagnosis and management of insect anaphylaxis is also expanding. Although not commonly used in the United States, the basophil activation test may be informative in managing individuals with a history of systemic reactions to insect stings without specific IgE (Kruse et al. 2009; Kosnik and Korosec 2011; Peternelj et al. 2009).

30.9 Conclusion

Insect allergy is one of the three most common triggers of life-threatening anaphylaxis and is by far the most treatable. It is crucial that physicians and the public understand proper diagnosis, treatment, and management of this potentially life-threatening allergy. While the other two causes, food and medication anaphylaxis, are managed primarily by avoidance, Hymenoptera allergy can be managed prospectively with VIT, which provides up to 98% protection from subsequent sting anaphylaxis. Effective management of the acute event, a thorough history of the sting circumstances, recognition of the likely culprit insect, appropriate venom testing, VIT, and optimal use of auto-injector epinephrine are necessary for ideal outcomes. Acute management includes establishing the presence of a Hymenoptera sting-related anaphylactic event, followed by appropriate use epinephrine. Occult mast cell disease may be playing an important role in Hymenoptera sting reactions, and a basal tryptase level may be very helpful. However, long-term management does not end with the dispensing of an epinephrine auto-injector but includes appropriate referral, determination of venom-specific IgE, and, if indicated, IT.

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Allergy from Ants and Biting Insects

31

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Abstract

Allergy to stinging ants and biting insects is a worldwide problem that is likely to increase due to urbanization and human disruption of insect environments. This leads to inevitable contact with a variety of insect species that may trigger adverse reactions. While most human reactions to insects are generally mild in nature, the potential for severe and life-threatening allergies exists for some. The importance of further evaluation for a potential stinging insect allergy is highlighted by the reported fatalities to stinging and biting insects. Knowledge of insect taxonomy and life cycles is important as they play a vital role in guiding the evaluation of insect allergy. The evaluation of stinging insect allergy is largely guided by a history of potential exposure to an insect, resulting symptoms, availability of diagnostic resources, and risk of potential future reactions. In addition to avoidance measures and symptomatic treatment of an acute adverse reaction to a stinging insect, long-term treatment protocols that utilize immunotherapy are recommended if available. Further research into the production of diagnostic extracts, in vitro testing, and commercial extracts for insect allergen immunotherapy should be conducted in order to provide all venom-allergic individuals standardized evaluation and treatment options.

Keywords

Hymenoptera · Ants · Biting · Insects · Allergy · Hypersensitivity

31.1 Introduction

Human disease from the sting or bite of insects is a common problem worldwide. Insects make up the largest class of the Arthropod family. With over 2 million species of insects discovered, members of this diverse class include bees, beetles, flies, and ants. While the vast majority of human and insect interactions are no more than a nuisance, the potential for human envenomation by several insect species exists. Clinical symptoms range from mild cutaneous reactions to allergic and non-allergic processes that can involve multiple organ systems, may become life-threatening, and pose an ongoing public health concern. The following is a review of the most common ant and biting insect species associated with human disease, the medical evaluation to further investigate insect reactions and the available treatment options that exist.

31.2 Order Hymenoptera

The Arthropoda phylum makes up the most diverse and largest group of described animal species in the world. They are invertebrates that have an exoskeleton, a segmented body and paired appendages. The Insecta class, within the Arthropod phylum, includes the largest group of hexapod invertebrates. Hexapoda, or true insects, are characterized by having three pairs of legs and three distinct body segments: the head, thorax, and abdomen. Within the Insecta class, Hymenoptera make up the third largest order with over 100,000 different species described (Fig. 1). Over 17,000 Hymenoptera

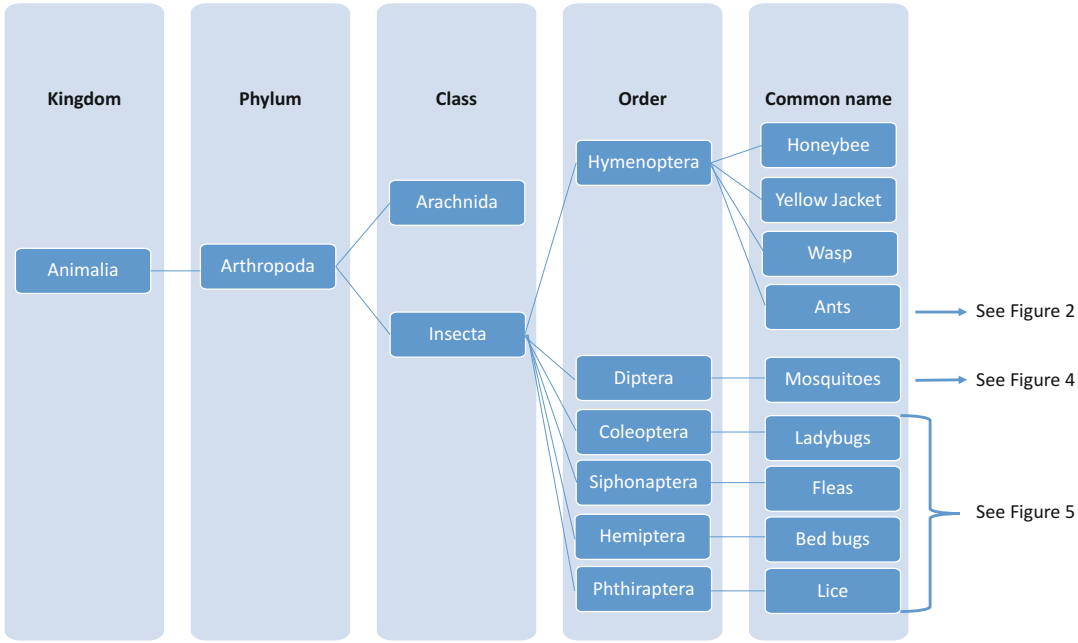

Fig. 1 Overview of insect taxonomy

species reside in North America alone. The Hymenoptera order can be further divided into two suborders: Symphyta (sawflies and horntails) and Apocrita (bees and wasps). Members of the Apocrita suborder have a characteristic waist or petiole due to narrowing between their thorax and abdomen. The Apocrita can be further divided into two subdivisions: the Terebrantia and Aculeata. An important distinction between these two subdivisions is the role of the ovipositor. The Terebrantia are mostly parasitic and use their ovipositor to lay eggs on other insects. The Aculeata have an evolved ovipositor that is used to sting and deposit venom. Another important distinction is the development of highly socialized behavior seen in some members of the Aculeata subdivision such as honeybees and ants. It is the members of the Aculeata subdivision that pose the most direct threat to humans.

31.2.1 Family Formicidae (Ants)

Families within the Hymenoptera order include the Apidae, Vespidae, and Formicidae families (Fig. 1). Flying Hymenoptera such as honeybees and wasps fall under the Apidae and Vespidae families, respectively. Ants fall under the Formicidae family and include over 14,000 described species. Of these, only a few ant species are associated with human allergic disease. Primarily five genera comprise the stinging ants that produce allergy; three are the most prevalent, with various forms of protein-containing venom capable of evoking a specific IgE response in humans. Fig. 2 reviews the taxonomic relationships in the Formicidae family.

31.2.1.1 Genus *Solenopsis*

In the United States, the imported fire ant (IFA) is the most relevant stinging ant (Fig. 6). *Solenopsis invicta* (red imported fire ant) is a native species to Brazil that was inadvertently introduced to the United States through the port of Mobile, Alabama, between 1930 and 1940. Since then it has spread throughout the southeastern United States, and its habitat has extended into the arid southwest and as far north as Maryland (Fig. 3). The IFA can be spread inadvertently by the movement of soil and vegetation. Entire colonies may be

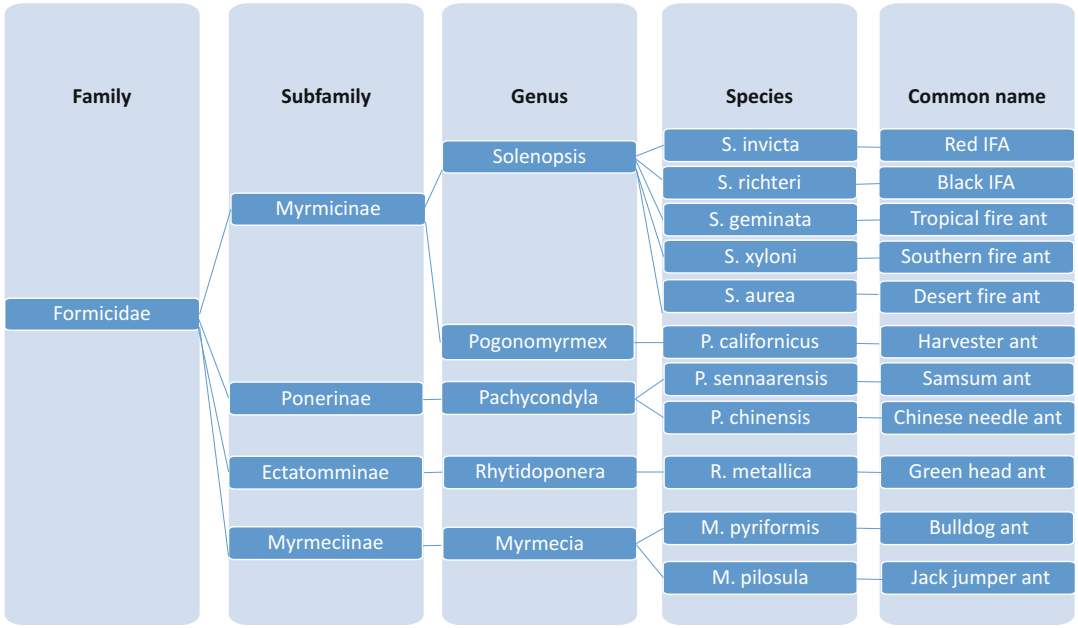

Fig. 2 Taxonomy of common stinging ants

displaced due to a natural phenomenon such as flooding. Fig. 3 shows the current IFA quarantine map for the United States. Worldwide the IFA has been found in Australia, New Zealand, China, and the Caribbean. The black fire ant, *Solenopsis richteri*, is also native to South America and was introduced to the United States around 1918. Its distribution in the United States is more limited as it is only found in northeastern Mississippi and northwestern Alabama.

The *Solenopsis* life cycle is important as it directly affects natural spread and distribution of this invasive species. Like other eusocial species, division of reproductive labor is seen with the queen being the only one capable of laying eggs. After a mating flight, the winged queen may travel away from the site of her original colony in search of a new colony location. Once a suitable location is found, the queen sheds its wings and begins to lay eggs underground. Initial workers emerge within 1–2 weeks. As these workers mature, they take over care of the brood, forage for food, and expand the nest. In the first year, a colony may rapidly grow in size and include 10,000 or more workers. After a few years, a mature colony can contain as many as 500,000 workers. The characteristic IFA mound is formed as workers excavate, and the soil is brought to the surface. Disruption of the mound by animals or humans results in swarming of ants to the surface as a defensive posture to protect the colony. In order to sting, the IFA will first anchor itself by biting with its mandible. Once anchored, it will arch its back then drive its stinger into the skin by curving its lower abdomen (Fig. 7). The stinger is removed and using its anchored mandible to pivot, the ant will then continue to sting in a circular pattern. IFA venom contains a mixture of piperidine alkaloids and proteins. The alkaloids, which make up 90–95% of IFA venom, are responsible for the characteristic pseudopustule seen after a sting.

Native *Solenopsis* species in the United States include *S. xyloni*, *S. geminata*, and *S. aureus* (Hoffman 1995). Mounds of these native species tend be smaller and more scattered than the dome-shaped IFA mound. Native species tend to be less aggressive than IFA. These native species are also distributed throughout the world and thus can pose a risk in susceptible individuals. Table 1 shows the worldwide distribution of ant species associated with human disease.

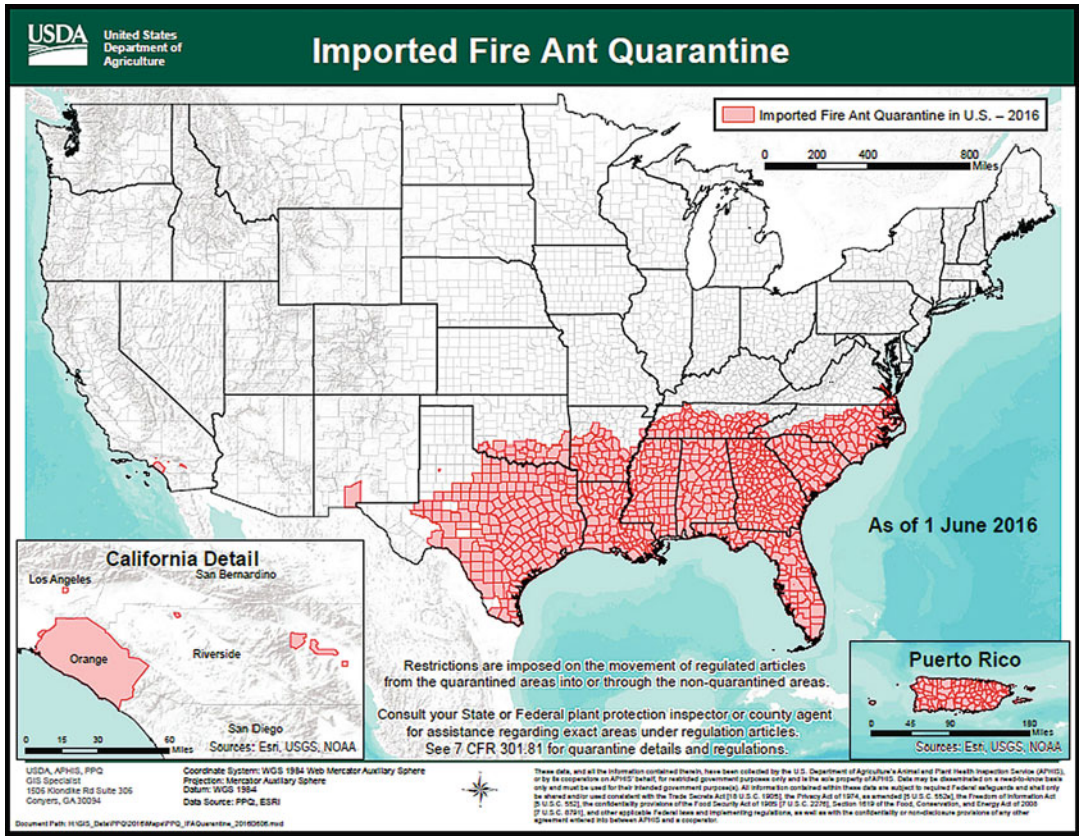

Fig. 3 Current map of imported fire ant quarantine areas in the United States. USDA, Accessed 7 Feb 2018. https://www.aphis.usda.gov

31.2.1.2 Genus *Myrmecia*

In Australia, the usual culprits for ant-related stings are members of the *Myrmecia* genus. The most commonly implicated species are *Myrmecia pilosula* (jack jumper ant) and *Myrmecia pyriformis* (bull ant). Jack jumper ants are aggressive foragers that move with a jumping motion. Bull ants are typically larger than jack jumper ants, have a powerful sting, and are also foragers. These two species make up the leading cause of allergic reactions in Australia affecting up to 3% of the population in endemic areas (Brown et al. 2011). In some areas of Australia, the prevalence of ant-triggered anaphylaxis exceeds the prevalence of anaphylaxis due to other causes such as bee stings and food allergy.

31.2.1.3 Genus *Pachycondyla*

Members of the *Pachycondyla* genus associated with allergic reactions include *Pachycondyla chinensis* (Chinese needle ant) and *Pachycondyla sennaarensis* (samsum ant). *P. chinensis* is commonly found in China, Japan, and Korea. It is also found in the southeastern United States as it was inadvertently introduced to North America prior to 1930 (Nelder et al. 2006). A prevalence rate of 2.1% for systemic allergic reactions after *P. chinensis* stings was noted in an endemic area (Cho et al. 2002). *P. sennaarensis* is found in Africa and the Arabian Peninsula where it poses a major public health concern as severe reactions leading to death have been reported (Dib et al. 1995).

31.2.1.4 Other Genera

Other ant species associated with allergic reactions include *Pogonomyrmex* species (harvester ant) which are found throughout the United States, Canada, and Mexico (Pinnas et al. 1977).

Table 1 Common stinging ants and worldwide distribution

Ant genus and species	Distribution
Solenopsis richteri; *Solenopsis invicta*	North and South America, Caribbean, Australia, China, Asia, Spain, Taiwan, New Zealand
Solenopsis geminata	North, Central and South America, Caribbean, Indonesia, Taiwan, Thailand, India
Solenopsis xyloni	Southwestern US, Mexico
Myrmecia pilosula; Myrmecia pyriformis; Rhytidoponera metallica	Australia
Pachycondyla sennaarensis	Africa, Arabian peninsula
Pachycondyla chinensis	Japan, Korea, New Zealand, China, Korea, Vietnam, Southeastern US
Pogonomyrmex species	North America

The sting from harvester ants is similar in mechanism to the IFA sting and tends to be quite painful with symptoms lasting up to 4 hours. The green head ant, *Rhytidoponera metallica*, has also been implicated in allergic reactions in Australia (Brown et al. 2011; Mehr and Brown 2012). Members of the *Hypoponera* genus are widely distributed across the world including the United States. *Hypoponera punctatissima* has been associated with adverse reactions in humans during swarming (Klotz et al. 2005). More recently, the twig or oak ant, *Pseudomyrmex* species has also been implicated in allergic reactions. These ants live in hollow twigs and trees and have unique venom that contains polysaccharides (Klotz et al. 2005).

31.2.2 Ant Venom Antigens

Ant venoms have unique contents and characteristics. The venom of the IFA is a complex blend of alkaloids with limited protein contents. The alkaloid component can vary among different species of ants. Only 10–100 ng of protein are injected per IFA sting (Hoffman 1995). This is in contrast to vespids who deliver 2–20 mcg of venom protein per sting (Golden et al. 2017). Four allergenic proteins have been described for *S. invicta*: *Sol i* 1, *Sol i* 2, *Sol i* 3, and *Sol i* 4 (Table 2) (Hoffman et al. 1988). *Sol i* 2 makes up the majority of allergenic venom protein in *S. invicta*. *Sol* i 1 is a phospholipase that is related to flying Hymenoptera phospholipases. *Sol i* 3 shares homology with the vespid antigen 5 molecules (Hoffman 1995). For *S. richteri*, *Sol r* 1, *Sol r* 2, and *Sol r* 3 are homologous to *Sol i* 1–3. *S. richteri* venom does not contain an analogous *Sol i* 4 antigen, whereas *S. geminata* contains a similar fourth antigen. Among other *Solenopsis* species, *Sol i* 1 and 2 are the most variable among species, whereas *Sol i* 3 tends to be conserved (Hoffman 2010). Cross-reactivity between members of the *Solenopsis* genus is common.

Table 2 *Solenopsis invicta* venom antigens. *Solenopsis* venom contains a mixture of piperidine alkaloids (these make up 90–95% of the total venom contents) and proteins. Listed are the proteins found in *Solenopsis* venom

Solenopsis invicta venom antigens	Percentage of protein components	Function
Sol i 1	2–5%	Phospholipase, related to flying Hymenoptera venom phospholipases
Sol i 2	60–70%	Function unknown
Sol i 3	20%	Shows homology with the vespid group 5 allergens
Sol i 4	9%	Shows homology with *Sol i* 2

Myrmecia ant venoms are different from other ants and flying Hymenoptera. *Myrmecia* venom contains phospholipase and a complex mixture of basic proteins. Several allergenic peptides have been described for jack jumper ants. One of the most important allergens is *Myr p* 2 or pilosulin 3 which is cytotoxic and has strong microbicidal activity (Hoffman 2010). There appears to be no cross-reactivity between IFA and *Myrmecia* venom allergens (Hoffman 2006). The major allergen for *P. chinensis* is *Pac c* 3 which is a member of the *Sol i* 3/vespid antigen

5 family (Lee et al. 2009). *P. sennaarensis* venom and *Sol i* 3 cross-react (Hoffman 2006). Venom from harvester ants appears to be more toxic than other insect venoms including hornets and honeybees (Schmidt and Blum 1978). The venom contains a mixture of phospholipases, hyaluronidase, acid phosphatases, and lipases.

31.2.3 Epidemiology and Risk Factors

While the exact prevalence of Hymenoptera stings is unknown, in IFA-endemic areas, it is estimated that up to 58% of individuals are stung on an annual basis (deShazo et al. 1984). In children, close to 40% reported an IFA sting within the preceding summer month, and when stung 23.9% of them reported multiple stings (Partridge et al. 2008). A 51% sting rate over a 3-week period was also reported in adults new to an IFA-endemic area (Tracy et al. 1995).

In the United States, prevalence of allergic sting reactions due to Hymenoptera in adults who are stung is 3.3% (Golden et al. 1989). In children who are stung, the estimated prevalence ranges from 0.15% to 0.8% (Bilo and Bonifazi 2008). In IFA-endemic regions, most allergic insect reactions are due to IFA stings (Freeman 1997). Systemic allergic reactions were reported in 16% of those stung by IFA with 0.6% of these reactions meeting criteria for anaphylaxis (Triplett 1976). Large local reactions occur in up to 56% (deShazo et al. 1984). A physician survey showed that 2% of patients who seek care after an IFA sting required treatment for anaphylaxis in endemic areas of the United States (Stafford et al. 1989).

The incidence of flying Hymenoptera-related fatalities varies by country. In a recent review of fatal anaphylaxis, venom-related fatalities occurred at a rate of approximately 0.1 cases per million population in several countries including the United States, United Kingdom, Canada, and Australia (Turner et al. 2017). The exact prevalence of sting-related fatalities, however, is unknown due to likely underreporting in cases where a sting is not recognized to precede a death or overreporting in cases where death may result from other mechanisms not related to an insect sting. In a 1989 survey of physicians, 83 fatal and 2 near-fatal reactions to the IFA were reported with the majority of reactions occurring in 2 states, Florida and Texas (Rhoades et al. 1989).

Several risk factors are associated with increased severity of a Hymenoptera-related reaction. Some of these factors may include older age, male sex, the use of angiotensin-converting enzyme inhibitors, vespid venom allergy, elevated serum baseline tryptase levels, and a history of one or more preceding field sting reactions (Rueff et al. 2009). An additional consideration for individuals that reside in IFA-endemic areas is the risk of indoor sting attacks which to date have been reported in the extremes of age (infants and elderly) and in individuals who are immobile or otherwise incapacitated (Rupp and deShazo 2006).

Mast cell disorders are associated with increased risk of anaphylaxis and increased severity of anaphylaxis. This increased risk is highlighted by insect-related fatalities in patients with mastocytosis (Oude Elberink et al. 1997). Though the exact prevalence of Hymenoptera venom allergy in patients with systemic mastocytosis is unknown, it is estimated to be tenfold higher than the general population (Brockow et al. 2008). Conversely, the prevalence of mastocytosis in venom-allergic patients is estimated to be 1–5% (Dubois 2004; Bonadonna et al. 2009). Hymenoptera stings are one of the most common triggers for anaphylaxis in mastocytosis patients (Brockow et al. 2008).

Pre-existing cardiovascular disease and the use of cardiovascular medications such as beta blockers and angiotensin-converting enzyme inhibitors may be risk factors for systemic reactions and increased severity of reactions in patients with venom allergy. Antihypertensive medications were associated with increased organ system involvement and increased risk for hospitalization in a group of patients that presented with anaphylaxis due to a variety of etiologies (Lee et al. 2013). Other studies, however, have not shown increased risk in venom-allergic patients who are also on beta-blockers or angiotensin-converting enzyme inhibitors (Stoevesandt et al. 2012).

31.2.4 Clinical Associations

Reactions to ant stings can range from localized pain, redness, and itching at the site of the sting to systemic reactions that can be allergic or non-allergic in nature. For IFA stings, the initial cutaneous response consists of a localized wheal with erythema at the site of the sting. A vesicle will develop over several hours that is initially filled with clear fluid that then becomes cloudy. The characteristic sterile pustule from the IFA occurs 1–2 days after a sting and represents localized cellular toxicity from the piperidine alkaloids found in the venom. A large local reaction (LLR) is generally described as contiguous swelling and erythema of 10 cm or greater. LLRs typically peak at 48–72 h and resolve over the course of days. LLRs are immunologically mediated and most likely represent a late-phase IgE-dependent response. Data from flying Hymenoptera venom-allergic patients indicate that despite evidence of venom-specific IgE in individuals with LLRs, the risk of a systemic reaction with a subsequent sting is less than 10%, with less than a 5% chance of anaphylaxis (Mauriello et al. 1984; Golden 2015).

Systemic reactions vary in presentation. On the mild spectrum of disease is the development of a full body urticarial rash with or without angioedema, also referred to as a systemic cutaneous reaction. More severe anaphylactic reactions are characterized by the rapid onset of multi-system symptoms that can include cutaneous symptoms (e.g., urticaria and angioedema), upper airway symptoms (e.g., rhinitis, congestion, conjunctivitis), lower airway symptoms (e.g., cough, wheezing), abdominal symptoms (e.g., nausea, vomiting, diarrhea), and cardiovascular symptoms (e.g., hypotension, loss of consciousness). While most insect-related systemic reactions are quick in onset (often within minutes), biphasic reactions (e.g., 12–24 h after the inciting event) have also been described in 1–20% of individuals (Bilo and Bonifazi 2008). With a history of previous insect sting anaphylaxis, the risk of recurrent anaphylaxis with subsequent stings is 30–60% (Reisman et al. 1985; Franken et al. 1994).

While toxic reactions to flying Hymenoptera are recognized and may lead to significant morbidity from massive envenomation, the clinical sequela from a large amount of IFA stings is not as clearly defined. Some individuals are able to tolerate such exposures with no significant sequela, while others may succumb to death (More et al. 2008).

Other reported reactions to IFA stings include the development of nephrotic syndrome, rhabdomyolysis with acute renal failure, neuropathy, seizures, and hemolytic uremic syndrome (Fox et al. 1982; Swanson and Leveque 1990; Koya et al. 2007; Lee et al. 2014). Finally, while most reactions to ants are due to a sting, IgE-mediated respiratory allergy from indoor exposure to ants and reactions after ingestion of ants or their eggs have also been described (Kim et al. 2005; Chansakulporn and Charoenying 2012; Nandhakumar 2013).

31.2.5 Evaluation

Evaluation for venom allergy is highly dependent on the clinical history. Sensitization, or evidence of positive specific IgE (sIgE) to venoms without a correlating clinical history, can be found in up to 15% of the general population (Golden et al. 1989). In IFA endemic areas, the finding of IFA sIgE is 1.7 times more common than other allergens in a random sampling of blood donors (Caplan et al. 2003). After an IFA sting without systemic symptoms, evidence of IFA sIgE was detected in 16% of adults (Tracy et al. 1995). In fact, in endemic areas, sensitization occurs within the first few years of life (Partridge et al. 2008).

An important historical fact to obtain in determining whether an IFA sting occurred includes the presence or absence of a pustule at the sting site as this is virtually pathognomonic for IFA stings. The absence of a sterile pustule, however, does not rule out a possible IFA sting as rarely these may not form or may not be noticed by the patient.

A diagnosis of IFA hypersensitivity can be made when the clinical history confirms anaphylaxis after an IFA sting and evidence of IFA sIgE is obtained via serologic and/or skin testing.

Skin testing to IFAs is done in a stepwise fashion in individuals that have a clinical history that would warrant venom immunotherapy. Timing of testing is important as venom skin testing may be negative in the first 4–6 weeks after a sting for unclear reasons. A negative skin test done in this time period should be repeated at a later date, or other testing modalities (i.e., serologic testing) should be done. IFA whole-body extract (WBE) to *S. invicta* and *S. richteri* is available for skin testing. Initially, prick testing with IFA WBE at a concentration of 1×10^{-3} wt/vol is done. If prick testing is negative, then intracutaneous or intradermal testing can be conducted starting at a concentration 1×10^{-6} wt/vol and then increased by tenfold serial concentrations until a positive test is achieved or up to a maximum concentration of 1×10^{-3} wt/vol.

Serologic testing is another testing mechanism to further evaluate for IFA hypersensitivity and is the test of choice in individuals that are unable to undergo skin testing. In the setting of clinical symptoms of insect allergy and negative skin testing, serologic testing is positive in about 10% of individuals. In individuals with positive skin tests to insects, up to 20% may have negative serologic testing. For this reason, experts recommend that regardless of which test is performed first, individuals with a convincing history of Hymenoptera venom allergy should undergo the alternative test to insect allergens that tested negative initially (Golden et al. 2017).

Obtaining a baseline tryptase level as part of the evaluation is also a consideration for patients with venom allergy as an elevated serum baseline tryptase level is associated with increased severity of reactions in untreated patients and in some undergoing venom immunotherapy (Rueff et al. 2009, 2010). The likelihood of finding an elevated tryptase level is increased in individuals who experience severe venom reactions (e.g., hypotension), individuals with clinical reactions to venom but no evidence of sIgE on serology or skin testing, and in individuals who experience systemic reactions while on immunotherapy (Golden et al. 2017). An elevated baseline tryptase level should prompt further consideration for an underlying mast cell process, and additional evaluation should be considered.

Evaluation of systemic reactions due to ant species other than IFA thus far has been region specific. Skin testing to extracts and serologic testing have been diagnostic for several ant species such as *P. chinensis*, *P. sennaarensis*, *Pogonomyrmex* species, and *Myrmecia* species (Pinnas et al. 1977; Dib et al. 1995; Kim et al. 2001; Klotz et al. 2005). Standardization and availability of skin test reagents and commercial serologic tests for the evaluation of allergic reactions to ants other than IFA is an area that requires additional investigation.

31.2.6 Treatment

Immediate treatment of an IFA sting involves removal of the ant which may require brisk rubbing of the skin or actually picking off individual ants as attachment via their mandibles may make it difficult to remove by simply shaking or washing them off. Local cutaneous reactions and the pseudopustule following an IFA sting can be managed conservatively. While pruritus is common, care must be taken not to disrupt the sterile pustule as a secondary bacterial infection may then occur. The pustule itself will self-resolve over days to a week or two. LLRs can be more cumbersome depending on their location (e.g., lower extremity). Symptomatic treatment with elevation of the affected extremity, cold compresses, topical corticosteroids, and oral antihistamines can aid in reducing the swelling and pruritus associated with these reactions.

Systemic reactions to insect stings require prompt recognition and treatment in order to prevent further morbidity and mortality. Intramuscular epinephrine is the first-line treatment and initial drug of choice for the treatment of an allergic systemic reaction. In children, the recommended dose is 0.01 mg/kg, up to a maximum dose of 0.5 mg per dose. In adults, the recommended dose is 0.3–0.5 mg. Epinephrine should be delivered via intramuscular injection and may be repeated as needed for persistent or recurrent symptoms. Additional adjunct treatments include

antihistamines, intravenous fluids, H2-blockers, bronchodilators, and corticosteroids. Following a stinging insect reaction, referral to an allergist is indicated to further investigate the history, discuss additional evaluation, and provide guidance on treatment options.

In general, recommendations for the initiation of immunotherapy for IFA allergy follow recommendations for flying Hymenoptera with a few exceptions as the natural history of IFA hypersensitivity has not been clearly described (Table 3). IFA immunotherapy is recommended for individuals who have experienced an anaphylactic reaction to IFA and who show evidence of sIgE to IFA. In general, individuals who have experienced LLRs to IFA have a low risk of future systemic reactions; therefore, additional testing or consideration for immunotherapy is not indicated. In certain cases where an individual may experience repeated or debilitating LLRs, testing and immunotherapy may be a consideration as it has been shown to be effective at decreasing size and duration of LLRs due to flying Hymenoptera insect stings (Golden et al. 2009). Similar results were noted in a case report of a child with debilitating LLRs due to IFA (Hagan 2000). Recent data investigating the natural history of systemic cutaneous reactors to flying Hymenoptera have determined that the risk of progression for these individuals is low. Hence, with the most recent update to the stinging insect practice parameter, further testing and treatment with venom immunotherapy are no longer recommended for these individuals regardless of their age (Golden et al. 2017). Children who experience systemic cutaneous reactions to IFA usually do not progress to more severe reactions if re-stung (Nguyen and Napoli 2005). However, given the incompletely elucidated natural history of IFA allergy, additional testing and treatment with immunotherapy should be considered in individuals living in IFA-endemic areas who experience systemic cutaneous reactions. Factors that may influence this decision include patient or parental preference, lifestyle, and the presence of other risk factors that may place the individual at risk of complications from repeated IFA stings.

Table 3 Imported fire ant (IFA) hypersensitivity reactions, evaluation and treatment recommendations

Patient history	Test and treat with immunotherapy	Notes
No history of previous reaction to IFA sting	No	Increased sensitization to IFA seen in individuals living in endemic areas
Large local reaction (LLR)	Not generally, consider case by case	Due to low risk of progression with subsequent stings, testing is not indicated in general. If an individual is experiencing debilitating or recurrent LLRs, can consider testing and offering immunotherapy on case by case basis
Systemic cutaneous symptoms	Consider	Testing is no longer recommended for individuals of all ages with systemic cutaneous reactions to flying Hymenoptera. However, given natural history of IFA hypersensitivity is unknown could consider testing/treating depending on patient preference, risk of recurrence and presence of additional risk factors
Anaphylaxis	Yes	Due to significant risk of reactions with subsequent stings, testing to IFA and treatment with immunotherapy is recommended

Venom immunotherapy for the treatment of Hymenoptera venom allergy is effective and has been shown to decrease the risk of subsequent reactions to less than 5% (Golden et al. 2017). For flying Hymenoptera, the use of WBE has proven ineffective when compared to the use of purified venom extracts (Hunt et al. 1978). Despite this, the use of WBE for the treatment of IFA hypersensitivity is considered effective (Freeman et al. 1992). The available IFA allergen extract is a non-standardized WBE that contains *S. invicta*, *S. richteri*, or both. Given the significant cross-reactivity between the two species, the use of *S. invicta* WBE is likely sufficient in most cases. A maintenance dose of 0.5 ml of a 1:100 wt/vol concentration is considered the therapeutic goal by most.

Conventional buildup protocols utilize increasing doses of allergen given one to two times per week until a maintenance dose is reached. Conventional buildup protocols typically take 3–6 months to complete depending on the schedule of injections. Once the maintenance dose is reached, the interval can be spaced out to monthly injections. In regard to the safety of IFA immunotherapy, one study showed rates of systemic reactions of 0.4% per injection and 9.1% per patient in a cohort of patients undergoing IFA WBE immunotherapy (La Shell et al. 2010). Most reactions to immunotherapy were mild in nature and did not result in significant morbidity.

Given the propensity for individuals to experience repeat IFA stings in an endemic area, accelerated 1- to 2-day protocols have also been described. These accelerated protocols carry the benefit of reaching the maintenance dose rapidly and hence provide protection to the individual within days of starting. An example of a 1-day IFA accelerated (rush) protocol is shown in Table 4. Premedication with oral antihistamines, oral corticosteroids, and H2-blockers starting a few days prior to an accelerated protocol decreases the risk for systemic reactions (Arseneau et al. 2013). In a patient with reactions to IFA immunotherapy, addition of omalizumab (anti-IgE monoclonal antibody) to a premedication regimen that consisted of antihistamines and corticosteroids allowed for the successful rapid desensitization to IFA (Tille and Parker 2014). No reactions were noted in a case series of three children 36 months of age and younger who completed a 1-day rush protocol (Judd et al. 2008).

Table 4 Imported fire ant 1 day rush immunotherapy protocol

Day	Volume (mL)	IFA whole body extract concentration (wt/vol)	Observation time after injection (minutes)
1	0.3	1:100,000	30
	0.1	1:10,000	30
	0.3	1:10,000	30
	0.05	1:1,000	30
	0.15	1:1,000	60
	0.3	1:1,000	60
	0.05	1:100	60
	0.1	1:100	60
	0.2	1:100	60
	0.3	1:100	120
8	0.5	1:100	30
15	0.5	1:100	30
29	0.5	1:100	30
50	0.5	1:100	30
Monthly maintenance dose (every 4 weeks)	0.5	1:100	30

The exact length of treatment for IFA WBE is unknown. When extrapolating data from studies of flying Hymenoptera allergy, a 3- to 5-year course of immunotherapy would be considered optimal for most individuals with a few exceptions. Risk factors associated with relapse after immunotherapy include the presence of mastocytosis, an elevated serum baseline tryptase level, severity of previous insect-related symptoms such as syncope, receiving less than 5 years of immunotherapy, and having a systemic reaction to a field sting or injection while on immunotherapy (Golden et al. 2017). Given insufficient data regarding the optimum duration of IFA WBE immunotherapy, longer treatment courses may be considered depending on identified risk factors and risk of future stings.

Immunotherapy for other ant species is limited due to lack of commercial extracts. In Australia, a

venom extract for *M. pilosula* was shown to be effective in a double-blind placebo-controlled trial (Brown et al. 2003).

31.2.7 Avoidance and Patient Education

Individuals with ant hypersensitivity should be counseled on avoidance measures to minimize future stings. Patients should be counseled to avoid going barefoot when outdoors. If working outdoors, care should be taken to wear protective gear such as work gloves to decrease the risk of inadvertent exposure to ants. Control measures such as the use of baits or chemical treatments for lawns and yards that are infested with IFAs should also be considered. Individuals who have experienced systemic reactions to IFA should be counseled to carry self-injectable epinephrine, obtain and wear a medical alert bracelet, and keep an updated anaphylaxis action plan available. In low-risk cases such as those with histories of LLRs to IFA stings, a self-injectable epinephrine kit may be considered for patient comfort.

31.3 Order Diptera (True Flies)

Members of the Diptera order are considered true flies because they have a single pair of wings, whereas other insects have more wing pairs. The back pair of wings in true flies has evolved into small structures called halteres that are used to stabilize the insect while flying. Additionally, the mouth parts of flies have evolved for different uses (e.g., suck up water or piercing for a blood meal). With over 4,500 species of flies described worldwide, this group of insects includes mosquitoes, the common housefly, fruit flies, midges, and black flies (Fig. 4).

Human disease associated with true flies includes the risk of spreading of food-borne illness as well as their function as vectors of disease (e.g., deer flies transmit tularemia). Cutaneous myiasis is due to a parasitic infestation of fly larvae on the skin. Flies may directly deposit eggs on the skin or may use an intermediate vector. After hatching, the larvae penetrate into the host's skin and produce a localized erythematous and edematous papule that can be associated with significant pruritus. Treatment requires complete removal of the larvae, though occlusion of the central hole in the papule may also be effective. Localized cutaneous reactions are common from other fly bites such as midges. Contact dermatitis to midge larvae (*Chironomus thummi thummi*) has also been described (de Jaegher and Goossens 1999). *Drosophila* species have proven helpful through their use as a model organism for research purposes. Occupational allergy to *Drosophila* has been described in laboratory workers. The overall prevalence of sensitization to *Drosophila* is estimated to be 6% in exposed lab workers, though an increase in sensitization up to 15% is seen in those with the highest exposure (Jones et al. 2017). IgE-mediated sensitization from occupational exposure to the tsetse fly (*Glossina morsitans*) resulted in anaphylactic symptoms in one patient (Stevens et al. 1996).

Members of the Tabanidae family include horse flies and deer flies which can cause painful bites that result in local reactions and may rarely cause anaphylaxis. Several specific allergens for these have been identified (Hemmer et al. 1998). Evaluation is difficult as skin testing to commercial WBE was not helpful at distinguishing clinically reactive patients from controls and serologic testing showed mixed results (Freye and Litwin 1996; Hrabak and Dice 2003). Immunotherapy using WBE to deer flies (*Chrysops* spp.) may be effective and safe (Hrabak and Dice 2003). Cross-reactivity between Diptera and flying Hymenoptera allergens has been described and clinically was deemed to be relevant in a patient with reactions to horse fly and flying Hymenoptera (Freye and Litwin 1996). In a patient with severe reactions to horse fly and mosquito bites, elevated serum basal tryptase levels and abnormal mast cell aggregates were noted on bone marrow biopsy though full diagnostic criteria for mastocytosis were not present (Potier et al. 2009). The bite of the blackfly (Simuliidae family) is initially painless though over time it can become extremely painful and produce a local inflammatory

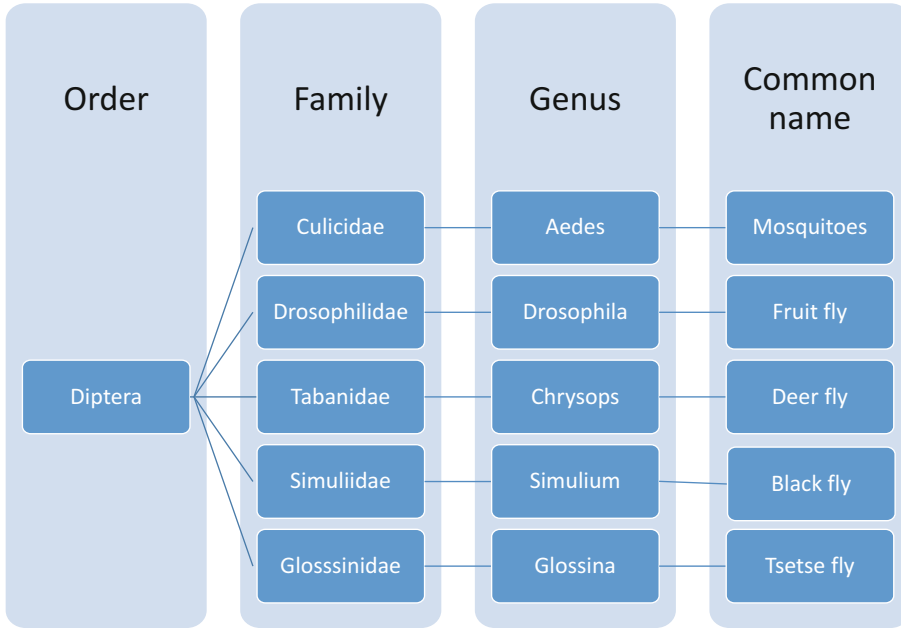

Fig. 4 Taxonomy of true flies

response. "Blackfly fever" is a systemic process characterized by fever, headache, nausea, malaise, and lymphadenopathy noted in some individuals after a blackfly bite. Cutaneous, neurologic, and renal symptoms were described in one patient after recurrent blackfly bites (Orange et al. 2004).

31.3.1 Family Culicidae (Mosquitoes)

31.3.1.1 Role in Human Disease

Over 3,500 different mosquito species have been described worldwide. They are members of the Insecta class, order Diptera, and family Culicidae (Fig. 4). While both males and females feed on flower nectar, some species are also hematophagous. In these species, the females use a proboscis to feed on the blood in order to complete the process of egg development. In humans, mosquito bites introduce salivary proteins that can lead to local and sometimes systemic symptoms in the host. Aside from the allergic or irritant effects that these bites produce, a larger and more concerning process is the role that mosquitoes play as vectors of disease. Mosquitoes are vectors for a variety of human-related infectious diseases to include the viruses that cause dengue fever, yellow fever, and Zika transmitted mostly by *Aedes* species and parasitic agents such as *Plasmodium* species that will result in malaria. Worldwide, members of the *Culex* and *Aedes* genera are the most important mosquito species.

Localized and systemic reactions to mosquito bites are due to the salivary proteins that are introduced into the host during a bite. More than 30 salivary proteins have been described for *A. aegypti* (Fig. 9). These salivary proteins are utilized by the mosquito to aid with the feeding process and have several functions to include anticoagulant and vasodilatory effects. Salivary proteins lead to sensitization of the host and can elicit an immunologic response.

31.3.1.2 Natural History

The natural history of insect-related reactions has been described (Table 5). In stage 1, there is no reaction to a bite as the host has not been previously sensitized to that insect. Stage 2 describes a delayed reaction that starts 3–4 h after a bite and peaks at 18–24 h. Stage 3 is characterized by both immediate and delayed symptoms, whereas in stage 4, only

Table 5 Natural history of mosquito reactivity

Stage	Immediate reaction	Delayed reaction
1	No	No
2	No	Yes
3	Yes	Yes
4	Yes	No
5	No	No

immediate symptoms occur. Stage 5 is notable for non-reactivity (German 1986). In mosquito-related reactions, natural and ongoing exposure induces a state of non-reactivity consistent with stage 5 (Peng and Simons 1998). Therefore, natural desensitization is suspected to occur with age and ongoing exposure.

The exact prevalence of mosquito bites and reactions is unknown due to underreporting. One survey study reported 82% of participants developed local reactions with mosquito bites, whereas 2.5% reported LLRs (Arias-Cruz et al. 2006). Risk factors associated with increased severity of reactions to mosquito bites include younger age, lack of previous exposure to native mosquito species, increased frequency of exposure (e.g., outdoors workers), and individuals with abnormal immune function (e.g., individuals with primary or secondary immunodeficiency) (Peng et al. 2007). Increased severity of cutaneous reactions has been reported in individuals with human immunodeficiency virus (Diven et al. 1988).

31.3.1.3 Clinical Associations

Clinical symptoms of mosquito bites range from localized cutaneous reactions on exposed skin (e.g., papular wheal with surrounding erythema) to severe cutaneous symptoms that may also involve other organ systems. The cutaneous reaction can be immediate in nature, delayed or not occur at all. Immediate reactions tend to peak within 20 min. Delayed reactions start later, peak 24–36 hours after a bite and resolve over days to weeks. In some individuals, the localized wheal and flare reactions may be large and be better characterized as LLRs. Other cutaneous reactions that can be seen after a mosquito bite include vesicular, pustular, hemorrhagic bullae or necrotic lesions with surrounding erythema. Skeeter syndrome is characterized by large local cutaneous inflammation that may also be accompanied by a low-grade fever. Systemic urticaria and angioedema as well as anaphylactic reactions have also been described with mosquito bites (Peng et al. 2004a; Arias-Cruz et al. 2006). A case of recurrent anaphylaxis due to presumed mosquito bites in a patient with mastocytosis has also been reported (Reiter et al. 2013).

Robust reactions to mosquitoes have also been described in systemic diseases such as natural killer (NK) cell lymphocytosis related to chronic Epstein-Barr virus (EBV) infection. Skin lesions in these individuals are characterized by bullae that may be clear or hemorrhagic at the site of mosquito bites. Systemic symptoms include high fever, lymphadenopathy, hepatosplenomegaly, liver, and kidney dysfunction. Symptoms gradually resolve but can recur with repeat mosquito bites. Pathogenesis for this condition involves the reactivation of latent EBV in NK cells after stimulation by mosquito antigen-specific $CD4^+$ T cells (Asada 2007). Mosquito antigen-specific $CD4^+$ T cells can also induce the expression of a viral oncogene, latent membrane protein 1 in NK cells (Asada et al. 2005). Oncogenesis of NK cells may explain the progression to hemophagocytic lymphoproliferative syndrome that has also been described in some of these patients.

31.3.1.4 Evaluation

Natural exposure to mosquitoes induces mosquito-specific IgE as well as specific IgG. Both mosquito-specific IgE and IgG levels correlate with skin reactivity on natural exposure (Peng and Simons 1998). In fact, an inverse relationship is seen between age and levels of mosquito-specific IgE and IgG. Levels of mosquito-specific IgE and IgG gradually decline after the age of 5 years as natural desensitization is thought to occur (Peng et al. 2004b). Delayed reactions are due to T-cell-mediated immunity. Cross-reactivity exists between mosquito allergens from different species; however, species-specific allergens also exist (Peng et al. 2004a).

Testing for hypersensitivity reactions to mosquito should be considered in patients who present with unusual or robust reactions to mosquito

bites (Crisp and Johnson 2013). Testing that may be considered includes challenge testing or serologic or skin testing. While challenge testing may be necessary in controlled research studies, its role for the routine evaluation of mosquito hypersensitivity reactions is limited by the lack of availability of specific mosquito species, risk of disease transmission, and risk for inducing reactions that may include anaphylaxis (Levine et al. 2003). Serologic testing can be considered as a mosquito whole-body in vitro test is available in the United States. There are several commercial extracts available for skin testing for mosquito hypersensitivity in the United States (Crisp and Johnson 2013). Because these extracts are non-standardized, they may have variable allergen content which may limit their use in skin testing. Only 32% of patients with mosquito bite proven skin reactions also reacted to a skin test using WBE (Peng et al. 2006). The use of recombinant allergens may improve the diagnostic sensitivity of mosquito allergen extracts (Peng et al. 2006, 2007). Recombinant allergens for *A. aegypti* have been developed though they are not commercially available.

31.3.1.5 Treatment

Treatment of localized cutaneous reactions to mosquito bites is largely supportive. Oral antihistamines have been shown to decrease the pruritus and size of localized immediate and delayed cutaneous symptoms (Karppinen et al. 2006). Additional treatment options are similar to those of LLRs for other insect stings such as cold compresses and topical corticosteroids to decrease local inflammation and swelling. Antibiotics are not indicated for the treatment of LLRs without evidence of bacterial superinfection. In the rare case of systemic allergic symptoms such as anaphylaxis, the treatment algorithm follows the same pattern as for other causes of anaphylaxis with epinephrine given first and adjunct medicines used as needed.

Immunotherapy using mosquito WBE is an option for the treatment of mosquito hypersensitivity reactions. Non-standardized WBE has been proven effective to treat immediate and delayed cutaneous reactions as well as systemic reactions after mosquito bites (McCormack et al. 1995; Beaudouin et al. 2001; Ariano and Panzani 2004). Serum sickness was noted as a side effect of immunotherapy in a patient undergoing immunotherapy to *C. pipiens* and *A. aegypti* (McCormack et al. 1995). The lack of approved and standardized extracts for mosquito immunotherapy limits generalization of this procedure, however. Given that the natural history of cutaneous reactions supports natural desensitization over time, randomized controlled studies are needed to ensure that the benefit from immunotherapy is consistent with the procedure rather than what would be typically seen with natural desensitization.

31.3.1.6 Avoidance and Patient Education

Patients should also be counseled on avoidance of mosquito-infested areas and encouraged to wear protective clothing and to apply personal mosquito repellants such as N,N-diethyl-m-toluamide (DEET) on exposed skin. Clothing can also be treated with an insecticide prior to wear. If outdoor exposure is prolonged and unavoidable, the use of netting that has been pretreated with an insecticide may prove useful to decrease exposure. In cases where anaphylaxis has occurred, patients should be counseled to carry self-injectable epinephrine in case of future reactions.

31.4 Order Coleoptera (Beetles)

Beetles form the order Coleoptera, the largest order in the animal kingdom, with over 400,000 species of beetles described (Fig. 5). Some species secrete cantharidin, an odorless vesicant that produces a chemical burn if applied to the skin. While inadvertent exposure to cantharidin may be an unwelcome side effect of contact with a beetle, it has proven useful as a therapeutic agent for the treatment of molluscum contagiosum skin infections in humans.

31.4.1 Family Coccinellidae (Ladybugs)

More than 5,000 species of ladybugs have been described. The Asian lady beetle or *Harmonia*

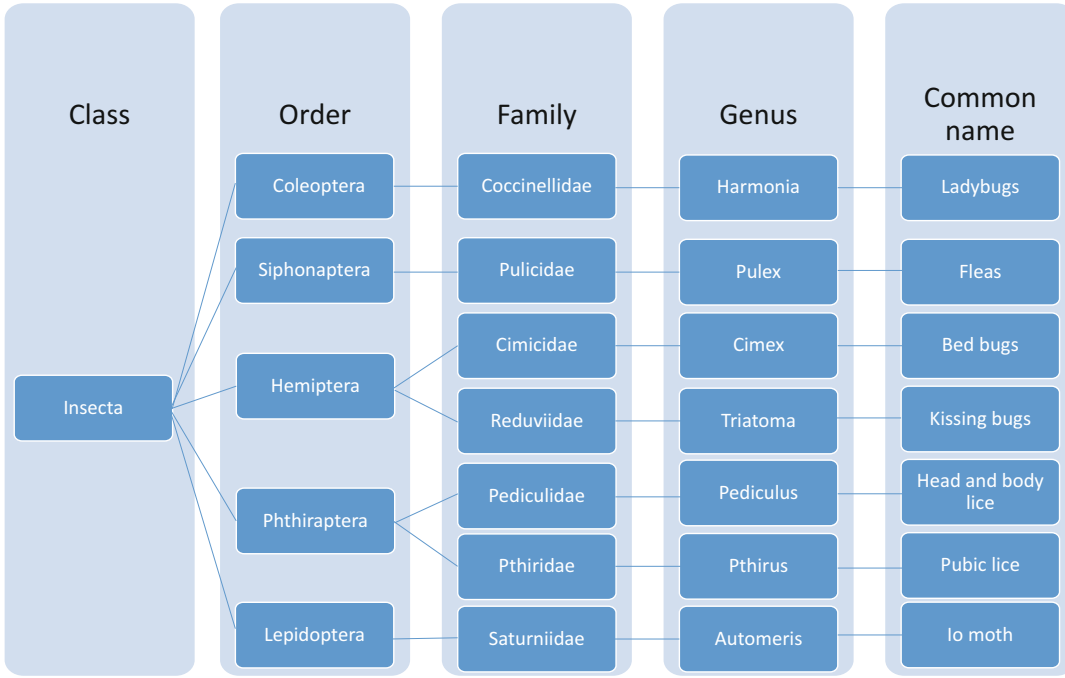

Fig. 5 Taxonomy of other biting insects associated with human disease

axyridis was introduced to North America from Japan in the 1970s in an attempt to control the population of aphids and soft-bodied insects (Fig. 8). *H. axyridis* has now established its own colonies throughout North and South America and is considered an environmental and invasive pest. The Asian lady beetle typically finds its way indoors during fall in order to survive the cold winter months. Indoor infestations tend to occur in the fall, winter, and spring months; however, year-round infestations have been reported (Sharma et al. 2006).

Allergic reactions to the lady beetle were first reported in 1999 (Yarbrough et al. 1999). Common symptoms associated with lady beetle allergy are limited to the upper respiratory tract (e.g., rhinoconjunctivitis symptoms), lower respiratory tract (e.g., asthma), and the skin (e.g., urticaria and angioedema). Reactions to ladybugs have occurred in adults as well as children (Yarbrough et al. 1999; Davis et al. 2006). Though rare, ladybug bites are reported and thought to be due to pinching of the skin by the insect's legs. A localized wheal and flare reaction may occur after these "bites." One case of presumed ladybug-triggered anaphylaxis associated with an elevated tryptase level has been reported (Albright et al. 2006).

As one of their defense mechanisms, ladybugs secrete a yellow fluid through the joints of their exoskeleton that is called reflex bleeding. The fluid includes hemolymph and noxious chemicals used to deter predators. The hemolymph contains the major allergenic antigens that trigger human disease, *Har a* 1 and *Har a* 2 (Nakazawa et al. 2007; Goetz 2009). Skin testing to a WBE of ladybug showed that sensitization can occur in up to 20% of exposed individuals, whereas an experimental whole-body IgE immunoassay was positive in 10% of blood bank donors (Drelich 2007; Clark et al. 2009).

Currently, there is no commercial extract for the diagnosis of ladybug hypersensitivity. Similarly, there is no commercial allergen immunotherapy extract to ladybugs though locally produced extracts have been utilized and have shown to be efficacious. Treatment recommendations include avoidance measures and symptomatic

treatments. As resolution of allergic symptoms is prompt after removal of ladybug exposure, household removal of these insects should be expeditious.

Elimination of ladybugs once an infestation has occurred may be difficult as insecticides may not be effective. Removal strategies should be done carefully to prevent crushing the ladybugs as this will release hemolymph and allergen. Prevention of infestations with the use of insecticides applied outside the home as well as closing cracks to prevent ladybugs from entering homes may be a cost-effective strategy.

31.5 Order Siphonaptera, Family Pulicidae (Fleas)

Over 2,500 species of fleas have been described. Fleas are small insects that parasitize mammals and birds. They are wingless and have mouthparts that are adapted to pierce the host's skin and suck blood. Their hind legs are also adapted for jumping, allowing them to jump distances up to 50 times their length. They are also vectors of disease and can transmit diseases like rickettsial infections. Most of the flea species that parasitize humans are found in the Pulicidae family. Common reactions in humans are pruritic papular urticarial lesions at the site of the flea bite. Treatment includes topical corticosteroids though most flea bites will resolve on their own. Elimination of fleas from a household involves removal of fleas at all stages of development.

31.6 Order Hemiptera

31.6.1 Family Cimicidae (Bed Bugs)

Bed bugs (order Hemiptera, family Cimicidae) pose an ongoing public health concern. Bed bugs were mostly eradicated in the developed world in the 1940s. Since the 1990s, however, a resurgence of infestations has been noted and is attributed to increased international travel, decreased presence of a natural predator (e.g., cockroaches), and increased resistance of bed bugs to extermination (Ter Poorten and Prose 2005). These ectoparasites are known for their propensity to feed exclusively on blood. The common bed bug, *Cimex lectularius*, feeds on humans, birds, bats, and other mammals. They are found in warm dark areas typically near their prey though are rarely seen as exposure to light makes them seek the dark. They feed on their host at night, preferring exposed areas of the skin such as the face and arms in humans. The bites tend to occur in a linear or clustered pattern of three to four lesions and are not typically felt by the host.

Clinical reactions can range from a pruritic papular rash on exposed areas of the skin to bullous dermatosis to rare cases of anaphylaxis (Parsons 1955; Ter Poorten and Prose 2005; deShazo et al. 2012). Multiple immunologic mechanisms are suspected. In vitro evidence of specific IgE to a salivary protein of *C. lectularius* has been identified. Biopsy of bullous lesions shows a leukocytoclastic vasculitis pattern (deShazo et al. 2012; Price et al. 2012).

Diagnosis requires a careful history of one or more house inhabitants affected by similar dermatologic complaints. Identification of the bed bugs can aid with the diagnosis though this may be a difficult endeavor that requires nocturnal searches. The finding of black specks on sheets, a mixture of bed bug feces and human blood, may be a clue as to their presence. Avoidance measures such as sleeping in long-sleeved shirts and pants may help decrease exposure. Treatment of papular lesions involves the use of topical corticosteroids and oral antihistamines, though the latter may not be as helpful at controlling the pruritus associated with these lesions. Oral corticosteroids may be helpful in cases of bullous eruptions.

Eradication of bed bugs can be problematic as adults may live up to a year without feeding and up to 2 years in cooler environments. Pesticide resistance has also been a concern that poses limitations on complete eradication of bed bugs. Pesticides including desiccants, pyrethrins, insect growth regulators, and pyrroles have proven helpful with eradication though a combination of products may be needed to combat resistance.

31.6.2 Family Reduviidae (Kissing Bugs)

Another insect within the Hemiptera order that poses a risk to humans is the kissing bug or conenose bug (Triatominae subfamily, *Triatoma* genus). Like bed bugs, members of the Reduviidae family are also ectoparasites that feed on blood. Unlike bed bugs, members of the Reduviidae family can be vectors of disease through their transmission of the causative organism for Chagas disease, *Trypanosoma cruzi*. Like bed bugs, *Triatoma* typically feed at night on exposed areas of the skin including the face, hence the name "kissing bug."

Clinical cutaneous reactions to kissing bugs include papules, vesicles, and bullous lesions at the site of a bite. Systemic allergic reactions such as anaphylaxis have also been reported (Rohr et al. 1984; Anderson and Belnap 2015). A history of anaphylaxis that develops or wakes a patient from sleep may be a key piece of history that suggests the kissing bug as the culprit. Survey data noted 13% of exposed individuals reported allergic reactions to *Triatoma* in one county in the United States (Walter et al. 2012). Procalin, a member of the lipocalin family, has been isolated as a major allergen found in *Triatoma* saliva (Paddock et al. 2001).

Treatment for local reactions is supportive and follows the same recommendation as for other insect bites. There is no standardized testing available to further evaluate for allergy to *Triatoma*. Similarly, there is no commercial extract available for immunotherapy though immunotherapy with a salivary gland extract has been shown to be efficacious (Rohr et al. 1984).

31.7 Order Phthiraptera, Families Pediculidae and Pthiridae (Lice)

The louse is part of the Phthiraptera order of insects. In humans, infestations can occur by the head louse (*Pediculus humanus capitis*), body louse (*Pediculus humanus humanus*), and pubic louse (*Pthirus pubis*). The head and body louse tend to be indistinguishable, whereas the pubic louse is wider and has a crablike appearance. Infestations with lice are also referred to as pediculosis and affect millions of individuals yearly. The life cycle of lice includes three stages. A nymph is a newly hatched louse that feeds on the blood and takes 9–12 days to mature to an adult louse. Female adult head lice can lay 50–150 eggs over an average lifetime of 2 weeks, whereas the female body louse can lay up to 300 eggs in their lifetime. When the eggs, or nits, are laid, they are attached to hair shafts (head or pubic lice) and clothes (body lice) and take 1–2 weeks to hatch. Head and body lice are spread through direct contact or through fomites. The pubic louse can be transmitted through sexual contact or through fomites. Pubic lice prefer short, coarse hair so they may also be found in other areas of the body such as body hair, axillary hair, beards, and eyelashes. Separation of the louse from its host usually leads to death of the louse though in favorable conditions the head and body louse can live a few days.

Infestation is characterized by intense pruritus of the scalp and for the body louse a pruritic erythematous macular rash. Cervical lymphadenopathy and conjunctivitis may also be reported. One case of possible IgE-mediated reaction to *Pediculus humanus capitis* presented with upper and lower airway symptoms that disappeared with treatment of the lice infestation (Fernandez et al. 2006). In cases of pubic lice, a blue to gray macular rash called macula cerulea may be present due to a reaction between lice saliva and the blood. Intense itching is the characteristic symptom of pubic lice that typically starts within 2–3 weeks of an infestation. Chronic infestations may lead to the development of hyperpigmented and thickened skin. Both the saliva and the feces of lice are thought to play a role in the development of hypersensitivity reactions (Peck et al. 1943).

Diagnosis of lice infestation includes finding of nits close to the hair shaft as well as evidence of adult lice seen on the scalp, pubic area, or seams of clothing. Extensive evidence of excoriation may be evident on exam as well. Once the diagnosis has been made, treatment must be instituted quickly to prevent further spread. Evaluation of family

members and close contacts should also be considered once lice infestation has been identified in an individual. Treatment of all infected individuals should occur at the same time.

Recommended treatment strategies include removal of adult lice and nits, elimination of reservoirs (fomites), and the use of pediculicides. Effective pediculicides that can be used include malathion, permethrin, and pyrethrins though recent concerns for resistant lice pose a public health concern. Failure of treatment may be due to reinfestation with close contact of an untreated individual, resistant ova, or lice or improper use of treatment strategies. Retreatment is recommended if agents that are only weakly ovicidal or not ovicidal are used, whereas strongly ovicidal agents may not need routine retreatment. If retreatment is needed, ideal timing should be once all eggs are hatched but before new eggs are made.

31.8 Order Lepidoptera (Caterpillars, Moths, Butterflies)

The order Lepidoptera are mostly winged insects and include moths and butterflies (Fig. 5). Their life cycle is characterized by complete metamorphosis. After a fertilized egg is laid on plants, the larva or caterpillar emerges and undergoes molting or transformations called instars. The mature instar of some species such as moths may create a cocoon prior to pupating. A pupating butterfly is called a chrysalis. An adult emerges from the cocoon or chrysalis once complete transformation occurs.

Human disease is due to contact with butterfly and moth larvae or the adults. Reactions after contact with the larval stages are called erucism. Stinging caterpillars may secrete venom through the hair (setae) or spines covering their bodies. Contact leads to stinging or burning pain with an accompanying punctate rash where direct contact has occurred. Vesicular, hemorrhagic bullous eruptions, lymphangitis, and lymphadenopathy may also be seen. Caterpillar hairs can become airborne and cause pruritus, ocular and respiratory symptoms. Immunologic or IgE-mediated contact urticaria and anaphylaxis have been described as an occupational hazard (Vega et al. 2004). Occupations that may be at higher risk include farmers, loggers, foresters, and entomologists. Systemic symptoms including malaise, nausea fever, and vomiting have also been described. Delayed contact reactions may also occur and are due to a toxic irritant mechanism.

In the United States, the four common caterpillars encountered include the saddleback caterpillar, the Io moth caterpillar, the Douglas-fir tussock moth caterpillar, and the puss caterpillar. Contact with the urticating larval stages of these species is associated with dermatitis. Treatment is largely supportive. Tape (e.g., duct tape) can be placed over the affected skin so that removal of the setae occurs as the tape is pulled off. The skin that came in contact with the caterpillar should be washed with soapy water to reduce exposure. Topical application of corticosteroids, cold compresses, and oral antihistamines may

Fig. 6 Imported fire ant. Photo by Scott Bauer, USDA Agricultural Research Service

Fig. 7 Fire ant sting apparatus. Photo by Justin Schmidt, USDA Agricultural Research Service

Fig. 8 *Harmonia axyridis*. Photo by Scott Bauer, USDA Agricultural Research Service

help with decreasing pruritus and inflammation. Systemic reactions concerning for anaphylaxis should be treated with injectable epinephrine similar to other causes of anaphylaxis. Avoidance measures should be encouraged.

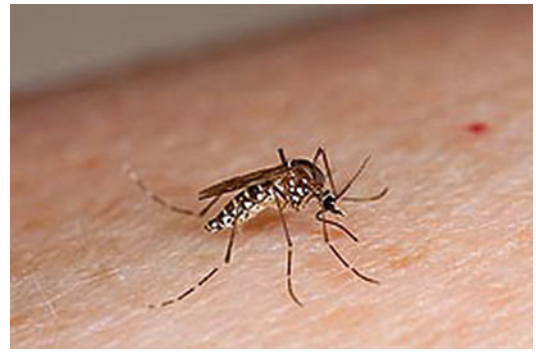

Fig. 9 *Aedes aegypti*. Photo by Stephen Ausmus, USDA Agricultural Research Service

31.9 Conclusion

Human allergic and non-allergic reactions to stinging and biting insects pose an ongoing public health concern that requires awareness and prevention strategies. Incidence of adverse reactions to insects is expected to increase with urban sprawl and its likely disruption of natural insect ecosystems. Human activities such as travel and trade can directly impact and promote the dispersal of invasive species across the world. While only a few species of insects are threats to humans, some of the reactions that they cause are life-threatening in susceptible individuals. Although the most common reactions are mild, the sheer number of affected individuals and the recurrent nature of these insect-triggered reactions make their impact on human life significant. Evaluation for insect-related reactions requires a high index of suspicion and careful consideration of potential exposures in order to evaluate fully. Information regarding the entomology of insects can help with determination of cross-reactivity patterns which may aid with testing and treatment options. Knowledge of insect life cycles can help with establishing exposure patterns and may guide the evaluation process. Research is needed to further characterize the exact prevalence of insect reactions, associated morbidity, cost, and impact on human life. There is also a need for standardized reagents for skin testing as well as the development of in vitro tests to aid with

the diagnosis of insect allergy. Finally, the process of immunotherapy needs to be investigated further in order to establish protocols that are safe and effective for the treatment of stinging and biting insect allergy.

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Part VIII

Allergy and Asthma Diagnosis

Allergy Skin Testing

32

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Contents

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Abstract

Allergy skin testing dates back to the late 1800s. Since then there has been advancement in technique and results using updated devices. This chapter will discuss the history of allergen skin testing, focusing mainly on IgE-mediated allergy, and review when best to test the patient, along with what may interfere with interpretation and with discussing possible side effects from testing and alternative tests. Later in the chapter, other modes of skin tests will be discussed including discussion for patch testing for contact dermatitis.

Keywords

Epicutaneous skin test · Patch testing · Hypersensitivity

32.1 Introduction

IgE-mediated allergen skin testing has been a vital tool dating back to Charles Blackley in 1865 through self-diagnoses that discovered a vital way to confirm allergies with underlying hypersensitivity as a mechanism. The most utilized skin test evaluating IgE-driven allergic disorders is through the epicutaneous (also referred to as the prick/puncture) route. Epicutaneous skin testing confirms the clinical diagnoses of allergic rhinitis, asthma, and atopic dermatitis to environmental triggers and the clinical diagnoses of hypersensitivity-driven food allergy, along with evaluating drug hypersensitivity reactions as well. Skin testing should be performed when benefits outweigh risk and when there are no confounding factors that may limit skin test interpretation. Other methods are available in addition to the epicutaneous route, including intradermal skin testing and endpoint titration. This chapter will review in detail these types of tests, along with how best to perform testing, which instruments are commercially available to perform the tests, and how to record the results in order for other allergists to interpret without difficulty. Additional tests for other allergic disorders are discussed at the end of the chapter.

32.2 History of Immediate Hypersensitivity Allergy Skin Testing

Skin testing is a fundamental diagnostic tool in immunoglobulin E (IgE)-mediated allergic diseases first described by Charles Blackley in 1865. Blackley, who suffered from hay fever and asthma, self-applied pollen specimens to his conjunctival, nasal, and buccal membranes to reproduce their respective symptoms. He was the first to demonstrate the skin as a modality for testing. He applied pollen grains over abraded areas of arm and later lower extremity as a means to evaluate allergies. He witnessed swelling and induration in association with pruritus at these sights (Blackley 1983). This was followed by the introduction of the intracutaneous test for tuberculosis

by von Pirquet (1907). Mantoux expanded upon von Pirquet's intracutaneous test, and in 1908, he introduced the intradermal test to evaluate immediate hypersensitivity disease (Mantoux 1908). The Mantoux test (also known as PPD test) is still used today as a screening tool for tuberculosis. The intradermal injection (Mantoux technique) involves injecting a standard dose of 5 tuberculin units (0.1 ml) intradermally and is read 48–72 h later. In 1912, Schloss expanded on von Pirquet's intracutaneous test and correlated a child's history of asthma, rhinitis, and eczema to be associated with egg, almond, and oats. Schloss introduced the scratch test which involved rubbing the suspected allergen into a small area of scratched skin for the diagnosis of food allergy in children (Schloss 1912). The scratch and intracutaneous tests remained the primary testing methods for about 60 years. The scratch test eventually fell out of favor due to patient discomfort, lack of reproducibility, and potential for scarring. In the 1950s, Lewis and Grant first described the prick and puncture tests with vascular studies to induce wheals in attempts to evaluate capillary circulatory mechanisms (Lewis and Grant 1927). Eventually in the 1970s, the prick and puncture tests evolved to be adapted as the diagnosis of immediate hypersensitivity allergy skin testing supported by a pivotal study showing less variability in results compared to the earlier skin test technique through scarification (James and Simons 1979). Currently, the two major allergy skin tests used are the prick/puncture and intradermal techniques. In most situations, the prick/puncture method is the initial diagnostic test. Skin tests are practical for diagnosis as they are quick and easy to perform, cheap, and sensitive.

32.3 Indications for Immediate Hypersensitivity Skin Testing

Immediate hypersensitivity skin testing is utilized in diagnosing disorders associated with an IgE-mediated component. The most common conditions requiring IgE-mediated skin testing include allergic rhinoconjunctivitis, asthma, and atopic dermatitis. Skin testing can also be used for the diagnosis of certain food, medication (only penicillin allergy has been validated), and venom allergies (Kowal and DuBuske 2018).

Patients diagnosed with asthma and/or allergic rhinitis suffer from bouts of the symptoms common for these conditions, including sneezing, rhinorrhea, nasal congestion, itching eyes/nose/throat, cough, wheezing, or other symptoms of dyspnea. It is important to obtain a complete history regarding when these symptoms are most prevalent. Based on a good history, IgE-mediated skin testing can be used to confirm diagnoses of allergic rhinitis and/or asthma to triggers.

Common triggers could explain intermittent and/or perennial symptoms. Intermittent symptoms can be associated with aeroallergen sensitivity. For example, tree pollens tend to predominate early in the year, followed by grass in the spring and summer and then weeds in the latter half of the year. The type of aeroallergens that predominate varies between different climates and locations. Persistent year-round symptoms could be associated with perennial environmental allergens, which could include dust mites, molds, animal dander, occupational allergens, and even pollens in areas where the pollen is present year-round (Wallace et al. 2008).

Skin testing is the preferred diagnostic test for determining the specific allergens. The type and number of allergens chosen for skin testing should be based on the patient's history and environment. Together with the patient's history, skin testing can be used to identify the suspected allergens causing a patient's symptoms. Symptoms can be ameliorated with general treatment such as intranasal corticosteroids, antihistamines, and oral antihistamines. More importantly, skin testing results can provide information regarding specific allergen avoidance measures and targeted therapy, such as allergen immunotherapy.

Atopic dermatitis affects 10–20% of children and 1–3% of adults (Schultz-Larsen and Hanifin 2002; Hanifin et al. 2007). In most patients, atopic dermatitis develops before 5 years of age; however it can develop in adulthood in 20% of patients (Bieber and Leung 2002). Atopic dermatitis is usually the first manifestation of atopic disease in patients who later develop allergic rhinitis and asthma. Atopic dermatitis presents with

chronic, relapsing courses of eczematous lesions with pruritic and scratching. In infants and young children, the skin of the face, neck, and extensor is often involved. In older children and adults, the lesions predominantly involve the flexural areas of the extremities. Common triggers such as temperature, humidity, and irritants can exacerbate symptoms. About one third of children with atopic dermatitis have food allergy; even patients can be sensitized to certain foods (detected by the presence of specific IgE) without clinical manifestations of food allergy. Food allergens can be triggers of atopic dermatitis in infants and young children; thus the clinician can consider limited food allergy testing for suspected foods. It is not recommended to eliminate foods based only on positive skin test (without clinical history) as potential nutritional deficiencies can occur (Schneider et al. 2013).

Environmental allergens, including dust mite and pollen, may have a role in precipitating atopic dermatitis (Schneider et al. 2013). Immunotherapy may be an option for treating atopic dermatitis patients, especially dust mite allergy (Schneider et al. 2013).

Patients with eosinophilic esophagitis usually present with feeding disorders and vomiting in younger children and dysphagia and food impactions in adults. The population of eosinophilic esophagitis patients are predominantly male and have a higher rate of atopic disease compared with patients with GERD. An extensive evaluation of eosinophilic esophagitis includes food allergen and aeroallergen IgE-mediated skin prick testing or measurement of allergen-specific IgE. Studies have shown that more than 75% of patients who eliminate potentially triggering foods based on testing have notable improved endoscopic findings (Adkinson et al. 2014; Rothenburg 2014).

32.4 Subjects at Greater Risk for Undergoing Immediate Hypersensitivity Skin Testing

Skin testing should not be performed in patients with high risk for anaphylaxis, medications that could antagonize the treatment of anaphylaxis or certain skin conditions.

32.4.1 Medications that May Put Patient at Risk

In the anaphylaxis practice parameter, the use of beta-blockers and ACE inhibitors is listed as a relative contraindication to perform skin testing (Lieberman et al. 2015). Although beta-blockers and ACE inhibitors do not interfere with skin testing results, theoretically, if an individual would experience an anaphylactic event from a placed allergen on the skin, beta-blockers could limit cardiac response to anaphylaxis by preventing tachycardia and could lead to unopposed alpha adrenergic activity (Coop et al. 2017).

Though there is a lack of evidence in evaluating the risk of anaphylaxis in patients on beta-blockers and ACE inhibitors who undergo skin testing, most of the studies evaluating whether patients on beta-blockers or ACE inhibitors are at increased risk for anaphylaxis have been limited to retrospective studies or case reports. A retrospective study by Fung and Kim showed that skin prick tests in patients on beta-blockers were relatively safe. They reviewed charts of the 191 patients that were on beta-blockers when they had allergy skin prick testing. Out of the 72 patients with positive skin tests, none of them had an adverse reaction (Fung and Kim 2010). The authors concluded that their data supported that skin prick tests are relatively safe in patients on beta-blockers; however this was a small retrospective study.

Bradykinin is a mediator that is generated in anaphylaxis and can contribute to hypotension and hypovolemia. ACE inhibitors can interfere with the catabolism of bradykinin, thus potentiating its effects during anaphylaxis. Most of the studies evaluating ACE inhibitors in the setting of anaphylaxis were conducted in patients on venom immunotherapy. Studies have shown more severe systemic reactions in patients who are on ACE inhibitors while on venom immunotherapy (Tunon-de-Lara 1992; Ober 2003). However, studies have not demonstrated a relationship between patients on ACE inhibitors and a higher rate of anaphylaxis during immunotherapy (Rank et al. 2008; White and England 2008).

Skin testing should be avoided in patients taking MAO inhibitors in patients more at risk to experience adverse events since these medications may potentiate the effect of epinephrine since they are known to interfere with the breakdown of sympathomimetic drugs (Livingston and Livingston 1996). If there is any concern for possible anaphylactic reaction when undergoing skin testing, an alternative would include checking a specific IgE to particular allergens in question.

32.4.2 Medical Conditions Placing Patients at Risk

Skin testing should not be performed routinely in patients who are at high risk for anaphylaxis. Patients at high risk for anaphylaxis could include those currently diagnosed with significant cardiopulmonary disease and poorly controlled asthma and a history of severe reactions following exposure to small amount of allergens, especially if multiple skin prick tests are performed simultaneously. For example, in a poorly controlled asthma patient with multiple allergies, testing with these trigger allergens can induce an episode of bronchospasm in the patient. In these patients, serum IgE testing can be the initial test of choice until their asthma is controlled before reconsidering skin testing.

Patients with relative contraindications to skin testing include patients with cardiovascular disease; this is relatively stable, geriatric patients with multiple comorbidities and pregnancy. In these patients, if the risk of anaphylaxis from skin tests outweigh the benefits, serum IgE testing to the allergens in question would be preferable.

32.4.3 Extremes of Age

Allergy skin testing is generally safe; nevertheless it can cause systemic reactions in very sensitive patients. Extremes of age including very young children and elderly patients with multiple comorbidities such as cardiovascular and pulmonary diseases, especially those with histories of severe reactions to suspected allergens, are at higher risk for adverse reactions, particularly if multiple skin prick tests are performed simultaneously. Skin testing should be performed in the setting where emergency medications (such as epinephrine) and equipment are available. Intradermal testing should only be completed after negative prick/puncture testing. Although fatal anaphylaxis secondary to allergy skin testing is very rare, it is almost always associated with intradermal testing without prior prick/puncture evaluation (Lockey et al. 1987, 2001). Higher rates of systemic reactions with intradermal tests of food allergens and latex, thus, are no longer recommended.

In a pediatric study of almost 6000 patients, the rate of systemic reactions to skin prick testing was 0.001%. The patients who had systemic reactions were children less than 1 year of age and had active eczema (Norrman and Falth-Magnusson 2009). There were two cases of anaphylaxis with skin prick testing to fish extracts; however both of these patients had asthma, and the other had atopic dermatitis as well (Pitsios et al. 2010).

There is a case report in an adult patient with asthma who developed anaphylaxis 2 h after skin prick testing to aeroallergens (Ricketti et al. 2013). There is one case report of fatal anaphylaxis in a young female patient with allergic rhinitis, moderate persistent asthma, and food allergy who received 90 food prick tests during one visit (Bernstein et al. 2004).

The overall rate of systemic reactions to skin testing in a prospective study of about 1500 patients was 3.6%; however none were life-threatening. Most of the systemic reactions were due to intradermal testing to aeroallergens (Bagg et al. 2009).

32.5 Contraindications: What May Interfere with Performing Skin Testing Thus Reverting to In Vitro Tests

32.5.1 Skin Disorders

Skin test interpretation could be difficult for patients diagnosed with specific skin conditions, including chronic or acute urticaria requiring

daily antihistamines. Dermatographism could present with a primary disorder, or a secondary disorder, i.e., patients diagnosed with cutaneous mastocytosis. Significant dermatographism could interfere with skin test results given highly likelihood of false-positive results along with positive controls. If skin tests are performed in the patients with mild dermatographism, the results should be interpreted with caution as there can be multiple false positives.

For patients diagnosed with chronic dermatitis, daily application of topical medications can modify the skin and affect skin test results. Skin testing should also be avoided in other skin disorders such as ichthyosis vulgaris. These conditions require serum IgE testing rather than skin testing to evaluate allergic triggers.

32.5.2 Medications

Patient medication should be reviewed prior to performing IgE skin test since certain medications could interfere with interpreting skin test results. First-generation H1 antihistamines (e.g., diphenhydramine) can suppress skin reactivity for 24 h or longer. Second-generation H1 antihistamines (e.g., cetirizine, fexofenadine, loratadine) can suppress skin responses for 3–7 days. Most clinicians recommend holding all oral antihistamines 1 week prior to skin testing. Antihistamine topical nasal sprays (e.g., azelastine) can be systemically absorbed and should be held for 3 days prior to testing. H2 antihistamines (e.g., ranitidine, cimetidine) should be discontinued 48 h prior to testing, although discontinuing on the day of testing is likely sufficient (Chirac et al. 2014; Kupczyk et al. 2007).

Tricyclic antidepressants may reduce skin reactivity 2 weeks or even longer. Patients requiring these medications should obtain the alternative IgE test if they are unable to discontinue these medications. Patients currently taking selective serotonin reuptake inhibitors (SSRIs) are not required to hold these medications as they do not interfere with skin testing (Chirac et al. 2014; Rao et al. 1988; Isik et al. 2011).

Medications applied directly to skin could interfere with skin test results. Topical corticosteroids applied for more than 7 days could reduce skin test reactivity. Data pertaining to the effect of topical calcineurin inhibitors on skin test interpretation is inconsistent. Tacrolimus was found to reduce allergen skin prick test results in children, though it did not affect histamine response (Gradman and Wolthers 2008). Pimecrolimus did not show effect on skin test results (Spergel et al. 2004). In general, skin testing should be performed over areas of skin that has not been treated with topical corticosteroids or calcineurin inhibitors for at least 7 days (Kowal and DuBuske 2016).

Patients on omalizumab have both decreased size of allergen-induced skin responses in the early and late phases. Skin reactivity can be decreased for up to 6 months, although skin reactivity can return earlier in some patients (Corren et al. 2008).

32.5.3 Anaphylaxis

An anaphylactic episode within 4 weeks may result in false-negative skin tests since anaphylaxis can cause the skin to be temporarily nonreactive. This nonreactive state can take 2 to 4 weeks to normalize.[7] After a systemic reaction secondary to an insect sting, a refractory period of up to 6 weeks was noted by Goldberg and colleagues. In this case, an early investigation can be performed if necessary; however only the positive skin tests should be accounted for, as negative skin tests may be secondary to false-negative results (Goldberg and Confino-Cohen 1997). If an early skin test results in negative readings, a repeat test in 4–6 weeks is warranted (Chirac et al. 2014).

32.6 Technical Aspects of the Allergen Skin Test

Several different devices and techniques exist to perform skin testing. Available methods have been modified to reduce pain tolerability, improve reproducibility, and reduce inaccurate results.

Skin prick testing may be performed with single-site or multiple-site devices (Carr et al. 2005).

Single-site skin prick devices include metallic lancets, allergen-coated lancets, plastic lancets, and steel lancets. Examples of such devices include Greer Pick (Greer Labs), Accuset (ALK-Abello, Inc), Sharpest (Paratrex), Quintip (Hollister-Stier), and smallpox needle (Hollister-Stier). These devices differ with regard to needle length, needle width, and point lengths, leading to the variability in size of skin punctures. Variation in puncture size is also user dependent given dependence of the pressure and angle of application (Nelson et al. 1998). Manufacturers may recommend different techniques for application, even for devices with a similar design.

Multiple-site skin prick devices, referred to as multiheaded devices, allow the user to perform up to ten tests in one application, reducing the testing time and increasing efficiency. In addition, multiheaded devices are often preferred in children due to easier application of a few multiple test devices rather than several individually applied tests (Carr et al. 2005). Multiple-site skin devices also reduce variation in individual prick sites given that the angle of insertion is fixed. Currently available devices differ in the numbers of lancets per stylus, lancet spacing, needle length, and the amount of antigen that is delivered. Examples of multiheaded devices include Quintest (Hollister-Stier), Quantitest (Panatrex, Inc), GreerTrack, and Multi-Test II (Lincoln Diagnostics, Inc).

Different skin prick test devices offer different potential advantages. Most devices feature "dip and apply" so that application of the allergen extract to the skin is done at the same time as the extract penetrates the epidermis. The smallpox needle, however, may be reused to perform all tests on one patient (Nelson et al. 1998).

Several studies exist that compare variability among skin test devices. In one prospective comparative study of eight skin test devices, there were statistically significant differences among drives in terms of patient discomfort, size of histamine wheal and flares, and intradevice variability (Tversky et al. 2015). The difference in the wheal and flare response has been shown in both the positive and negative sites and appears to result from the degree of trauma to the skin caused by the device. Histamine wheal response has clinical significance given that devices that produce smaller wheals are more likely to lead to false-positive reactions, whereas those that produce large wheals may, in turn, produce wheeling at the negative control site (Matsui and Keet 2015). Another study found variability with results of skin testing when performed by multiple operators, which is often the case in many allergy centers (Werther et al. 2012) (Table 1).

Skin prick test device performance depends on the technician's training and the methodology used to perform the test. Given the significant variation among operators, methods have been developed to improve operator proficiency. While in the USA or Canada there are no formal criteria required to verify operator proficiency, there are several publications that suggest best practice, including parameters offered jointly by the American Association of Allergy, Asthma, and Immunology (AAAAI) and the American College of Allergy, Asthma, and Immunology (ACAAI) (James and Simons 1979).

Skin prick test operator proficiency can be quantified via a coefficient of variation (CV). Multiple methods of proficiency testing are available. Turkeltaub et al. 1989 developed one method involving administering multiple dilutions of two

Table 1 Comparison of histamine and control wheals along with pain scale for available devices. (Adapted from Carr et al. 2005)

Device	Mean histamine wheal (mm)	Mean saline wheal (mm)	Mean pain (Wong-Baker FACES pain scale)
Sharptest	7.1	0.003	1.17
Greer Pick	6.6	0	0.88
Accuset	5.1	0.1	0.94
Quintip	4.8	0	1
Multi-test II	5.9	0.02	1.62
Quantitest	5.7	0.01	1.74
Quintest	4.3	0	1.45
Greer Track	3.2	0.012	2.04

different histamine concentrations on the same subject. When performed properly, the two different dose-response lines should be parallel. The Cox method requires the administration of ten alternative positive controls with ten alternating negative controls. Operators are considered proficient if the CV is less than 30% (Father et al. 2014). Interestingly, in a 2006 survey of physicians from the ACAAI, only 10% of respondents reported that they used an objective test protocol for quality assurance purposes (Oppenheimer et al. 2006b).

The prevalence of allergens varies among geographic regions as there is a relationship between the type of vegetation and the regional airspora. Thus, the common allergens in one region may be less useful in another region with different flora. Because of this, manufacturers often provide panels of aeroallergen extracts based upon regional differences.

32.7 How to Perform Skin Testing

32.7.1 Prick/Puncture Skin Testing

The prick/puncture (or epicutaneous) method is the preferred method and can be performed by placing a drop of antigen on the skin followed by a puncture from a solid bore needle or a lancet. Multiple head devices have the advantage of retaining the liquid antigen solution at their tip; thus rather than a two-step placement involving separate antigen solution followed by needle insertion at the sight, only one step placement is required (Bernstein et al. 2008).

32.7.2 Intradermal Skin Testing

Intradermal skin testing (IDST) involves the intracutaneous injection of a small volume (approximately 0.02–0.05 ml) of dilute allergens (approximately 100- to 1000-fold more dilute than the concentration used for SPT) into the dermis with a 0.5- or 1.0-ml syringe and 26- or 27-gauge hypodermic needle, producing a small superficial bleb (Chirac et al. 2014; Bernstein et al. 2008). A 2006 survey of 539 allergists suggests it is a widespread practice, with 85.2% of responders reportedly using IDST to detect aeroallergen sensitization that has not been picked up by SPT (Oppenheimer et al. 2006b). In defining a positive intradermal test, 85% of allergists used the criterion of 3 mm or greater than the negative control as a threshold for a positive result (Oppenheimer 2006); a wheal of 5 mm or larger has also been used as a positive result threshold (Nadarajah et al. 2001). Of note, intradermal testing should only be performed after negative SPT; though exceedingly rare, nearly all reported skin testing fatalities have been associated with IDST without prior SPT (Lockey et al. 2001).

The 2008 Allergy Diagnostic Testing practice parameter recognizes both intradermal and skin prick testing as preferred techniques for the evaluation of IgE-mediated sensitivity; intradermal testing is noted to be the more sensitive option and may identify a larger number of patients (Bernstein et al. 2008). However, though IDST is more sensitive than SPT, it is also less specific (Position Paper 1993) and may not correlate as well with symptoms (Dreborg et al. 1989). Studies assessing the value of IDST in timothy grass (Nelson et al. 1996b), mouse (Sharma et al. 2008), and cat (Wood et al. 1999) found IDST to be less valuable than SPT when correlated with exposure challenges. A later study evaluating tree, grass, ragweed, cat, house-dust mite, and Alternaria allergies similarly found that positive IDST results in patients with prior negative SPTs did not correlate with nasal challenge reactions; the study thus concluded that, in patients with negative SPT results, positive IDST results are unlikely to identify clinically relevant sensitivities (Schwindt et al. 2005). In the evaluation of food allergy, intradermal skin testing is inappropriate with both a higher risk of systemic reaction in allergic patients and false positives in nonallergic patients (Bock et al. 1977).

32.7.3 Alternative Evaluation of Aeroallergens

Currently, there is no universally accepted "gold standard" in the assessment of allergic rhinitis.

In addition to SPT as described above, other modalities may be used in the diagnosis of aeroallergen sensitization.

32.7.4 In Vitro IgE Testing

In vitro testing IgE is another available diagnostic tool for evaluating IgE-mediated hypersensitivity to inhalant allergens. Immunoassays, in various forms, are the most commonly used in vitro tests for IgE-mediated allergy. These tests detect allergen-specific IgE in a patient's serum by incubating the serum with the allergen of interest. Though the term "radioallergosorbent tests" or "RAST" is often used to refer to these types of tests, RAST is the earliest example of allergy immunoassay testing and rarely used today (Wide et al. 1967). The more commonly used present-day allergen-specific IgE antibody assays include the ImmunoCAP by Phadia (UniCAP100, ImmunoCAP250), the Immulite System from Siemens (Berlin, Germany), and the HYTEC-288 system from Hycor/Agilent Technologies (Santa Clara, Calif) (Hamilton 2010). All three systems use a solid-phase allergen to bind allergen-specific IgE in a patient's serum; a labeled anti-IgE antibody then binds the IgE, and the patient's serum allergen-specific IgE level is calculated via interpolation from a total serum IgE calibration curve linked to the World Health Organization IgE standard. Though ImmunoCAP is the most extensively studied assay, it is not known which of the major assays provides the most accurate evaluation of allergen-specific IgE, and previous studies have found that the results of one test are generally not comparable to those of another, even if the same units are used (Cox et al. 2008; Wood et al. 2007; Wang et al. 2008).

Currently, the American Academy of Pediatrics (Sicherer et al. 2012) and the National Lung and Heart Institute Asthma Management Guidelines (EPR-3 2007) recommend either SPT or in vitro IgE testing for allergic sensitization diagnosis. Similarly, the practice parameter states that "there are no clinical scenarios in which immunoassays for allergen-specific IgE can be considered either absolutely indicated or contraindicated (Bernstein et al. 2008)." In vitro IgE testing may be more reasonable in patients with underlying skin disease who do not have a sufficient area of normal skin for SPT, patients who may be in a refractory period after a severe allergic reaction leading to a falsely negative SPT, and patients who are unable or unwilling to hold medications that may interfere with SPT results (such as antihistamines) (Bousquet and Michel 1993). Interestingly, in vitro IgE testing is also perceived to have a safety benefit since it involves venipuncture only and no allergen exposure; however, one study of 16,205 patients found that the adverse reaction rates were significantly higher with venipuncture (0.49% vs 0.04% with SPT) with reported reactions including syncope, near syncope, malaise, and 1 episode of asthma (Turkeltaub and Gergen 1989). Potential drawbacks of in vitro IgE testing in comparison with SPT are greater expense, delayed results, and lower sensitivity (Hamilton and Adkinson 2003). Studies assessing the clinical utility of in vitro IgE found relatively poor correlations with skin tests to mouse and mold aeroallergens (Sharma et al. 2008; Liang et al. 2006). Studies assessing the clinical utility of in vitro IgE found relatively poor correlations with skin tests to mouse and mold aeroallergens (Sharma et al. 2008; Liant et al. 2006), but significant correlations with skin tests to cat, timothy grass, and birch pollen allergens (Wood et al. 1999; Hamilton and Adkinson 2003).

32.7.5 Endpoint Titration Method

Skin-endpoint titration (SET) is a variation of aeroallergen intradermal testing and is more commonly used among otolaryngology practitioners (Lin and Mabry 2006). In this method, progressive dilutions are made from the antigen of interest and then injected into the patient at increasing concentrations until a predetermined wheal size is obtained; the more sensitive the individual, the lower the concentration needed. One of the described protocols is to start with the antigen at a 1:20 weight/volume commercial concentration and then perform 1:5 serial dilutions (i.e., dilution #1 is 1:100, dilution #2 is 1:500, etc.)

until dilution #6 is obtained (1:312,500) (King et al. 2005). Approximately 0.04 ml of dilution #6 is then injected into the patient to create a 4- to 5-mm wheal and then observed for 10–15 min; assuming minimal growth in the wheal during this observation period, this process is then repeated with dilution #5, dilution #4, etc. until a significant 2-mm or more increase in wheal size is observed (termed the "endpoint" wheal). The next more concentrated dilution is then injected to produce a "confirmatory" wheal that is at least 2 mm greater than the previous wheal; however, the "endpoint" dilution is the one used to determine the antigen concentration at which immunotherapy can safely be initiated. If the endpoint wheal is not obtained with the more concentrated dilutions (i.e., dilution #1 or #2), then this is considered a negative result. The role for skin-endpoint titration in comparison to SPT is unclear; conflicting evidence exists comparing skin-endpoint titration to SPT in shortening immunotherapy courses (Kaffenberger et al. 2018; Seshul et al. 2006). One small study showed that skin-endpoint titration was both less sensitive and less specific than SPT, though the study was not sufficiently powered for statistical significance (Gungor et al. 2004).

32.8 Interpretation of Skin Testing

32.8.1 Sensitivity and Specificity

Between prick/puncture and intracutaneous tests, there are differences in sensitivity and specificity. In general, prick/puncture tests are less sensitive through more specific compared to intracutaneous skin testing performed by some clinicians following negative prick testing. This is partly related to the nature of the test itself. Intracutaneous tests require larger volumes of the injected allergens and are more prone to elicit and an irritant response (Bernstein et al. 2008). To adjust for the differences in volume, intracutaneous tests require a 50 to 100 times more concentrated antigen solution compared to the epicutaneous test extracts.

False-positive reactions seen more with intradermal tests may be due to histamine that is already present in the extract along with the direct irritant effect (Williams et al. 1992). Studies have shown that intradermal testing for grass and cat allergens do not contribute much to diagnostic utility (Nelson et al. 1996b; Wood et al. 1999). Also, intradermal tests are more reproducible than prick/puncture tests; however intradermal tests carry a higher risk of systemic allergic reaction.

Due to the differences between intracutaneous and prick tests, studies have been done in attempts to establish cutoff values, sensitivity, specificity, and predictive values of these tests. The interpretation of these tests is variable, depending on whether the comparison is a clinical history or controlled provocation challenge. Using positive nasal provocation challenges as a standard, the sensitivity of skin prick/puncture tests ranges from 85% to 87%, and the specificity of these tests is between 79% and 86% (Gungor et al. 2004; Krouse et al. 2004).

32.8.2 Location of Skin Placement

The location of skin test placement can affect the results. The skin on the forearm is less reactive than the skin on the back. The skin location on the forearm has different reactivity. The wrist is the least reactive, the antecubital fossa is the most reactive, and the ulnar side is more reactive than the radial side. Skin tests should be placed 5 cm from the wrist and 3 cm from the antecubital fossa. The upper and middle back skin is more reactive than the lower back (Chirac et al. 2014).

A study showed the diameter of the wheals to be 27% smaller and the flares to be 14% smaller on the forearm compared to the back with allergen skin prick testing. The differences were statistically significant ($P < 0.001$), though it would only be clinically relevant for borderline reactions. Similar results were also noted for histamine skin tests comparing the forearm and back. In a study with 76 patients who underwent skin testing to the same allergens on the forearm and back,

the results showed 2.3% more positive reactions on the back (164 on the forearm, 173 on the back) (Nelson et al. 1996a, 2001).

32.8.3 Race

Studies have shown that African-American subjects with darker skin coloration have increased histamine wheal response and are more likely to demonstrate positive skin prick and puncture tests compared to the Caucasian population counterparts (Joseph et al. 2000; Celedon et al. 2004; Demoly et al. 2003). Interpretation of skin test results may be affected by color of skin, since erythema is less obvious in darker vs lighter skin (Bernstein et al. 2008).

32.8.4 Circadian Rhythm and Seasonal Variation

The circadian variation of skin reactivity is negligible and does not affect the clinical interpretation of skin tests. Variations regarding testing during different times of the year with specific IgE antibody synthesis have been demonstrated with pollen and house-dust mite allergies. An example would be increased skin sensitivity for tree pollen following pollen season which diminishes further until the next season. These findings could be clinically significant for patients with a low level of sensitization or for allergen extracts that have weak potency. Ultraviolet B radiation significantly decreases wheal reactivities (Demoly et al. 2003; Sin et al. 2001; Vocks et al. 1999).

32.8.5 Anxiety

Studies have shown that stress can affect allergen-induced histamine release during skin testing. A prospective study by Heffner et al. evaluated allergic rhinitis patients and skin testing in response to stress. Their study showed that more anxious patients with atopy had a higher incidence of positive skin prick tests to allergens that previously tested negative (Heffner et al. 2014).

32.8.6 Age, Gender, and Phase of Menstrual Cycle

It is important to keep in mind that skin reactivity varies with age. Studies have shown that infants and younger children usually have smaller positive reactions compared to adults. Infants tend to develop a large erythematous flare and a small wheal; however studies have shown that prick/puncture skin tests in infants are reliable. In general, skin test wheals increase in size from infancy through adulthood and usually decline after 50 years of age. Patients with chronic kidney disease or renal failure on hemodialysis, malignancy, spinal cord injuries, and diabetic neuropathy can have decreased skin reactivity (Chirac et al. 2014; Bernstein et al. 2008).

In general, there are no strong variances in skin test reactivity based on gender. There are findings that suggest males to have higher histamine skin prick test reactivity compared to females (Bordignon and Burastero 2006). Studies have also shown that skin test reactivity can vary in females with their menstrual cycle. Females showed the highest reactivity with both histamine and allergen reactivity during midcycle (days 12–16) rather than during the menses (days 1–4 of the menstrual cycle) or the late progesterone phase (days 24–28). It is unclear if these findings bear any clinical implication (Chirac et al. 2014; Nelson 2001; Kalogeromitros et al. 1995; Kirmaz et al. 2004).

32.8.7 Extracts

Skin reactions to allergens depend on multiple variables. The quality of the allergen extract is extremely important. False-negative reactions can be caused by the lack of significant allergen content in nonstandardized extracts. In the past, skin test extracts were often made directly in the physicians' offices by extracting the allergenic

source directly; however given the many issues, this method is nonexistent. Established potency and concentration within the standardized extracts decreases variability; thus standardized allergen extracts should be used when available. There have been many methods proposed for standardizing extracts. The two that are more popular are the US and Nordic standardization system. Both are based on the wheal that is induced by skin testing; however the difference is in the evaluation of intradermal skin testing in the US standardization system and skin prick test in the Nordic standardization system (Chirac et al. 2014).

Mixtures of unrelated allergens should be avoided as this may result in false-negative results due to dilution of the allergens. Although there are cross-reactivities among different pollens, testing with multiple cross-reactive pollens does not add more information. Preservatives are used in allergen extracts for stability; glycerin is used for this purpose. Thimerosal can be irritating and cause a positive reaction in nonsensitized individuals. Extracts lose their potency over time with elevated temperatures; thus extracts should be refrigerated (Chirac et al. 2014; Tripathi and Patterson 2001). All extracts should be stored under 4 °C to maintain stability (Niemeijer et al. 1996).

32.8.8 Variability Based on Person Performing Test

For every skin test, it is essential to document the technician performing the test and the type of device used. Wheal size will vary among those performing the test, possibly from the amount of pressure placed for each antigen (Vohlonen et al. 1989). Also, those administering tests using the twist method will have larger reactions than those using the prick method. Different devices can lead to difference in size of wheals as well (Nelson et al. 1998). Information placed on skin test forms should include name of person administering the test, the test device, and the way that the device was utilized twist vs prick (Fig. 1). Technicians who perform skin testing should be evaluated regularly for consistency of their skin test results with skin testing proficiency protocols. In Europe, a coefficient variation of less than 20% after histamine control applications has been suggested versus 30% in a Childhood Asthma Management Study (Bernstein et al. 2008; Oppenheimer et al. 2006a).

32.8.9 Size of Wheal and Probabilities

Allergy skin testing correlates well with serum IgE testing; however skin tests are more sensitive and specific. Serum testing is helpful if skin testing cannot be performed. A positive skin test by itself does not confirm clinical sensitivity to the allergen; thus it is important to take the clinical history into context as well. With aeroallergens, a combination of the patient's history and skin test results can identify the allergens that are contributing to the disease. A study demonstrated that the predictive value of clinical history by itself for allergic rhinitis ranged from 82% to 85% for intermittent seasonal allergens (at least 77% for persistent allergens) and the rate increased to between 97% and 99% when skin prick tests (or serum IgE tests) were performed (Crobach et al. 1998). Alternatively, a negative skin test with a negative history is consistent with a nonallergic etiology.

Skin test sensitivities and specificities vary for aeroallergens and food allergens. Skin testing for food allergens needs to be interpreted cautiously. Skin test specificity and sensitivity values are 70–85% and 80–97% for aeroallergens and 30–70% and 20–60% for food allergens. These differences likely reflect the cross-reactions between aeroallergens and food allergens. In general skin tests with food allergens are less reliable than those with aeroallergens as only a small number of patients with positive skin test results for foods experience clinical reactions during an oral food challenge (Demoly et al. 2003; Ownby 1982). Skin testing for foods has a high negative predictive value but low positive predictive value. A positive skin test may represent sensitization but the absence of clinical allergy.

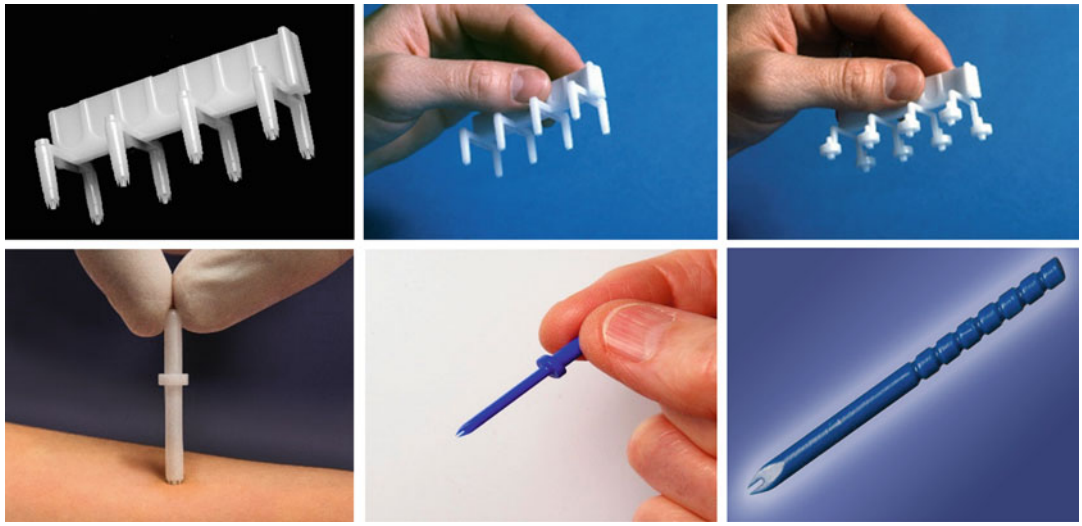

Fig. 1 Examples of Multi-Test devices (from left to right) Multi-Test® PC (Pain control), Multi-Test® II, Multi-Test®. Examples of single test devices (from left to right) UniTest® PC, Duotip-Test® II, Duotip-Test®. (Courtesy of Lincoln Diagnostics. Duotip-Test®-Available 1994)

Studies have investigated the association with wheal size from skin test and correlation with the probability of a true food allergy as documented in food challenge. There is a 95% positive association between food challenge to cow's milk of at least 8 mm, egg white of at least 7 mm, and peanut of at least 8 mm. No such studies have been performed for environmental allergens (Bernstein et al. 2008).

32.9 Definition of a Positive Test

A positive prick/puncture test appears as a raised wheal with surrounding erythema. The skin test should be read 15 to 20 min after application. Qualitative scoring (0 to 4+) is no longer used as there is variability in scoring among physicians. Positive skin test results should have high specificity and sensitivity along with high reproducibility so that providers could interpret skin test results without the need to retest patients. Currently based on studies showing high sensitivity and specificity, a positive prick/puncture test is defined as a response that is 3 mm in diameter greater than the control. Using the orthogonal diameter, which is based on the sum of the largest diameter wheal and its perpendicular diameter divided by 2, has proven more reproducible (Vanto 1982). The histamine control system in which an allergen wheal equal to or greater than the histamine control is considered positive has shown the best sensitivity and specificity when compared to a composite score based on specific allergen IgE level, provocation test, and clinical history (Osterballe et al. 2005).

For all skin tests, it is important to have both positive and negative controls for proper interpretation of the results. Histamine (preferably histamine dihydrochloride 10 mg/ml) is used as the positive control, and saline or 50% glycerinated human serum albumin saline is used as the negative control. For histamine, the maximum wheal and flare is at 15–20 min. Each individual allergen should be placed at a distance to avoid false-positive reactions. As per Nelson, the optimal distance between allergens is 2–5 cm apart (Nelson et al. 1996a; Tripathi and Patterson 2001).

Intradermal tests can follow negative prick tests. A positive intradermal result is a raised wheal that is 5 mm or larger in most cases (Ownby 1982). In general, most allergists use the criterion of 3 mm larger than the negative control as a positive test.

An example skin test form provided by the American Academy of Allergy, Asthma, and Immunology (Fig. 2) highlights the need to include the name of the ordering physician, the technician who placed the skin test, and the type of device, among other essential information.

Allergy Skin Test Report Form

Practice name Ordering physician:
Street address **City** **State** **Zip**
Telephone **Fax**

Patient name: ______________________________ **Date of birth: __/__/__** **Patient number**:____________________________
Testing Technician: _______________________
Last use of antihistamine (or other med affecting response to histamine): ___ days
Testing Date (s) and Time: **Percutaneous __/__/____________AM PM Intradermal __/__/____________AM PM**

1) **General information about skin test protocol**
   •**Percutaneous** reported as: **Allergen: Testing concentration: Extract compan**y (*see below)
   ○**Location**: back___ arm___ **Device**: ____
   •**Intradermal**: 0.__ml injected, **Testing concentration**: 1:_____w/v or BAU or AU/ml, PNU
2) **Results:** record longest diameter **or** longest diameter and orthogonal diameter (perpendicular diameters) of wheal (W) and erythema (flare) (F) measured in millimeters at 15 minutes
   ND or blank in results column indicates test was not performed, 0=negative

* Extract manufacturer abbreviations: G=Greer, AL=Allergy Labs, Ohio, LO Allergy Labs, Oklahoma, AK=ALK, HS=Hollister–Stier, , NE=Nelco, AM=Allermed, AT=Antigen Labs

Allergen: Concentration: Extract Manufacturer. *	Percutaneous W (mm) F		Intradermal W (mm) F		Allergen: Concentration: Extract Manufacturer. *	Percutaneous W (mm) F		Intradermal W (mm) F	
					Controls				
					Percutaneous				
					Negative:				
					Positive:				
					Intradermal				
					Negative				
					Positive:				

Interpretation:

Fig. 2 Allergy skin test report form

32.10 Oral Allergy Syndrome

Oral allergy syndrome (OAS), also known as pollen-food allergy syndrome (PFS), is a hypersensitive reaction to specific foods secondary to prior sensitization to pollen allergens. About 20–70% of patients who have pollen sensitivity have OAS symptoms after consuming raw fruits and vegetables (Osterballe et al. 2005; Czarnecka-Operacz et al. 2008). Birch pollen sensitization is very commonly seen in OAS, with cross-reactivities to Bet v1 (found in cherry, apricot, pear, peach, hazelnut, celery, carrot, parsley, and potato) and Bet v2 proteins (found in apple, pear, melon, carrot, celery, and potato) (Dreborg and Foucard 1983; Breiteneder and Ebner 2000; Tordesillas et al. 2010; Ebner et al. 1995). OAS and food allergies have different underlying mechanisms; OAS is secondary to cross-reactivity between food proteins and aeroallergens secondary plants, and food allergies are secondary to direct sensitization to the food protein itself.

32.11 Directed Therapy

The purpose of aeroallergen skin testing is useful for the diagnosis of allergic diseases such as asthma, rhinitis, and conjunctivitis. Patients who are both sensitized and clinically allergic to the allergens they test positive for can be started on direct therapy such as subcutaneous or sublingual immunotherapy if appropriate. For patients who are not candidates for immunotherapy, allergen avoidance (e.g., dust mite covers for dust must allergic individuals) and symptomatic treatment (e.g., intranasal steroids and/or antihistamines, oral antihistamines) are key to control disease.

32.12 Other Skin Tests Utilized

32.12.1 Prick-by-Prick Testing

Another variation of SPT is the prick-by-prick method (also known as prick-to-prick, prick-in-prick, or prick-prick). Prick-by-prick testing (PPT) is performed by inserting the test lancet directly into the food of interest, withdrawing it, and then immediately pricking the patient's cleaned skin. Though less convenient than standard SPT with commercial extracts, PPT is often used in the evaluation of hypersensitivity to fresh fruits and vegetables as the proteins in these foods are likely to degrade with commercial processing (Ortolani et al. 1989). Studies have shown that PPT is more sensitive (though often also less specific) when compared to SPT with commercial extracts in the assessment of cherry, orange, peach, apple, kiwi, tomato, celery, and carrot hypersensitivities (Ortolani et al. 1989; Lucas et al. 2004; Ferrer et al. 2008; Ballmer-Weber et al. 2000, 2001). The use of PPT has also been studied in the evaluation of other food allergies; PPT has been found to be comparable to SPT for hazelnut (Ortolani et al. 2000); more sensitive for egg white, seawater shrimp, and freshwater shrimp (Jirapongsananuruk et al. 2008; Rance et al. 1997); and less sensitive for cow's milk, pea, and walnut (1,8); conflicting evidence exists for peanut (Ortolani et al. 1989; Rance et al. 1997).

Of note, the use of PPT with fresh foods is complicated by additional variables that are not associated with SPT. Studies have shown that patients demonstrate different reactivity with PPT based on the fruit ripeness, the use of the peel or pulp of the fruit in question (Ferrer et al. 2008), the specific variety or cultivar of the fruit involved (Bolhaar et al. 2005; Le et al. 2011), the initial prick location relative to the fruit's stem (Vlieg-Boerstra et al. 2013), and even the handling of the fruit with latex gloves in patients with known latex allergy (Sanchez-Lopez et al. 2000). In the evaluation of seafood allergies, it may also be reasonable to perform PPT with both cooked and raw versions of the food in question; for instance, it has been noted that PPT for cooked fish can detect fish-collagen hypersensitivity unlike PPT for raw fish (Chikazawa et al. 2015). Regarding safety, PPT in the evaluation of food allergies has not been as extensively studied as SPT (Codreanu et al. 2006), but anaphylaxis has been reported with PPT (Pitsios et al. 2009; Haktanir Abul and Orhan 2016; Ciccarelli et al. 2014; Novembre et al. 1995; Tosca et al. 2013).

32.12.2 Patch Testing

A different form of skin testing, patch testing, is used in the evaluation of contact dermatitis. Contact dermatitis accounts for up to 30% of all cases of occupational disease in industrialized nations, making it the most common occupational skin disorder (Clark and Zirwas 2009). Contact dermatitis can be divided into either irritant or allergic. Irritant contact dermatitis is more common and involves multiple mechanisms including the innate immune system (Smith et al. 2002), whereas allergic contact dermatitis (ACD) is the classic presentation of a T-cell-mediated, delayed-type hypersensitivity response to exogenous agents (Rietschel and Fowler 2008; Mowad et al. 2016). In ACD, an exogenous substance penetrates the skin surface where it then is processed and presented by dendritic cells to naïve T-cells in regional lymph nodes; these T-cells then proliferate and recognize the antigen on future exposures inducing an immunologic cascade and subsequent dermatitis (Fonacier and Sher 2014).

The patch test, first introduced in 1896, is now considered the gold standard for confirming the diagnosis of ACD (Jadassohn 1969; Fonacier et al. 2015). It can be used to evaluate any chronic, pruritic, eczematous dermatitis concerning for ACD; it can also determine the causative agent and differentiate between irritant and allergic contact dermatitis. The most common patch test techniques are the TRUE test, the only FDA-approved screening method and the method using individual Finn Chambers (Bernstein et al. 2008). The TRUE (thin-layer rapid use epicutaneous) test is a commercially available test that consists of 35 allergen and allergen mixes that have been incorporated into a dried-in-gel delivery system; these patches are then coated onto polyester backing to form 3 patch templates; 2 of the patches contain 12 allergens and allergen mixes each, and the third patch contains 11 allergens and 1 negative control (TRUE Package Insert 2018). In contrast to preloaded TRUE test, the Finn Chamber is a small occlusive aluminum chamber that is filled with any allergen of interest for an individual patient and applied to the skin at the time of testing (Bernstein et al. 2008). Various panels are commercially available to use in filling Finn Chambers; these include the North American Contact Dermatitis Group series and the European standard series. False-negative and false-positive test results can occur with either the TRUE test or Finn chamber technique (Wilkinson et al. 1990; Goh 1992), but the TRUE test may have lower sensitivity than other testing options (Cohen et al. 1997). Studies of the older TRUE test consisting of 23 allergen and allergen mixes estimated it was only able to identify 25–30% of clinically relevant causes of ACD (Belsito 2004; Cronin 1978; Fisher 1986). One study comparing the 35 antigen TRUE test with the more extended North American Contact Dermatitis Group panel of 70 or more antigens found that the TRUE test can miss detection of approximately 26.7% of antigens (Warshaw et al. 2013).

Patient-specific measure can also affect patch test results. To improve patch testing sensitivity, patients would ideally refrain from systemic corticosteroid use. Small studies have found that patients taking prednisone or other immunosuppressants (such as adalimumab, azathioprine, cyclosporine, etanercept, infliximab, methotrexate, and mycophenolate mofetil) are still able to mount positive patch test results (Rosmarin et al. 2009; Wee et al. 2010). However, in adults, a dose of 20 mg in a 75-kg male has been found to suppress allergic contact reactions (Anveden et al. 2004). Patients should also refrain from use of topical steroids on the testing area for at least 3 days prior to patch testing (Fowler et al. 2012). Oral antihistamines can be used to manage pruritus symptoms and should not alter patch testing results.

Regarding the placement of either the TRUE test templates or Finn chambers, the patch tests should be placed on the upper or middle back areas (approximately 2.5 cm lateral to the spine on either side) in an area free of dermatitis and hair (Bernstein et al. 2008). After placement, the patch tests should remain in place for 48 h (Skog and Forsbeck 1978); the patches may then be removed and read for potential positive reactions. Currently, a nearly universal nonlinear descriptive scale is used to read patch testing results and to discern and describe positive findings (Mathias and Maibach 1979; Fregert et al. 1984).

- A doubtful reaction consists of faint macular erythema alone.
- A weak positive (1+) reaction is erythema with mild infiltration with or without discrete nonvesicular papules.
- A strong positive (2+) reaction consists of erythema and mild infiltration with vesicles and papules.
- An extreme positive reaction (3+) is a coalescing vesicular and papular plaque with deep erythema and significant infiltration that may become bullous or ulcerative and often expands past the margins of the original patch.

Later readings at 96 h (48 h after the removal of the patch and original 48-h reading) are also recommended by both the International Contact Dermatitis Research Group and the North American Contact Dermatitis Group since approximately 30% of relevant allergens that are negative 48 h will become positive at 96 h (Pratt et al. 2004; Britton et al. 2003). If a reaction was initially positive at the original 48-h read but then resolves at the subsequent 96-h read, this is suggestive of an irritant reaction. Of note, if there are one or two strongly positive reactions, this can sometimes lead to an array of false-positive reactions at nearby patches (Barbaud 2005); this reaction is called "angry back" or "excited skin syndrome" (Dawe et al. 2004). A prospective study found that this phenomenon occurs in roughly 6.2% of patients undergoing patch testing and is more common in patients who have experienced dermatitis for a longer duration (Duarte et al. 2002). The exact mechanism of this reaction remains unclear; one hypothesis is that the strongly positive reactions lead to nonspecific hyperreactivity of the surrounding skin (Mitchell 1975). These patients with "angry back" may benefit from repeat separate testing to each positive allergen.

On the opposing end of the spectrum, doubtful and weak positive reactions are difficult to reproduce and may also often be false positives; the accuracy of weak positive (1+) reactions has been estimated to be as low as 20%, whereas 2+ and 3+ reactions are estimated to be accurate 80–100% of the time (Fischer and Maibach 1991). For weak sensitizers, other options such as a 7-day reading time or a different technique called the repeated open application test (ROAT) may be appropriate (Hannuksela and Salo 1986; Villarama and Maibach 2004). The repeated open application test (ROAT) or exaggerated use test is performed by repeatedly applying the test substance to a specified area twice daily for up to 1 week or until an eczematous reaction develops (Farage and Maibach 2004); this is often done in areas that easily accessed and observed by the patient, such as the antecubital fossae. ROAT is designed to determine a patient's biologic threshold to the suspected allergen and is often used to assess topical leave-on products such as mascara or lotions (Schnuch et al. 2005).

Non-standardized forms of patch testing have also been used in other applications. For instance, drug patch tests use relatively high concentrations of the commercial form of the drug; after test placement, reactions are assessed at 20 min (as some drugs may cause immediate reactions) and then again at 48 and 96 h to assess for delayed reactions (Barbaud 2005). In the diagnosis of drug rash with eosinophilia and systemic symptoms (DRESS), 1 study of 56 patients found it to be a safe and useful method in confirming DRESS induced by antiepileptic drugs but not DRESS induced by allopurinol (Santiago et al. 2010).

Patch testing has also been used in the assessment of food allergy in atopic dermatitis; this testing is performed by mixing 2 g of dried or desiccated foods with 2 ml of an isotonic saline solution and then placing the mixture into a Finn Chamber and placing the chamber on the patient's back with standard patch readings (Bernstein et al. 2008). Studies have generally concluded that patch testing is more sensitive than skin prick testing for the diagnosis of food-associated atopic dermatitis (Stromberg 2002) but also likely less specific (Giusti and Seidenari 2005; Mehl et al. 2006). Patch testing's role in eosinophilic esophagitis (EoE) has also been evaluated, with conflicting evidence on the negative and predictive value of patch testing in comparison to skin prick testing (Spergel et al. 2002, 2007, 2012). The more recent of these studies was published in 2012 and evaluated 941 pediatric patients with

EoE; it concluded both skin prick and patch testing were acceptable testing methods (Spergel et al. 2012).

32.13 Conclusion

Our chapter provided detailed information on how best to utilize the epicutaneous skin tests in diagnosing hypersensitivity disease. Other tests to evaluate allergic disorders were discussed as well. These tests play a vital role in every allergist practice and should available for years to come.

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In Vitro Allergy Testing

33

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Abstract

In vitro allergy testing has been utilized, in various methods, for almost 100 years. This chapter will primarily focus on clinically available laboratory allergy testing. Details on how the specific allergy tests are conducted and performed will be reviewed. Current clinical correlation of specific allergy test results is discussed. Practical utilization and limitations on in vitro IgE and IgG testing will be explored. Brief introduction to experimental in vitro allergy testing for research is covered.

Keywords

Laboratory allergy testing · In vitro allergy testing · IgE allergy testing

33.1 Introduction

In vitro allergy testing has been developing and continuously refined for almost 100 years. There presently exists no in vitro test, which can definitively predict if a patient will experience an allergic reaction after being exposed to a potential allergen. The gold standard for food allergies remains a double-blinded, placebo-controlled oral food challenge (DBPCOFC) to an allergen to determine the patient's allergic status. However, in vitro allergy testing has excelled in providing the clinician and patient with a predictive value or risk of an allergic reaction occurring following exposure to a potential allergen. In vitro testing can be conducted on a vast range of environmental and food allergens with a single blood draw. The advantages include testing patients with equivocal or negative skin test results in the presence of a strong clinical history, positive skin tests but missing or poor clinical correlation, patient or parental preference, relative contraindications such as active skin disease, or history of anaphylaxis on prior skin testing. This chapter will not discuss in vivo, please see ▶ Chap. 32, "Allergy Skin Testing" for more on this topic.

The classical type I Gell-Coombs hypersensitivity allergic reaction is mediated by IgE antibodies. The main challenges in studying allergens and respective antibodies in vitro stem from the fact that both are proteins. As with all proteins, they are prone to irreversible denaturing during handling and isolation, which alters binding of IgE antibodies specific to the denatured allergen. Similarly, it is possible to denature the antibody rendering its binding to an allergen unreliable. This problem is further compounded by the fact that within the same allergen source, there are likely different proteins of interest with varying similarities in chemical properties which makes purification difficult and unwanted contamination in creating appropriate standards. For these reasons, one of the main differences for commercial versus research in vitro testing is reproducibility and standardization. The FDA has certain criteria for premarket approval in order for in vitro lab testing to be commercially available for clinical practice (510(k)) (Bernstein et al. 2008).

This chapter will focus primarily on in vitro testing that is available for clinical practice. Immunoassays are one of the most commonly used in vitro allergy tests today. Immunoassays have changed over time, but each variation can be traced back to a process first published in 1959 by Yalow and Berson. As will be further discussed, immunoassays operate on comparing an unknown concentration sample with a standard concentration curve generated from a known concentration sample of the same substance. The properties of the standard concentration curve are unique to each substance being investigated and sample run. The necessity to have purified and known concentrations of the protein in question was one of the drawbacks to 1977 Nobel Prize-winning immunoassay and remains a complication over 50 years later in the current immunoassays. However, immunoassays are an elegant solution to a complex problem and remain a powerful qualitative and quantitative tool.

33.2 Immunoassay

Enzyme-linked immunosorbent assays (ELISA) is one of the more commonly used forms of immunoassay today with multiple variations available. The ELISA test does not directly measure the amount of unknown protein in a sample

but rather compares the amount of signal produced by that sample with the signal that was produced by a standard or control sample(s). The standard or control sample must be of the same purified substance with a known concentration.

If all steps in the ELISA were performed equally, the unknown concentration samples will then be compared with the standard curve produced by various known concentrations of the standard samples. Because of unique chemical properties that characterize each protein, the standard sample again must be same purified substance as the unknown or test sample. The test sample may be crude or minimally purified. To further explore this concept, Fig. 1 depicts the basic overall process.

The top pathway shows the standard sample for "Protein A," while the bottom pathway shows the unknown sample. In Fig. 1, we are testing to determine if "Protein A" is in the unknown sample and, if so, how much. Each step is performed identically with each sample (it is crucial that each step is done identically for comparing signal strength at the end, especially for quantitative tests). Step 1 illustrates "Protein A" of known concentration being placed into a testing well. After a period of time the well is emptied and washed several times in step 2 in order to ensure all of the original solution was removed. The resultant well although appearing empty is actually coated with "Protein A" on its surface. The exact amount of protein coating is unknown for both pathways at this point. Step 3 adds "Protein B" for a period of time and the solution is again removed with washing in step 4. Step 3 attempts to occupy empty well surface area not previously occupied by "Protein A" in step 1 ("Protein B" is assumed to be inert in subsequent steps). By further occupying potentially unused well wall space, "Protein B" will be blocking additional binding of other proteins, such as antibodies in the next step. In Step 5, an antibody to "Protein A" (commonly IgG or IgE are used) of known concentration, with an enzyme attached to it, is added to each well. The well is again emptied in Step 6 and washed.

Within each well there is now an unknown amount of "protein A" and "protein B" coating the walls. Protein B prevents the antibodies to "protein A" from adhering to the walls rather than binding to "protein A." Thus we assume that all the antibodies remaining in the well after step 6 is noncovalently attached to our "Protein A" and not readily displaced by our washing step. In step 7, a solution containing a known concentration of a substrate to the enzyme tethered to our antibody is added. As the substrate is metabolized, it will add pigmentation to the solution inside each well (colorimetric analysis). The pigmentation is read by an instrument in step 8. The amount of pigmentation created in a given amount of time is directly related to how much enzyme is present in the well. It is not directly related to how much "Protein A" is present. However, if there is pigmentation in the unknown sample, then you can at least conclude that "Protein A" is present in a qualitative sense.

In order to determine quantitatively how much "Protein A" is present, a standard curve

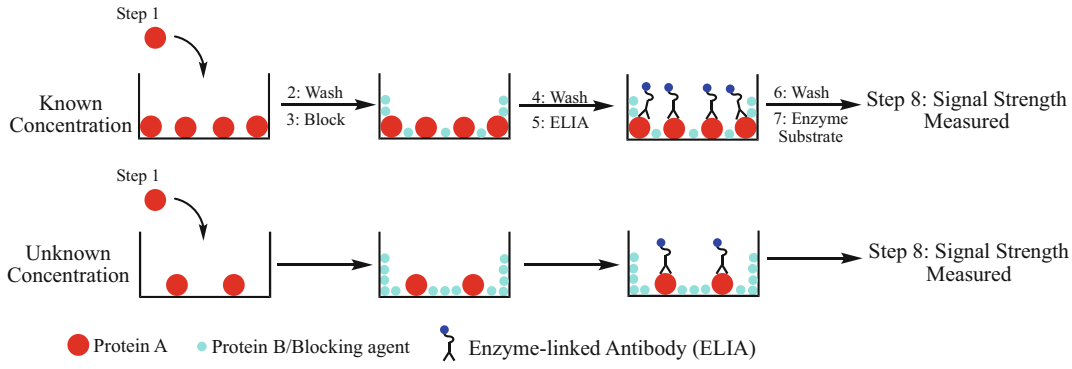

Fig. 1 Basic immunoassay principles

is required. This is accomplished by serial dilutions of the standard sample into different wells at step 1. Likewise, it is customary to do the same with the unknown sample to ensure the signal in the end is neither too high nor too low for comparison with the standard curve.

Figure 1 shows that the end degree of pigmentation on the standard curve does not directly indicate how much "Protein A" is physically in the wells. Rather, it operates on the assumption that if everything was done identically at each step then the same concentration of "Protein A" in both the standard and the unknown sample in step 1 will produce the pigmentation at the same rate in step 7 and give you the equal signal strength in step 8. Seemly trivial differences in timing of each step, subtle run, or operator-specific techniques along with microscope variability in each ELISA plate create additive errors that necessitate the creation of a standard curve for each run. Standard ELISA plates are made of polystyrene and have 96 wells per plate (12 × 8 format).

The chance for additive errors in an ELISA is why the FDA 501(k) premarket approval of test kits is critical. Commercial tests today are semiautomatic to fully automatic, which helps to reduce errors. To further ensure reliability, additional safe guards are in place for IgE testing (whether in total or for a specific antigen) at various laboratories under the Federal Clinical Laboratory Improvement Act (CLIA) originally passed in 1988 (Peddecord and Hammond 1990). For IgE testing, this act means that each individual commercial laboratory must compile with the College of American Pathology's (CAP) tri-annual surveys (Patrick et al. 2014). These surveys include the running of known and "unknown" standards in the laboratory to ensure proper quantitative measurements and techniques. Additional and most current specification and policies are located on the CAP website (College of American Pathologists [www.CAP.org]).

Figure 1 is also the classic example of a direct ELISA. By replacing the enzyme linked to the antibody with a fluorescent enzyme or radioactive element (Classically ^{125}Iodine), the test would be similar to a direct fluorescent enzyme immunoassay (FEIA) or radioallergosorbent test (RAST) respectively. Historically, the RAST test was first created in 1967 and was widely used for decades, but not commonly used in practice today. Covalently linking "Protein A" rather than noncovalently coating a well wall (paper disks and capsule are also used rather than wells) is also possible.

There are four different main types of immunoassays: direct, indirect, sandwich, and competitive. Figure 1 depicts the basic concept of a direct immunoassay. The three other forms will be reviewed at the end of the chapter in the research section. Of the four, the most common form used for commercial testing is the sandwich immunoassay. Appreciating how much optimization must go into each immunoassay available for commercial use will help to understand the reason skin testing has stood the test of time and is still highly supported in the literature. However, neither test can determine the severity that an allergic reaction will occur in patient, but rather these tests can provide information as the likelihood that an allergic reaction to a specific allergen will develop by providing positive and negative predictive values.

33.3 Clinical Practice and Common Laboratory Testing

33.3.1 IgE Values and Clinical Correlation

The original RAST immunoassay came with six arbitrary classes, which categorized respective IgE levels (Table 1). These classes were originally arbitrarily divided based on birch pollen IgE (Bernstein et al. 2008).

Table 1 RAST classes

Class rating	PRU/mL	Interpretation
0	<0.1	Absent or undetectable
0/1	0.1–0.35	Very low
1	0.35–0.7	Low
2	0.7–3.5	Moderate
3	3.5–17.5	High
4	>17.5	Very high

Phadebas RAST unit = (PRU)

The classes were not determined by stratifying severity of reactions from a double-blind, placebo-controlled challenge among allergic individuals. This remains true for today's in vitro tests (Table 2), however the units are reported based on the World Health Organization (WHO) standards of IU/mL (Thorpe et al. 2014). The International System of Units (SI), in contrast to the WHO, recommends IgE be reported in nanogram per milliliters (ng/mL) (Lundberg et al. 1986). Clinical research has helped to determine to some degree the clinical correlation with total IgE, allergen-specific IgE, and specific allergen component IgE levels using FDA approved immunoassays. There are however a very limited number of allergen-specific IgEs that have been prospectively studied. One barrier to double-blinded, placebo-controlled oral food challenges (DBPCOFC) are the ethical consideration involved in the studies. As pointed out by Sampson in 2001, parents were likely to opt out of oral food challenge based on predictions from retrospective studies on specific IgE levels and failing an oral food challenge (Sampson 2001).

Total IgE levels have virtually no clinical value for determining the likelihood of a specific allergy but may be useful in diagnosing and treating several allergy-related disorders. Should the total IgE be significantly high, such as >20,000 IU, the specific IgE measurements may be falsely positive (Bernstein et al. 2008). In general, individuals with environmental allergies, asthma, and atopic dermatitis will have higher levels of IgE than patients without these ailments. However, total IgE levels can be useful in diagnosing allergic bronchopulmonary aspergillosis (ABPA), a medical condition related to the allergic sensitization to *Aspergillus fumigatus* (Patterson and Strek 2010). A total IgE level of >1000 IU/mL is considered one of several clues for presence of ABPA (Reddy and Greenberger 2017). However, other criteria are required for the diagnosis of ABPA (please see ▶ Chap. 20, "Allergic Bronchopulmonary Aspergillosis").

The total IgE level is utilized in determining the appropriate dosage of omalizumab in treating allergic asthma (Table 3) (Busse et al. 2001). The dosing is determined predicated on weight, age, and serum total IgE levels. Separate nomograms are published for both adult and pediatric patients (Tables 3 and 4) (Omalizumab [PDF file]). For individuals 12 years and older, dosing starts at 150 mg every 2 weeks for those with IgE levels > or equal to 30–100 IU/mL and weighing 30–60 kg.

For individuals 6 and under 12 years, dosing starts at 75 mg every 2 weeks for those with IgE levels > or equal to 30–100 IU/mL and weighing 20–25 kg (Table 4). The first cutoff for when omalizumab is not indicated for all approved age groups is serum IgE levels ranging from 300 to 400 with an individual weight of >90–125 Kg. However, higher serum IgE levels are approved for use provided the individual's weight is less as seen in Tables 3 and 4.

Table 2 CAP system scoring scheme

Class rating	IgE level (kIU/L)	Interpretation
0	<0.35	Absent or undetectable
1	0.35–0.69	Low level
2	0.70–3.49	Moderate level
3	3.50–17.49	High level
4	17.50–49.99	Very high level
5	50–100.00	Very high level
6	>100.00	Very high level

World Health Organization IgE standard = 1 kIU/L = 2.44 ng/mL

33.3.2 Food Allergies and Specific Allergen IgE Levels

Class 0 for any IgE test (less than 0.35) is considered absent or nondetectable. However, nondetectable specific IgE does not necessarily eliminate the risk of an allergic reaction occurring upon exposure (Fig. 2). With a strongly suggestive history, skin prick testing is recommended if the Immunocap is negative or low titer before proceeding to an oral food challenge (top orange arrow, Fig. 2). Studies confirm a risk of between 5% and 20% of a positive oral challenge occurring with a Class 0 sIgE, negative skin testing and a strong clinical history suggesting allergic sensitization (Sampson et al. 2014). If there is no

Table 3 Omalizumab dosing and frequency for those 12 years or older with asthma

Pre-treatment Serum IgE IU/mL	Body Weight			
	30–60 kg	>60–70 kg	>70–90 kg	>90–150 kg
≥30–100	150 mg	150 mg	150 mg	300 mg
>100–200	300 mg	300 mg	300 mg	225 mg
>200–300	300 mg	225 mg	225 mg	300 mg
>300–400	225 mg	225 mg	300 mg	
>400–500	300 mg	300 mg	375mg	
>500–600	300 mg	375 mg		
>600–700	375 mg			

2 week Dosing
4 week Dosing
Do Not Dose

Table 4 Omalizumab dosing and frequency for those 6 and under 12 years old with asthma

Pre-treatment Serum IgE (IU/mL)	Body Weight (Kg)									
	20-25	>25-30	>30-40	>40-50	>50-60	>60-70	>70-80	>80-90	>90-125	>125-150
	Dosing (mg)									
30 - 100	75	75	75	150	150	150	150	150	300	300
>100 - 200	150	150	150	300	300	300	300	300	225	300
>200 - 300	150	150	225	300	300	225	225	225	300	375
>300 - 400	225	225	300	225	225	225	300	300		
>400 - 500	225	300	225	225	300	300	375	375		
>500 - 600	300	300	225	300	300	375				
>600 - 700	300	225	225	300	375					
>700 - 900	225	225	300	375						
>900 - 1100	225	300	375							
>1100 - 1200	300	300								
>1200 - 1300	300	375								

2 week Dosing
4 week Dosing
Do Not Dose

history of reaction and/or history of tolerance to the food in question, an oral food challenge or food avoidance is not required (bottom green arrow, Fig. 2).

Figure 3 describes the clinical decisions required when sIgE levels are detectable between Class I and VI. Specific IgE assays should be obtained based on the patient history rather than

obtaining a panel of allergens unrelated to the history because of the risk of confirming immunologic sensitization rather than allergic sensitization which may incorrectly result in unnecessary dietary restrictions or avoidances.

The green pathway to the left outlines the common occurrence of a positive sIgE result within a large food panel assay in the absence of a positive history. If a patient has a reliable history of frequent *and* current ingestion without *any* adverse reaction, a positive result may be interpreted as tolerance and/or potential irrelevant sensitization. Recommending an oral food challenge or avoidance is not warranted (Sampson et al. 2014). Education for the patient should, however, be provided if symptoms do unexpectedly occur.

When a questionable, inconsistent, remote, or absent history of ingestion is obtained, the bottom orange pathway would be most appropriate. Under these circumstances, an oral food challenge (OFC) should be a consideration. History of recent anaphylaxis of any severity or remote history of severe anaphylaxis or failed OFC with clear temporal correlation with ingestion of the food in question negates the need for an OFC (Sampson et al. 2014). In these cases, serial sIgE testing and skin prick testing can be useful to monitor both decreasing sIgE levels as well as skin test positivity. The frequency of testing is determined by the age of the patient and severity of the allergic reaction, but testing every other year is generally not considered unreasonable. Traditionally a decrease of >50% in sIgE level is suggestive that an allergic response is less likely during a subsequent oral challenge. Skin prick testing does have excellent positive predictive value (PPV) for some foods based on diameter and needs to be considered together with sIgE levels. Additional factors such as poor asthma control, mast cell disorders, and beta-blocker administration are considerations when deciding to perform an OFC (Santos and Brough 2017).

Currently there are only four allergens with specific IgE antibody levels that have widely recognized positive and negative predictive values based on failing (positive) or passing (negative) an oral food challenge (Fig. 3, right red arrow). These allergens are egg white, cow's milk, peanut, and fish. The significance of the specific IgE levels changes based on the particular allergen for a 95% predictive decision point to an OFC from retrospective study by Sicherer et al. (2000). All 95% predictive decision point with respect to IgE levels had a respective PPV of >95%. The IgE levels recommendation are based on the retrospective studies presumably secondary to

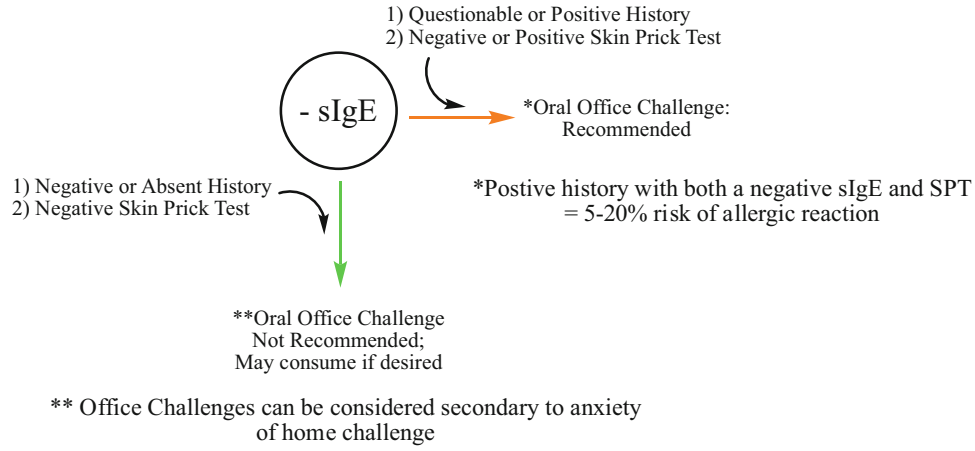

Fig. 2 Oral challenge guidance based on Class 0 specific IgE level and history. Bottom green pathway: risk of reaction is negligible and routine office challenge is not recommended. Right orange pathway: some risk, up to 20%, office challenge is recommended

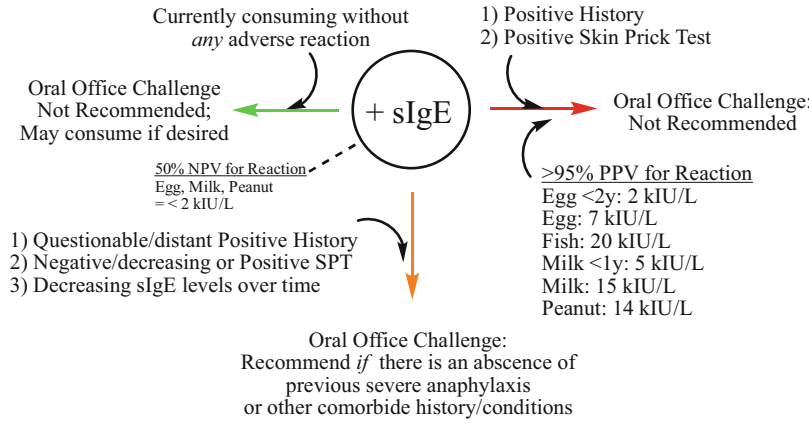

Fig. 3 Oral challenge guidance based on Class I–VI specific IgE levels and history. Left green pathway: risk of allergic reaction is negligible and routine office challenge is not recommended. Bottom orange pathway: increased risk, office challenge may be recommended. Right red pathway: high risk of allergic reaction, office challenge is not recommended

low patient enrollment in the subsequent prospective studies (Sampson 2001). It is important to note that sIgE levels for any food allergen has predictive value that is subject to regional fluctuations (Vereda et al. 2011). The sIgE levels vary depending on race as well (Branum and Lukacs 2009; Du Toit et al. 2013). The PPV depicted in Fig. 3 above are for the United States.

For fish levels at or above 20 kIU/L with a positive history, an oral challenge is not recommended as the risks of a positive reaction are considerable approaching 100% (Sampson et al. 2014). Any level at or above 0.35, but less than 20 kIU/L, may warrant in office oral challenge for fish, unless there is a reliable history of current tolerance or allergic reaction (Fig. 3, bottom orange pathway). The risk assessment and recommendations for eggs, milk, and peanuts remain the same; however, the IgE levels for >95% PPV vary by food and age of the patient. Egg white with an IgE level greater that 7 kIU/L has a >95% PPV for a positive oral food challenge. However, someone under the age of 2 would have a >95% PPV with an IgE level above 2 kIU/L for egg whites. For cow's milk, a level above 5 kIU/L for an infant is >95% PPV, while above 1 year of age the level moves up to 15 kIU/L. Peanut has been reported to have a >95% PPV with an IgE level above 14 kIU/L.

For eggs, milk, and peanut, an IgE level less than 2 kIU/L has a 50% negative predictive value (NPV). The 50% NPV improves for peanuts to less than 5 kIU/L if there is no prior history of reaction. With essentially only a 50% NPV for IgE levels of these four food allergens residing in Classes II and I, clinical correlation is vital (Sampson et al. 2014).

33.3.3 Environmental- and Hymenoptera-Specific IgE Levels

For clinical purposes, environmental allergen-specific IgE testing can be divided into two categories: detectable (class I–VI) and non-detectable (class 0). Clinical correlation is just as important as with specific food allergy testing. Currently, it is only recommended to initiate immunotherapy for patients with a clinically positive history that is consistent with positive skin and/or IgE testing (Cox et al. 2011). Despite a strong clinical history, immunotherapy is not indicated in patients with a negative skin tests or nondetectable specific IgE testing for the respective allergen(s). A uncommon condition known as local allergic rhinitis (entopy) does exist where both skin testing and sIgE are negative

but allergic sensitization is present, which can only be documented with nasal provocation with the suspected allergen (Rondón et al. 2012).

The recommendations for environmental allergies and immunotherapy are similar. They, however, differ due to the consideration of the patients' age and severity of the allergic reaction to envenomation as to whether or not to initiate hymenoptera immunotherapy (Golden et al. 2017). Another difference is the recommendations on repeating testing if negative results are obtained initially in the presence of a strong or repeated and severe clinical history of anaphylaxis after envenomation. As with environmental allergies, starting immunotherapy in these settings of repeated negative skin and in vitro testing is not advised. There is, however, even with repeated negative test results, a chance of systemic anaphylaxis with subsequent envenomation (Golden et al. 2001). It is suggested in these cases to consider investigation into mastocytosis (Golden et al. 2017). The option for a live sting challenge has been reported but is not routinely performed in clinical practice (Golden et al. 2001, 2017; Ruëff et al. 2001).

33.4 Interface of Clinical Practice and Research Today

33.4.1 Specific IgG/IgG4 Values and Clinical Correlation

The IgG testing is carried out by ELISA in much the same way as IgE above. In general, it is not recommended to test specific IgG to food, environmental, and hymenoptera allergens. To date, the main consensus by allergy and immunologists regarding the presence of allergen-specific IgG is that it is not an indication of sensitization or intolerance but rather an indicator of past exposure (Bernstein et al. 2008). There are notable exceptions when testing for specific antigen; IgG is performed to as part of the diagnostic evaluation including hymenoptera, celiac disease (nonallergic disease), ABPA, and suspected adverse reactions to trace amounts of IgA in IVIG (anti-IgA) (Wells et al. 1977).

It has been reported that as the duration of venom immunotherapy progresses, specific IgE levels will decrease and reciprocal specific IgG4 levels will increase. This helps to support that IgG/IgG4 levels are protective rather than an indicator of an allergy, intolerance, or sensitivity. However, serial specific IgG/IgG4 level testing to monitor immunotherapy is currently not recommended for the purpose of guiding care decisions (Golden et al. 2017).

Using food-specific IgG levels to help investigate food sensitivities or intolerances is not recommended. Studies to date have been unable to show correlation with food-specific IgG and allergies, intolerance, or sensitivities in a reliable or consistent manner in order to support their use in routine clinical practice (Zeng et al. 2013).

It is accepted that positive results for specific IgGs, but not a specific level, indicate an individual's past exposure to the respective protein (such as in celiac disease, ABPA, and anti-IgA). Furthermore, the absence of IgG does not indicate that past exposure has not occurred. It does not by itself indicate allergic or nonallergic disease status.

33.4.2 Component-Resolved Diagnosis

Component-resolved diagnosis (CRD) or component testing is clinically used to investigate if specific allergen IgE testing or positive skin prick testing indicate a heightened risk for an allergic reaction that will result in anaphylaxis rather than a pollen cross-reactive driven process such as oral allergy syndrome (Borres et al. 2016). It is the only in vitro ELISA test that attempts to provide information that cannot be ascertained by skin testing (Muraro et al. 2017). This is because skin testing, with routine commercial allergen extracts, is unable to distinguish a positive test to the whole protein allergen from various allergen protein components. The components used are a reflection of the major allergen components in each specific allergen as experimentally determined from those with the respective allergy.

Component testing is currently used to help differentiate patients with positive testing by skin

or sIgE that may be able to tolerate the allergen prior to deciding to proceed to a challenge. A good example of the clinical use of component testing can be seen with peanuts (Table 5). The peanut allergen component Ara h 8 is associated with the oral allergy syndrome, whereas Ara h 2 > Ara h 1, 3, 9 is correlated to a greater risk of anaphylaxis. Individuals with class 0 sIgEs to Ara h 1, 2, 3, but positive to the Ara h 8 component are reported to have a lower risk of anaphylaxis during an oral food challenge (Glaumann et al. 2015). This is of particular clinical interest when providing recommendations to patients that have a questionable, but positive peanut sIgE and/or skin prick testing (Fig. 3, bottom orange pathway). The level of Ara h 8, however, does not apparently correlate well with the risk of positive oral allergy symptoms (OAS) during a challenge. In these cases, the amount of peanut ingested as been suggested as more of a determinant of OAS than the sIgE level of the Ara h 8 component (Glaumann et al. 2015). Depending on the region of the Ara h 1, 2, 3 and 9, sIgE level has been shown to have predictive value to a positive oral food challenge (OFC), particularly with Ara h 2 (Ara h 9 in southern Europe) (Ballmer-Weber et al. 2015). The Ara h 2 levels for a 90–95% PPV to an oral challenge to peanut, however, vary greatly depending on the region from >0.35 to 42.2 kUI/L (Borres et al. 2016). Similar tests and reports exists for milk (Bos d 4, 5, 6, 8), egg (Gal d 1, 2, 3, 4) (Haneda et al. 2012), as well as others (Borres et al. 2016). Currently guidelines do not support their routine use but state that it can be considered especially with peanuts (Sampson et al. 2014).

Table 5 Specific IgE food component levels and predictive interpretations

	Component	Clinical significance	Note
Peanut	Ara h 8	Predict OAS	Must have negative Ara h 1, 2, and 3
Milk	Bos d 8	Positive OFC	95% PPV with 10 kU/L
Egg	Gal d 1	Baked egg tolerant	90% NPV with 0.35 kU/L or less

33.5 Research

33.5.1 Basophil Histamine Release

As indicated by the name, this test measures the histamine released from basophils upon stimulation by an allergen (Muraro et al. 2017). The test requires live basophils, which are exposed to the allergen in question. After a period of incubation, the histamine released is measured. This test has not been standardized to any allergen.

33.5.2 Basophil Activation Testing

Basophil activation test or BAT uses a flow cytometry functional assay to gage the degree of activation after exposure to stimuli of interest (McGowan and Saini 2013). Specifically, the assay traditionally uses two cluster differentiation (CD) markers, 63 and 203c, on the basophil to monitor reactivity. When the high-affinity IgE receptors (FcεRI) on a basophil become stimulated by cross-linking of an allergen, the cell degranulates by two possible pathways: piecemeal or anaphylactic degranulation. Cluster differentiation marker 63, which is located on the membrane of the intracellular secretory granules, is found on the basophils' cell surface due to upregulation and exocytosis in anaphylactic degranulation. On the other hand, CD 203c, a transmembrane type II glycosylated protein, is always present on the cell surface in small amount. It is upregulated quickly on exposure to an allergen or potentially more slowly through Interleukin (IL)-3 stimulation.

In piecemeal degranulation, it has been observed that exocytosis is not present, making the presents of CD203c without CD63 supportive evidence of a nonanaphylactic degranulation. In contrast when both are present this supports the potential of an anaphylactic degranulation. Thus the aim is to predict by incubating a patient's blood in the presents of a suspected allergen to determine if they will have a potential of an allergic reaction (increase in CD203c and/or CD63 on the basophils surface). If there is an increase in the CD markers, the ultimate goal

would be to determine if the allergic reaction predicted piecemeal (Increase in CD 203c only) versus anaphylactic degranulation (increase in both CD 203c and 63). Reproducible and standardized achievement of this goal would help to eliminate or reduce the need for an oral challenge to a suspected allergen.

33.5.3 Immunoblot

This technique, also commonly referred to as a western blot, is useful in the research realm when complex mixtures of proteins that are potentially allergenic require separation in order to confirm allergen status (Bernstein et al. 2008). The mixture is separated by gel electrophoresis. The resultant protein bands within the gel are transferred (blotted) to nitrocellulose membrane. The nitrocellulose membrane is then incubated with serum containing sIgEs to allergenic proteins. Once the incubation is completed, the membrane is washed and once again allowed to incubate but with labeled IgE specific to human IgE. The bands that the labeled IgE detected helps to direct investigators to the proteins that are more likely to be the allergens.

33.5.4 Microarray

Microarray assays have been developed with the hope of detecting epitope patterns and testing for multiple allergens in one assay or chip (Hamilton 2017). The test has not yet been approved by the FDA.

33.5.5 Nanoallergen Platform

Nanoallergen platform uses synthetically made liposome with single or multiple allergenic epitope peptides or proteins dispersed around the liposome (Deak et al. 2017). One advantage this method has is reducing the concern of allergic aggregates or different sized particle that can cross-link IgE receptors differently within the same sample. This technique has the ability to probe which epitope of an allergenic protein has the highest immunogenicity to an individual's own IgE binding epitope(s) profile. The general approach in the laboratory would be to titrate the synthetically made, allergen-infused liposomes into an individual's serum. The mast cell degranulation would then be measured. The titration of a known allergen-specific epitope of near uniform-sized allergenic particles and spatial concentration on the liposome are the aspect that makes it possible to probe immunogenic response of the individual's IgE epitope(s) more precisely.

In Deak et al.'s research, they used the different Ara h2 peptide sequences known for the eight Ara h2 IgE epitopes. The peptides were synthetically made and incorporated into liposomes individually. The liposome containing one Ara h2 peptide epitope was then titrated into an individual's sera to see if that epitope was the match for their Ara h2 IgE epitope. Repeat tests with other liposomes provide the profile of Ara h2 IgE epitopes present in a person. Additionally, by using an individual's own sera the degree of mast cell degranulation also aids in measuring the severity in the reaction and the amount of the allergen needed to create the response. One of the ultimate goals for nanoallergen platform testing, similar to the basophil activation test, is to remove the need of oral food challenges as the gold standard. It, however, is one of the more recent methods being researched and remains experimental.

33.5.6 Different Forms of Immunoassays

Indirect immunoassay (ID) can be seen as an extension of the direct immunoassay with one additional step (Fig. 1). The first antibody added (now called primary antibody) does not have the enzyme tethered to it, rather a secondary antibody, which detected the primary antibody, has the enzyme linked to it (Meurant 2012). Obviously, this adds additional washing steps. The benefit is that ID allows amplification, making it easier to detect a protein even in low quantities.

Sandwich immunoassays use an antibody to coat the well of an assay to capture the allergen

of interest (Meurant 2012). Then a second antibody, to the same allergen, is added to the assay, thus "sandwiching" that allergen between two antibodies. The second antibody is normally linked to an enzyme.

Competitive immunoassays are used traditionally for measurement of small molecules such as chemical compounds (medications, toxins, hormones). A use of a competitive immunoassay is most applicable when the possibility of more than one allergenic epitope is low owing to the small size of the molecule or compound (O'Kenndy and Murphy 2017). A tracer for the analyte being measure is used. A known amount the of the analyte and tracer is initially used (Meurant 2012). The tracer itself is a combination of the analyte linked to a signal generating element, such as an enzyme. The sample containing the analyte in question competes with the known concentration of the pretreated tracer. The amount of signal produced is inversely proportional to the concentration of the analyte being introduced.

33.6 Conclusion

"In vitro allergy testing has made significant advances in the past 60 years. Much of the progress has been in the way of improved ease, reproducibility, safety, sensitivity, and specificity of detecting an allergen in question. Clinical history remains paramount for management guidance in regard to when it is safe and appropriate to offer oral food challenges or initiate environmental and venom immunotherapy. An absent or negative in vitro allergy test should not be interpreted as a zero risk of allergic reaction to a suspected allergen. A positive history with negative testing still carries a risk of an allergic reaction during oral food challenges. This risk has been reported as high as 20%.

33.7 Cross-References

- ▶ Allergic Bronchopulmonary Aspergillosis
- ▶ Allergic Rhinitis
- ▶ Allergy Skin Testing
- ▶ Asthma Phenotypes and Biomarkers
- ▶ Biologic and Emerging Therapies for Allergic Disease
- ▶ Ige Food Allergy

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Pulmonary Function, Biomarkers, and Bronchoprovocation Testing

34

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Abstract

The diagnosis and management of pulmonary disease is essential to the practice of modern clinical allergy and immunology. In addition to the history and physical examination, appropriate use of diagnostic testing augments diagnostic efforts and enhances management of a variety of common and rarer illnesses, from asthma to hypersensitivity lung disease. Physiologic testing, such as spirometry, complete lung function testing, and bronchial provocation, is often the next step after the clinical examination. Establishing (or excluding) obstructive or restrictive defects will either validate the "clinical" impression or suggest the need for further studies. The evolving understanding of asthma pathogenesis has led to development of numerous biomarkers that complement spirometry as a diagnostic tool. Noninvasive biomarkers isolated from blood, sputum, or breath enhance insights into asthma pathophysiology. These tools may be crucial to select and refine therapy, thereby optimizing and personalizing asthma treatment.

Keywords

Pulmonary function · Bronchoprovocation · Biomarkers · Asthma · COPD

34.1 Introduction

The practice of allergy and clinical immunology encompasses a wide range of disease affecting the lung. Combining pulmonary function testing modalities and biomarker assessment will assist the provider in refining the diagnosis and management of these conditions. Accordingly, the ability to understand both the physiology and also the pathophysiology of lung function in this context is a vital tool for the specialist. Learning objectives in the first and second sections of this chapter include understanding the basics of obstructive and restrictive pulmonary pathophysiology; recognition of how these conditions manifest in the pulmonary function test; recognition of the indications, strengths, and limitations for spirometry; complete lung function analysis; and bronchial provocation testing. The third section will review the science and clinical application of biomarkers, particularly as they may be applied to asthma, and how they can be used to select specific treatments.

34.2 The Pulmonary Function Test

34.2.1 Overview

Conceptually it is useful to divide lung function testing into four categories. These include, in order of complexity, spirometry, complete lung function

analysis, bronchial provocation, and exercise testing. Exercise testing, as a form of bronchial challenge, will be reviewed, but cardiorespiratory exercise testing (as a measure of ventilation and oxygen consumption) is beyond the scope of this chapter, and its application is generally beyond the purview of the practicing allergist. Spirometry may be readily performed in an ambulatory care setting, such as an allergy office, with relatively affordable and accurate equipment. Spirometry data depends upon measuring the volume and rate of airflow at the mouth. The complete pulmonary function test (PFT) which includes measurement of total lung capacity (TLC), diffusing capacity (DL,CO), and airway resistance (R_{aw}) requires more complex equipment in order to determine the residual volume (RV) (the amount of air remaining in the lung after full exhalation) and its derivatives the functional residual capacity (FRC) and total lung capacity (TLC) which will be described below in more detail. Modern PFT laboratories utilize a combination of gas diffusion and body plethysmography to determine these measures. Cost, frequency of need, and technical expertise relegate these tests often to hospital or pulmonary medicine venues, but allergists often will need to order and understand these results in the diagnosis and management of their patients; hence they are relevant to this discussion. Bronchial provocation studies will be addressed at the end of the first part of the chapter, including indications, contraindications, and interpretation.

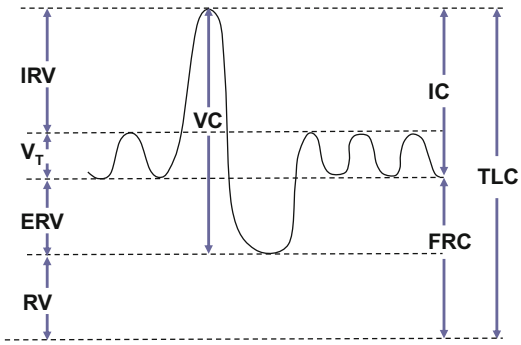


Fig. 1 Lung volumes and capacities. *ERV* expiratory reserve volume, *FRC* functional residual capacity, *IC* inspiratory capacity, *IRV* inspiratory reserve volume, *RV* residual volume, *TLC* total lung capacity, V_T tidal volume, *VC* vital capacity. (Republished with permission. John Wiley and Sons Inc. ©2006. Lung Function: Physiology, Measurement and Application in Medicine. 6th Edition. Cotes, JE, Chinn D.J Miller M.R. Permission conveyed through Copyright Clearance Center, Inc.)

34.2.2 Lung Volumes and Capacities

Conceptually and practically, it is useful to divide the lung into volumes, and these volumes, when combined, comprise "capacities." Figure 1 reveals that the TLC is the sum of all lung "compartments" or volumes (Cotes et al. 2006). The tidal volume (TV) is the amount of air inhaled or exhaled with each breath during quiet breathing and is approximately 0.5 L in a normal adult. The inspiratory reserve volume (IRV) is the additional volume inhaled after quiet inspiration (approximately 2 L). The expiratory reserve volume (ERV) is the additional volume exhaled after quiet expiration (approximately 1.2 L). The residual volume (RV) is the amount of air remaining in the lungs following maximal expiration (approximately 2 L). Capacities are as follows: TLC is the volume of gas in the lungs after maximal inspiration (RV + ERV + TV + IRV). The functional residual capacity (FRC) is the lung volume present at end-expiration during tidal breathing (RV + ERV). The vital capacity (VC) is the volume change at the mouth between full inspiration and full expiration (ERV + TV + IRV). The most clinically useful form of VC is the forced vital capacity (FVC) wherein the patient is instructed to exhale as rapidly and forcibly as possible from full inspiration (TLC) to full exhalation (RV). It may also be performed as a slow inspiratory or expiratory capacity (MacIntyre et al. 2005).

34.2.3 Specific Spirometric Tests

FEV1 is defined as the forced exhaled volume in the first second. The FEF_{25-75} is the average flow rate over the mid 50% of the FVC. It is also referred to as the MMEF or maximum mid-expiratory flow. The FEV1/FVC ratio or the FEV1% is the ratio of the volume of air exhaled

under maximal effort in the first second of the FVC maneuver divided by the FVC itself. This is a very useful indicator of obstructive disease. The PEF or PEFR is the peak expiratory flow rate, defined as the maximum flow rate generated from a forceful expiration. By convention, it is recorded in L/s in the laboratory, but handheld devices are usually expressed in L/min, so the conversion from laboratory to handheld device may be accomplished by multiplying by a factor of 60. The MVV or maximum voluntary ventilation is the maximum volume of air a subject can breathe over a specified period of time (usually 12 s) expressed as L/min. The MVV may be abnormal if there is almost any perturbation in lung function, such as restriction, obstruction, reduced effort, and certainly weakness.

34.2.4 Clinical Aspects of Spirometry

Spirometry is defined as a physiological test measuring inhaled and exhaled volumes of air as a function of time (Miller et al. 2005b). Measurements that are derived from spirometry include FVC, FEV1, PEFR, MVV, FEV1/FVC, and flow-volume loops. Any measurement dependent upon residual volume (TLC, FRC) cannot be determined by spirometry since the RV is "hidden" air trapped in the lung at the end of exhalation. Indications include diagnostic evaluations of signs or symptoms (e.g., dyspnea, wheeze), monitoring disease natural history (e.g., asthma progression, COPD, occupational impairment, response to therapy), perioperative risk assessment, prognosis, etc. The principal output is both graphic (analog) and numeric (digital). The spirometer can display volume as a function of time or flow as a function of time (flow-volume loop) (Fig. 2). Response to bronchodilator is also valuable. The American Thoracic Society and European Respiratory Society (ATS/ERS) consensus statement defines reversible obstruction as a minimal increase of *both* 200 mL and 12% in either FEV1 or FVC from baseline following administration of a bronchodilator (Pellegrino et al. 2005). Pattern recognition of the flow-volume loop is essential diagnostically as well as assisting in quality control. Standards of quality are published and are essential to insure that misinterpretation due to poor quality does not occur (Miller et al. 2005b). That being said, spirometry is of great value in determining obstructive disease, but the diagnosis of restrictive pulmonary dysfunction is dependent upon a precise TLC, which must involve assessment of the RV (and FRC) only available in complete lung function testing.

34.2.5 Complete PFT Components

Recall that the TLC determination is dependent upon measuring the RV. In order to measure the air remaining within the lung after complete exhalation, indirect methodologies must be employed. Since FRC contains both the ERV and the RV, the FRC and RV will be explored next. Gas dilution (helium), nitrogen washout, and plethysmography will be briefly reviewed. Helium dilution allows for determination of the FRC as follows. The PFT device is of known volume, and the concentration of helium in the machine at outset is known. The patient then breathes the gas mixture from the machine, and when the mixture comes to new equilibrium (helium will be diluted into the new volume including the patient lung) with the patient and the machine combined, the second helium concentration is measured. Thus, with concentrations 1 and 2 and volume 1 (machine) known, one can solve for volume 2 (patient + machine) and by subtraction determine the patient's lung volume ($V1 \times C1 = V2 \times C2$). Nitrogen washout methods depend on inhalation of 100% oxygen and measuring nitrogen concentrations as nitrogen is "washed out" of the lung. This allows inferences about lung volumes. Both the nitrogen washout and helium dilution methods are subject to error especially in obstructive lung diseases. This is primarily the case when the, e.g., helium cannot readily diffuse into poorly or non-ventilated areas of the lung (due to obstruction, small airway

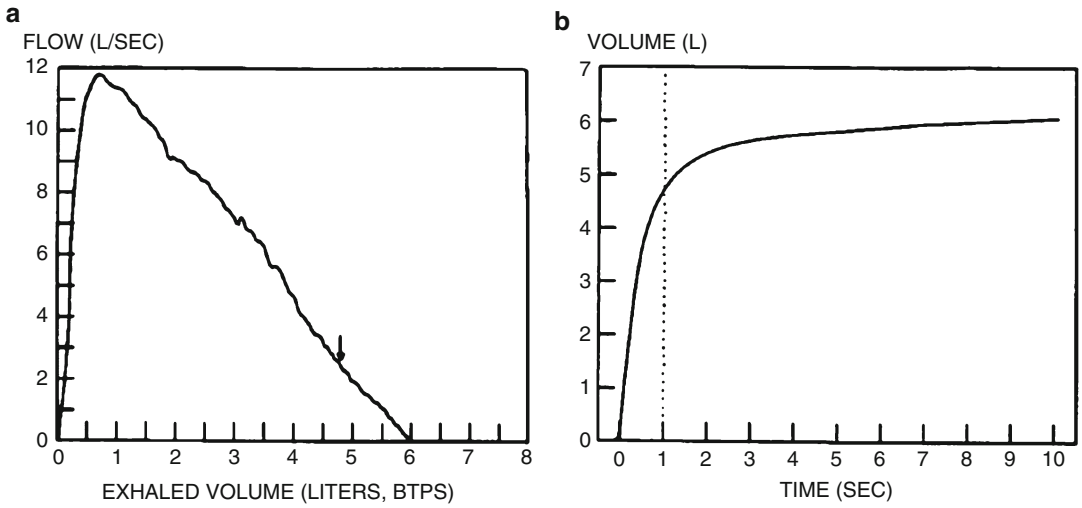
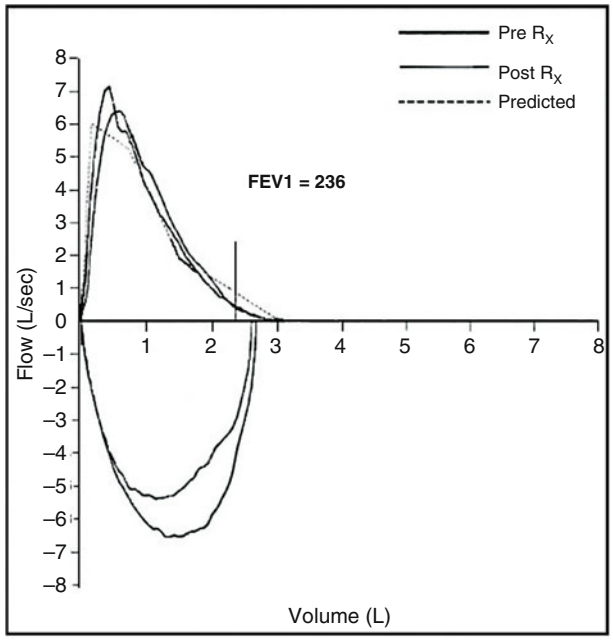


Fig. 2 Spirometry generates a flow volume loop (**a**). Flow is represented in L/s on the y-axis, with lung volume represented on the x-axis. TLC is at 0 and residual volume at 6. The same data is simultaneously depicted in **b**, where the output is in volume (y-axis) plotted against time on the x-axis. Note only the exhalation portion of the respiratory cycle is shown. Note the normal contour of the flow volume tracing with a very steep rise in flow rate, and a linear or fixed maximal flow rate through full exhalation. The arrow in **a** depicts 1 s duration, similarly shown as a dashed vertical line in **b**. The area under the curve in **a** reflects actual volume

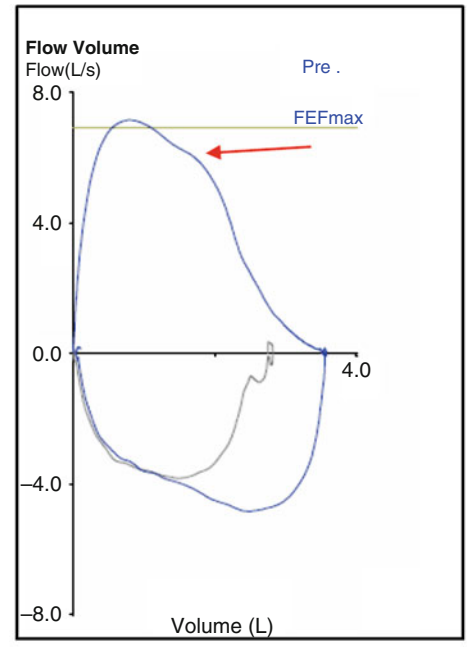
closure, bullae/blebs). As a result, the gas is diluted less than what reflects the "true" lung volume so lung volumes (TLC, FRC, and RV) are underestimated. Fortunately, body plethysmography is not subject to that limitation. When lung volumes are obtained by plethysmography, the designation FRC_{pleth} is used in the report. The plethysmograph utilizes Boyle's Law, which allows one to calculate volume based on changes in pressure during the respiratory maneuvers. Complete descriptions of this are readily available but beyond the scope of this discussion (Cotes et al. 2006; Wanger et al. 2005). Measurements from the plethysmograph also include specific conductance (SG_{aw}) the inverse of which is SR_{aw}, or specific airway resistance, which is a very sensitive measurement of airway obstruction. The diffusing capacity (DL, CO) is the measurement of carbon monoxide uptake in the lung. It reflects the capacity of the lung to exchange gas between the alveolus and the capillary. DL,CO may be increased or decreased in disease. Factors decreasing DL,CO include reduction in lung inflation (effort, weakness, deformity), anemia, pulmonary emboli, carboxyhemoglobin pretest, lung resection, emphysema, interstitial lung disease, pulmonary edema, vasculitis, and pulmonary hypertension. Conditions increasing DL,CO include polycythemia, left-right intracardiac shunts, pulmonary hemorrhage, and asthma (due to decreased intrathoracic pressure from Muller maneuver). Corrections in the laboratory for hemoglobin concentration and ventilation are performed to allow for more precise reflection of the lung's ability to absorb CO. This allows for inferences about gas exchange in disease states (Wanger et al. 2005).

34.2.6 The Flow-Volume Loop

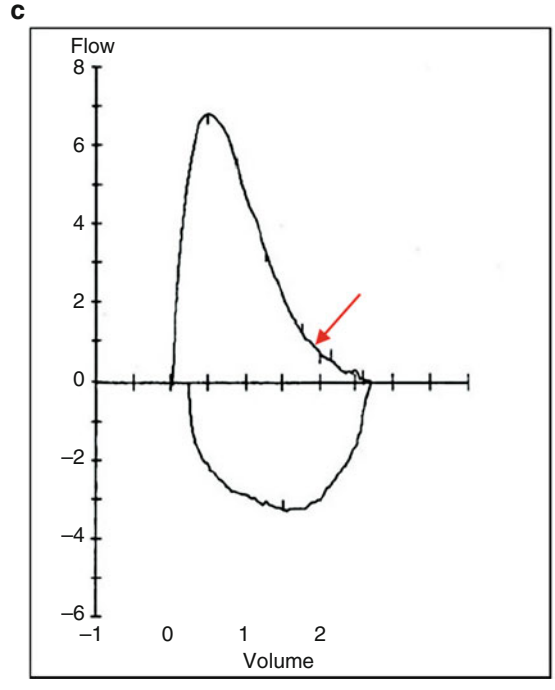
In addition to numeric readouts of the various tests described above, spirometry (or the complete PFT) will generate a flow-volume loop. As the name indicates, the readout plots inspiratory and expiratory flow on the vertical axis against lung volume on the horizontal axis. One of the valuable aspects of the flow-volume loop is that it affords the ability to do "pattern recognition." Restrictive, obstructive, or mixed defects have distinct shapes, and also technical errors may be readily identified.



Normal with no bronchodilator response



Normal with 'shoulder' high flows



Normal low flow at terminus in elderly

Fig. 3 (continued)

In Fig. 3, one sees the normal-shaped expiratory loop which is above the horizontal axis, and inspiration is below the axis. Note the "shark-fin" shape of the normal expiratory loop, reflecting a very rapid rise in flow from 0 at TLC to peak expiratory flow, after which the slope is relatively straight, during exhalation. Normal variants can include slight flattening or a "shoulder" early in exhalation, particularly seen in young healthy subjects. In normative aging, due to loss of elastic recoil and tethering by the lung itself, there can be some inward concavity at the very end of the loop.

34.2.7 Overview of Obstructive and Restrictive Pulmonary Disease

Obstructive lung disease is described in the 2005 ATS/ERS task force on standardization of lung function testing as follows: "An obstructive ventilatory defect is a disproportionate reduction of maximal airflow from the lung in relation to the maximal volume that can be displaced from the lung. It implies airway narrowing during exhalation and is defined by a reduced FEV1/VC ratio below the 5th percentile of the predicted value" (Pellegrino et al. 2005). A more functional description would be to state that obstructive disease manifests in a reduced flow rate during exhalation which then results in less volume of air being exhaled, for example, in the first second of exhalation relative to the entire (forced) vital capacity. Hence, the FEV1/FVC would be reduced due to the numerator being relatively lower than the denominator. These types of changes result in a concavity to the expiratory flow-volume loop (Fig. 4) reflecting reduced flow rates relative to normal. These reduced flow rates in obstructive disease can be seen to reflect differential rates of flow and lung emptying regionally. Thus from collapse, mucus plugging, airway narrowing, and loss of tethering, some airways will take longer to fully empty. One can observe very low flow and long expiratory cycles in COPD, for example. During an FVC maneuver, forcible exhalation may further exacerbate this phenomenon, and intrathoracic pressure delivered to the external portion of the airway further compresses it, such that when the compressive pressures begin to exceed the pressures within the airway, flow declines and then ceases. Often the flow rates diminish earlier in disease (COPD, asthma) along the mid and terminal portions of the expiratory loop, even prior to FEV1 reductions, but the FEF_{25-75} lacks good reproducibility and thus is not useful in defining severity or presence of obstructive diseases. Typical flow-volume loops in COPD and asthma are depicted in Fig. 4. Less common but important patterns of obstruction include variable and fixed intrathoracic obstruction (Miller and Hyatt 1973). These patterns are depicted in Fig. 5. Fixed intrathoracic obstruction (Fig. 5a) may be seen when there is compression of the central intrathoracic trachea, such as tumor compression just proximal to the carina. Flow rates are impaired on both inhalation and exhalation. Variable obstruction may be "extra-thoracic" which may occur in vocal cord dysfunction (Mikita and Mikita 2006), as well as other circumstances (Fig. 5b). Note here how the exhalation loop is preserved but the inspiratory loop is flattened reflecting paradoxical vocal cord adduction during inhalation, hence increasing inspiratory airway resistance and reduced flow rates (Pellegrino et al. 2005). Variable intrathoracic obstruction may occur if during inhalation the airway collapses/narrows during exhalation. A clinical example of this would be relapsing polychondritis. During exhalation, the pressure external to the trachea

Fig. 3 Panel **a** depicts good reproducibility in expiratory flow loops. Dashed line reflects reference normal. The solid lines reflect pre- and post-albuterol. There is no bronchodilator response. Panel **b** is a normal variant, often seen in young patients, where there is a "shoulder" of very high flow rates (arrow) then the slope increases to residual volume. Panel **c** demonstrates attenuation of flow rates near residual volume (arrow) due to normative aging and loss of tethering and elastic recoil

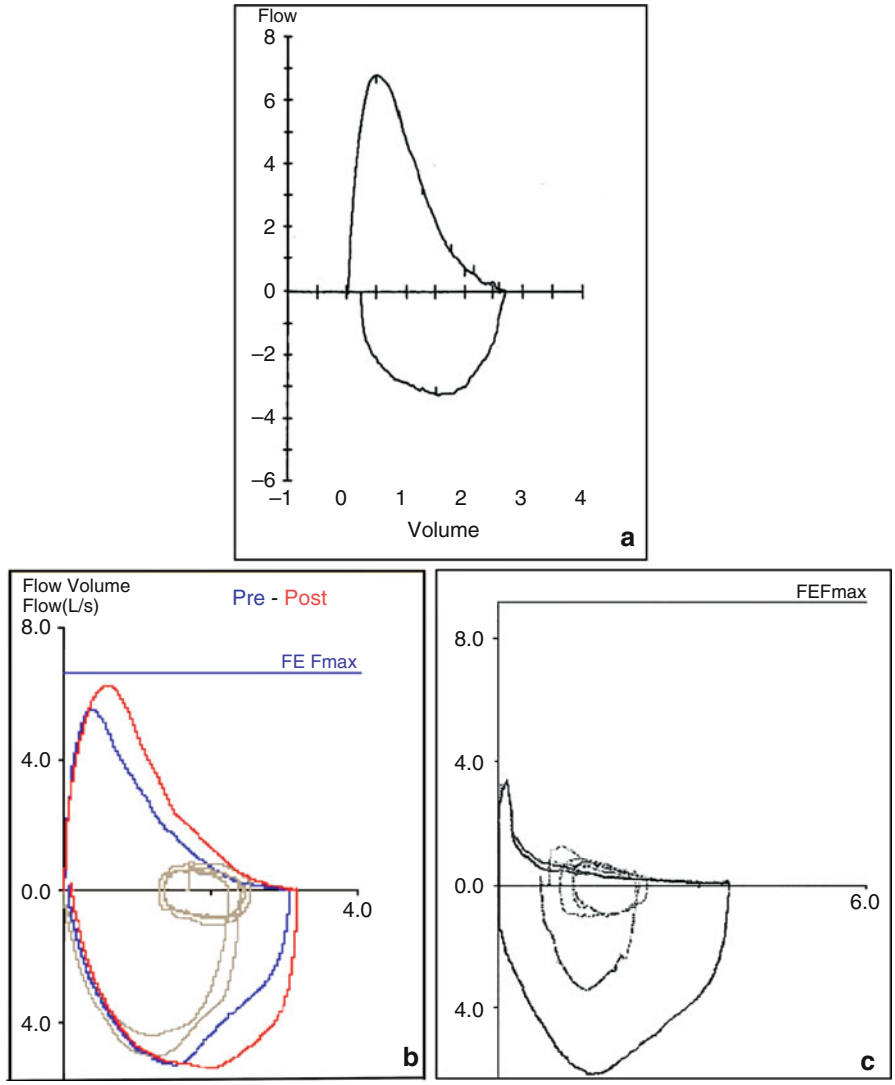


Fig. 4 Patterns of obstructive lung disease. Panel **a** depicts a normal expiratory loop with reduced terminal flows seen as a function of lost tethering/recoil with aging. Panel **b** reveals moderate obstruction with post-albuterol partial reversibility. Note preservation of flow on inspiratory loop (below the x-axis). Panel **c** depicts severe obstruction in COPD. Peak flows are impaired as are all flow rates in exhalation. The loop is very concave. There is minimal reversibility. Note also that the FVC maneuver results in dynamic compression of the smaller airways and flows are actually lower than during tidal breathing seen as the smaller central loops

exceeds that within the trachea, worsened during forcible exhalation, and the no-longer rigid trachea is compressed making airflow worse during exhalation (Kapnadak and Kreit 2013; Miller and Hyatt 1973).

Restrictive lung disease is defined as a reduction in the TLC below the 5th percentile of predicted value (based on reference group) in the presence of a normal FEV1/VC (Pellegrino et al. 2005). Spirometry alone is not sufficient to establish a diagnosis of restriction because a reduced VC may be the result of a submaximal effort (which might be difficult to detect). Note that the classic pattern of true restriction on spirometry is a

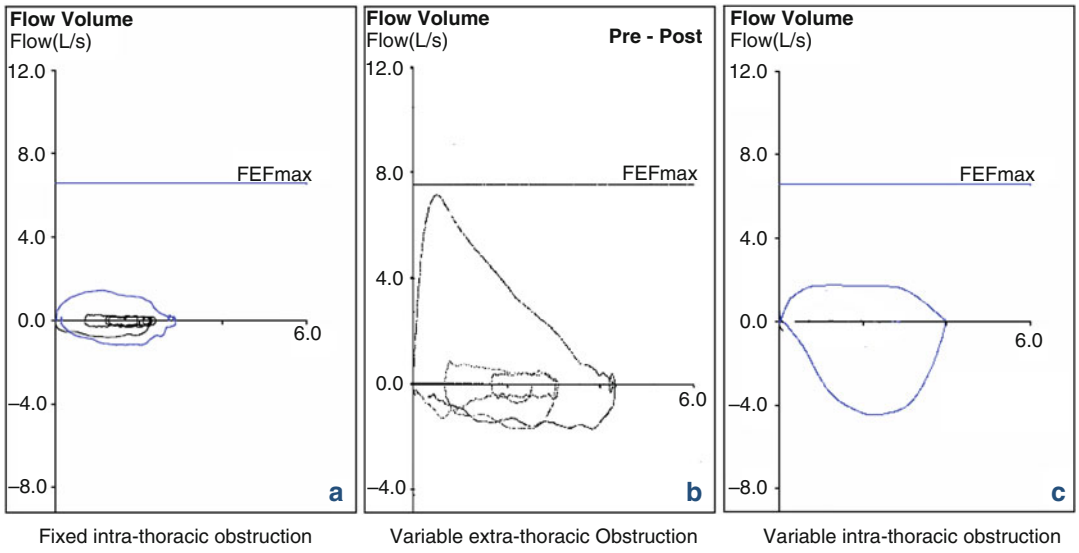


Fig. 5 Panel **a** depicts a fixed intra-thoracic obstruction from malignant tumor and lymph node compression of the trachea just proximal to the carina. Note the severely reduced inspiratory and expiratory flows. Panel **b** demonstrates variable extra-thoracic obstruction, in this case secondary to vocal cord dysfunction. Note the preserved expiratory flow pattern with impaired inspiratory flows secondary to partial adduction of the vocal cords during inspiration. Panel **c** represents variable intra-thoracic obstruction

low VC relative to FEV1; hence the FEV1/VC ratio may be normal or >85–90. In addition, the flow-volume loop is convex, rather than concave in shape, or has more of a vertical ellipse-type pattern (Fig. 6). This convexity may be explained by the fact that due to the stiffer lung (parenchyma, pleura, or chest wall), there is a tendency for recoil pressures to generate higher emptying flow rates relative to a given lung volume than normal or obstructed patients' lungs. Hence, the TLC is the most reliable measure of restrictive disease and, when combined with the described spirometric data, is reliable. In addition, the presence or absence of reduced DL,CO indicates if the lung parenchyma are the cause. So restrictive disease may be "intraparenchymal" due to a diseased lung itself, such as with interstitial diseases (sarcoidosis, hypersensitivity pneumonitis, fibrosing alveolitis), or due to "extra-parenchymal" processes. Restrictive disease is associated with reduced lung compliance or increase stiffness of the lung, defined as reduced change in volume relative to change in pressure ($\Delta V/\Delta P$). Stated more intuitively, it takes a greater change in pressure to generate a given change in volume in a stiff or restricted lung relative to a normal. From a clinical perspective, it is useful to subdivide the reduced lung volume entities into alteration in lung parenchyma (low DL,CO) or "extra-

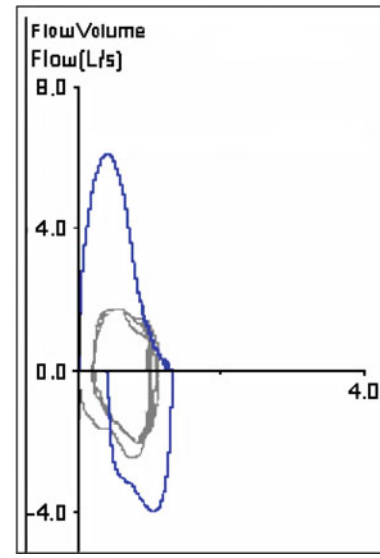


Fig. 6 Restrictive pulmonary flow pattern. Note the vertical elliptical shape of the loop and the low volume on the x-axis

parenchymal" disorders such as disease of the pleura, chest wall, or neuromuscular apparatus. Examples of extra-parenchymal disease include skeletal (kyphoscoliosis), pleural (pleural effusion, mesothelioma, pleural fibrosis), or neuromuscular impairment such as seen in diaphragmatic paralysis, myasthenia gravis, or Guillain-Barre. Pleural effusion causes restriction by extrinsically compressing the lung, even when the parenchyma itself is not primarily diseased. If the lung cannot inflate, a restrictive physiologic insult occurs. In the presence of a mesothelioma, the pleura is thickened and becomes inelastic. The lung then becomes encased in a restrictive envelope. When neuromuscular weakness is suspected, the patient may be asked to generate a maximal inspiratory and expiratory effort on a pressure-sensing device. This will generate a negative inspiratory pressure (NIF) and positive expiratory pressure (PIF). If these are impaired, it supports a neuromuscular etiology. A summary diagnostic algorithm (modified here with permission) from the European Respiratory Society has been published to assist in navigating this diagnostic path (Pellegrino et al. 2005) (Fig. 7).

Because some conditions are associated with both restriction and obstruction, there may be "mixed" data generated. For example, the FEV1/FVC may be reduced in the face of a low TLC. In obstruction, particularly more severe cases, there is air trapping so the TLC should be increased. When the opposite occurs, a "mixed" defect is diagnosed (i.e., the FEV1/VC and TLC are both <5th percentile predicted) (Fig. 7). Clinical examples of mixed defects include sarcoidosis and hypersensitivity pneumonitis. In these conditions, the interstitium becomes inflamed and may then enter a fibrotic phase with reduced DL,CO and reduced compliance. Obstruction may occur due to bronchiolitis, and narrowing/obstruction, particularly in the smaller airways, and in some cases the lung may take on a "Swiss-cheese" or mosaic appearance on CT scanning, with many blebs intermixed with increased density parenchyma.

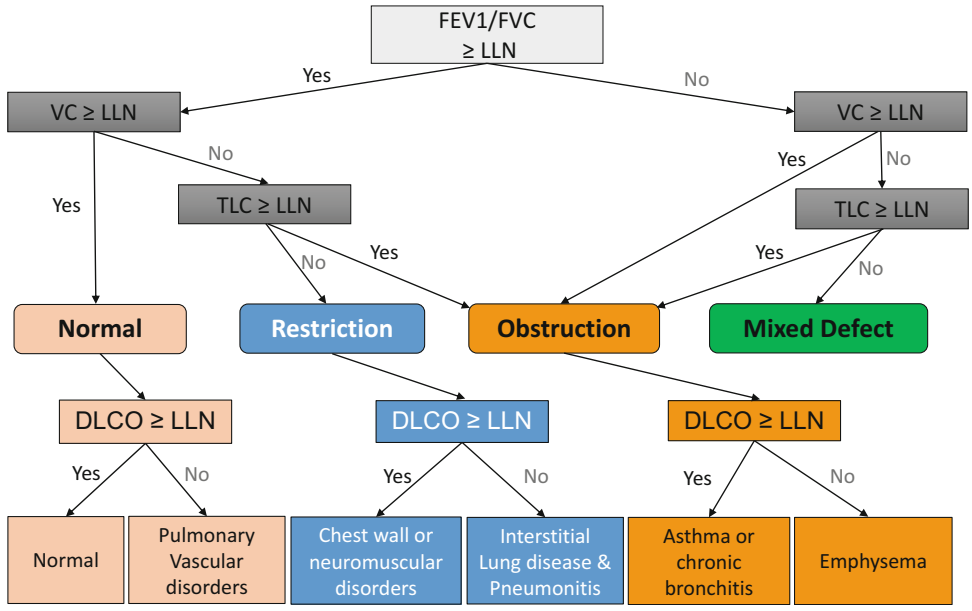


Fig. 7 An interpretation algorithm for Pulmonary Function Testing. *FEV1* forced expiratory volume in 1 s, *VC* vital capacity, *LLN* lower limit of normal, *TLC* total lung capacity, *DLCO* diffusing capacity. (Reproduced (in modified form) with permission from the ©ERS 2005. European Respiratory Journal Nov 2005, 26(5): 948–968; https://doi.org/10.1183/09031936.05.000 35205)

34.2.8 Quality Control Essentials in Spirometry

Because spirometry is so often utilized in the care of allergy patients, the approach to insuring a good-quality study is worth reviewing. Quality assurance (QA) begins with the recognition that there are both instrumentation and also patient-derived considerations. Three concepts must be integrated into the quality process. These are *accuracy* (closeness of agreement between the result of a measurement and the true value), *repeatability* (closeness of agreement between the results of successive measurements), and *reproducibility* (closeness of results of successive measurements but not under identical conditions). Accuracy for VC, for example, would be determined by comparing the volume readout to a known volume delivered from a large-volume calibration syringe. Repeatability would be determined by comparing a PFT under identical circumstances – repeating a test within a short time frame, for the same patient, technician, and equipment. Reproducibility of a test might allow for changed conditions such as the method, or equipment, or technician (Miller et al. 2005a). There are clinical considerations as well. Contraindications to spirometry (or a full PFT) would include chest or abdominal pain, oral or facial deformity or pain making use of a mouthpiece uncomfortable or impossible (lack of tight seal), stress incontinence, or altered mental states such as dementia or confusion, recent (1 month of) myocardial infarction, and unstable aortic aneurysm (Miller et al. 2005a). Current convention is to perform these tests in a sitting position (although standing can be done). Not only does this avoid the issue of position affecting reproducibility, but patients may become dizzy or syncopal during hyperventilation or valsalva-inducing maneuvers (such as MVV or FVC). Reference ranges depend upon age, height, weight, gender, and ethnicity, so it must be recorded/entered into the PFT device, which has programmed nomograms. Bronchodilator type/route of delivery (meter dose inhaler or nebulizer) should be recorded or whether the patient used these prior to the test. Temperature and barometric pressure are important and may be measured by the instrument. Infection control and other technical issues are discussed in more detail in the ATS/ERS combined standards publications (Miller et al. 2005a). Reference ranges are very important to appropriate interpretation of test results. Comprehensive lists of reference range citations are available (Pellegrino et al. 2005). In the United States, the NHANES III (National Health and Nutrition Examination Survey) provides reference ranges for ages 8–80 years (Pellegrino et al. 2005; Hankinson et al. 1999). Similarly for pediatric patients under 8 years of age, equations of Wang et al. are usually recommended (Wang et al. 1993; Pellegrino et al. 2005).

As stated above, the responsibility of insuring good data cannot be taken lightly, and thus the process of instrument calibration, infection control, and then test performance must all be continuously practiced. Taken as a whole process, stages include equipment validation, quality control, subject/patent maneuvers, measurement procedures, acceptability, reproducibility, reference value interpretation, and then clinical assessment. There are many publications on this, including the American Thoracic Society (ATS) official statement (re)issued in 1994, which is comprehensive (Crapo 1995). The most recent, and definitive, update is contained in the ATS/ERS task force publications of 2005 (Miller et al. 2005b). Knowledge of issues of calibration, sensitivity to ambient temperature, and humidity are important. Some spirometers measure volume, while many office-based units utilize a pneumotachometer device, which employs a "grid" which senses flow and converts this to volume. Attention to testing conditions, and manufacturer's specifications, and these guidelines will allow the provider to insure generation of accurate and reproducible data (Crapo 1995).

Patient maneuvers are crucial and require skill in real-time assessment by the person performing the test and then during interpretation (Tables 1 and 2) (Miller et al. 2005b). A variety of common technical errors are demonstrated (Fig. 8). Insufficient inhalation prior to the FVC maneuver, visible in the flow-volume loop as a shallow or poor inspiratory curve (below the x-axis)

Table 1 ATS/ERS criteria for single spirometry maneuvers

Satisfactory start (EV[a] <5% of maneuver or <0.15 L)
Absence of cough in first second of exhalation
No early termination of the VC
Minimum 6-s exhalation time
No valsalva/glottis closure
No air leak at mouthpiece
No extra breath

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[a]*EV* extrapolated volume

Table 2 ATS/ERS criteria for between-maneuver acceptability criteria

After three acceptable spirograms (do not exceed four attempts)
Two largest values of FVC within 0.150 L of each other
Two largest values of FEV1 within 0.150 L of each other
Two (of three) largest PEF values reproducible within 0.67 L/s (up to five PF attempts). Select best of three
MVV should be 12-s duration with TV ~50% of VC, breathing rate 90 breaths/min

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(Fig. 8a), causes a low FVC and likely low FEV1 and a "pseudo-restrictive pattern." Hesitation (Fig. 8b) can reduce the FEV1 and possibly the FEF_{25-75}. Early termination would reduce the FVC, and hence increase the FEV1FVC %, possibly masking obstruction (Fig. 8c). This reflects the need for a minimum of 6-s exhalation time. Figure 8d demonstrates inconsistent/non-reproducible flows which, if not compared, would lead to spurious results. Mouthpiece obstruction, from tongue protrusion, causes a completely flattened peak flow shelf after an initial rise in peak flow (not shown). Figure 8e demonstrates non-reproducible FVCs. Figure 8f shows a "sawtooth" pattern of coughing. An additional common disqualifying problem includes a submaximal effort often typified by a low peak flow and rounded exhalation loop. Coughing can result in secondary inhalation, hence affecting volume and flow, and submaximal effort will markedly reduce peak flow as well as FEV1.

34.2.9 Pulmonary Function in Specific Clinical Contexts

Asthma and smoking-related conditions account for the majority of obstructive lung diseases which will present to the primary care or allergy provider. In 2010, the prevalence in the United States of cigarette smoking was 19.3% of adults, and asthma prevalence in 2009 was estimated at 8.2% (24.6 million) for all ages (Sands 2014). Smoking in US asthmatics is generally estimated to be similar to non-asthmatic populations (Eisner et al. 2001). It is important to also recognize that of COPD patients about 10–20% are estimated to have ACOS (asthma-COPD overlap syndrome) (Barrecheguren et al. 2015). ACOS is recently defined as persistent airflow limitation with several features usually associated with asthma and several features associated with COPD. In the clinical arena, a COPD patient may demonstrate enhanced airway obstructive reversibility, or an asthmatic patient with smoking history developing only partially reversible airway obstruction (Barrecheguren et al. 2015). The pulmonary function test cannot fully differentiate these conditions, but it allows clinical inferences which are important. In the absence of tobacco smoke exposure, the demonstration of a 12% and 200 mL increase in FEV1 *or* FVC from baseline following the administration of a bronchodilator (such as albuterol or ipratropium) meets the ATS/ERS definition of reversible obstruction and would be consistent with a diagnosis of asthma, recognizing that the clinical context is critical (Pellegrino et al. 2005). Pretest abstinence from short-acting bronchodilators for 4 h and long-acting bronchodilators (such as formoterol or salmeterol) for at least 12–24 h and tobacco use (24 h) is necessary to avoid confounding test utility (Miller et al. 2005b). It is also important to recognize that incremental changes in FEV1 or FVC of 8% or <150 mL may be within the variability of the test itself, so these criteria are helpful in avoiding a threshold which is too low, which

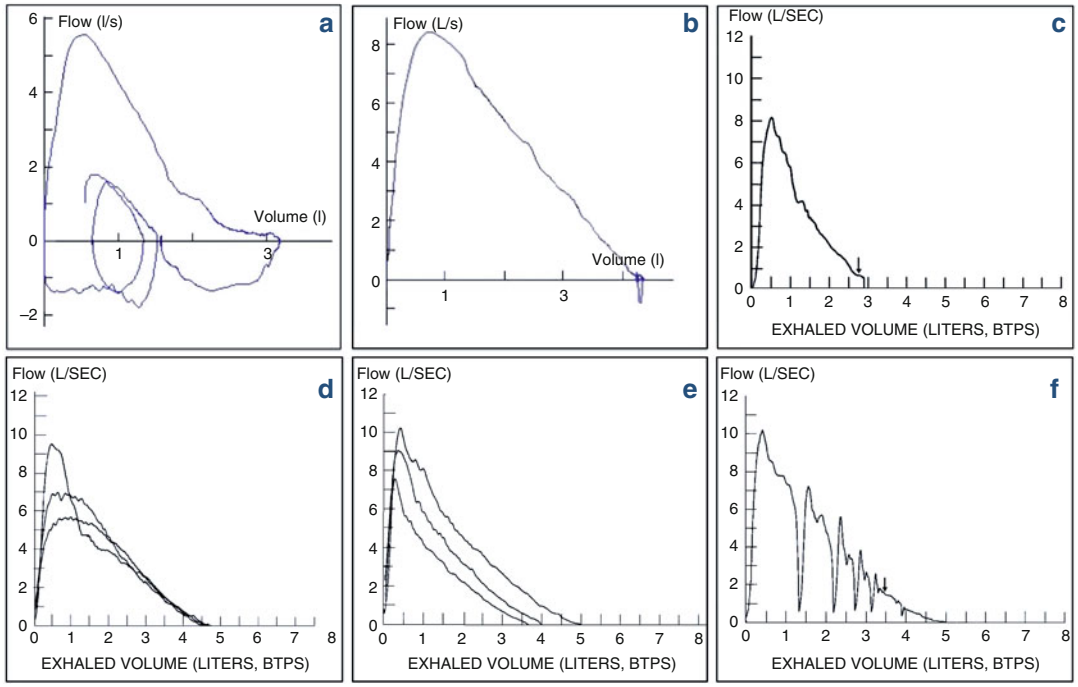

Fig. 8 Panel **a**, insufficient inhalation; Panel **b**, Hesitant start (note slow rise in peak flow rate); Panel **c**, Early termination; Panel **d**, Nonreproducible peak flows; Panel **e**; Nonreproducible FVC; Panel **f**, Cough

might yield false-positive results. The FEV1/FVC ratio is problematic. The use of a 0.70 lower limit of normal for this ratio (as an indicator of obstruction) has fallen somewhat into disfavor due to false positives on males >40 years or females >50 years of age (Miller et al. 2005b; Pellegrino et al. 2005). Furthermore, when examining the bronchodilator response, or lack thereof, this index is not useful as both the FEV1 and FVC may increase substantially after bronchodilator; hence the ratio may not be substantively altered during the test. This has led to a more narrow recommendation for interpretation by ATS/ERS (Pellegrino et al. 2005). It is also important to recognize that the absence of a bronchodilator response does not exclude the diagnosis of asthma, which may be variable in presentation. Additionally, the natural history of asthma, even in the absence of tobacco smoke or other noxious exposures, may lead to an advanced rate of decline in lung function (e.g., FEV1) over time. This is attributed to airway remodeling, including subepithelial fibrosis and smooth muscle hypertrophy. Improved endotyping, in the future, will offer more insight into individual variability of remodeling (Lange et al. 1998; Pascual and Peters 2005).

34.2.10 Severity Ranking

Severity of obstruction by convention is somewhat arbitrary, but it does correlate to prognosis and survival. The FEV1 definitions of severity (as % predicted) are as follows: mild >70, moderate 60–69, moderately severe 50–59, severe 35–49, and very severe <35 (Pellegrino et al. 2005). The FEF_{25-75} may decline in obstructive lung disease earlier than the FEV1 and during methacholine (Mch) challenge may decline sooner and by larger percentages than the FEV1, but due to a high degree of variability, including dependence upon a consistent FVC, effort over the mid-exhalation portion of the FVC maneuver, and hesitation or delays in commencing the FVC, it lacks utility in terms of defining a bronchodilator response (Pellegrino et al. 2005). The degree

of severity in DL,CO impairment is divided into mild (>60% and <lower limit normal), moderate (40–60%), and severe (<40%). Adjusting the DL,CO for lung volume is controversial. Adjustment for Hb concentration is mandatory.

34.2.11 Summary of the PFT Interpretation Process

When commencing the formal interpretation of a PFT, it is important to follow a stereotypic approach, in order to avoid errors of commission or omission. It is not dissimilar to the concept of interpreting a radiograph, where one needs to avoid looking initially at an abnormality while missing critical information in the periphery. Upon inspection of the demographic data and assurance the correct ethnicity, gender, age, height, etc. were entered, review the flow-volume loop(s). The check list (Tables 1 and 2) for technical adequacy must be completed. Determine if there is a discrete pattern to the flow-volume loop, such as obstruction, or restriction, or a subset of these disorders (such as variable extra-thoracic). Next review the spirogram. Look at the FEV1 and the percent predicted, and do the same for FVC. Examine the FEV1/FVC (or FEV1/VC) to determine if there is overt evidence of obstruction or restriction (<70 or >85). Compare this to the loop for pattern recognition and internal consistency. If the FEV1 is disproportionately reduced relative to the FVC or VC and the loop looks concave (reduced flow rates on exhalation), then the likelihood of obstruction is very high. If both are reduced, proportionately, or the VC is normal or low, consider restriction and move to TLC values. If the TLC is less than the lower limit of normal, there is a restrictive defect. In the presence of restriction, the DL,CO differentiates intrinsic from extra-parenchymal etiologies. A low DL,CO indicates interstitial lung disease or pneumonitis. If there is an obstructive spirometric pattern, a low DL,CO suggests emphysema due to loss of cross-sectional alveolar area. This would not be seen in asthma where the DL,CO is preserved (or occasionally increased if high intrathoracic pressure results in augmented lung blood volume). In the event there is chronic bronchitis without emphysema, the DL,CO would be normal. If the spirometry and TLC are normal, but the DL,CO is abnormal, insure that anemia is excluded (Hb correction). If this is excluded, then pulmonary vascular diseases such a pulmonary emboli or other obliterative processes are in the differential diagnosis, as well as early interstitial disease (Pellegrino et al. 2005) (Fig. 7). Disorders with both low TLC and low FEV1/FVC are deemed mixed defects. Examples of a mixed defect include hypersensitivity pneumonitis or allergic bronchopulmonary aspergillosis, in more advanced stages, which may be mixed processes reflecting a fibrotic response to inflammation, and admixture of airway and interstitial injury. Thus, in the diagnostic armamentarium, one may use simple spirometry to rule in obstructive disease, document reversibility, and then with additional lung volume and DL,CO measurements (complete PFT) diagnose parenchymal (emphysema) obstructive disease, restrictive or mixed disease, while differentiating parenchymal from non-parenchymal causes of low lung volumes. If the diagnosis of asthma is suspected and spirometry is normal, additional testing such as bronchial challenge would need to be considered. In the next section, the types of bronchial provocation will be reviewed and placed into clinical context.

34.3 Bronchial Challenge Tests (Bronchoprovocation)

34.3.1 Introduction

Bronchial challenge testing is a method of determining airway reactivity or airway hyperresponsiveness (AHR). The clinical context for needing to determine this is that asthma is characterized by AHR. It is important to recognize that there is a spectrum of AHR, and AHR itself is not synonymous with asthma. Other conditions other than asthma result in AHR, including COPD, patients with allergic rhinitis, cystic fibrosis (CF), and even normal patients with sequelae from recent respiratory infection. The primary purpose of developing and applying these tests is

to improve the ability to exclude the diagnosis of asthma or to confirm it when clinical findings and standard spirometry do not explain compatible, active symptoms. The types of bronchial challenges will be reviewed, along with indications and contraindications and interpretation of test results (Crapo et al. 2000).

Bronchial challenge (or provocation) tests are divided conceptually into either *nonselective* or *selective* categories. The nonselective group is divided into direct or indirect. A *direct* stimulus acts *directly* upon airway smooth muscle. An *indirect* stimulus i*nduces* bronchoconstriction by intermediate pathways. Direct stimuli include methacholine and histamine, as they work directly on muscle receptors (muscarinic) (Hargreave et al. 1981; Cockcroft and Davis 2009). Indirect stimuli include exercise, cold air, eucapnic hyperventilation, adenosine monophosphate (AMP), hypertonic saline, and mannitol (Cockcroft and Davis 2009; Barrecheguren et al. 2015; Covar 2007). Selective stimuli are divided into immunologic (such as allergens or low molecular weight sensitizers) or non-immunologic (including aspirin or NSAIDs).

Direct stimuli (which include methacholine (Mch) as well as histamine, prostaglandins, and leukotrienes) act directly upon the bronchial smooth muscle to induce contraction. In clinical use, histamine has been supplanted by methacholine, which is in general use worldwide and has been for over 30 years. Methacholine has an extremely high sensitivity and negative predictive value, so if a patient has *active* respiratory symptoms, consistent with asthma and a negative test, the probability of the patient having asthma is very low. Thus it is good for ruling out asthma. However, there are false positives, because allergic rhinitis, COPD, cystic fibrosis, and even recent rhinovirus infection are all associated with enhanced AHR, even in the absence of clinical asthma. One exception is that it is not good at excluding exercise-induced asthma (Joos et al. 2003). Indirect tests, such as mannitol (currently not available in the United States), are more specific but are less sensitive. Thus a positive test helps to rule in asthma (Cockcroft and Davis 2009).

Indirect challenges, including mannitol, exercise, eucapnic voluntary hyperpnea (EVH), cold air, distilled water, hypertonic saline, and adenosine monophosphate, induce constriction through mediator release which then induces bronchoconstriction (Joos et al. 2003). Both exercise and EVH dry the airway, causing a hyperosmolar stimulus, inducing mediator release. Hypertonic saline and mannitol also induce a hyperosmolar airway trigger. Adenosine is a non-osmotic stimulus (Cockcroft and Davis 2009; Joos et al. 2003). Indirect challenges may correlate with airway inflammation, by virtue of the dependence upon inflammatory cell infiltrates to modulate the mediator release. They have a theoretical advantage in terms of specificity for this reason. They may be better able to discriminate between COPD and asthma accordingly. Exercise challenge is very specific for exercise-induced asthma (Cockcroft and Davis 2009) as well.

34.3.2 Clinical Contexts and Specifics of Challenges: *Direct Challenges*

34.3.2.1 Methacholine Challenge

Indications for the methacholine challenge test (MCT) include clarification of the diagnosis of asthma when there is clinical doubt, but symptoms are present despite normal spirometry. It may be used to quantify the severity of AHR, for meeting military service requirements, or for SCUBA certification eligibility (Crapo et al. 2000). The test is best interpreted when the diagnosis of asthma is suspected and spirometry pre-/post-bronchodilator is nondiagnostic. Relevant symptoms include wheeze, dyspnea, chest tightness, and cough, particularly in the context of known asthma triggers such as cold air exposure, post-exercise symptoms, respiratory infectious exacerbation of above symptoms (wait 4–6 weeks after infection to avoid false positives), or allergen-induced asthma-like symptoms. It may also be utilized in the context of occupational asthma to confirm AHR, used serially to identify possible sensitizer exposure, or serial measures to determine adequacy of environmental controls or long-term impairment (Cartier et al. 1989;

Crapo et al. 2000). It is equally important to recognize the following contraindications for Mch challenge, including severe airflow impairment (FEV1 < 50% predicted or <1.0 L), myocardial infarction within 3 months, uncontrolled hypertension (>200/100), any condition resulting in increased intracranial pressure from an FEV1 effort, recent eye surgery, or aortic aneurysm (Coates et al. 2017). Relative contraindications include FEV1 < 60% predicted or 1.5 L, inability to perform acceptable quality spirometry, pregnancy, or breastfeeding and current use of a cholinesterase inhibitor for treatment of myasthenia gravis (Crapo et al. 2000).

The selection of prior test methodologies has been well described (Cockcroft and Davis 2009; Crapo et al. 2000) but was very recently updated in an ERS statement paper (Coates et al. 2017). This very significant publication resolves several long-standing issues related to the method of methacholine delivery, and test interpretation is discussed below. Because transitioning to the new guidelines may not be immediate, and clinical care has depended upon historical testing, a review of old and current methodologies is timely. Two general methods have been in use. The dosimeter method, wherein increasing doses of methacholine are administered via a nebulizer driven by a dosimeter, generates a short, timed burst of pressurized air, nebulizing a known quantity of Mch, repeated five times, followed by a spirometry. Thus a known volume multiplied by a known concentration delivers an inhaled "dose." This generates a provocative dose (PD). The other method is the tidal breathing method. No dosimeter is used, but a quiet breathing maneuver via mask is performed for sequentially increasing doses. These methods have been compared, and the major differences in response between methods were found primarily for those with milder AHR. The deep breath from the dosimeter method resulted in some reflex bronchodilation, blunting the fall in FEV1 during the next maneuver, hence shifting the PD_{20} to the "right" of the dose-response curve or increasing the PD_{20}. This made the test less sensitive, possibly resulting in a false-negative challenge. This confounder can be minimized when during the dosimeter breath, a maximal inhalation is avoided (reducing a neurogenic bronchodilator effect which blunts constriction) (Cockcroft and Davis 2006; Cockcroft 2014; Coates et al. 2017). Test interpretation based upon tidal breathing was based upon an estimated methacholine dose expressed as the PC_{20} which is the provocative concentration at which a 20% decrease in FEV1 from baseline at test onset was achieved. Potential errors in this method resulted from variable output of the nebulizer over the 2-min dosing cycles and difficulty correlating a "concentration" to an actual delivered dose. The readout (y-axis) is FEV1 plotted against the log of the Mch dose (x-axis) (Fig. 9). The concentration at which the decline in FEV1 crosses 20% mark on the plot is calculated by the computer (interpolated) to determine the PD_{20}. A normal PD_{20} is >16 mg/mL; borderline between 4 and 16 mg/mL; mild AHR between 1 and 4 mg/mL; moderate AHR 0.25–1 mg/mL; and marked AHR <0.25 mg/mL. It is important to understand the historical aspects of the MCT, in light of the modified guidelines from the ERS task force report.

Essentially three fundamental modifications are now put forward. The use of the PC_{20} is now supplanted for the tidal breathing method, and both dosimeter and tidal breathing will be reported as a provocative dose (PD_{20}). This allows better comparability between dosimeter and tidal breathing. Secondly, tidal breathing will be performed with either a breath-actuated or continuous nebulizer (but for 1, not 2 min). This will reduce variance on the delivered methacholine dose. The nebulizer outputs must be from devices with known characteristics of modern design. Tests previously requiring inhalation to TLC are replaced by shallow breathing methods to prevent the "bronchoprotective" effect of the deep breath as described above (Coates et al. 2017). The new ERS guidelines provide a referenced method for converting the PC_{20} from tidal breathing to PD_{20} (see Table 6 of the task force report) (Coates et al. 2017).

From an interpretive standpoint, it is important to avoid the following pitfalls. This test does not diagnose the severity of asthma, only documents the presence and severity of AHR. Additionally,

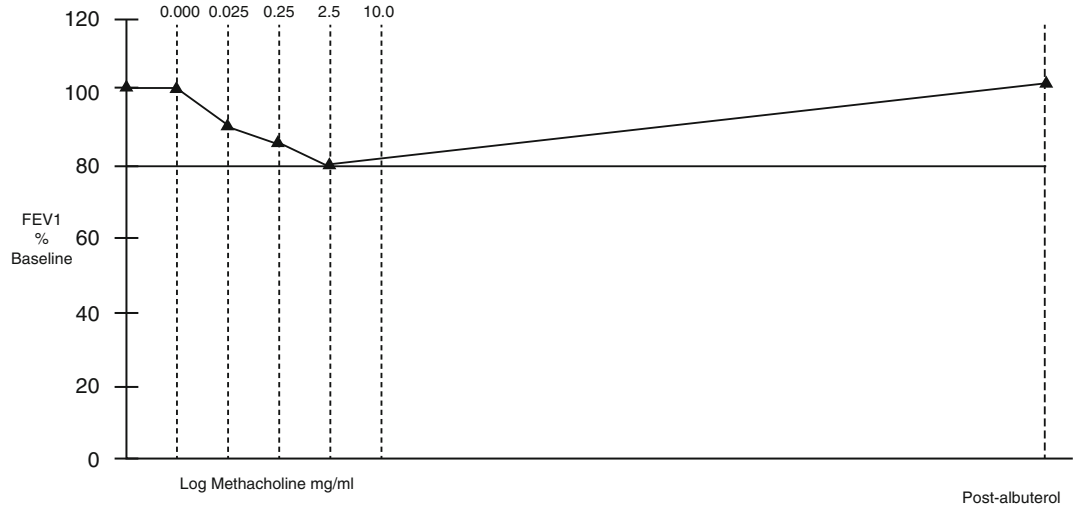

Fig. 9 Methacholine challenge. PD_{20} is 2.5 mg/mL. Positive study

the patient should abstain from medications which may block AHR, including bronchodilators and possibly caffeine (Crapo et al. 2000).

34.3.3 Clinical Contexts and Specifics of Challenges: *Indirect Challenges*

Indirect challenges are generally used in clinical practice to duplicate/mimic exercise-based pulmonary symptoms. They may be used in epidemiologic studies to determine AHR of clinical relevance. Airway narrowing in elite athletes who can perform extreme minute ventilation rates with cold air, hyperventilation, or exercise may be due to a different mechanism than inflammatory asthma. By creating a similar physiologic stress to the lung, it may better correlate with this clinical framework.

34.3.3.1 Exercise Challenge

The exercise challenge is the prototype in this category (Joos et al. 2003). It mimics "real-world" exercise. It can utilize a treadmill, bicycle, or free running. An FEV1 decrease of 10% or more from baseline is a positive (abnormal) response. ATS guidelines were generated in 1999 and describe this in detail (Crapo et al. 2000).

34.3.3.2 Eucapnic Voluntary Hyperpnea (Hyperventilation) and Cold Air Hyperpnea

The patient inhales dry air, at room temperature, with 4.9–5% CO_2 to maintain normal CO_2 levels or may be adjusted with end-tidal CO_2 monitoring. A 6-min protocol with a maximum intensity of 30 times the FEV1 would exclude exercise-induced asthma (EIA) in elite athletes, and 21 X FEV1 is sufficient in most patients. Post-challenge measures of FEV1 at 5, 10, 15, and 20 min are obtained (or sooner if symptoms occur). A 10% fall in FEV1, as in exercise, is considered a positive test. This test may have a lower false-negative rate than exercise. If asthma is already treated, sensitivity declines. Cold air hyperpnea is similar to eucapnic voluntary hyperventilation but uses refrigeration to cool inspired air to −20 °C. Interpretation is the same.

34.3.3.3 Hypertonic Saline Challenge and Distilled Water Challenge

About 4.5% saline is preferred. It correlates better with some inflammatory asthma markers, but is not in wide clinical use. It correlates with patients responding to moderate to high doses of Mch (Anderson et al. 1997; Cockcroft and Davis 2009). Distilled water responsiveness correlates

better with exercise and eucapnic hyperventilation than with Mch (Anderson et al. 1997).

Adenosine challenge is not approved for clinical use in the United States. Like other indirect stimuli, it correlates better with inflammation than does Mch. It uses a PC_{20} endpoint (Van Den Berge et al. 2001).

34.3.3.4 Mannitol Challenge

The mannitol challenge was developed in Australia and is described in a 1997 publication (Anderson et al. 1997). As noted above, it has utility in identifying exercise-induced asthma, a benefit which it shares with other indirect challenges such as exercise, hypertonic saline, and eucapnic hyperventilation (hyperpnea) (Joos et al. 2003). It was developed as a simpler test to administer, as well. It currently is not available in the United States. The mannitol challenge protocol involves administering doubling doses of dry powder mannitol through a proprietary device, starting at 5 mg, and ending at 160 mg (total dose 635 mg) or until a 15% fall in FEV1 from baseline occurs. Reversal after a beta-2 agonist inhalation is measured after 10 min. Positive tests correlate well with inhaled steroid responsiveness in patients suspected of having asthma. There has been correlation with step-up steroid dosing in already known asthmatics. A negative test suggests that active airways inflammation is unlikely, or actively treated asthma is controlled.

34.3.3.5 Allergen Challenge

Although primarily a research tool (Diamant et al. 2013), inhaled allergen challenge offers insights into the physiology of allergic airways disease, as well as will have ongoing value in pharmaceutical efficacy testing. In specialized centers, tests using sensitizers for occupational asthma may be performed. By definition, it is the quintessential indirect challenge test, because it depends upon immune reactivity to a highly specific antigenic stimulus to precipitate airway hyperreactivity. It is important to recognize that the physiologic relevance making the test valuable also increases the risk. Unlike pharmacologic or physical agents used in direct and other indirect challenges, allergen challenges produce early (immediate) and often late phase responses, which may persist for days (to weeks) (Diamant et al. 2013; Cockcroft and Murdock 1987). Allergen challenges fall into three categories: nasal, segmental lung challenge, and total lung (inhaled challenge). Total lung challenge types include incremental and bolus challenge, repeated low-dose challenge, and exposure rooms (e.g., live cat exposures). Only total lung challenges will be further reviewed. Precautions to be taken include immediate access to care of anaphylaxis and severe/persistent bronchospasm and continuous monitoring for complications for not less than 7 h after exposure. Bronchodilators are administered after the 7-h observation period (if not already needed). Proper ventilation to protect medical personnel from passive exposure is needed. Rapid access to intensive care facilities is needed. Patient selection excludes those with severe or unstable asthma. Need for safety and efficacy dictate that standardized protocols be utilized. These have been published (Sterk et al. 1993). Detailed inclusion and exclusion criteria are published recently (Diamant et al. 2013) in this extensive updated review. Like the Mch challenges, both dosimeter and tidal breathing methods have been utilized successfully. PC_{20} for the FEV1 is determined for the higher-dose bolus or incremental challenges. For repeated low-dose challenges, felt to better mimic the chronic/repeated exposures to allergens in the normal course of activity, protocols identifying a 5% drop in FEV1 exist, and monitoring at 5, 7, and 10 days is done. These are particularly useful for correlating to biomarkers such as airway eosinophilia, increases in exhaled nitrogen oxide (eNO), and airway hyperreactivity. Biomarkers will be extensively explored in part II of this chapter.

Data reporting from these challenges underscores pathophysiology, offering further insight into mechanism and possible treatment. The early asthma response (EAR) usually occurs within 10 min of exposure. The FEV1 decline from the post-diluent exposure by 20% is the hallmark. It usually is maximal by 30 min. It may also be described as $AUC_{0-2\ h}$ (area under the curve of the % FEV1 vs. time over 2 h). An isolated EAR response occurs in 50–70% of patients, but the remaining substantial group has a late asthmatic

response (LAR) (Cockcroft and Murdock 1987). This FEV1 decline defined by at least 15% may commence from hour 3 to 7, lasting 8–12 h post-exposure, but as noted earlier could persist for days (Diamant et al. 2013). In distinction to these higher-dose acute challenges, the lower-dose challenges can be reported out as alterations in Mch challenge PD_{20} or PC_{20}. Other biomarkers for sputum eosinophils, IL-5, ECP (eosinophil cationic protein), and eNO have been evaluated.

Finally, there is a clinical application of allergen testing to evaluate patients for occupational asthma (and occupational rhinitis). It is sometimes necessary to confirm the culprit allergen. Testing for diisocyanates (as an example of a low molecular weight sensitizer) or high molecular weight agents like flour or enzymes (detergent) has been done (Diamant et al. 2013; Seed et al. 2008). Again, these carry risk and are usually only performed in specialized testing sites, after appropriate evaluation and screening.

34.3.3.6 Summary

Sections 2 and 3 have reviewed the fundamentals of spirometry, pulmonary function and physiology, and bronchoprovocation. Spirometry yields valuable graphic and numerical data to diagnose obstructive lung defects and reversibility if present. In order to accurately diagnose restrictive defects, the TLC must be measured, and since this depends upon measuring air contained in the lung after full exhalation (RV), methods including gas dilution or plethysmography are required. The DL,CO measurement when corrected for Hb, in obstructive diseases, helps differentiate emphysema (low DL,CO) from asthma or chronic bronchitis. In restrictive disease, it can differentiate parenchymal disease (low DL,CO) from extra-parenchymal disorders of the pleura, chest wall, or neuromuscular apparatus (normal DL,CO).

Symptoms consistent with asthma, in the absence of abnormal resting PFT data, may be further elucidated by bronchoprovocation studies. These may be divided into direct (such as Mch) or indirect (including exercise, hyperventilation, mannitol, or allergen). Indirect studies with non-specific stimuli (including exercise, mannitol) are felt to be more sensitive for exercise-induced asthma than methacholine and also more specific. Allergen challenge (a specific stimulus) is primarily a research tool and can result in prolonged bronchospasm due to late phase allergic reactions not seen in direct stimuli. Allergen challenge may also be utilized in occupational asthma evaluations in appropriate testing venues. In the third section, the role of biomarkers will be explored to extend the diagnostic avenues just reviewed.

34.4 Biomarkers in Asthma

34.4.1 Introduction

With recent insights into the heterogeneous nature of asthma, there has been a reinvigorated effort to identify biomarkers that can characterize asthma and guide selection of treatment. The asthma "syndrome" comprises multiple phenotypes that encompass distinct disease pathogenesis, which can have varying responses to current treatment modalities. Utilization of noninvasive biomarkers may be the key to understand these phenotypes, gauge asthma severity, and predict treatment responses. In this section, we will review the utility and limitations of varying asthma biomarkers including fractional exhaled nitric oxide (FE_{NO}), sputum and serum eosinophils, immunoglobulin E (IgE) levels, as well as newly emerging biomarkers.

34.4.2 Fractional Excretion of Nitric Oxide

Nitric oxide (NO) formation is catalyzed by nitric oxide synthase (NOS), which coverts L-arginine into NO and L-citrulline in the presence of O_2 and NADPH (Luiking et al. 2010). NOS-2, the inducible isoform of NOS, is expressed in fibroblasts, endothelial cells, monocytes, macrophages, antigen presenting cells, and natural killer cells (Coleman 2001). In humans, NO can relax smooth muscle, inhibit mast cell activation, and dilate blood vessels. It is also involved in regulating immune cell death via apoptosis (Coleman 2001).

In the respiratory tract, NO regulates vascular and bronchial tone and coordinates the beating of ciliated epithelial cells (Belvisi et al. 1992; Jain et al. 1993). Fractional excretion of nitric oxide (FE_{NO}) is the amount of NO in exhaled breath in parts per billion (ppb). FE_{NO} is measured by chemiluminescence, which is produced when NO molecules in a gas sample react with ozone (O_3) that is generated in the instrument (Maniscalco et al. 2016). This method is highly sensitive and is the current gold standard method for quantifying exhaled NO.

Measurement of FE_{NO} may have diagnostic utility in asthma. The optimal reported cutoff for a clinical significant FE_{NO} is estimated to be >25 ppb, above which a patient is more likely to have asthma (Dweik et al. 2011). However, there is some overlap between levels in healthy patients and in those with stable controlled asthma. The main utility of FE_{NO} may be as a surrogate marker of Type 2 inflammation and eosinophilic airway inflammation. A relationship between FE_{NO} and airway eosinophils in induced sputum and BAL has been reported, which is a correlation of 0.78 ($P < 0.001$) and 0.59 ($P < 0.001$), respectively (Dweik et al. 2011). Elevated FE_{NO} levels may also reflect IL-4- and IL-13-driven airway inflammation (Malinovschi et al. 2013).

There is evidence that FE_{NO} can be used to predict response to inhaled corticosteroids (ICS). In a single-blind placebo-controlled trial by Smith et al., ICS response was measured by peak flow, spirometry, and bronchodilator response in 52 individuals with undiagnosed respiratory symptoms (Smith et al. 2005). They found that steroid responsiveness correlated with a cutoff point of >47 ppb. Based largely off of this study, a cut point of >50 ppb is suggested to predict ICS responsiveness and <25 ppb to predict ICS insensitivity (Dweik et al. 2011). It has also been demonstrated FE_{NO} level may be used to assess adherence to ICS, which can assist clinicians in decisions about modifying therapy in uncontrolled asthma. McNicholl et al. identified asthmatics as adherent and non-adherent to ICS based on prescription filling and measured FE_{NO} before and after directly observed ICS therapy (DOICS) (McNicholl et al. 2012). They found that non-adherent patients had a greater FE_{NO} suppression after DOICS. Utility of FE_{NO} to guide step-down of asthma medications has also been studied. The BASALT trial, a randomized placebo-controlled double-blind trial that sought to evaluate if FE_{NO} biomarker-based step-down therapy in mid-to-moderate asthmatics was superior to physician assessment-based, found no significant difference between the two groups (Calhoun et al. 2012).

With the emergence of multiple monoclonal antibodies that target specific inflammatory pathways, the question of whether FE_{NO} measurements may allow us to predict response to biologics has arisen. Given the expected role of FE_{NO} in eosinophilic asthma, this measurement has been used as part of the inclusion criteria for anti-eosinophilic drugs, including anti-IL-5 and anti-IL-5 receptor (Castro et al. 2014; Pavord et al. 2012). It is possible that FE_{NO} may also help to predict responses to other medications. Patients with high FE_{NO} measurements showed 53% reduction in exacerbations on omalizumab compared to 16% in the placebo group (Hanania et al. 2013).

Although FE_{NO} is a noninvasive and relatively inexpensive biomarker, there are some limitations that are important to consider. As discussed above, published studies show variable utility of FE_{NO}. There are a number of diseases and comorbidities that can alter FE_{NO} levels, including smoking, atopy, sepsis, trauma, obesity, and vascular disease (Jatakanon et al. 1998; Sanchez-Garcia et al. 2017; Yao et al. 2011). Furthermore, medications like glucocorticoids lower levels. As a result, FE_{NO} levels need to be interpreted with these factors in mind, and the test is best used in conjunction with other objective measures and patient history.

34.4.3 Sputum Eosinophils

Characterizing the cellular profile of airway inflammation can be a critical component to understand disease pathogenesis to help guide disease monitoring and management. High-quality sputum induction can provide a noninvasive mechanism to determine the distribution of

leukocytes that contribute to airway inflammation. Sputum eosinophils can be measured from induced sputum after centrifugation, staining, and analysis of cell types (Gershman et al. 1996). Determining whether a patient has eosinophilic asthma is particularly important; it may predict disease course, help guide treatment, predict treatment response and could be used to quantify response to treatment.

Sputum eosinophil percentage (usually ≥2–3%) is a marker for airway eosinophilia and correlates with multiple asthma outcome measures. A multivariate analysis of data by Woodruff et al. showed that eosinophilia in induced sputum was independently associated with lower FEV1 ($r = -0.15$, $P = 0.005$) and lower methacholine responsiveness ($r = -0.21$, $P = 0.005$), even after controlling for common confounders like ICS therapy, age, sex, and ethnicity (Woodruff et al. 2001). These findings have been replicated, and additional studies have also found an association between sputum eosinophilia and worse asthma control ($r = 0.43$, $p < 0.001$) (Louis et al. 2000).

Sputum eosinophils may be useful in predicting glucocorticoid responsiveness. In a population of mild-to-moderate asthmatics, eosinophilic asthmatics showed a significant improvement in their FEV1 after 2 weeks of 0.5 mg/kg/day of prednisone, 800 μg budesonide, and 20 mg zafirlukast when compared to the same treatment regimen in non-eosinophilic asthmatics (McGrath et al. 2012). In addition, sputum eosinophilia could help to assess effectiveness of treatment. A randomized controlled trial showed that sputum eosinophils were significantly decreased after treatment with 2400 μg of budesonide as well as a >2-fold improvement in airway responsiveness (Gibson et al. 2001). Routine monitoring of sputum eosinophils may be used to guide treatment more effectively. In a randomized controlled trial with moderate-to-severe asthmatics, individuals whose controller medications were adjusted based on changes in sputum eosinophil counts saw a reduction in severe asthma exacerbations when compared to current management strategies (Green et al. 2002). Some of these findings may also apply to biologics in asthma, where sputum eosinophils can also be considered as biomarkers for predicting treatment responsiveness (Flood-Page et al. 2007). For example, in a trial of reslizumab, asthmatics with a sputum eosinophilia percentage ≥3% saw a significant reduction in exacerbations and better quality of life compared to those with lower eosinophil percentage (Castro et al. 2011).

There are a number of important factors that limit the use of sputum eosinophils in routine care. Acquiring high-quality sputum can be time-intensive and difficult. Sputum eosinophil measurements can vary with bronchoconstriction inadequate specimens and between operators (Green et al. 2002; Lacy et al. 2005). In addition, multiple eosinophilic sub-phenotypes may exist, so it is important to interpret sputum eosinophil levels in the context of other data and patient history (Moore et al. 2010). Despite these limitations, testing is recommended by current guidelines to guide treatment in experienced centers (Chung et al. 2014).

34.4.4 Blood Eosinophils

In contrast to sputum eosinophils, blood eosinophils can be easily and readily obtained. Blood eosinophils have been evaluated as a potential biomarker to characterize asthma and guide treatment. Similar to what was observed sputum eosinophilia, blood eosinophilia has also been shown to be inversely related to FEV1 in multiple studies (Horn et al. 1975; Ulrik 1995). In addition, higher blood eosinophil levels have been associated with increased bronchial hyperreactivity (Ulrik 1995). Along these lines, elevated blood eosinophil levels have also been shown to be related to poor asthma control and severe asthma exacerbations. A large cohort study in the United Kingdom demonstrated that asthmatics with >400 peripheral eosinophil cells/μL had more severe asthma exacerbations and acute respiratory events when compared to asthmatics with 400 cells/μL or less (Price et al. 2015). High blood eosinophil count may also be a risk factor for future exacerbations and increased beta-2 agonist usage. One retrospective study saw that asthmatics who had exacerbations in 2011 and more than seven short-acting bronchodilators prescribed were

found to have eosinophil counts >400 cells/μL in the year prior (Zeiger et al. 2014).

A blood eosinophil level that corresponds to eosinophilic asthma has not been well established. A number of studies have used a level of 400 cells/μl, and this was the cutoff used for studies with reslizumab, the anti-IL5 inhibitor. Treatment with reslizumab in subjects with blood eosinophil levels ≥400 cells/μl resulted in improved FEV1 and asthma quality of life (Bjermer et al. 2016; Castro et al. 2015; Corren et al. 2016). Studies using mepolizumab showed efficacy with blood eosinophil cutoffs ≥300 cells/μl and in fact as low as 150 cells/μl. Along these lines, we found that the median eosinophil count in our asthma population was 200 cells/μl, and that asthma-related outcomes were similar regardless of whether a cutoff of 200 or 400 cells/μl was used as the threshold for eosinophilia (Mukadam et al. 2017). These findings raise the possibility that eosinophilic asthma may exist even in the setting of a low blood level. Furthermore, blood eosinophil levels can be altered by medications, other diseases, and time of blood draw. It has been shown that there may be up to 40% diurnal variation in blood eosinophil count (Winkel et al. 1981).

34.4.5 IgE Levels

Allergy testing, either skin testing or blood testing (specific and total IgE), has long been an important tool to aid diagnosis and management of asthma. In addition to identifying allergic triggers for asthma, total and specific IgE have predictive roles in the disease. In children, assessing atopy may have important implications for risk of developing asthma (Sly et al. 2008). In 3-year-old children, increased levels of cat-, dog-, and mite-specific IgE were shown to correlate with a 1.33-fold increase in wheezing by the age of 5 (Simpson et al. 2005). Other aeroallergen sensitivity, like *Alternaria* mold, also correlates with the likelihood of developing asthma (Huss et al. 2001; Sporik et al. 1990; Wahn et al. 1997). Total IgE levels can also help to rule in, rule out, and consider diagnoses other than allergic asthma. Low IgE levels (<30 IU/mL) argue against allergic asthma, while high IgE levels (particularly >400–500 IU/mL) raise the suspicion for allergic bronchopulmonary aspergillosis. In addition, it has been shown that elevated IgE levels may predict likelihood of response to ICS (Szefler et al. 2005). Furthermore, IgE levels are essential to the selection of monoclonal antibody therapy in asthma. Measures of IgE, particularly in combination with measures of eosinophilic inflammation, can help to identify Type 2 inflammation. Omalizumab, an anti-IgE monoclonal antibody, is selected based on blood level of total IgE (30–700 IU/mL) and specific IgE to perennial aeroallergens (Busse et al. 2001).

However, it should be pointed out that the optimal IgE cutoff for allergic asthma is still unclear, and the specificity of IgE for asthma is low. Other allergic diseases can produced elevated IgE levels, and medications like corticosteroids can affect levels (Zieg et al. 1994).

34.4.6 Emerging Biomarkers

34.4.6.1 Periostin

Identification of biomarkers in asthma has been challenging as mediators of airway inflammation are rarely detectable in the blood at clinically useful levels. In recent years periostin has emerged as a potential blood marker of IL-13 and Type 2 inflammation. Periostin was found to be elevated in asthmatics with high airway IL-13 expression and subsequently found to be induced in airway epithelial cells and secreted into the blood after IL-13 stimulation (Woodruff et al. 2007). The clinical utility of periostin as a biomarker was observed in early phase studies of anti-IL13. Subjects with higher periostin levels were found to have a better response to anti-IL13 than those with lower levels, indicating the potential to identify IL-13/Type 2 inflammation (Corren et al. 2011). The clinical utility of periostin still remains to be validated, but it may be a powerful blood marker.

34.4.6.2 Exhaled Breath Condensates

Exhaled breath condensate (EBC) is a noninvasive mechanism to obtain material from the lower lung: Physiologically, the exhaled breath is constituted predominately by water vapor and aerosolized particles, generated by airway lining fluid (ALF). By cooling breath vapor, EBC can be collected, and its biochemical composition has been found to be very similar to ALF (Bajaj and Ishmael 2013). Numerous mediators have been detected in EBC, and as detection methods have improved with better technologies in the past few years, it is now possible to quantitatively measure cytokines, nucleic acids, leukotrienes, pH, and other small molecules. Quantitation of these mediators is emerging as a means of phenotyping asthma. Measurement of eicosanoids in EBC has been demonstrated to differentiate aspirin-sensitive and aspirin-tolerant asthmatics (Sanak et al. 2011). Cytokine profiling has been shown to identify T_H2 signatures and may be useful to distinguish T_H2 high and T_H2 low phenotypes (Shahid et al. 2002). MicroRNAs (miRNAs) have also emerged as novel potential biomarkers. miRNAs are small (~20 base-long), noncoding RNAs that are present in all biofluids. These nucleic acids are synthesized from noncoding regions of the genome and can arise from introns or from their own gene. Over 1500 miRNAs have been identified in humans, though only a subset is detectable in EBC. We have identified signatures of miRNAs which correspond to T_H2 inflammation and are different in EBC of asthmatics, patients with COPD, and healthy subjects (Pinkerton et al. 2013). miRNAs are also found in serum and saliva, and measurement of their expression from these sources has also been shown to have utility in asthma (Panganiban et al. 2012).

34.4.6.3 Circulating MicroRNAs

Circulating miRNAs are produced from secretion of miRNAs from multiple cells and organs. Approximately 150 miRNAs are readily detectable in the blood (Panganiban et al. 2016). They are encapsulated by exosomes and thus are protected from nuclease degradation. They can be isolated in the blood using stand RNA isolation techniques and quantified by quantitative real-time PCR. We found that plasma miRNAs are differentially expressed in asthma, allergic rhinitis, and non-asthma nonallergic rhinitis subjects (Panganiban et al. 2016). In addition, we found that subsets of miRNAs were able to distinguish eosinophilic from non-eosinophilic asthma, suggesting that these could be diagnostic and phenotypic biomarkers (Panganiban et al. 2016). Davis et al. subsequently demonstrated that circulating miRNAs were associated with airway hyperresponsiveness in children (Davis et al. 2017). Larger validation studies are needed to confirm the utility of blood miRNAs as biomarkers, but they have potential to be highly useful markers.

34.4.7 Composite Biomarkers

Currently, no single biomarker is optimal in asthma. Each has limitations and drawbacks but may be more powerful when used in combination, particularly in the setting of complex asthma phenotypes. For instance, eosinophilic asthma in the setting of atopy and early onset may be responsive to inhaled corticosteroids, while eosinophilic asthma without atopy, particularly with late onset asthma, may be very difficult to treat and require anti-IL-5 therapy. Thus, measuring a combination of markers that includes specific IgE, total IgE, blood eosinophils (and/or sputum eosinophils), and FE_{NO} would be helpful to distinguish these scenarios. Furthermore, combining these established biomarkers with emerging biomarkers may be necessary to fully characterize asthma. For instance, a recent study demonstrated that a composite panel of FE_{NO}, blood eosinophils, serum CCL26, and CCL17 expression had a 100% positive predictive value for identifying asthmatics with Type 2/IL-13-driven inflammation, which was confirmed by airway biopsy. As more targeted therapies to specific inflammatory pathways emerge, the need to measure specific biomarkers to characterize asthma will become a vital part of personalizing asthma care.

34.4.8 Summary

The evolving understanding of asthma pathophysiology and the heterogeneous nature of the disease has necessitated the development of noninvasive biomarkers to characterize asthma and help guide therapy. Established biomarkers such as blood eosinophils, total and specific IgE, and FE_{NO} are readily obtainable in most allergy offices and can provide insight to asthma pathophysiology and may help to predict treatment responses. However, there are limitations in the clinical utility of these tests, as no single test can diagnose or fully characterize asthma. Sputum cell measures may be very useful but are difficult to perform in routine clinical practice. As new asthma therapies targeting specific immune cells and inflammatory mediators are rapidly emerging, use of biomarkers will be crucial to select the right treatment for the right patient. The solution may involve using composite measures of multiple biomarkers as a panel, possibly with incorporation of some of the new biomarkers that are now in the validation phase of study.

34.5 Conclusion

When evaluating a patient for respiratory complaints, the clinical history and physical examination often require supplemental information to refine the differential diagnosis and gain insight into pathophysiologic mechanisms of specific disease states. Pulmonary function testing will help confirm or exclude the presence of obstructive or restrictive diseases. Bronchoprovocation can further clarify the presence of airway hyperreactivity through either direct or indirect challenges. With the evolving use of biomarkers, the diagnosis of asthma may be further refined. Utilization of biomarkers not only assists in the diagnosis but also reflects the increasing recognition of asthma heterogeneity and, with this recognition, offers the promise of more refined and hence personalized therapeutic approaches to this condition.

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Part IX

Treatment of Asthma and Allergy

Primary and Secondary Environmental Control Measures for Allergic Diseases

35

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Contents

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Abstract

Atopic diseases, such as allergic rhinitis, asthma, atopic dermatitis, and food allergy, prevalence continues increasing worldwide. They are characterized by the production of IgE to diverse allergens. Atopic diseases represent an important health and economic burden in our population. The development of atopic diseases is a consequence of the interactions of multiple factors, including genetic predisposition, environment, infections, microflora, diet, and use of different medications. Great effort has been placed in the development of diverse strategies to prevent these atopic diseases. Primary prevention is focused in the development of measures to avoid sensitization. The goal of secondary prevention is to avoid the development of symptoms once sensitization is present. However, due to pathogenesis complexity of these diseases diverse results have been reported. In this chapter, the effectiveness of different primary and secondary interventions and control measures of common allergens will be discussed in detail.

Keywords

Atopy · Asthma · Rhinitis · Atopic dermatitis · Food allergy · Allergens · Primary prevention · Secondary prevention

35.1 Introduction

The prevalence of allergic diseases is increasing worldwide (Akinbami et al. 2016). Houses in the United States have a high allergen burden, even more so if they have pets or pests (Salo et al. 2018). The cure for allergic diseases has not been identified, representing a major challenge in our society. Allergic diseases play a significant role in our health, economic conditions, and quality of life. Therefore, it is imperative to discuss prevention interventions for these diseases. Primary prevention develops strategies to avoid sensitization, while secondary prevention interventions assist with symptom avoidance once an allergen sensitization is present. Tertiary prevention aims to decrease morbidity and complications once the diseases have developed (Fig. 1).

Herein, we will discuss environmental control interventions for allergic diseases used in the broadest sense of the concept. The first section will summarize the available data on different primary and secondary interventions used in specific atopic diseases. The second part discusses the primary, secondary, and tertiary prevention interventions focusing on the most common inhaled allergens. A discussion on future areas of investigation to prevent allergic sensitization completes this chapter.

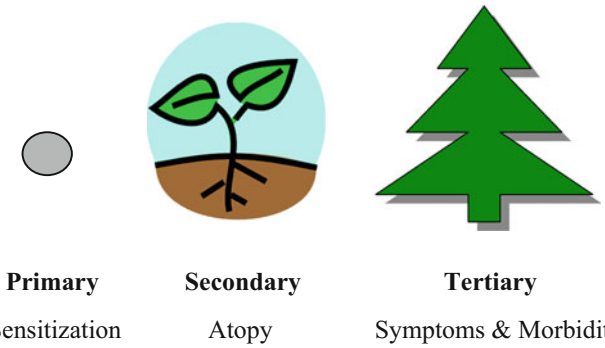

Fig. 1 Primary, secondary, and tertiary interventions

35.2 Primary Prevention and Secondary Prevention of Atopic Dermatitis

Atopic dermatitis (AD) is one of the most prevalent skin disorders worldwide. Because its prevalence continues to increase, the associated economic burden is estimated at approximately $5 billion annually (Adamson 2017). It typically starts during early childhood and commonly resolves during adolescence, although some subjects have it throughout their lifetimes. AD is characterized by intense pruritus and dry skin. Asthma, allergic rhinitis, and food allergy are usually associated with AD. Genetic, environmental, and immune factors are part of this disease pathogenesis. There is no disease-modifying treatment. Therefore, prevention interventions are important since they could also prevent the progression of the atopic march.

35.3 Primary Prevention

35.3.1 Use of emollients

Emollient use is a key component in the treatment of AD since it restores the epidermal barrier. The use of emollients as a preventive intervention has demonstrated a positive result. Simpson et al. conducted a randomized controlled study on the daily use of emollients on infants born to atopic families. Both groups received education on skin care measures. At the end of 6 months, the children in the intervention group had a 50% reduction in the incidence of atopic dermatitis compared to the controls (Simpson et al. 2014). The beneficial effect of moisturizer among high-risk infants was confirmed when infants at high risk for atopic dermatitis were randomized to receive an emulsion-type emollient or regular skin care daily or on an as-needed basis. After a 32-week intervention, the infants receiving emollient had a 32% lower incidence of atopic dermatitis (Horimukai et al. 2014). A more recent study using a ceramide-based emollient twice a day for 6 months among high-risk infants showed a trend toward the reduced incidence of AD after 1 year (Lowe et al. 2018). Differences in these studies may be related to sample size, compliance with treatment, and outcome measures. Nevertheless, they demonstrated the benefit of at least daily use of emollients on high-risk infants as primary prevention for atopic dermatitis.

35.3.2 Dietary Factors

35.3.2.1 Prebiotics and Probiotics

Composition of intestinal microflora in allergic patients differs from nonallergic patients. Attempts to restore beneficial flora have been studied in relation to atopic dermatitis (Ouwehand et al. 2001). The mechanism of the protective effect of probiotics has been evaluated. A comparison of three different probiotics in their potential to avoid skin inflammation in a murine model showed that *Lactobacillus salivarius* and *Lactobacillus rhamnosus* limited skin inflammation macro- and microscopically and reduced the

inflammatory cytokines in serum compared to *Bifidobacterium bifidum* (Holowacz et al. 2018). Understanding and manipulating gut microbiome by the administration of these protective bacteria may become another primary and secondary prevention.

Studies of the probiotic effects on AD have been controversial. A systematic review analyzing the use of probiotics, particularly *Lactobacillus rhamnosus GG,* was effective for the prevention of AD, especially when it was administered to both pregnant mothers and infants at risk for AD (Foolad et al. 2013). The use of prebiotic supplementation during early infancy also demonstrated a preventive effect for AD (Foolad et al. 2013). Avershina et al. conducted a subanalysis of the Prevention of Allergy among Children in Trondheim (ProPACT) study evaluating stool bacterial 16S rRNA among infants with and without AD whose mothers received probiotics or placebos during pregnancy. Infants who received probiotics and developed AD had a higher divergence from infants who did not develop AD at 10 days in bacterial stool microbiota and had a higher prevalence of *Bifidobacterium dentium*. The divergence disappeared with time, supporting an interaction between a neonate's microbiota and probiotics early in life, which is important in AD development (Avershina et al. 2017). A Cochrane review failed to show any benefit of probiotics in AD (Osborn and Sinn 2007). Supplementation with prebiotics mixed with neutral short-chain galacto- and long-chain fructo-oligosaccharides for 6 months in infants of atopic parents reduced AD and wheezing development, a beneficial effect that persisted for up to 2 years after concluding the intervention (Arslanoglu et al. 2006).

35.3.2.2 Breast-Feeding

The role of breast-feeding as a primary prevention intervention for AD is controversial. A birth cohort of 4089 children concluded that exclusive breast-feeding for longer than 4 months decreased the risk of AD by age 4 (Kull et al. 2005). A meta-analysis demonstrated a lower incidence of AD in children with a family history of atopy who were exclusively breast-fed for the first 3 months of life (Gdalevich et al. 2001). A prospective cohort also showed that children with prolonged breast-feeding had the lowest prevalence of AD among the groups analyzed (Saarinen and Kajosaari 1995). However, other studies failed to demonstrate an association between breast-feeding and the prevention of AD. An observatory cohort of 1314 infants showed that the prevalence of atopic eczema in the first 7 years of life increased with each additional month of breast-feeding (Bergmann et al. 2002). Similar results were found in the Auckland Birthweight Collaborative study (a case-control study) of risk factors for small for gestational age infants. Duration of breast-feeding was associated with an increased risk of AD (Purvis et al. 2005).

35.3.2.3 Vitamin D

The use of vitamin D during pregnancy for AD prevention has no solid evidence to support it. As in other diseases, the recommendation to use vitamin D as a primary intervention for AD remains inconsistent. Lower cord blood vitamin D levels were observed in patients who developed eczema (Jones et al. 2012). However, supplementation with vitamin D at 27 weeks of gestation showed no difference in eczema when compared to control groups (Goldring et al. 2013). A recent systematic review of randomized and non-randomized studies demonstrated no primary prevention effects of vitamin D supplementation in pregnant women for the development of AD (Yepes-Nunez et al. 2018).

35.3.3 Animals

The association of farm environments with atopy has demonstrated a protective effect. Specifically, the GABRIEL Advanced Study reported the beneficial effect of exposure to farm environments in the development of atopic diseases. For AD specifically, exposure to horses, manure, and silage prevented the onset of disease (Illi et al. 2012). The Auckland Birthweight Collaborative demonstrated that AD was more likely to develop at 3.5 years of age if a child was exposed to cats but not to dogs (Purvis et al. 2005). A similar result was

Table 1 Effect of interventions for atopic dermatitis prevention

Intervention	Effect	Target prevention	Reference
Emollients	+++	Primary	Lowe et al. 2018; Horimukai et al. 2014; Simpson et al. 2014
Pre- and probiotics	+/−	Primary	Foolad et al. 2013; Avershina et al. 2017; Osborn and Sinn 2007; Arslanoglu et al. 2006
Breast-feeding	+/−	Primary	Purvis et al. 2005; Bergmann et al. 2002; Saarinen and Kajosaari 1995; Gdalevich et al. 2001; Kull et al. 2005
Vitamin D	−	Primary	Goldring et al. 2013; Yepes-Nunez et al. 2018
Farm and domestic animals	+	Primary	Illi et al. 2012; Purvis et al. 2005; Zirngibl et al. 2002; Langan et al. 2007
Immunizations	+/−	Primary	Martignon et al. 2005; Anderson et al. 2001; Farooqi and Hopkin 1998; Olesen et al. 2003
Allergen avoidance	−	Primary	Bremmer and Simpson 2015

found in a cohort of 4578 children. A negative association of keeping any pets, particularly dogs, with AD was observed in the first and second years of life (Zirngibl et al. 2002). Additionally, a systematic review concluded that having a pet early in life was protective for atopic dermatitis (Langan et al. 2007). It has been proposed that exposure to endotoxins protects children from atopy development, although the timing dose and route of exposure are crucial to determine the outcome.

35.3.4 Vaccines

The possible association of immunization with the development of AD is debatable. Two studies demonstrated an increase in AD in patients vaccinated for pertussis, measles, mumps, and rubella (Farooqi and Hopkin 1998; Olesen et al. 2003). Other studies demonstrated no relationship between vaccines and AD (Anderson et al. 2001). A more recent study demonstrated a protective effect for atopic disease development (Martignon et al. 2005).

35.3.5 Allergen Avoidance

Can we prevent atopic dermatitis by initiating house dust mites (HDM) environmental control measures prior to sensitization? Bremmer et al. conducted a meta-analysis of randomized controlled trials of high-risk infants treated with HDM avoidance and followed prospectively. Seven trials were evaluated including 1587 infants in the intervention and 1473 in the control. The interventions included the use of impermeable covers and some additional measures. Despite decreased exposure to HDM in the intervention group, sensitization or atopic dermatitis was not prevented (Bremmer and Simpson 2015). Thus far, primary and secondary measures against HDM have failed to prevent sensitization and atopic dermatitis (Table 1).

35.4 Secondary Prevention

Secondary prevention intervention in AD is difficult to achieve. Secondary AD prevention involves interventions to avoid the onset in this disease in sensitized patients. However, specific

IgE sensitization is not the only factor associated with AD initiation. In fact, sensitization can occur secondary to the permeability defects in the epithelium of AD patients. Therefore, this definition cannot be applied to this disease as in other atopic diseases discussed in this chapter.

35.5 Primary and Secondary Prevention of Food Allergy

Food allergy (FA) is defined according to the National Institute of Allergy and Infectious Diseases (NIAID) expert panel as "an adverse health effect arising from a specific immune response that occurs reproducibly on exposure to a given food" (Boyce et al. 2010). Data from the U.S. Food and Drug Administration's National Electronic Injury Surveillance System of emergency department encounters suggest that there are approximately 125,000 visits per year for food-induced allergic reactions, 14,000 visits per year for food-induced anaphylaxis, and 3100 hospitalizations per year related to food allergy (Ross et al. 2008).

Varying patterns of consumption may lead to different food allergens in other countries and parts of the world. In Western countries, the following eight allergens cause the most cases of food allergy: cow's milk, hen's eggs, soy, wheat, peanuts, tree nuts, fish, and shellfish (Sampson et al. 2014). Although the majority of children with food allergy eventually tolerate milk, egg, wheat, and soy, the rate of resolution has become slower in the past decade (Savage et al. 2016). In most patients, peanut allergy begins at a young age and persists as a lifelong problem.

Prevention entails intervention to reduce risks or threats to health. Primary prevention involves preventing the onset of IgE sensitization. Secondary prevention interrupts the development of FA in IgE-sensitized children. Tertiary prevention seeks to reduce the expression of allergy in children with established FA.

Allergic patients develop loss of tolerance to foods for unknown reasons. Sensitization to food antigens may occur in the gastrointestinal tract, oral cavity, skin, and respiratory tract. Percutaneous exposure to food proteins rather than enteral exposure may lead to food allergy, especially in patients with atopic dermatitis (AD) through the activation of thymic stromal lymphopoietin (TSLP) and basophils secreting interleukin (IL)-4 (Hussain et al. 2018). A T helper cell type 2 (Th2) milieu arises with OX40L-activated dendritic cells, IL-4 from activated innate lymphoid cells (ILCs) type 2 , natural killers T (NKT) cells and basophils, down-regulation of regulatory T cells (Tregs), B cell proliferation and class switch to immunoglobulin E (IgE) eventually leading to mast and basophil degranulation, and epithelial cells secreting TSLP, IL-25, and IL-33. Interrupting this immunological cascade may prevent food allergy.

Food allergy occurs more commonly in association with other atopic diseases, thus, among children with established food allergy, 29% have asthma, 31% have rhinitis, 28% have eosinophilic esophagitis, and 27% have eczema (Akinbami et al. 2016). Children with moderate to severe AD have a higher risk (35%) of food allergy (Breuer et al. 2004).

In the Canadian Healthy Infant Longitudinal Development (CHILD) study, a multicenter prospective birth cohort, children with AD who were also sensitized to inhalant or food allergens were more likely to develop asthma or food allergy at age 3 (Tran et al. 2018).

Transepidermal water loss (TEWL), a measure of skin barrier disruption, is increased in those with AD at both lesional and nonlesional sites. Infants in the Babies after Scope: Evaluating the Longitudinal Impact using Neurological and Nutritional Endpoints (BASELINE) birth cohort had TEWL measured in the early newborn period and at 2 and 6 months of age. At age 2, the infants had skin-prick tests and oral food challenges. Even in the infants without AD, those with increased TEWL were 3.5 times more likely to have FA at 2 years of age (Kelleher et al. 2016). Filaggrin gene mutation associated with a defective skin barrier in patients with atopic dermatitis was also associated with peanut sensitization at age 4, and sensitized children with a history of preschool eczema were more often polysensitized (Johansson et al. 2017). Interventions that might

interrupt the atopic march, which usually begins with eczema, could influence the risk of other allergic diseases, including food allergy.

35.6 Primary Prevention

35.6.1 Early Introduction of Foods

As the immune system of the infant develops, there is a window of opportunity to introduce food tolerance. There has been a paradigm change from avoiding allergens early in infancy to the introduction of solid foods, including potentially allergenic foods, at 4–6 months of age (Thygarajan and Burks 2008). Maternal allergen avoidance or avoidance of specific complementary foods at weaning do not prevent food allergy (Sampson et al. 2014). Recent cohort studies suggested that extended exclusive breast-feeding may increase the likelihood of food allergy secondary to the delayed timing of first complementary foods (de Silva et al. 2014). In a prospective birth cohort of 856 children from rural areas in five different European countries, increased food diversity between 3 and 12 months of age was inversely associated with food allergy (Roduit et al. 2014).

Early introduction to cow's milk, within 14 days of birth, protected against developing cow's milk allergy in an Israeli cohort (Katz et al. 2010). A case-control study also showed that the delayed introduction of cow's milk formula was an independent risk factor for an IgE-mediated cow's milk allergy (Onizawa et al. 2016).

There has been conflicting data on early egg introduction. Early introduction of egg in infants 3–6 months of age did not prevent egg allergy at 12–36 months in the Enquiring About Tolerance (EAT) study, but compliance with the amount of allergen protein per week in the intervention group was low, and the age of allergen introduction in the intervention (5 months) and control arms (introduced from 6 months) might not have been sufficiently varied to have a biological impact (Perkin et al. 2016a). In two other randomized control trials (RTCs) designed as primary prevention trials that included nonsensitized infants, there was no difference in the risk of IgE-mediated egg allergy at 12 months between the group with early egg consumption at 4–6.5 months compared to the group with egg ingestion at 10 months or 12 months (Palmer et al. 2017; Perkin et al. 2016b). However, different studies found that the introduction of eggs at age 4–6 months was associated with a lower prevalence of egg allergy compared to later introduction after 12 months (Bellach et al. 2017; Koplin et al. 2010). In both the Beating Egg Allergy Trial (BEAT) and the Prevention of Egg Allergy with Tiny Amount Intake (PETIT) study, early egg introduction at 4–12 months in high-risk infants prevented egg sensitization or allergy, respectively (Wei-Liang Tan et al. 2017; Natsume et al. 2017).

After observing that the prevalence of peanut allergy was ten times higher in London than in Tel Aviv, where infants had early exposure to peanuts, the Learning Early About Peanut Allergy (LEAP) study was designed to study the early introduction of peanuts in high-risk infants. It served as an effective primary and secondary strategy for the prevention of peanut allergy. Infants were randomized to consuming peanut products at least three times a week or completely avoiding any peanut until 60 months of age. Infants 4–11 months old with either eczema or egg allergy or a skin-prick test (SPT) to peanuts <5 mm were included. Among the 530 infants who initially had negative peanut skin test results, the prevalence of PA at 60 months of age was 13.7% in the avoidance group and 1.9% in the consumption group. Among the 98 infants who initially had positive skin test results, the prevalence of peanut allergy was 35.3% in the avoidance group and 10.6% in the consumption group. Based on these data, the authors concluded that the early introduction of peanuts significantly decreased the frequency of peanut allergy, even in already sensitized infants (Du Toit et al. 2015). Official guidelines now recommend the early introduction of peanuts starting at 4–6 months of age in children with severe eczema as a preventive measure of peanut allergy. Evaluation of peanut-specific IgE, SPT, or both should be considered prior to introducing peanuts to an infant with severe eczema, egg allergy, or both. If the IgE to peanuts is less than 0.35 kU/L, the introduction of peanuts may occur

at home. If the peanut IgE measurement is 0.35 kU/L or greater, the child should be referred to an allergist for skin-prick testing. If the wheal of the skin-prick test for peanuts is 2 mm or less, peanuts can be introduced to the infant's diet. If the wheal diameter produced by skin testing for peanuts is 3 mm greater than the saline control, up to 7 mm, supervised peanut feeding or graded challenge should be done (Togias et al. 2017). If SPT to peanut produces a wheal diameter 8 mm or greater than the saline control, the likelihood of peanut allergy is high. This category should be followed by allergists. The LEAP-ON study demonstrated that the oral tolerance of peanuts persisted after 1 year (Du Toit et al. 2016).

35.6.2 Use of Emollients

The use of skin moisturizes is a key component in the treatment of AD. Interestingly, the use of daily emollients in high-risk infants led to a 50% reduction in risk of AD at 6 months of age (Simpson et al. 2014). Daily moisturizer with petrolatum may prevent eczema in infants and thus food sensitization by upregulating antimicrobial peptides such as human B-defensin 2 and innate immune genes and by inducing the expression of the key barrier proteins filaggrin and loricrin (Czarnowicki et al. 2016).

35.6.3 Dietary Factors

35.6.3.1 Breast-Feeding

The use of breast-feeding to prevent the development of atopy, including food allergy, has been controversial. Most of the available studies did not consistently demonstrate the protective effect of breast milk on the development of food allergy (Lodge et al. 2015; Pesonen et al. 2006).

35.6.3.2 Use of Prebiotics and Probiotics

There is insufficient evidence for the supplementation of the maternal or infant diet with probiotics or prebiotics to prevent atopy (Sampson et al. 2014). A recent meta- analysis, however, concluded with low evidence that probiotics can reduce the risk of eczema when used by women during the last trimester of pregnancy, while breast-feeding, or when given to infants (Cuello-Garcia et al. 2015). Other atopic conditions are not influenced by probiotics consumption. The World Allergy Organization recommended probiotics for pregnant women at high risk of having an allergic child, for women who are breast-feeding a high-risk infant, and to prevent eczema in infants at high risk of developing allergy. There is no guidance on specific probiotic strains or dosages (Bridgman et al. 2016).

35.6.3.3 Hydrolyzed Formula

Partially hydrolyzed formula may decrease eczema in infants at age 6 but the benefit is not long-standing, as seen in the follow-up of the German Infant Nutritional Intervention (GINI) study, a double-blind randomized controlled trial (DBRCT) of 2252 infants with a family history of allergy (von Berg et al. 2013). Moreover, the Australian guidelines for feeding infants to prevent food allergy do not recommend hydrolyzed formulas for the prevention of allergy (Netting et al. 2017).

35.6.3.4 Vitamin D

Different studies assessing the role of vitamin D supplementation in atopy suggest an increase change of sensitization if supplemented (Milner et al. 2004; Wjst 2005; Hypponen et al. 2004). However, an Australian population study found that children with low levels of serum vitamin D were more likely to develop peanut and egg allergy than those with normal levels (Allen et al. 2013). In addition, a low level of vitamin D was associated with persistent egg allergy (Neeland et al. 2018) (Table 2).

35.7 Secondary Prevention

Few secondary prevention interventions have been studied for food allergies. However, as previously mentioned, the LEAP study results showed that the early introduction of peanuts prevented the development of peanut allergy in those already sensitized to this food (Du Toit et al. 2015).

Table 2 Effect of interventions for food allergy prevention

Intervention	Effect	Target prevention	Reference
Emollients	+	Primary	Czarnowicki et al. 2016
Pre- and probiotics	+/−	Primary	Sampson et al. 2014; Cuello-Garcia et al. 2015; Bridgman et al. 2016
Breast-feeding	−	Primary	Lodge et al. 2015; Pesonen et al. 2006
Vitamin D	+/−	Primary	Milner et al. 2004; Wjst 2005; Hypponen et al. 2004; Allen et al. 2013; Neeland et al. 2018
Early food introduction	+++	Primary and secondary	Roduit et al. 2014; Katz et al. 2010; Onizawa et al. 2016; Perkin et al. 2016a, b; Palmer et al. 2017; Bellach et al. 2017; Koplin et al. 2010; Wei-Liang Tan et al. 2017; Natsume et al. 2017; Du Toit et al. 2015, 2016
Hydrolyzed formula	+/−	Primary	von Berg et al. 2013; Netting et al. 2017

35.8 Primary and Secondary Prevention of Allergic Rhinitis

Allergic rhinitis is characterized by frequent sneezing, nasal congestion, runny nose, and itchy eyes. It is secondary to overreaction to the presence of different allergens. This allergic disease affects approximately 10–30% of the U.S. population (Settipane 2001; Singh et al. 2010; Meltzer et al. 2009). Allergic rhinitis is associated with loss of quality of life. Patients with uncontrolled rhinitis report loss of sleep, fatigue, decreased school and work productivity, and problems with social activities (Leynaert et al. 2000; Majani et al. 2001). This disease also accounts for a significant economic burden. The annual cost related to allergic rhinitis medications and medical expenses has been estimated at approximately $3.5 billion (Ray et al. 1999).

Several primary and secondary prevention interventions for allergic rhinitis have been studied. However, many of the interventions continue to be inconclusive concerning the effectiveness of allergic rhinitis prevention. Different primary and secondary interventions are discussed below.

35.9 Primary Prevention

35.9.1 Allergen Avoidance

Studies to determine the effectiveness of the primary prevention of allergic rhinitis have been limited. The use of anti-dust mite encasing vs. education as a primary prevention intervention was studied in a newborn cohort. A prospective, randomized, controlled birth cohort of 696 newborns at a high risk of developing atopic disease was randomized to either intervention. No difference in the rates of sensitization or the development of allergic rhinitis was seen when comparing both groups at 2 years of age (Horak et al. 2004).

Interestingly, instead of allergen avoidance, exposure to a high dose of certain antigens may prevent further sensitization. A study assessed the association between cat and dog ownership in childhood and early adulthood and the development of atopy in a population-based birth cohort of 1037 subjects. The study showed that living with both cats and dogs was associated with a lower risk of developing atopy during childhood (at age 13) and young adulthood (at age 32). However, living with only one dog or cat was not protective against atopy. Among adults, a parental history of atopy seemed to modify the association (Mandhane et al. 2009).

35.9.2 Breast-Feeding

Breast-feeding as a primary intervention for allergic rhinitis has not been proven to be effective. A meta-analysis of six prospective studies that evaluated the association between exclusive breast-feeding for at least the first 3 months of life showed only a borderline statistically significant protective effect for allergic rhinitis (Mimouni Bloch et al. 2002). With a similar conclusion, the Tasmanian Asthma Study, a prospective cohort that followed subjects from the age of 7–44 years showed that breast-feeding did not protect against the development of allergic rhinitis in the long term (Matheson et al. 2007). Only one study has demonstrated a protective effect of breast-feeding against allergic rhinitis, but it was only seen at 3 years of age in an African American subpopulation (Codispoti et al. 2010).

35.9.3 Other Dietary Factors

35.9.3.1 Different Milk Formulas

One randomized controlled study reported a modest reduction in rhinitis symptoms (not related to colds) at 1 year of age in high-risk allergy patients. The intervention group avoided house dust mites and pet allergens, tobacco exposure limitation, encouragement of breast-feeding, or supplementation with hydrolyzed formula (Chan-Yeung et al. 2000). A German birth cohort of participants with a first-degree family history of atopy was randomized to consume different hydrolyzed formulas and cow's milk formula for the first 4 months of life. At a 10-year follow-up, no preventive effect was observed in the subjects who consumed hydrolyzed formulas compared to cow's milk formula (von Berg et al. 2013). Interestingly, in the same cohort followed 5 years later, the group that consumed extensive whey hydrolysate formula and partially casein hydrolysate formula had a lower prevalence of allergic rhinitis (von Berg et al. 2016). A Cochrane review comparing the use of soy-based formula versus cow's milk formula for at least the first 6 months of life showed no difference in the prevention of allergic rhinitis (Osborn and Sinn 2006).

35.9.3.2 Vitamin D

At present, there is insufficient evidence to recommend Vitamin D supplementation during pregnancy or childhood to prevent allergic rhinitis. A cross-sectional Korean study demonstrated that participants with atopic dermatitis had lower Vitamin D levels. However, similar results were not observed in those with allergic rhinitis (Cheng et al. 2014). A Finland cohort of subjects due to be born in 1966 and supplemented with Vitamin D for 1 year was evaluated 31 years later. It found that those supplemented with vitamin D had a higher prevalence of atopy as demonstrated by the skin-prick test and allergic rhinitis (Hypponen et al. 2004). Furthermore, a Danish longitudinal cohort showed that supplementation of Vitamin D during pregnancy had no effect in the prevention of allergic rhinitis in their offspring by 7 years of age (Maslova et al. 2013).

35.9.3.3 Antioxidants

The hypothesis that changes in the Western diet, especially with a lower level of antioxidants, play a role in the development of allergic disease has been studied. Antioxidant intake on allergic rhinitis prevention is very limited. A cross-sectional study of 2633 adults showed that higher consumption of vitamin E was associated with lower IgE serum levels and a reduction in the risk of atopy (Fogarty et al. 2000). Additional cross-sectional studies have demonstrated that adherence to a Mediterranean diet during pregnancy and childhood was inversely associated with allergic rhinitis (De Batlle et al. 2008; Chatzi et al. 2007) (Table 3).

35.10 Secondary Prevention

Prevention interventions for allergic rhinitis mostly focus on primary and tertiary strategies. Secondary prevention interventions have been mostly focused on other atopic diseases. Allergy-specific immunotherapy as a secondary prevention of allergic rhinitis has been proposed as soon as the patient becomes sensitized and before any clinical symptoms develop (Matricardi 2014). However, no results concerning this hypothesis are available.

Table 3 Effect of interventions for allergic rhinitis prevention

Intervention	Effect	Target prevention	Reference
Allergen avoidance approach Encasing bedding	–	Primary	Horak et al. 2004
Allergen exposure: pets and pests	+/–	Primary	Mandhane et al. 2009
Breast-feeding	+/–	Primary	Mimouni Bloch et al. 2002; Matheson et al. 2007; Codispoti et al. 2010
Hydrolyzed formula	+/–	Primary	Chan-Yeung et al. 2000; von Berg et al. 2013, 2016
Vitamin D	–	Primary	Hypponen et al. 2004; Maslova et al. 2013
Antioxidants	+	Primary	Fogarty et al. 2000; De Batlle et al. 2008; Chatzi et al. 2007

35.11 Primary and Secondary Prevention of Asthma

Asthma is a chronic respiratory disease characterized by a reversible bronchi obstruction manifested by recurrent attacks of wheezing and difficulty breathing. It is estimated that approximately 300 million people worldwide suffer from asthma (WHO 2007), which is associated with 250,000 annual deaths worldwide. It is related to different comorbidities including limited physical activity, obesity, a decrease in school attendance, an increase in work absence, and hospitalizations, among others. According to the Centers for Disease Control and Prevention (CDC), in 2015, approximately 24,633,000 people, or 7.8% of the U.S. population, were affected by this chronic disease. Approximately 50% of those with asthma reported having at least one exacerbation per year. This translates to a significant economic burden leading to more than 10 million physician office visits and 1.5 million emergency department visits per year (CDC).

Primary and secondary prevention strategies have been developed to improve the outcomes discussed above. However, asthma is considered a multifactorial disease. Therefore, single interventions have demonstrated ineffective results for its prevention. Furthermore, none of the prevention intervention strategies involving RCTs have contributed enough evidence to be implemented in clinical practice.

35.12 Primary Prevention

35.12.1 Allergen Avoidance

Classically, asthma phenotypes have been divided into allergic vs. nonallergic asthma. Several groups have studied allergen avoidance as a primary prevention of asthma. Overall, multifaceted interventions have demonstrated better outcomes for the risk of childhood asthma (Van Schayck et al. 2007; Maas et al. 2009). A Cochrane review of three multifaceted studies (the Canadian Asthma Primary Prevention Study [CAPPS], the Isle of Wight study, and the Prevention of Asthma in Children [PREVASC] study) of children at a high risk of developing asthma demonstrated that multifaceted interventions are superior to mono-allergen reduction for the prevention of asthma (<5 years: OR 0.72, 95% CI 0.54–0.96; >5 years: OR 0.52, 95% CI 0.32–0.85). Mono-aeroallergen interventions were not superior to the controls (Maas et al. 2009).

Mite sensitization is a risk factor for atopy. The primary prevention of sensitization is of paramount importance. Gehring et al. randomized pregnant atopic mothers to receive impermeable mattress covers, placebo covers, or no intervention upon the birth of their infants (Gehring et al. 2012). The children were followed for 8 years for the onset of asthma, allergic rhinitis, allergen sensitization, and bronchial response. The impermeable covers group had a lower concentration of Der f 1 but not Der p 1 and fewer asthma

symptoms at 2 years but not at 8 years of age. Over the long term, no differences between the groups were noted in sensitization or atopic disease onset. The study failure may be explained because sensitization could have occurred at places other than the child's bedroom.

Recent reports have suggested that early exposure to high indoor levels of pet and pest allergens in the first 3 years of life protected children from developing asthma by the age of 7 (O'Connor et al. 2018). Perzanowski et al. found that living with a cat was inversely related to having a positive skin test to cat and incidence of physician-diagnosed asthma (RR, 0.49 [0.28–0.83]); this effect was most pronounced among the children with a family history of asthma. Weaker protective trends were seen with dog ownership in this study (Perzanowski et al. 2002). The association between exposure, sensitization, and atopy is not linear (Schram-Bijkerk et al. 2006). Other host and environmental factors may play a role in establishing atopic disease, as discussed in the last section.

35.12.2 Breast-Feeding

Breast-feeding as the primary prevention of allergic diseases and asthma has been a popular topic of investigation. However, its effectiveness remains controversial. Two cohort studies showed that exclusive breast-feeding until 4 months of age led to a substantial reduction in the risk of developing asthma by 6 years of age (Oddy 2000; Silvers et al. 2012). Similarly, another cohort study demonstrated that breast-feeding for at least 4 months reduced the risk of asthma by 8 years of age and had beneficial effects on lung function (Kull et al. 2010). In addition, a longer duration of breast-feeding despite the introduction of other food groups was associated with protection from non-allergic asthma but not allergic asthma (Nwaru et al. 2013). On the contrary, a different cohort study demonstrated that children breast-fed for more than 4 months had greater environmental sensitization and increased risk of developing asthma (Sears et al. 2002). A recent cohort study of more than 300,000 participants showed no evidence of asthma protection from breastfeeding (Ek et al. 2018).

35.12.3 Maternal Smoking During Pregnancy

Maternal smoking during pregnancy has been associated with fetal lung structure development, increased risk of preterm birth, and reduced lung function (Lodrup Carlsen et al. 1997; Broughton et al. 2007). Maternal smoking during pregnancy was associated with fetal epigenetic changes in areas related to different diseases, including asthma (Joubert et al. 2016). These factors translate to an increase risk of asthma development not only during childhood but also in adulthood (Miyake et al. 2005; Gilliland et al. 2001; Grabenhenrich et al. 2014; Xepapadaki et al. 2009).

35.12.4 Other Dietary Factors

The role of multiple vitamins and supplements has been assessed as a preventive intervention for asthma. Contradictory or insufficient data have led to inconclusive roles of different dietary factors for the prevention of asthma.

35.12.4.1 Vitamin D

Low levels of vitamin D, especially during pregnancy, have been associated with different aspects of allergy. Although a Cochrane review found that Vitamin D supplementation reduced the risk of asthma exacerbation, prevention of this disease and the use of this vitamin has not been found (Martineau et al. 2016). Most of the available studies have been performed in pregnant women with the objective of studying the role of primary prevention of allergic diseases in their offspring with prenatal vitamin D supplementation. However, these studies have not shown an effect in reducing the risk of asthma or wheezing in their children (Gale et al. 2008; Chawes et al. 2016; Litonjua et al. 2016).

Table 4 Effect of interventions for asthma prevention

Intervention	Effect	Target prevention	Reference
Allergen avoidance approach Multifaceted	+/−	Primary	Van Schayck et al. 2007; Maas et al. 2009; Gehring et al. 2012
Allergen exposure: pets and pests	+	Primary	O'Connor et al. 2018; Perzanowski et al. 2002
Breast-feeding	+/−	Primary	Oddy 2000; Silvers et al. 2012; Kull et al. 2010; Nwaru et al. 2013; Sears et al. 2002; Ek et al. 2018
Maternal smoking in pregnancy	−	Primary	Lodrup Carlsen et al. 1997; Broughton et al. 2007; Joubert et al. 2016; (Miyake et al. 2005; Gilliland et al. 2001; Grabenhenrich et al. 2014; Xepapadaki et al. 2009
Vitamin D	−	Primary	Martineau et al. 2016; Gale et al. 2008; Chawes et al. 2016; Litonjua et al. 2016
Omega 3 supplements	+/−	Primary	Gunaratne et al. 2015; Hansen et al. 2017; Bisgaard et al. 2016
Pre- and probiotics	−	Primary	Osborn and Sinn 2007; Cuello-Garcia et al. 2017
Immunotherapy	+/−	Secondary	Jacobsen et al. 2007; Valovirta et al. 2018
Pharmacotherapy			
Cetirizine Ketotifen Inhaled corticosteroids	+ + −	Secondary	Wahn 1998; Warner and Child 2001; Iikura et al. 1992; Bustos et al. 1995; Murray et al. 2006

35.12.4.2 Fish Oil

Different RCTs about supplementation of n-3 (or omega 3) long-chain polyunsaturated fatty acids (LCPUFA) during pregnancy were evaluated in a 2015 Cochrane review (Gunaratne et al. 2015). It concluded that the available data were limited to support fish oil supplementation during pregnancy to reduce asthma onset in offspring. However, other studies demonstrated a primary prevention of asthma with supplementation of n3-LCPUFA during pregnancy (Hansen et al. 2017; Bisgaard et al. 2016). However, long-chain polyunsaturated fatty acid supplementation during infancy did not affect the risk of developing asthma (Schindler et al. 2016).

35.12.4.3 Prebiotics and Probiotics

The disruption of human microbiota has been associated with numerous metabolic and immune disorder, including the development of allergies. However, the data available about the use of prebiotic or probiotic as a primary prevention of asthma do not support the use of these products for this objective (Osborn and Sinn 2007; Cuello-Garcia et al. 2017) (Table 4).

35.12.5 Secondary Prevention

Secondary prevention of asthma is concentrated in sensitized patients with a high risk of developing this disease but who have not yet presented any kinds of symptoms. The development of asthma in patients with allergic rhinitis and atopic dermatitis has been well documented. The Modified Asthma Predictive Index (mAPI), which includes inhalant allergen sensitization as a major criteria, showed a high predictive value after a positive test (with a positive likelihood ratio ranging from 4.9 to 55) for asthma development at years 6, 8, and 11 (Chang et al. 2013; Guilbert et al. 2004). We will discuss the evidence of different approaches to prevent asthma in high-risk individuals.

35.12.5.1 Immunotherapy

Allergen-specific immunotherapy has long been studied for the control of asthma and allergy symptoms. It is the only treatment available that has disease-modifying potential. Immunotherapy to aeroallergens can prevent new sensitizations in recipients (Des Roches et al. 1997; Eng et al. 2002; Pajno et al. 2001). However, its role in the

prevention of asthma remains debatable. A 3-year course of specific subcutaneous immunotherapy in patients with allergic rhinoconjunctivitis showed fewer subjects developing asthma at a 10-year follow-up (Jacobsen et al. 2007). However, treatment with sublingual immunotherapy tablets for 5 years did not lead to differences in the time of asthma onset in children with rhinoconjunctivitis (Valovirta et al. 2018).

35.12.5.2 Pharmacotherapy

As discussed above, atopic dermatitis and allergic rhinitis usually precede the development of asthma. The use of cetirizine in patients with atopic dermatitis prevented a subgroup of patients from developing asthma. This subgroup of children was sensitized to grass pollen or house dust mites (Wahn 1998; Warner and Child 2001). Similar results were observed in a small study of patients with atopic dermatitis with elevated IgE serum levels who received oral ketotifen for 1 year. At the end of the study, ketotifen use was associated with asthma prevention in patients with atopic dermatitis (Iikura et al. 1992; Bustos et al. 1995).

The use of on inhaled corticosteroids (ICS) has been studied to determine whether they can prevent the development of asthma later in life. However, early ICS use did not prevent the development of asthma later in childhood (Murray et al. 2006).

35.13 Allergy-Specific Measures

35.13.1 House Dust Mites

Mites are one of the most prevalent allergens worldwide, particularly in the tropics, with a mean prevalence of 21.7% according to the European Community Respiratory Health Study (Bousquet et al. 2007) (Table 5). The most two

Table 5 Effect of interventions for allergens

Intervention	Effect	Allergen target	Reference
Tightly woven encasing bed cover	++/–	Mites	Peroni et al. 2004; Arroyave et al. 2014; Tsurikisawa et al. 2016; Murray et al. 2017; Barry 2017; Marx and Sloan 2003; Woodcock et al. 2003
Air conditioner and high efficiency dehumidifiers	+/–	Mites	Arlian et al. 2001b; Custovic et al. 1995
Washing bedding in detergent	+	Mites	Arlian et al. 2003; Choi et al. 2008
	+	Pets	Patchett et al. 1997
Filtered vacuums	+	Mites	Vaughan et al. 1999; Hegarty et al. 1995; Ong et al. 2014; Colloff et al. 1995
	+/–	Pets	Portnoy et al. 2012; Popplewell et al. 2000; Woodfolk et al. 1993
Acaricides	–	Mites	Woodfolk et al. 1995; Rebmann et al. 1996
HEPA filters	–	Mites	Mcdonald et al. 2002
	+/–	Pets	Sulser et al. 2009
Education and home testing	+	Mites	Winn et al. 2016
	+	Roaches	Jeong et al. 2006
	+/–	Rodents	Matsui et al. 2017
Multifaceted intervention	+/–	Mites	Gotzsche and Johansen 2008; Dimango et al. 2016; (El-Ghitany and Abd El-Salam 2012; Stillerman et al. 2010
	+/–	Rodents	Dimango et al. 2016
	+	Pets	Francis et al. 2003; Wood et al. 1998; Green et al. 1999
Mitigation	+	Pets	Arlian et al. 2001a
	+	Mold	Sauni et al. 2015
Removal pets	+	Pets	Portnoy et al. 2012; Wood et al. 1989
Washing pets	+/–	Pets	Hodson et al. 1999; Avner et al. 1997

important dust mites are *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae.* They thrive in hot, humid, dark, and poorly ventilated places. Control, mitigation, and abatement measures consider these environmental factors.

35.13.1.1 Allergens

More than 30 allergens have been recognized in mites based on IgE binding among sensitized individuals. These allergens have been sequenced, and their structures and functions are defined. Although an extensive description of allergens is not in the scope of this chapter, the most important ones will be emphasized.

Der p 1 and Der f 1 are cysteine proteases capable of breaking mucosal epithelial integrity (Wan et al. 1999). They release low-affinity IgE from B cells, induce higher IgE production, and promote eosinophil survival and activation (Shakib et al. 1998; Wang 2013). Der p 2 and Der f 2 are lipid-binding proteins. They are homologous to MD-2-related lipid-recognition (ML) domain, a toll-like receptor (TLR) 4 cofactor that induces Th2 inflammation independent of IgE (Ichikawa et al. 2009).

Groups 3, 6, and 9 allergens are serine proteases, while groups 2, 7, and 10 are nonprotease allergens that interact with lipopolysaccharides and increase inflammation through TLR 2 upregulation. Proteases activate the epithelium through protease activation receptor (PAR) (Yin et al. 2018; Dumez et al. 2014). Both types of antigens are synergistic in their inflammatory effects.

Groups 5 and 21 are the dominant allergens in *Blomia tropicalis*, a mite species prevalent in the tropics (Kidon et al. 2011). Der p 10 is a tropomyosin common to many arthropods and crustaceans and is responsible for cross-reactivity. Der p 11 is homologous to paramyosins localized on the mite's muscles and is a major allergen in patients with atopic dermatitis (Banerjee et al. 2015). Der p 23 is an important allergen localized in the mite midgut and fecal particles that induces basophil activation in vitro and is highly allergenic (Weghofer et al. 2013). Der f 31, or cofilin, is a novel allergen that plays a role in Th2 inflammation by ILC 2 in the lungs (Lin et al. 2018; Wang et al. 2017). Der f 35, an MD-2 allergen, cross-react with Der f 2 and play an important role in storage mite allergy (Fujimura et al. 2017).

A dose above 1.2 μg/g Der p 1 or 0.2 μg/g Der f 1 exposure is considered the threshold for sensitization (Filep et al. 2012; Platts-Mills et al. 1995; Rosenstreich et al. 1997; Vervloet et al. 1991). Once sensitized, lower doses of exposure are sufficient to increase the use of rescue medications in asthmatic children.

35.13.1.2 Avoidance Measures

Several interventions have been used to control mite populations. These methods include physical measures (humidity, temperature control, and vacuum cleaning), barrier methods (mattress and pillow covers), air filtration systems, and chemical methods (acaricides). These measures along with the role of education will be discussed in this section.

Mites grow exponentially with increasing relative humidity (Oribe and Miyazaki 2000). Maintaining a relative humidity below 50% in a temperate climate with a high-efficiency dehumidifier (100 pints of water/day) and air conditioning achieved a significant decrease in mite levels compared to air conditioning alone or opening windows (Arlian et al. 2001b). Maintaining such humidity levels is particularly daunting during the summer months or in tropical environments worldwide. A single portable dehumidifier placed centrally in the house was unable to decrease indoor humidity to levels required to prevent mitigation (Custovic et al. 1995). Air leakage and condensation from the cooling units provided additional sources of water that contributed to the indoor relative humidity level. However, in semiarid environments, this is not a concern since evaporative cooling does not achieve sufficient relative humidity to support mite growth (Johnston et al. 2016).

Mites are temperature sensitive. Extreme temperatures above 130 °C or below −70 °C are lethal. Washing bedding in cold or warm water with a detergent or a combination of detergent and bleach killed most mites (Arlian et al. 2003). Increasing the number of rinses improved mite killing, regardless of the laundering temperature,

except for steam cleaning (Choi et al. 2008). Freezing food or stuffed animals killed mites but did not eliminate them (Feichtner et al. 2018).

Even dead mites can induce symptoms. Removal of infested furniture, carpets, and mattresses is important. Single-layer vacuum cleaners perform poorly compared to 2–3 layers of microfiltration (Vaughan et al. 1999). Filtered vacuums and steam vapor produce lower concentrations of airborne Der p 1 compared to conventional vacuums (Hegarty et al. 1995; Ong et al. 2014; Colloff et al. 1995). Of note, personal exposure to HDM increased even while cleaning with high-efficiency vacuum cleaners (Gore et al. 2006).

Acaricide treatment of carpets including tannic acid had limited effectiveness and duration of activity (Woodfolk et al. 1995). Benzyl benzoate was not more effective than frequent cleaning for mite control (Rebmann et al. 1996). Air filtration with high-efficiency particulate air (HEPA) filters was of limited benefit as a single measure (Mcdonald et al. 2002).

Impermeable mattress covers for dust mite control are widely recommended by professional groups and physicians. There are wide variations in the covers available in the market. Tightly woven (<6 μm), air permeable, and washable covers provide optimal allergen control (Peroni et al. 2004). Arroyave et al. conducted a meta-analysis evaluating whether impermeable mattress covers were effective at reducing allergic symptoms or avoiding their development (Arroyave et al. 2014). The pooled data failed to demonstrate any benefit from the use of impermeable covers compared to placebo for the prevention of dust mite sensitization, allergic rhinitis, wheezing, asthma, and atopic dermatitis onset. Moreover, no effect was found on peak flows or nasal or asthma symptom scores despite a notable decrease in mite levels in the mattresses of the treatment group. The study was criticized for how the authors selected research for inclusion, the heterogeneity of the exposure data, and the health outcomes selected (Van Boven 2014; Platts-Mills 2008). Tsrikisawa et al. compared the effect of impermeable covers, vacuum cleaning, and placebo in Der p1 levels, peak flow, and fractional exhaled nitric oxide (FeNO) measures among 111 adult asthmatics (Tsurikisawa et al. 2016). Murray et al. randomized 284 mite-sensitized children who presented at hospital emergency departments for asthma exacerbation into those receiving mite-impermeable or placebo bed encasing (Murray et al. 2017). After a 12-month intervention, asthma exacerbations requiring emergency room care were significantly reduced by 45%. Hospitalizations decreased in the bed encasing group from 41.5% to 29.3% in the control group, although not by a statistically significant difference. The need for steroid rescue for asthma exacerbation was similar in both groups. Subgroup analysis suggested that the intervention was most effective in younger children, those not exposed to tobacco, mite monosensitized subjects, and those with more severe asthma. Similarly, mite-sensitized children who had been previously hospitalized for asthma were randomized into groups using impermeable or permeable covers. Those who received the impermeable covers had decreased exacerbations requiring hospital visits (29% vs. 42%, number to treat 9). The cost of the impermeable covers and compliance with their use were potential concerns for broad utilization (Barry 2017). However, asthmatic adults recruited from general practice and randomized to receive bed covers or placebos had no significant improvement in symptoms, peak flows, or mite level reduction after the intervention (Marx and Sloan 2003; Woodcock et al. 2003).

Educational interventions to decrease HDM allergen content have been examined. Winn et al. conducted a randomized clinical trial of HDM education with the addition of an HDM rapid immunoassay kit for determination of mite levels in the homes of HDM-sensitized children (Winn et al. 2016). Dust samples were collected 1 year after intervention and the allergen levels were compared among the groups. The intervention group had lower concentrations of dust mites compared to the group receiving education alone. Unfortunately, no assessment of the clinical symptoms was done prior to or after intervention. The study supports the beneficial role of kits for the assessment of HDM levels to increase compliance with educational recommendations.

35.13.1.3 Multifaceted Interventions

Gotzshe et al. conducted a meta-analysis that failed to show the benefit of physical or chemical methods to decrease HDM exposure in asthma outcomes (Gotzsche and Johansen 2008). DiMango et al. failed to show any benefit of two multifaceted interventions or placebo in asthma clinical outcomes and sensitization to common aeroallergens among asthmatics residing in New York (Dimango et al. 2016). The multifaceted measures involved an educational module on allergen control, mattress covers, cleaning products, Electrolux® vacuums, Swiffer mops, and HEPA filters in the bedroom. However, a different randomized placebo-controlled experiment evaluated physical (mattress and pillow covers, washing bedding and toys, removing carpets, and/or vacuuming more than once per week), chemical (tannic acid), both, or no interventions in peak expiratory flow, forced expiratory volume (FEV) 1, and hospitalizations for asthma among 160 children (El-Ghitany and Abd El-Salam 2012). All the intervention groups had decreased HDM concentrations in collected dust, particularly in the physical measure groups. The subjects in the physical measure intervention group had decreased asthma severity and improved FEV1 compared to the controls, whereas those in the chemical intervention group had only improved lung function. Thus, contrary to the meta-analysis, simple physical measures effectively reduced asthma symptoms in a pediatric population in Egypt with high mite sensitization rates and humidity levels (74%).

Sheik et al. conducted meta-analyses of the effect of HDM control measures on allergic rhinitis (Sheikh et al. 2007, 2010). Among seven studies evaluated, intervention measures included mattress covers, acaricides, HEPA filters, and a combination of interventions. Most of the trials effectively reduced mite concentrations, particularly those using acaricides. Isolated use of mattress covers was not effective. No change in specific IgE or sensitization was noted between the groups. In another study, a 2-week crossover trial was conducted on the use of personal air filtration within a pillow encasement or placebo in adults (Stillerman et al. 2010). Allergic rhinitis symptoms, quality of life, and allergen dust content were compared. The intervention group had a decrease in allergen size particles and nasoocular symptoms and improved quality of life compared to the placebo group.

To summarize, although meta-analysis failed to show the benefits of most physical methods, selected populations of symptomatic high-risk subjects, particularly children, may benefit the most from the use of mattress covers and other environmental control measures. Multiple interventions are costly and require sustained application to maintain their effectiveness.

35.13.2 Roaches

Roach allergy is associated with asthma morbidity and poor health outcomes, particularly in inner cities. Recent articles demonstrated the increasing rate of roach infestation in human dwellings worldwide (Nasirian 2017). More than 30 roach species infest human dwellings, and 4 are particularly common: *Periplaneta americana*, *Blomia germanica*, *Blomia orientalis*, and *Supella longipalpa*.

Roaches grow in small tight spaces in tropical and subtropical regions. They require water, food, and access to buildings. Carlson et al. evaluated the origin of roach infestations in inner-city homes. By marking and collecting roaches in homes, it was determined that they entered from backyards instead of sewers (Carlson et al. 2017). Once roaches inhabit a building, humans may not notice their presence until elevated levels are reached, mostly during infestations. Asking patients to place bait or measuring roach antigens in dust samples is advised to assess levels of roach antigen exposure in houses and buildings.

35.13.2.1 Allergens

Roaches cross-react among themselves as well as with other insects and arthropods. Bla g 1 is found in roaches' fecal material and induces Th2 inflammation. Bla g 2 is an inactive aspartic proteinase found in roach feces. Bla g 4 is a calycin. Bla g 5 is a glutathione-S-transferase. Bla g 7 is a tropomyosin, as are Per 7 and Der p 10 (Arruda et al. 2001;

Arruda and Chapman 2001). Most of the other roach allergens are found in their bodies. Per a 2 and 10 are markers of long-term roach infestation while Per a 9 is a marker of current roach control, providing help in evaluating the status of roach infestation by measuring component analysis from dust samples (Lee et al. 2016).

Bla g 2 levels above 0.04 μg/g in dust are linked to sensitization and above 0.08 μg/g to disease and symptoms. Children sensitized and exposed to cockroaches have increased risk of hospitalizations and unscheduled visits to physicians for asthma care (Portnoy et al. 2013) (Rosenstreich et al. 1997; Eggleston et al. 1998).

35.13.2.2 Avoidance Measures

The elimination of food and water reservoirs, entrance pathways, and environments that enable roaches' growth and reproduction are important mitigation measures. Integrated pest-management programs, preferably by professional personnel, combined with the judicious use of pesticides with bait stations and gels are useful (Appel 1992). However, continued application is required. Although boric acid effectively kills roaches, it paradoxically increases the production of roach allergens among the survivors (Zhang et al. 2005). HEPA filters do not effectively reduce roaches' allergen levels due to the large size of the particles, although they have not been evaluated in a randomized trial (De Lucca et al. 1999).

For abatement, infested materials should be removed. Carpets should be removed or cleaned with a HEPA vacuum, and mattress covers and mattresses should be replaced (Brown et al. 2014).

Effective integrated pest-management programs decrease roach infestations, asthma symptoms, and morbidity (Zha et al. 2018; Wang and Bennett 2006), but their ample implementation is limited by cost. Rabito et al. conducted a randomized controlled trial on the effect of insecticidal bait pheromone sticky traps on morbidity among inner-city children with moderate to severe asthma. Asthma morbidity and symptoms decreased in the intervention group particularly after the first 6 months of the intervention (Rabito et al. 2017). Entomologist placed baits were more effective than commercial exterminators in achieving a reduction in roach antigens (Sever et al. 2007). Traditional insecticides are effective but toxic to humans. The natural pesticide 2-undecanone is a biopesticide that effectively reduces roaches (Zhu et al. 2018).

The role of a 2-year education program on mite and roach control on the levels of allergen in houses was tested. Education included the use of bed covers, washing bedding weekly, decreasing humidity below 50%, removing carpets, vacuuming frequently, the use of roach traps and insecticides, and protecting stored food. The participants answered questions during each home visit for allergen measurement. At the end of 2 years, the levels of mite and roaches had decreased significantly from the baseline value (Jeong et al. 2006).

To summarize, roach infestation is associated with asthma onset and severity. Integrated pest-management measures, although effective, are limited by the cost and need for continued application. New strategies that can be widely applicable must be entertained for roach control.

35.13.3 Rodents

Rodent allergy is a recognized cause of occupational health disease. Exposure and sensitization outside of the workplace has recently been recognized as a cause of asthma, particularly in urban settings. Exposure in the first year of life is an independent risk factor for wheezing and atopy later in life (Phipatanakul et al. 2000; Sedaghat et al. 2016).

35.13.3.1 Allergens

Urine is the main source of allergens in rodents. Allergens can also be found in dander, hair, saliva, and serum. Allergen size ranges from 0.4–10 μm and thus can remain airborne for an extended time. The major allergen is Mus m 1, a prealbumin member of the lipocalin family. Mus m 2 1 is an albumin found in serum, dander, and hair (Wood 2001).

Sensitization occurs at levels higher than 1.6 μg/g dust (Phipatanakul et al. 2000; Pongracic et al. 2008). Exposure not only takes place at home or in the workplace; elevated levels of

rodent allergen have been detected in schools where children could become sensitized.

35.13.3.2 Avoidance Measures

Integrated pest management has been recommended to reduce allergen exposure (Krieger et al. 2010). It involves mitigation, elimination of infested sources, and removal of reservoirs. Rodent traps include snap traps, live traps, and glue boards. Rodenticides may be required if traps are ineffective but must be used with caution.

DiMango et al. conducted a randomized controlled trial comparing multifaceted indoor allergen avoidance against pets, mites, roaches, and mice with pharmacologic guideline-based asthma treatment in adults and children living in New York. Allergen levels decreased after the intervention, but asthma outcomes and need for medication did not differ among the groups (Dimango et al. 2016).

The role of education compared to integrated pest-management was evaluated among mouse-sensitized children with asthma (Matsui et al. 2017). After a 1-year intervention, a 50% reduction in mouse allergen levels reduced asthma symptoms and morbidity significantly, although no difference in outcomes was identified in the intervention groups. Implementation of educational measures for rodent control is more affordable than pest-management programs and can play a broader role in communities, particularly in those with restricted budgets.

35.13.4 Molds

Molds are ubiquitous in nature. Although found in large concentrations in the environment, most are not implicated in human disease. However, dampness has been associated with increased asthma morbidity and impaired lung function and airway hyperreactivity, particularly in children.

Mold sensitization is close to 10% among those with atopy within the general population worldwide (Salo et al. 2011). Several issues have limited the study of molds, including multiple life forms and difficulty with quantification, identification, and growth requirements. Mold-sensitized subjects had poor asthma control and earlier disease onset and increased risk of mechanical ventilation and intensive care use compared to nonsensitized subjects (Byeon et al. 2017; Masaki et al. 2017). Sensitization to *Aspergillus spp.* and *Penicillium spp.* was a risk factor for asthma severity (Tanaka et al. 2016). Mold exposure enhances Th2 response independent of mold sensitization. β-glucan mediates IL-17A activation and promotes steroid resistance (Zhang et al. 2017).

35.13.4.1 Allergens

Alt a 1 is a nonspecies-specific allergen recognized in *Alternaria alternata*, *Botrytis spp.*, and *Stemphyllum botryosom*. It is a marker of primary sensitization and the main cause of airborne mold allergy (Moreno et al. 2016; Gabriel et al. 2016). Alt a 6, Cla h 6, Hev b 9, Asp f 22, and Pen c 22 are enolases. Other allergens include dehydrogenases, antioxidants, and heat shock proteins, among others (Kespohl and Raulf 2014).

35.13.4.2 Avoidance Measures

Mold remediation involves building design and ventilation that avoids dampness (Small 2003). Flooding, uncontrolled airflow, or inadequate barriers to rainwater are the most common causes of molds. Attention must be paid to window installation, heating, ventilation, and air conditioning, with assessment by an indoor environmental professional. Remediation involves eliminating sources of water damage and contaminated materials (Barnes et al. 2016).

Remediation decreases indoor spore concentration, symptoms, and health care use among asthmatic children in homes with mold after a 1-year intervention (Barnes et al. 2007; Kercsmar et al. 2006). Sauni et al. conducted a meta-analysis of the effect of mold remediation in houses and schools by the removal of wet structures, use of fungicides, and prevention of further damage by correcting water leakage (Sauni et al. 2015). They concluded that there is moderate quality evidence that remediation measures decrease asthma-related symptoms and medications, although not in children (Sauni et al. 2015). Large randomized controlled trials to evaluate the effect of primary, secondary, and tertiary measures against mold damage are needed.

35.13.5 Pollen

Pollen sensitization is one of the main triggers of seasonal allergies. It is estimated that 10–30% of the global population is affected and this is expected to increase (WAO 2011). Importantly, due to global warming, the pollen seasons are changing (Lake et al. 2017). Climate changes can cause a variety of effects on pollen, which might be significant for pollen-allergic patients. New allergenic pollen types may appear, and trees might produce larger quantities of pollen, which could result in more severe symptoms. The pollen season could become longer, extending the period during which patients suffer from allergy symptoms (De Weger and Hiemstra 2009).

35.13.5.1 Allergens

Most known pollen allergens predominantly come from wind-pollinated angiosperms and gymnosperm grasses, weeds, and trees. Pollen allergens can be classified as three types: those that are ubiquitous, those that are present in a limited number of plant families, and those that are restricted to a single plant family or order (Grote et al. 2003). Most pollen allergens are distributed within 29 protein families from a total of 2615 seed plant families. The major pollen allergen families include pathogenesis-related group 10 (PR-10 proteins), profilins, calcium-binding proteins, and expansions (Chapman et al. 2007). Exposure to pollen can be seasonal, as seen with tree pollen in spring and grasses and weeds from summer through autumn. Perennial exposure is also seen since pollen allergens have been found in house dust in combination with pet, dust mite, and cockroach allergens. Humidity, rain, and/or thunderstorms can cause the rupture of pollen grains, releasing hundreds of small starch particles into the air. These particles have high allergenic potential because they can move into the respiratory tract and cause disease (Knox 1993).

35.13.5.2 Avoidance Measures

Once disease has developed, there are measures that can be followed to diminished pollen allergens at home. Allergen avoidance is difficult.

HEPA filters are frequently recommended as a component of environmental control measures for patients with allergic diseases. However, there is no specific evidence of using HEPA filters to decrease pollen allergens indoors, as is seen with cats and dogs.

It is known that pollen is found indoors through wind entering by opening doors, windows, or any other place that allows entrance. Reducing ventilation could reduce levels of indoor pollen allergens. However, no studies support this.

Available pollen immunotherapy has been successful in preventing the development of new sensitizations and provides long-term relief after discontinuation (Eng et al. 2002).

35.13.6 Pets

Approximately 50% of U.S. households have pets, and more than 161 million of these are cats and dogs. According to the American Pet Products Association (APPA), as of June 2017, approximately 47% of households owned dogs, while approximately 37% owned cats (APPA 2018). The prevalence of allergy to furry animals has been increasing, and cats and dogs are major risk factors for the development of atopic diseases including asthma and rhinitis (Perzanowski et al. 2002). Sensitization to cats and dogs is relatively common; approximately 12% of the general population and 25–65% of children have persistent asthma due to these pets. In addition, 44.2% and 30.0% of asthma attacks were attributable to exposure to high levels of dog and cat allergens in the bedroom among patients with asthma sensitive to dogs and cats, respectively (Gergen et al. 2018).

35.13.6.1 Allergens

Both cats and dogs have many recognized allergens with a variety of biologic and immunologic characteristics. The significant cat allergens are Fel d 1 (uteroglobin), Fel d 2 (albumin), Fel d 3 (cystatin), Fel d 4 (lipocalin), Fel d 5 (IgA), Fel d 6 (IgM), Fel d 7 (lipocalin/Von Ebner's gland protein), and Fel d 8 (latherin). However, the major cat allergen is Fel d 1; up to 90% of

cat-allergic individuals are sensitized to it (Reininger et al. 2007). The major dog allergens include Can f 1 (lipocalin), Can f 2 (lipocalin), Can f 3 (albumin), Can f 4 (odorant binding/prostatic kallikrein lipocalin), Can f 5 (trypsin-like protease), and Can f 6 (lipocalin). Can f 1 and Fel d 1 are found in the hair, dander, and saliva of dogs and cats, respectively. Can f 1 and Fel d 1 are universally present in U.S. homes because they are transported on small particles (<10–20 μm) that allow airborne dispersion (Arbes et al. 2004; Custovic et al. 1997). Due to the transportability of these allergens on clothing and surfaces, even if patients without a dog or cat live in communities with a high prevalence of pet ownership, their pet allergen exposures at home will likely be above allergic sensitization thresholds and may possibly induce allergic symptoms (Arbes et al. 2004).

There is controversy regarding whether early dog and cat exposure can reduce the risk of development of sensitization. However, multiple studies have shown that early life exposure to cats and dogs is associated with a reduced risk of later allergic disease. Hesselmar et al. assessed the relationship between exposure to pets in early life, family size, allergic manifestations, and allergic sensitization at 7–9 and 12–13 years of age. They found that children exposed to cats during the first year of life were less often SPT positive to cats at 12–13 years (Hesselmar et al. 1999). Another study investigated the relationship between current exposure to cat allergens and sensitization to cats through a questionnaire, skin-prick testing, and home visits for the collection of dust samples. It found that prevalence of sensitization to cats was significantly decreased in the lowest and the highest exposure groups (Custovic et al. 2001). Similarly, the prevalence of any skin-prick test positivity at age 6–7 years was 33.6% with no dog or cat exposure in the first year of life, 34.3% with exposure to 1 dog or cat, and 15.4% with exposure to 2 or more dogs or cats (Ownby et al. 2002). These results suggest that the degree of sensitization is not associated with increasing or decreasing concentrations of these allergens, although other studies identified dose effect related to sensitization.

35.13.6.2 Avoidance Measures

Once allergic disease has developed, avoiding exposure is the most important measure. Pet avoidance is the most effective long-term approach to manage dog and cat allergy. Patients should be advised to consider removing the cat or dog from the environment (Portnoy et al. 2012). There is one prospective, nonrandomized, non-blinded observational study that examined the effect of pet removal from homes on pulmonary function testing, airway hyperresponsiveness, and medication use. It included 20 symptomatic patients with newly diagnosed pet allergic asthma who had domestic animals, including hamsters, cats, dogs, and ferrets and were sensitized to them. The clinical characteristics were compared between the patients who gave away their pets and those who refused to give away their pets. It was found that removal of pets from homes reduces airway responsiveness in patients with pet allergic asthma more than optimal pharmacotherapy alone, thus allowing a decrease in inhaled corticosteroid doses (Shirai et al. 2005). The effect of cat removal on cat allergen content in the home was evaluated. Serial house dust samples were collected from 15 homes during a 9- to 43-week period after cat removal. Fel d 1 levels dropped gradually in most homes, and by 20–24 weeks after cat removal, 8 of 15 reached levels consistent with those found in control homes without cats (Wood et al. 1989).

As stated above, removing the pet is the best alternative for long-term control. However, many patients are unwilling to remove their pets from their home. Therefore, other alternatives must be offered. The pet should be kept out of the bedroom, if possible outdoors or in a well-ventilated area of the house. This at least will decrease allergen load in the bedroom where people spend most of their time.

Washing dogs and cats has been an alternative suggested to patients sensitized to them. There are studies of dogs that concluded that washing a dog reduces allergen from dog hair and dander. However, a dog needs to be washed at least twice a week to maintain low levels of Can f 1 from its hair (Hodson et al. 1999). Washing cats by immersion will remove significant amounts of allergens,

preventing Fel d 1 from becoming airborne. Nevertheless, the decrease is not sustained at 1 week (Avner et al. 1997). Washing pets regularly can be complicated, especially cats. This measure does not provide a durable benefit as a sole measure.

The use of HEPA filters for the reduction of indoor pet allergens has been established but no significant clinical benefits have been appreciated (Sulser et al. 2009). The effect of a using a HEPA cleaner on cat-induced asthma and rhinitis demonstrated a reduction in airborne allergen levels but no difference was detected in settled dust allergen levels, nasal symptom scores, chest symptom scores, or rescue medication use. More benefit was seen when HEPA cleaner was combined with mattress and pillow covers and cat exclusion from the bedroom (Wood et al. 1998). Similar results were seen with dog allergens. HEPA air cleaners alone reduced airborne Can f 1 in homes with dogs. However, preventing the dog from accessing the bedroom and possibly the living room in combination with HEPA air cleaners was more effective in reducing the total allergen load inhaled (Green et al. 1999). The use of HEPA air cleaners in the living room and bedroom for 12 months combined with HEPA vacuum cleaners compared to HEPA vacuum cleaners alone in the homes of asthmatics with pets showed the effectiveness of combination therapy. Approximately two-thirds of the subjects in the HEPA filter with vacuum cleaner group showed clinical improvement compared to less than one-third of those using a HEPA vacuum alone after a 12-month intervention. No difference in lung function was seen between these groups (Francis et al. 2003).

Removing pet reservoirs is an additional recommendation to patients sensitized to pets. It includes the removal of furnishing, beds, clothing, and carpets. Carpets were the main reservoir for pet allergens in homes with pets (Arlian et al. 2001a). Furthermore, a carpet accumulates cat allergen at ~100 times the level of a polished floor. Moreover, air filtration was effective only if carpeting was not used (De Blay et al. 1991). Changing and washing clothes regularly is recommended since Fel d 1 is transported from the home to schools, offices, hospital corridors, and stores (Patchett et al. 1997). Fel d 1 also has been found in T-shirts and its concentration increases with exposure to cats. Therefore, it is said to be ubiquitous due to its presence in cat-free places as it is transported on the clothing of people with cats (Enberg et al. 1993).

The consistent use of high-efficiency vacuum cleaners or central vacuum cleaners is associated with reduced exposure to dog and cat allergens in homes where cats and/or dogs are present. This does not translate to clinical benefits (Portnoy et al. 2012). There are several studies using different vacuum systems: high efficiency, central, and microfilter. Their efficacy on reducing pet allergen loads or allergic diseases varied. In one study with allergic children and no pets, none of the three vacuum systems reduced Fel d 1 and Can f 1 (Popplewell et al. 2000). Nevertheless, vacuum cleaners with HEPA filters and double thickness bags removed allergens from dust without leaking Fel d 1 and Can f 1 (Woodfolk et al. 1993). Interestingly, one study demonstrated clinical the benefits of the long-term use of high-efficiency vacuum cleaners. Popplewell et al. reported a significant reduction in Fel d 1 in dust samples from the living room, bedroom carpet, mattress, and living-room sofa after 12 months of using high-efficiency cleaners but only in the mattress sample using standard cleaners. Can f 1 was reduced in the mattress sample after using high-efficiency vacuum cleaners but not at other sites. Patients in the high-efficiency group showed improvements in peak expiratory flow rates, FEV1, and bronchodilator usage after 12 months (Popplewell et al. 2000).

There is no evidence of the differential shedding of allergens by dogs clustered as "hypoallergenic." Allergists should advise patients that they cannot rely on breeds considered "hypoallergenic" to have lower allergen concentrations (Nicholas et al. 2011). It has been demonstrated that "hypoallergenic" dog breeds have higher Can f 1 levels in their hair and coat samples (Vredegoor et al. 2012). Similar results have been observed with cats (Butt et al. 2012).

35.14 New Frontiers: Microbiome and Cytokine Milieu Manipulation

According to the hygiene hypothesis, children exposed to vaccines and clean environments maintain a Th2-allergy predominance instead of a protective Th1 milieu; this was seen among children exposed to farm environment, pet endotoxins, and parasites (Feng et al. 2016). The protective effect of exposure to barn environments has been recently elucidated. Lipopolysaccharide exposure prior to or during allergen stimulation attenuated the inflammatory response of dendritic cells, reducing the nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB) and subsequent CCL20 and granulocyte-macrophage colony-stimulating factor (GM-CSF) production. The enzyme A20 encoded by the gene *TNFAIP3* is at least partially responsible for NFκB inhibition (Holt and Sly 2015). Microbial components interact with allergens to alter the inflammatory pathways in atopy.

Lynch et al. reported on the EUREKA study, a longitudinal birth cohort evaluating the interaction of allergen levels and microbiome profiles from dust samples in the households of infants born to atopic parents. The outcomes were the development of allergen sensitization, wheezing, and asthma at 3 years of age. As expected, cumulative exposure to mites, roaches, and mice were associated with wheezing and asthma by age 3. The authors also found an inverse relationship between the levels of allergen exposure during the first year of life and the likelihood of wheezing but not to exposure in the second or third year of life. The relative bacterial richness of dust samples was lowest in the atopic children compared to the nonatopic. The identification of certain protective bacterial species (*Bacteroidetes spp.* and *Firmicutes spp.*) in samples of dust protected infants from developing atopic wheezing. When bacterial microbiome and allergen levels in dust were combined, the group with the highest levels of allergen exposure and the highest microbial species in dust samples collected in the first year of life had the lowest likelihood of wheezing or asthma. The authors suggest that in environments with high allergen exposure, manipulating the bacterial milieu could be a better strategy than environmental control of allergens (Lynch et al. 2014).

Several studies evaluated the role of the microbiome in sensitization and atopy. Turturice et al. hypothesized that the perinatal milieu could influence an infant's atopic predisposition. The authors compared cord blood bacterial 16S ribosomal DNA among infants with T cell response to Bla g 2 or D far 1 and nonresponders. Major differences in bacterial diversity and species predominance were noted among the infants, supporting the hypothesis that perinatal bacterial exposure was an important determinant for allergen sensitization (Turturice et al. 2017). Avershina et al. evaluated the gut microbiome among pregnant women and their infants and reported differences in gut microbiome diversity according to the frequency of vacuuming. Thus, alteration in gut microbiome could be associated with exposure to inhaled allergens (Avershina et al. 2015). Sugan et al. used a house dust mite-sensitized murine model to test the effect of schistosoma infection on atopy. *Schistosoma japonicum* infection prior to mite sensitization reduced Th2 and Th17 cytokine patterns, both of which are involved in asthma. Similarly, infection with *S. japonicum* after mite sensitization abrogated the Th2 and Th17 cytokine shift and led to a Treg-predominant IL-10 protective response (Qiu et al. 2017). These studies suggest that allergen sensitization occurs even before birth, targeting primary prevention strategies to the prenatal period.

Studies on the effect of prenatal exposure on allergen sensitization are conflicting. In utero exposure to HDM increases airway hyperactivity, Th2 inflammation, and immunoglobulin levels in a dose-dependent fashion (Richgels et al. 2017). However, other studies reported that uterine exposure prevented development of atopy but decreased inhibitory FcγRIIb expression (Lira et al. 2014). Prenatal allergen exposure affects cord blood IgE levels. HDM cord blood IgE levels correlate with maternal HDM exposure but a similar correlation was not observed with cockroaches (Peters et al. 2009). Timing, dose, allergen exposure, and host microbiome affect atopic predisposition.

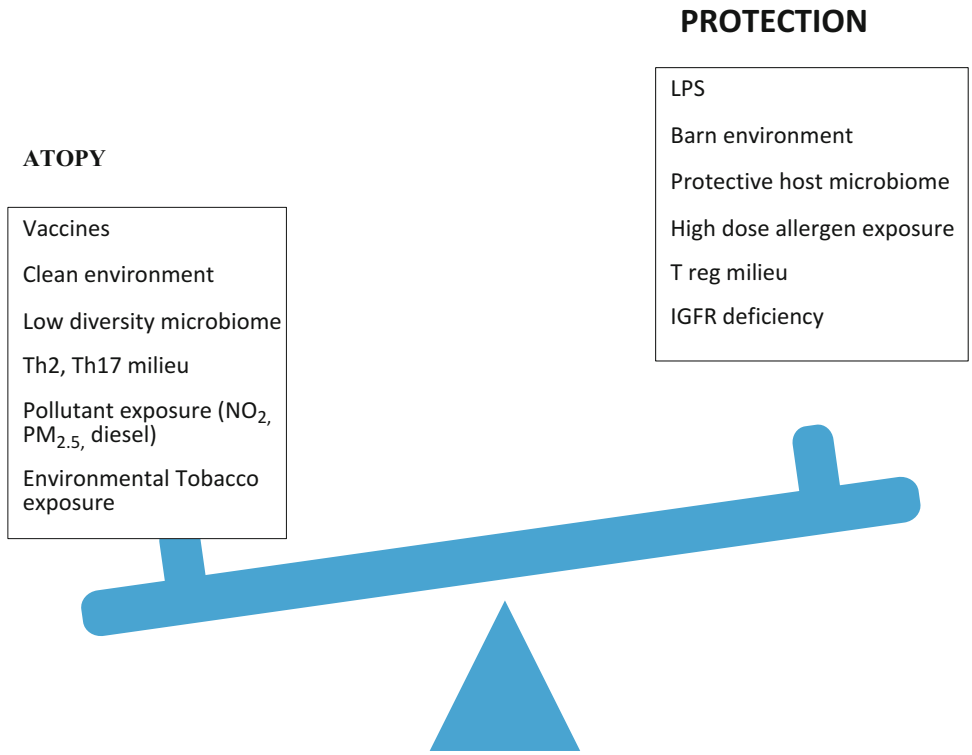

Fig. 2 Factors associated to atopy or protection

Environmental factors and pollutants also affect atopic predisposition. Tobacco exposure in utero increases the risk of allergen sensitization and asthma development in infants (Lannero et al. 2008). Christensen et al. demonstrated epigenetic changes in a murine model of asthma exposure in utero and after birth to environmental tobacco. Changes occurred in the methylation of genes associated with asthma such as IL-4, 5, 13, interferon γ (INF-γ), and FOXP3 (Christensen et al. 2017). Exposure to nitric oxide, particulate matter ($PM_{2.5}$), and diesel particles had a similar effect (Gruzieva et al. 2012; Sbihi et al. 2015; Zhang et al. 2015).

Hormonal factors also influence atopic sensitization. Pineiro-Hermida et al. tested the effect of insulin growth factor-1 receptor (IGFR1) deficiency in HDM-induced inflammation and asthma using a murine model. Compared to control mice, IGFR1-deficient mice or treatment with antibody against IGFR1 abrogated the inflammatory infiltrate characteristic of asthma. The authors proved that IGFR-1 deficiency abrogated IL-33 production, an important epithelial-derived cytokine that initiates Th2 inflammatory cascade (Pineiro-Hermida et al. 2017) (Fig. 2). Atopic sensitization depends on timing, particularly prenatal exposure, allergen dose, the host's microbiome, exposure to pollutants and irritants, and hormonal factors. Studies evaluating the interaction of these factors are required to prevent the development of allergy.

35.15 Conclusion

The pathogenesis behind atopic diseases is complex. The prevalence of atopic diseases is elevated. This translates to negative health, psychological, and economic consequences. Research has been focused in different strategies to prevent them. Many of the primary and secondary prevention interventions and their effectiveness remain controversial. Similarly, many of the recommended measures to decrease allergen burden are not

completely effective. At this moment, it has been demonstrated that single measures are not as effective as combination therapies. These multifaceted interventions should be emphasized as main preventive interventions. In recent years, attention has been given to the positive effect of immune modulation in the prevention of atopy. Changes of these microorganism pre- and postnatal may be modulating the immune system and the mechanisms of allergen tolerance. Importantly, all interventions should be accompanied by education to the patients and their families.

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Pharmacologic Therapy for Rhinitis and Allergic Eye Disease

36

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Abstract

Allergic rhinitis and allergic eye disease affect the lives of many worldwide. They are Type I IgE-mediated hypersensitivity reactions. Allergic rhinitis occurs after sensitization of the mucosal lining of the nasal cavity to allergens. Likewise, allergic conjunctivitis occurs after sensitization of the ocular epithelium to allergens. Avoidance of allergens is the key in prevention of sensitization and the ensuing allergic responses. Various pharmacologic agents are developed to target the different underlying allergic mechanisms that cause the many symptoms of allergic rhinitis and allergic eye disease: antihistamines, mast cell stabilizers, anticholinergics, decongestants/vasoconstrictors, corticosteroids, multimodal anti-allergic agents, NSAIDs, and immunomodulators. Oral, intranasal, and topical formulations are available for certain agents. Complementary and alternative form of therapy can provide additional symptomatic relief. Furthermore, at the forefront of research for the treatment and management of allergic diseases including allergic rhinitis and allergic eye disease, allergen-specific immunotherapy with subcutaneous or sublingual immunotherapy can offer potential treatment and cure.

Keywords

Allergic rhinitis · Allergic conjunctivitis · Rhinitis · Conjunctivitis · Antihistamines · Intranasal corticosteroids

36.1 Allergic Rhinitis

36.1.1 Introduction

When irritants such as allergens enter the nasal passage, the nasal cavity transforms into a state of inflammation or rhinitis. Allergic rhinitis is a specific type of rhinitis that is an IgE-mediated reaction caused by the sensitization of the mucosal lining of the nasal cavity to allergens. Patients with allergic rhinitis display symptoms localized to the upper airway, including nasal congestion, rhinorrhea, sneezing, and itching of the nose and often accompanied by ocular symptoms such as itching, increased lacrimation, and conjunctival injection of the eyes.

The type of allergic rhinitis is determined by the temporal pattern of symptoms. Seasonal allergic rhinitis is caused by aeroallergens, from trees, ragweed, and grass, and occurs at the same time each year. Perennial allergic rhinitis describes persistent year-round symptoms and is caused by household allergens such as molds, dust mites, cockroaches, and cat and dog dander. Risk factors include atopic disorders such as asthma and atopic dermatitis as well as a family history of allergic rhinitis and other allergic diseases (Wallace and Dykewicz 2008).

Allergic rhinitis is associated with allergic conjunctivitis (Leonardi et al. 2015) and can lead to complications such as exacerbation of asthma, rhinitis or rhinosinusitis, and serous otitis media (Bousquet et al. 2008). A thorough understanding of the pathophysiology of allergic rhinitis can explain the clinical manifestations, the relation to coexisting conditions including allergic eye diseases, and the treatment modalities.

36.1.2 Pathophysiology

Allergic rhinitis is an IgE-mediated Type I hypersensitivity reaction leading to the release and cellular influx of inflammatory mediators after repeated exposure of a specific allergenic antigen in an allergic individual (Fig. 1). T-helper 2 cells are the key lymphocyte responsible for the cascade of allergic events, secreting cytokines,

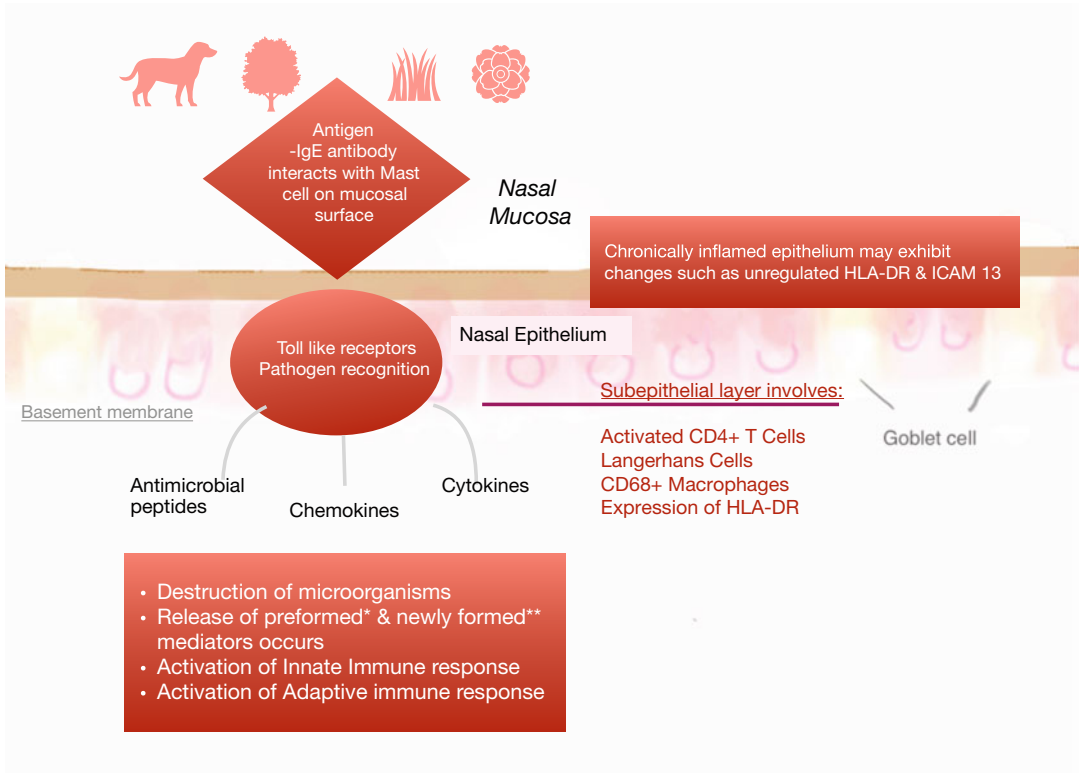

Fig. 1 Nasal epithelium: a simplified rendering of the normal nasal epithelium and impact of chronic inflammation in allergic rhinitis. The barriers and immune response are similar in allergic conjunctivitis, which features mucosa connected by the nasal lacrimal duct. Degranulation of mast cells triggers several allergic cascade events. *Preformed mediators: tryptase, chymase, kininogenase, histamine, and heparin, for example. **Newly formed mediators: prostaglandins, leukotriene, C4, LTD4, LTE4, for example

mainly interleukin (IL)-4, IL-5, and IL-13, which play a pivotal role in IgE and eosinophil production (Wynn 2015). The process in which the allergen binds to the allergen-specific receptor site on the antigen-specific IgE antibodies linked to basophils and mast cells is known as cross-linking. Cross-linking sets forth the early- and late-phase responses and its associated symptoms (Wallace and Dykewicz 2008).

Early-phase reactions occur within minutes as a result of the immediate release of preformed and newly formed inflammatory mediators from mast cells and basophils including histamine, tryptase, cysteinyl leukotrienes, prostaglandins, and cytokines (Prussin and Metcalfe 2006). These mediators cause symptoms such as sneezing, vasodilation, edema, and pruritus. Cytokines released from mast cells and Th2 cells also upregulate vascular endothelial adhesion molecules and, through chemotaxis, direct inflammatory cells to the targeted nasal mucosa. This late-phase reaction occurs within hours and is characterized by the cellular influx of inflammatory cells including mononuclear cells, neutrophils, eosinophils, basophils, and mast cells, to the nasal epithelium, leading to the common symptom of nasal congestion (Dvoracek et al. 1984). Less amount of the specific intranasal allergen is required to trigger mast cell degranulation leading to shorter time of onset of symptoms with each allergen season. This phenomenon is due to mast cells having the ability to "prime" itself for further allergen exposure (Wachs et al. 1989). These inflammatory mediators often cause simultaneous irritation to the entire airway due to the nasal mucosa's proximity to the lower airway tract

Table 1 Common workplace triggers in work-related rhinitis

Category	Triggers
Irritants	Gypsum dust, grain dust, flour dust, fuel oil ash, ozone, cosmetic powder, perfume, tobacco smoke
Corrosives	Ammonia, hydrochloric acid
Immunologic, IgE-mediated responses	Flour, laboratory animals (rats, mice, guinea pigs, etc.), animal products, coffee beans, natural rubber latex, storage mites, mold spores, pollen, psyllium, enzyme, acid anhydrides, platinum salts, chloramine

(Bousquet et al. 2008). Clinical manifestations of lower airway disease may arise or may become exacerbated, such as wheezing in asthmatics.

36.1.3 Differential Diagnosis

The symptoms of allergic rhinitis overlap with those of other rhinitis. The presentation of the symptoms is usually the key to narrowing the differential diagnosis, with the use of physical examination and testing to further make the correct diagnosis.

Patients affected with work-related rhinitis typically have nasal symptoms which occur or worsen during the days of the week at work (Table 1). Work-related rhinitis is divided into rhinitis caused by work, or occupational rhinitis, and rhinitis exacerbated by work, or work-exacerbated rhinitis (Sublett and Bernstein 2011). Occupational rhinitis can be further divided into those caused by a nonallergic or IgE-mediated allergic response. Nonallergic occupational rhinitis may be caused by irritants such as volatile organic compounds or corrosives such as chemical gases (Sublett and Bernstein 2011). Serum IgE testing or skin-prick testing may be used to confirm the suspected diagnosis, with positive results signifying an allergic response and negative results a nonallergic etiology.

Treatment modalities for symptomatic relief of rhinitis are often the same regardless of exact etiology. Nonallergic rhinitis, or vasomotor rhinitis, is differentiated from allergic rhinitis to minimize the risk of occurrences and exacerbations of symptoms. Nonallergic rhinitis includes those patients with nasal symptoms that occur after exposure to nonspecific particles such as cigarette smoke, alcohol, and perfumes as well as nasal symptoms occurring after exercising, ingesting certain food especially spicy meals, and exposure to cold air (Greiwe and Bernstein 2016).

Patients who use topical or oral alpha-adrenergic decongestants for greater than the recommended number of days may have severe nasal congestion as the chief compliant, due to rebound nasal congestion or "rhinitis medicamentosa (Morris et al. 1997)." This condition may predispose individuals to atrophic rhinitis, chronic sinusitis, otitis media, and nasal polyposis (Toohill et al. 1981).

In patients with significant nasal crusting, atrophic rhinitis should be considered especially in those with history of chronic bacterial infection leading to primary atrophic rhinitis or of multiple nasal sinus surgeries leading to secondary atrophic rhinitis (Moore and Kern 2001).

Nonallergic rhinitis with eosinophilia (NARES) is a condition with increased eosinophils on nasal smears in the absence of allergy skin or serum IgE tests (Gröger et al. 2012). Elderly patients are more prone to age-related rhinitis given the structural and physiological changes of the nasal mucosa associated with aging. Other rhinitis may occur from hormonal triggers associated with pregnancy. In children, foreign objects obstructing the nasal passageway should be considered as a non-rhinitis etiology. Other non-rhinitis causes can be discerned upon examination such as septal deviation, nasal polyp, and adenoidal enlargement (Wallace and Dykewicz 2008).

36.1.4 Treatment

36.1.4.1 Primary Treatment

The primary treatment is avoidance of all indoor household allergens and outdoor aeroallergens. Lifestyle changes are necessary to prevent exposures and to remove allergens. Recommendations to reduce house dust mite allergens include

Table 2 First-generation oral antihistamines

Chemical groups	First-generation antihistamines	General warnings/precautions of first-generation antihistamines
Alkylamines	Brompheniramine Chlorpheniramine maleate Dexchlorpheniramine	May cause CNS depression • Avoid performing tasks which require physical coordination or mental alertness such as operating machinery or driving • Effects may be potentiated with sedatives or alcohol • Monitor for drowsiness or irritability in breast-feeding women and nursing infants • May cause excitation in young children • Listed in Beers criteria • Monitor for anticholinergic effects or toxicity in elderly patients (65 years or older) • Use with caution in patients with: • Cardiovascular disease • Increased intraocular pressure or glaucoma • Prostatic hyperplasia/urinary obstruction • Respiratory disorders • Thyroid dysfunction
Ethanolamines	Carbinoxamine Clemastine Dimenhydrinate Diphenhydramine Doxylamine	
Ethylenediamines	Pyrilamine Tripelennamine	
Piperazines	Buclizine Cyclizine Hydroxyzine Meclizine	
Piperidines	Cyproheptadine Diphenylpyraline	
Phenothiazines	Methdilazine Promethazine	
Other	Doxepin (potent H1 and H2 receptor antagonist activity; also a tricyclic antidepressant)	

use of high-efficiency particulate arrestance (HEPA) filters, dehumidifiers, and air conditioners to maintain room humidity below 50%. Use of impermeable (<10 μm pore tightly woven fabric) encasements for pillows and mattresses and routine vacuuming with HEPA-filtered vacuum and washing of beddings in hot (130 °F) water are helpful (Arlian and Platts-Mills 2001).

Removal of offending pet allergens from the home followed by the washing of the walls and other surfaces as well as using HEPA filters may reduce exposure to animal dander. A professional pest control program has been shown to reduce cockroach and rodent allergens exposure. Avoidance of moisture, keeping humidity <50%, and using HEPA filters may also reduce fungal spores. Combination therapy such as the use of encasement for pillows and air filtration has been shown to effectively reduce nighttime allergen exposures and symptoms (Stillerman et al. 2010).

Limiting outdoor exposure during pollen season is essential for those patients with seasonal allergic rhinitis. Closing windows, using air conditioners, and washing outdoor clothes may also reduce the amount of pollen that is carried indoors. For patients with occupational rhinitis, avoidance of occupational allergens is essential.

Often it is difficult to maintain the level of reduction of allergens in the environment. This result in the reduction of the patient's quality of life and pharmacotherapy may be required.

36.1.4.2 Pharmacotherapy

Oral Antihistamines and decongestants: Histamine is one of the preformed inflammatory mediators released from mast cells and basophils in Type II IgE-mediated allergic diseases. Antihistamines are commonly used to mitigate mast cell and basophil degranulation products such as histamine, tryptase, cysteinyl leukotrienes, prostaglandins, and cytokines and are more effective in the first several days of an allergic reaction.

Histamine exerts its effects through four types of receptors: H1, H2, H3, and H4 (Hoyte and Katial 2011). The H1 receptor is a G-protein-coupled receptor, which activates intracellular signals including Ca^{2+}, cGMP, phospholipase A2, C, D, NF-κ, cAMP, and NOS (Simons 2004). These are widely expressed throughout various cell types, including neurons and smooth muscle.

Table 3 Second-generation oral antihistamines for treatment of allergic rhinitis

Generic	Brand (strengths and dosage form)	Dosing and administration	Contraindications; adverse reactions
Cetirizine	Children's Zyrtec® Allergy (5 mg/mL, syrup/solution) Children's Zyrtec® (5 mg and 10 mg, chewable/tablet) Zyrtec® (10 mg, ODT) Zyrtec® (10 mg, liquid gel)	6–12 mo: 2.5 mg qd 12–23 mo: Initial 2.5 qd, may be increased to 2.5 mg bid 2–5 yr: 2.5 mg/day to maximum of 5 mg/day in single dose or divided into two doses ≥6 yr: 5–10 mg/day as single dose or divided into two doses	Hypersensitivity; Drowsiness, headache
Desloratadine	Clarinex® (0.5 mg/mL, solution) Clarinex Reditabs® (2.5 mg, tablet) Clarinex® (5 mg, tablet)	6–11 mo: 1 mg qd 12 mo–5 yr: 1.25 mg qd 6–11 yr: 2.5 mg qd ≥12 yr: 5 mg qd[a]	Hypersensitivity; Pharyngitis, dry mouth, myalgia, fatigue, somnolence, dysmenorrhea
Fexofenadine	Children's Allegra® (30 mg/5 mL, suspension) Children's Allegra® (30 mg, ODT) Children's Allegra® (30 mg, tablet) Allegra Allergy® (30 mg, 60 mg and 180 mg, tablet)	6 mo–<2 yr: 15 mg q12h >2–11 yr: 30 mg q12h ≥12 yr of age: 60 mg q12h; 180 mg qd	Hypersensitivity; Headache, vomiting
Levocetirizine dihydrochloride	Xyzal® (0.5 mg/mL, solution) Xyzal® (5 mg, tablet)	6 mo–5 yr: Max 1.25 mg qd in the evening 6–11 yr: 2.5 mg qd in the evening ≥12 yr: 5 mg qd in the evening[b]	Hypersensitivity, end-stage renal impairment less than 10 mL/min CrCl or patients undergoing dialysis, children 6–11 yr of age with renal impairment; Somnolence, fatigue, asthenia
Loratadine	Children's Loratadine® (5 mg/5 mL, solution/syrup) Claritin® (5 mg/5 mL, syrup) Claritin Reditabs® (5 mg and 10 mg, ODT) Claritin® (5 mg, chewable) Claritin® (10 mg, tablet) Alavert® (10 mg, ODT) Alavert® (10 mg, tablet Loradamed® (10 mg, tablet)	2–5 yr: 5 mg qd Claritin Reditabs® ≥6 yr: 10 mg qd or 5 mg bid	Hypersensitivity; Headache, fatigue, dry mouth

bid twice daily, *h* hour, *mL* milliliter, *mg* milligram, *mo* month(s), *q* every, *qd* every day, *yr* year
[a]Dose adjustment required for renal and hepatic impairment
[b]Dose adjustment required for renal dose adjustment

H1 antihistamines act as inverse agonists that interact with and stabilize the inactive form of the H1 receptor (Leurs et al. 2002), preventing unwanted effects of increased vasodilation, vascular permeability, pruritus, bronchoconstriction, pain, flushing, headache, etc. (Simons 2004). H1 antihistamines exhibit both anti-allergic and anti-inflammatory activities. The anti-allergic activity of H1 antihistamines likely involves directly inhibiting calcium-ion channels preventing the accumulation of intracellular calcium stores. This prevents mast cells and basophils from releasing mediators and leads to reduction in itching, rhinorrhea, and sneezing, though minimal relief from nasal congestion. Downregulation of the H1-receptor-activated nuclear factor-κB

contributes to the anti-inflammatory effects, including expression of cell adhesion molecules and eosinophil chemotaxis (Leurs et al. 2002).

H1 antihistamines are divided into first-generation drugs (Table 2) or second-generation drugs (Table 3). First-generation oral drugs are highly lipophilic agents, able to readily cross the blood-brain barrier and exert its highly sedative effect by blocking the effect of histamine in the central nervous system (Chen et al. 2003). In addition, first-generation agents show poor selectivity for H1 receptors and also bind to muscarinic cholinergic, α-adrenergic, and serotonin receptors (Simons 2004). This leads to a wide range of potential side effects associated with these receptors. These symptoms include dry eyes, dry mouth, constipation, urinary hesitancy and retention, and mydriasis associated with anti-muscarinic effects and orthostatic hypertension and dizziness associated with anti-α-adrenergic effects (Shi et al. 2011). Anti-serotonin effects include increased appetite and weight gain (Ratliff et al. 2010).

The development of the newer, less lipophilic, non-sedating second-generation antihistamines in the 1980s reduced these unwanted side effects associated with first-generation antihistamines (Timmerman 2000). Second-generation antihistamines are the preferred antihistamines of choice.

Oral antihistamines provide relief from nasal pruritus, rhinorrhea, and sneezing with less effect on nasal congestion. During an allergic response, the small blood vessels become swollen, narrowing the nasal passageways, which leads to difficulty breathing. Oral decongestants, such as pseudoephedrine hydrochloride and phenylephrine, are specifically used to reduce nasal congestion by inducing vasoconstriction of the blood vessels via stimulating alpha-adrenergic receptors (Jackson 1991). As these agents do not alleviate the other symptoms of allergic rhinitis, oral decongestants are often combined with an oral antihistamine. As an alpha-adrenergic mild stimulant, side effects include insomnia and irritability with precautions to be taken in patients with hypertension and heart disease due to its propensity for increased blood pressure and risk of cardiac arrhythmias (Mortuaire et al. 2013).

Nasal antihistamines, decongestants, and anticholinergics: Antihistamines and decongestants may also be administered directly to the nasal mucosal with nasal sprays. Intranasal H1 antihistamine reduces both nasal congestion and rhinorrhea, itching, and sneezing and has a more rapid onset of action than oral antihistamines (Kaliner 2009). Azelastine is a second-generation H1 antihistamine that significantly reduces nasal congestion as well as other symptoms. Side effects include headache, dysgeusia, and sedation (Ellis et al. 2013).

Olopatadine hydrochloride is a newer second-generation intranasal H1 antihistamine that also has inhibitory effects on other inflammatory mediators such as platelet-activating factor, leukotrienes, and thromboxane from human polymorphonuclear leukocytes and eosinophils (Maiti et al. 2011). Adverse effects are similar to that of azelastine with sedation and headache (Maiti et al. 2011).

Intranasal decongestants such as phenylephrine, xylometazoline, and oxymetazoline have a more rapid onset of action and more potent effect than oral decongestants, though repeated use of 3 days or more can cause rhinitis medicamentosa (Mortuaire et al. 2013). Rhinitis medicamentosa is likely to occur with oral decongestants (Hendeles 1993). If rhinorrhea is the major complaint as opposed to nasal congestion, nasal anticholinergic such as ipratropium bromide can be used to reduce nasal discharge (Kaiser et al. 1998).

Corticosteroids: Intranasal corticosteroids (Table 4) are used if symptoms persist after use of antihistamines, decongestants, and/or anticholinergic or for moderate to severe allergic rhinitis. Corticosteroids have potent anti-inflammatory effects, reducing the number of T-lymphocyte, mast cells, basophils, and eosinophils, preventing preformed and newly generated mediators, and inhibiting production of cytokines and chemokines (Meltzer 1997). Corticosteroids, regardless of the route of administrations, consistently show greater anti-inflammatory effects as compared to H1 antihistamines (Greiner and Meltzer 2011). Side effects include nasal irritation, epistaxis with prolonged use, and rare

Table 4 Intranasal corticosteroids for treatment of allergic rhinitis

Generic	Brand (dosage forms and strengths)	Dosing and administration	Contraindications; adverse reactions; comments
Beclomethasone	Beconase AQ® (42 mcg/spray) Qnasl (80 mcg/spray)	Beconase AQ >6 yr: 1–2 sprays per nostril bid Qnasl 4–11 yr: 1 spray per nostril qd >12 yr: 2 sprays per nostril qd	Hypersensitivity; Nasopharyngitis, epistaxis, dizziness, headache, increased intraocular pressure, sneezing
Budesonide	Rhinocort Allergy® (32 mcg/spray)	6–12 yr: 1–2 sprays per nostril qd >12 yr: 1–4 sprays per nostril qd	Hypersensitivity; Epistaxis, pharyngitis, bronchospasm, cough, nasal mucosa irritation
Ciclesonide	Omnaris® (50 mcg/spray) Zetonna® (37 mcg/spray)	Omnaris 2–11 yr: 1–2 sprays per nostril qd ≥12 yr: 2 sprays per nostril qd Zetonna ≥12 yr: 1 spray per nostril qd	Hypersensitivity; Epistaxis, nasopharyngitis, nasal discomfort, headache
Flunisolide	Generic (solution, 25 mcg/spray)	6–14 yr: 2 sprays per nostril bid or 1 spray per nostril tid; maximum 4 sprays per nostril/day ≥15 yr: 2 sprays per nostril bid or 2 sprays per nostril tid; maximum 8 sprays per nostril/day	Hypersensitivity; Burning and stinging sensation of nose, nasal congestion
Fluticasone			
Fluticasone furoate	Flonase® Sensimist (suspension, 27.5 mcg/spray)	2–11 yr: 1–2 sprays per nostril qd; maintenance – 1 spray per nostril qd ≥12 yr: Initial – 2 sprays per nostril qd; maintenance – 1 spray per nostril qd	Hypersensitivity; Pharyngitis, epistaxis, headache, acute asthma Use with caution with patients using ketoconazole, ritonavir, or other cytochrome P450 3A4 inhibitor which increases plasma concentrations of fluticasone
Fluticasone propionate	Flonase® Allergy Relief (suspension, 50 mcg/spray) GoodSense® Nasoflow™ (suspension, 50 mcg/spray Ticaspray® (nasal therapy pack, 50 mcg/spray)	4–11 yr: 1 spray per nostril qd ≥12 yr: 2 sprays per nostril qd for 1 week; may adjust to 1 or 2 sprays per nostril qd	
Mometasone furoate	Propel Mini (implant, 370 mcg 1 each) Nasonex (suspension, 50 mcg/spray)	2–12 yr: 1 spray per nostril qd >12 yr: 2 sprays per nostril qd Seasonal allergic rhinitis (prophylaxis) Adults: 2 sprays per nostril qd; treatment to begin 2–4 weeks prior to start of pollen season	Hypersensitivity; Headache, viral infection, pharyngitis, cough, epistaxis

(*continued*)

Table 4 (continued)

Generic	Brand (dosage forms and strengths)	Dosing and administration	Contraindications; adverse reactions; comments
Triamcinolone acetonide	GoodSense Nasal Allergy Spray (aerosol, 55 mcg/spray) Nasacort Allergy 24HR (aerosol, 55 mcg/spray) Nasacort Allergy 24HR Children (aerosol, 55 mcg/spray) Nasal Allergy 24 Hour (aerosol, 55 mcg/spray) Generic (aerosol, 55 mcg/spray)	2–6 yr: 1 spray per nostril qd 6–12 yr: 1–2 sprays per nostril qd; maintenance – 1 spray per nostril qd ≥12 yr: 2 sprays per nostril qd; maintenance – 1 spray per nostril qd	Hypersensitivity; Headache, pharyngitis

bid twice daily, *mcg* microgram, *qd* daily, *yr* year, *tid* three times daily

Table 5 Major systemic side effects of long-term treatment with glucocorticoids

System	Side effects
Dermatologic	Acne, alopecia, cushingoid appearance, hirsutism, hypertrichosis, skin atrophy and purpura, striae
Cardiovascular	Arrhythmias, congestive heart failure, hypertension
Endocrine	Adrenal suppression, diabetes mellitus, hyperglycemia, growth restruction in children, weight gain
Gastrointestinal	Gastritis, pancreatitis, peptic ulcer disease, steatohepatitis, visceral perforation
Eye	Cataract, glaucoma, increased intraocular pressure
Genitourinary and reproductive	Amenorrhea, infertility, intrauterine growth retardation
Infectious disease	Increase risk of infections, i.e., herpes zoster, measles, opportunistic infections
Musculoskeletal	Avascular necrosis, myopathy, osteoporosis
Neuropsychiatric	Akathisia, behavioral disturbances, dysphoria, depression, euphoria, insomnia, irritability, mania, psychosis
Renal	Hypokalemia, fluid volume shifts

complication of nasal septal perforation (Wallace and Dykewicz 2008). Aqueous-based formulations lacking phenylethyl alcohol such as budesonide nasal or triamcinolone acetonide may reduce local nasal irritation and burning sensations (Shah et al. 2003; Stokes et al. 2004).

Systemic corticosteroids are indicated for those who presents with severe nasal obstruction. A short burst of oral prednisone can be used to allow penetration of intranasal agents (Wallace and Dykewicz 2008). Intramuscular corticosteroids are rarely indicated due to the long-term systemic effects steroids (Table 5). Other treatment options for allergic rhinitis include leukotriene inhibitors such as zileuton, montelukast, and zafirlukast, used in combination with an antihistamine, or intranasal cromolyn sodium for prophylaxis of allergic symptoms.

36.1.4.3 Allergen-Specific Immunotherapy

Allergen-specific immunotherapy (AIT) is reserved for moderate to severe perennial or seasonal allergic rhinitis. It is indicated in those patients refractory to environmental controls and/or unable to tolerate the side effects of pharmacologic treatments. AIT is the only potential treatment and cure for allergic disease as it alters the underlying immunologic response of not only allergic rhinitis but also that of asthma. It has been shown to relieve symptoms, improve the quality of life, and reduce the use of medications including topical, oral, and inhaled steroids. Furthermore, AIT may induce long-term remission after treatment completion (Nelson 2016).

The specific allergen is identified prior to initiation of immunotherapy. An adequate dose of the purified allergen extract is administered either

subcutaneously or sublingually. The immune system responds by forming Th1 and regulatory T cells which releases IL-10 and transforming growth factor-ß (TGF-ß) (Jutel et al. 2003). These immunosuppressive cytokines limit local inflammatory reaction by inducing increased levels of IgG4 which competes with IgE and by inhibiting mast cells, basophils, and eosinophils recruitment within the nasal mucosa (Burks et al. 2013).

Subcutaneous immunotherapy: Subcutaneous immunotherapy (SCIT) is more commonly used in the United States to treat Americans with multiple environmental allergens, while both SCIT and sublingual immunotherapy (SLIT) are used in Europe. SLIT is shown to be more effective at treating patients with a single environmental allergen and is used more frequently in Europe as Europeans often only have one environmental allergen.

For SCIT, regular subcutaneous injections of the allergen are injected weekly (buildup) during initiation of therapy and monthly (maintenance) after 1 year. It is then continued for at least 3–5 years (Cox et al. 2011). SCIT is typically performed in a controlled setting such as in the physician's office, with epinephrine and other life-resuscitation equipment readily available. The patient waits onsite for at least 30 min after injection due to increased risk of systemic allergic reactions including anaphylaxis (Cox et al. 2011).

The rate of anaphylaxis as well as other systemic events decreases with SLIT. Per the World Allergy Organization, the rate of anaphylaxis with SLIT is estimated to be at 1 case/100,000,000 administrations (Calderon et al. 2012). While the safety profile of SLIT is better than SCIT in terms of serious systemic reactions, local adverse effects such as oromucosal itching and swelling are frequent (~35%) though typically subside after the first week of treatment (Brozek et al. 2010).

Sublingual immunotherapy: Sublingual immunotherapy may be given as a liquid extract or tablets and like SCIT, therapy is continued for at least 3 years. The first dose is administered by a healthcare professional in the physician's office where the patient may be monitored for any adverse reactions. Subsequent dosing is self-administered outside of a healthcare setting with the ease and convenience of administration serving as one of the main benefit in choosing SLIT over SCIT. In the United States, tablets composed of grass, ragweed pollen, and most recently dust mites have been FDA-approved (Table 6). Unlike SCIT, SLIT does not provide a potential for a therapeutic cure of allergic rhinitis (Greenhawt et al. 2017).

Contraindications to AIT: Allergen-specific immunotherapy is not recommended in patients with severe or uncontrolled asthma who are at increased risk of systemic reactions to immunotherapy. AIT is also relatively contraindicated in patients with underlying medication conditions such as severe lung or cardiovascular diseases that compromise the patient's ability to survive a systemic allergic reaction or the treatment for the systemic reaction. Additionally, any history of eosinophilic esophagitis (EoE) is a contradiction to initiation of SLIT. In such cases, alternative treatment options should be considered (Cox et al. 2011).

36.1.4.4 Complementary and Alternative Treatments of Allergic Rhinitis

A complementary and alternative form of treatment may be considered in certain population with allergic rhinitis. These patients may have symptoms unamenable to pharmacotherapy, difficulties adhering to medications due to side effects and unable to tolerate desensitization with either SCIT or SLIT. Outside of the United States, in Eastern Asia, ailments are commonly treated or supplemented with the use of traditional medicine. Osteopathic manipulative medicine (OMT) may also be of added benefit in chronic rhinosinusitis, a complication of allergic rhinitis.

Acupuncture and herbal medicine: Historically, acupuncture is a complementary therapy involving the introduction of fine needles into the body for the management of pain (Wilkinson and Faleiro 2007). Studies have shown its effectiveness in treatment of allergic rhinitis in comparison with or in addition to standardized treatment (Chen et al. 2016). Acupuncture is

Table 6 Allergen-specific immunotherapy sublingual immunotherapy (SLIT)

Sublingual tablet (brand/strength)	Indication	Comments	Boxed warning
Timothy grass pollen extract (Grastek®/2800 bau)	Grass pollen-induced allergic rhinitis	Start ≥12 weeks before expected onset of each pollen season and continue throughout season In clinical trials, interruptions ≤7 days were allowed	Autoinjectable epinephrine should be prescribed to all patients undergoing (SLIT) in case of anaphylaxis • May not be suitable for patients with conditions that may reduce their ability to survive a serious allergic reaction • Use may not be suitable for patients who may be unresponsive to epinephrine or inhaled bronchodilators due to concomitant drug therapy • Monitor all patients at least 30 min after initial dose
House-dust mite extract of *Dermatophagoides farinae* or *D. pteronyssinus* in a 1:1 mixture (Odactra™/12 SQ-HDM)	House-dust mite-induced allergic rhinitis	In clinical trials, interruptions ≤7 days were allowed	
Five-grass pollen allergen extract: sweet vernal, orchard, perennial, rye, timonthy, Kentucky blue grass (Oralair®/100 IR and 300 IR)	Grass-pollen-induced allergic rhinitis	Start 4 months before expected onset of each grass pollen season and continue throughout pollen season	
Ragweed pollen extract of *Ambrosia artemisiifolia* (Ragwitek®/12 AMB A1-U)	Ragweed pollen-induced allergic rhinitis	Start ≥12 weeks before expected onset of each ragweed pollen season and continue throughout pollen season In clinical trials, interruption ≤7 days were allowed	

AMB A1-U Ambrosia A1-Unit, *bau* bioequivalent allergy units, *IR* index of reactivity, *qd* daily, *SQ-DM* standardization of biological potency, major allergen content and complexity of the allergen extract, house-dust mite, *yr* year

relatively safe with adverse effects usually limited to local site irritation or minor bleeding (Wilkinson and Faleiro 2007). Patients who require blood thinners are to withhold anticoagulation prior to treatment or advised against acupuncture.

Herbal formulations and acupoint herbal patching, or direct application of the herbs to the body's acupuncture points, are other options that have shown potential in relieving nasal symptoms, recurrence rate, and quality of life (Zhou et al. 2015). To date, there remains insufficient evidence to completely support or reject acupuncture and herbal medicine treatment for allergic rhinitis (Chen et al. 2016); these alternative forms of therapy may be used with caution.

Osteopathic manipulative medicine: Osteopathic manipulative medicine is a hands-on holistic approach to treating somatic disorders. OMT as it pertains to chronic rhinosinusitis is thought to improve lymphatic and venous congestion by targeting the musculoskeletal and autonomic nervous systems. No present consensus exists for or against the use of OMT on the direct treatment of allergic rhinitis (Méndez-Sánchez et al. 2012).

36.2 Allergic Eye Diseases

36.2.1 Introduction

Allergic eye diseases are a group of ocular inflammatory disorders characterized by itching of the eye, conjunctival injection, and increased lacrimation. Allergic conjunctivitis is the most common type of allergic eye disease with seasonal allergic conjunctivitis as the most frequent type (Leonardi et al. 2015). It is associated with personal and/or family history of atopic disorders including allergic rhinitis, atopic dermatitis, and asthma. Allergic conjunctivitis is an acute inflammatory condition, whereas atopic keratoconjunctivitis (AKC), vernal keratoconjunctivitis (VKC), and giant papillary conjunctivitis (GPC) are more severe, less common, chronic inflammatory conditions.

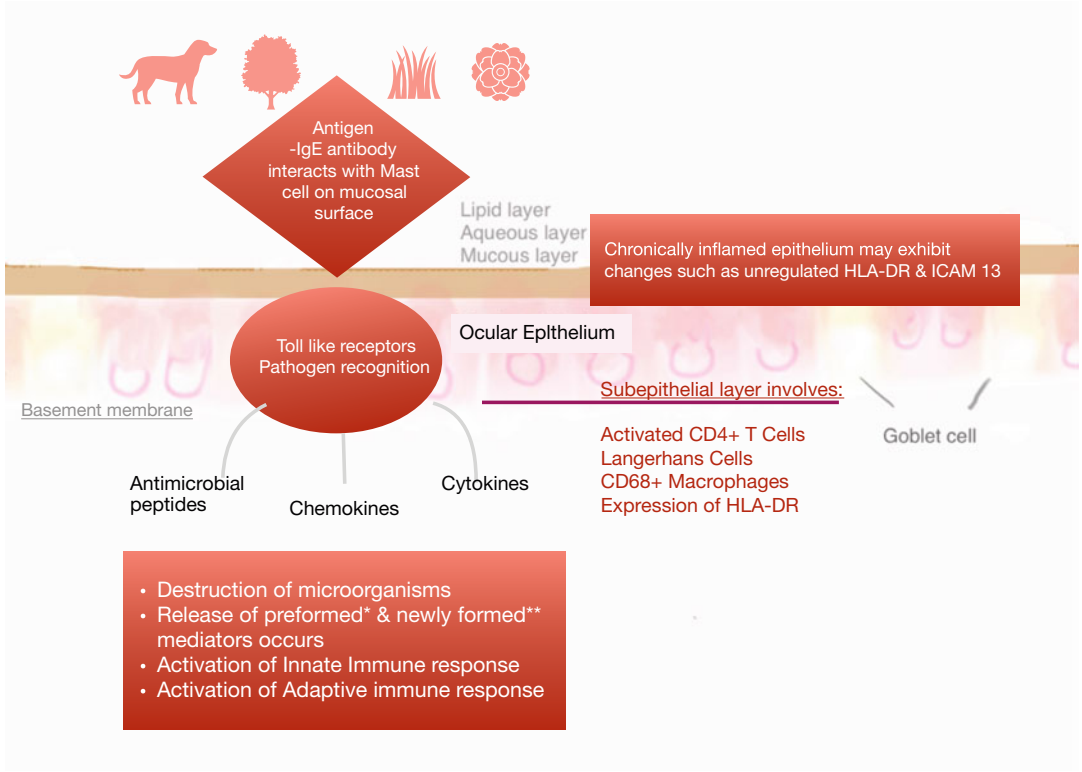

Fig. 2 Ocular epithelium: a simplified rendering of the normal ocular epithelium and impact of chronic inflammation in allergic conjunctivitis. The barriers and immune response are similar in allergic rhinitis, which features mucosa connected by the nasal lacrimal duct. Degranulation of mast cells triggers several allergic cascade events. *Preformed mediators: tryptase, chymase, kininogenase, histamine, and heparin, for example. **Newly formed mediators: prostaglandins, leukotriene, C4, LTD4, LTE4, for example

36.2.2 Pathophysiology

Allergic conjunctivitis is an IgE-mediated reaction. The pathophysiology parallels that of allergic rhinitis with sensitization of the ocular mucosal surface (Fig. 2). This is typically followed by exposure of the allergen to the conjunctiva and release and infiltration of inflammatory mediators to the conjunctiva by mast cells. Mast cells are the predominant finding during immunostaining of the conjunctival epithelium (Fukuda et al. 2009).

The classification of allergic conjunctivitis is also similar to that of allergic rhinitis. It is subdivided based on the predominance of symptoms during certain seasons or throughout the year, seasonal allergic conjunctivitis and perennial allergic conjunctivitis, respectively. Since only the conjunctival is affected, visual acuity is intact, as opposed to the other allergic eye disorders where involvement of the cornea leads to visual changes and loss.

36.2.3 Differential Diagnosis

Atopic keratoconjunctivitis, VKC, and GPC are the chronic inflammatory eye disorders marked by additional symptoms of ocular pain, photophobia, periocular redness and edema involving eyes and eyelids, and blurred/impaired vision. These physical findings can be used to distinguish chronic inflammatory eye disorders from allergic conjunctivitis. They are IgE- and T cell-mediated allergic reactions, with a shift toward Th1 in AKC and toward Th2 in VKC (Calder et al. 1999).

On immunostaining, mast cells, eosinophils, and T cells predominant (Leonardi et al. 2006).

Atopic keratoconjunctivitis is a severe, chronic, IgE, and delayed-hypersensitivity-mediated condition affecting patients with history of atopic dermatitis or asthma. Eyelid skin lesions reflecting signs of dermatitis, severe blepharitis, ectropion/entropion, trichiasis, and conjunctival injection are some of the common findings on exam. The cornea is often affected due to the persistent inflammation leading to epithelial defects, ulceration, and scarring (Chen et al. 2014).

Patients with VKC complain of similar symptoms as atopic keratoconjunctivitis and may also develop damages to the cornea. VKC is the chronic inflammation of specifically the upper conjunctival with "cobblestoning" appearance reflecting papillary hypertrophy. It affects male patients between the ages of 10 and 20 in warm climates, with the disease resolving before adulthood as opposed to the lifelong condition of AKC (De Smedt et al. 2013).

Giant papillary conjunctivitis is also a chronic inflammatory disease affecting the upper conjunctiva with "cobblestoning" papillae. Unlike VKC, GPC develops in contact lens wearers (Donshik 2003).

36.2.4 Treatment

Identification of the type of allergic eye diseases dictates the choice of treatment. Management of allergic conjunctivitis is similar to that of allergic rhinitis, as the two disorders are connected anatomically by the lacrimal duct. They are both caused by like allergens and share similar pathophysiology.

Treatment of allergic conjunctivitis consists of (1) prevention of allergen sensitization by avoiding or discontinuation of allergen, (2) mediating the mast cell response and inflammatory cascade, and (3) modifying the underlying mechanism of the immune response. Patient education also plays an important factor in the correct use of and adherence to medications and therapies of both allergic conjunctivitis and allergic rhinitis.

Management for the chronic inflammatory ocular disorders, AKC, VKC, and GPC, does not involve immunotherapy. The goal of treatment for these disorders is to limit prevention of corneal damage and prevent visual changes and progression to visual loss. Ophthalmological consultation is often recommended in cases involving these pathologies.

36.2.4.1 Primary Treatment

Avoidance of the allergen(s) is the primary treatment for allergic conjunctivitis. Methods of prevention which depends on the inciting antigen include using HEPA air filters, limiting outdoor exposures, removing animal dander, routine cleaning, and vacuuming, among others.

36.2.4.2 Pharmacotherapy

Topical solution is most commonly used for the treatment for allergic eye diseases. Preservative-free topical eye drops are preferred to avoid the risk of allergic responses or damages to the ocular surface. Ocular lubricating agents such as saline solution or artificial tears are often the initial therapy used for allergic conjunctivitis. These over-the-counter agents limit the exposure of the eye to allergens by dilution, irrigation, and removal of allergens and inflammatory mediators on the ocular surface (Bielory et al. 2012). Artificial tears and/or saline solution also serve as a barrier against allergens.

Various agents are used for the management of allergic conjunctivitis with the mainstay of treatment involving topical antihistamines, mast cell stabilizers, and multimodal anti-allergic agents. Other drugs such as topical vasoconstrictors, NSAIDs, and corticosteroids may be used in acute, severe, or refractory cases. Combination therapies with topical antihistamine/vasoconstrictor and topical antihistamine/mast cell stabilizer are also implemented to improve efficacy and optimize relief of ocular symptoms. Immunotherapy with immunomodulators is also used for allergic eye disorders, mainly in the treatment of severe AKC and VKC. Furthermore, AIT with SCIT or SLIT may serve as a potential treatment.

Antihistamines, mast cell stabilizers, and multimodal agents: Oral antihistamines are

typically used for the management of allergic rhinitis. It may be used in allergic conjunctivitis especially with the concomitant use of an eye drop as second-generation antihistamines can induce ocular dryness (Welch et al. 2002). Ocular dryness leads to removal of the protective barrier against allergens and worsening of symptoms.

Topical H1 antihistamines such as ketotifen ophthalmic and olopatadine ophthalmic are often used over systemic antihistamines due to its fast onset of action (Ackerman et al. 2016). Most have other mechanism of action and are classified as multimodal anti-allergic agents. Topical H1 antihistamines act directly on the ocular surface and deliver the drug to the site of allergic inflammation. They are reversible H1-receptor antagonists and act on the capillaries of the conjunctival epithelium causing vasoconstriction, reduction in vascular permeability, and decrease in edema. Topical H1 antihistamines also relieve ocular itching. Symptoms are alleviated for only a short duration, requiring dosing of up to four times a day (La Rosa et al. 2013). The repeated dosing can sometimes be irritating to the eyes, and the once-daily oral antihistamine can be used in patients who have difficulty in adherence to the regimen or who are unable to tolerate the side effects. Newer topical H1 have been developed for singular dosing.

Topical mast cell stabilizers such as cromolyn sodium, lodoxamide, and nedocromil sodium are one of the treatment options for allergic conjunctivitis. The exact mechanism of action is unknown though they have been shown to reduce the degranulation of mast cells and prevent the release of histamine and additional inflammatory mediators. In this way, mast cell stabilizers prevent both the early and late phases of the allergic responses while reducing conjunctival injection and itching. Because of the slow onset of action, they are not effective against existing symptoms and require a loading period prior to antigen exposure (Ackerman et al. 2016).

The use of mast cell stabilizers as prophylactic agents renders them particularly beneficial toward the management of perennial allergic conjunctivitis. It also leads to poor compliance given the long onset of action and repeated dosing. Topical mast cell stabilizers are generally safe with transient burning or stinging upon initial administration.

Multimodal anti-allergic agents are often the drug of choice for patients and providers. These agents have multiple pharmacologic effects that target different allergic pathways, such as having both the combined action of histamine receptor antagonist and mast cell stabilizers in addition to other drug-specific mechanisms of actions (Table 7).

Topical vasoconstrictors, combination therapy, and anti-inflammatory agents: Topical vasoconstrictors such as naphazoline and oxymetazoline effectively reduce hyperemia and ocular redness via alpha adrenoreceptor stimulation, with little to no relief on ocular pruritus. Like nasal decongestants, the chronic use of topical vasoconstrictors can lead to rebound symptoms or in this case rebound hyperemia or "conjunctivitis medicamentosa" (Spector and Raizman 1994). Topical vasoconstrictors are not preferred for the treatment of allergic conjunctivitis due to their rebound effects and less efficacies in controlling ocular itching and lacrimation than the other topical preparations. Due to the over-the-counter availability of topical vasoconstrictors, and like intranasal decongestants, they are at an increased risk of overuse and misuse.

Combination therapy such as topical antihistamine with a vasoconstrictor or topical antihistamine with a mast cell stabilizer can be used to further alleviate ocular symptoms. Combination treatments with antihistamines and vasoconstrictors have been shown to be more effective than single-agent administration (Abelson et al. 1990). However as this combination treatment contain a vasoconstrictor, side effects such as conjunctivitis medicamentosa can also occur with chronic use. Combination treatments with antihistamines and mast cell stabilizers improve patient compliance as these agents have both the benefits of the rapid onset of antihistamines used to treat existing symptoms and the prophylactic action of mast cell stabilizers to prevent future symptoms (Bielory et al. 2012).

Anti-inflammatory drugs such as topical NSAIDS and corticosteroids are used in addition to the main treatment options for allergic

Table 7 Topical multimodal anti-allergic agents for treatment of allergic conjunctivitis

Generic	Brand (strength and dosage form)	Mechanism of action	Administration[a]	Contraindications; adverse reactions
Alcaftadine	Lastacaft® (0.25%, 3 mL solution)	Second-generation histamine H1 receptor antagonist; mast cell stabilizer	≥2 yr: 1 drop qd	Hypersensitivity; Burning sensation of eyes, eye irritation, eye pruritus, eye redness, stinging of eyes
Azelastine hydrochloride	Generic (0.05%, 6 mL solution)	Second-generation histamine H1 receptor antagonist; mast cell stabilizer	≥3 yr: 1 drop bid	Hypersensitivity; Transient burning/sting, headache, bitter taste
Bepotastine besilate	Bepreve® (1.5%, 5 mL and 10 mL solution)	Second-generation histamine H1 receptor antagonist; mast cell stabilizer	≥2 yr: 1 drop bid	Hypersensitivity; Dysgeusia, headache, eye irritation, nasopharyngitis
Epinastine hydrochloride	Elestat® (0.05%, 5 mL solution) Generic (0.05%, 5 mL solution	Second-generation histamine H1 receptor antagonist; mast cell stabilizer; also has affinity for the H_2, alpha$_1$, alpha$_2$, and the 5-HT$_2$ receptors	≥2 yr: 1 drop bid	Hypersensitivity; Cold symptoms, upper respiratory infection
Ketotifen fumarate	Alaway® (0.025%, 10 mL solution) Alaway Childrens Allergy® (0.025%, 5 mL solution) Claritin Eye® (0.025%, 5 mL solution) Eye Itch Relief® (0.025%, 5 mL solution) GoodSense® Itchy Eye (0.025%, 5 mL solution) TheraTears® Allergy (0.025%, 10 mL solution) Zaditor® (0.025%, 5 mL solution) Generic (0.025%, 5 mL solution)	Histamine H1 receptor antagonist; mast cell stabilizer; additional anti-inflammatory actions including interacting with chemokine-induced migration of eosinophils into conjunctiva	≥3 yr: 1 drop bid q8–12h	Hypersensitivity; Headache, conjunctival injection, rhinitis
Olopatadine hydrochloride	Pataday® (0.2%, 2.5 mL solution) Patanol® (0.1%, 5 mL solution) Pazeo® (0.7%, 2.5 mL solution) Generic (0.1%, 5 mL solution; 0.2%, 2.5 mL solution)	Second-generation histamine H1 receptor antagonist; mast cell stabilizer; inhibits histamine-induced effects on conjunctival epithelial cells	Pataday, Pazeo ≥2 yr: 1 drop qd Patanol ≥3 yr: 1 drop bid	Hypersensitivity; Cold symptoms, flu-like symptoms, pharyngitis, superficial punctate keratitis

bid twice daily, *h* hour, *mL* millimeter, *qd* daily, *yr* year

[a]Instill amount of drops into each eye

Table 8 Topical corticosteroids for treatment of allergic conjunctivitis

Generic	Brand (strength and dosage form)	Administration	Contraindications; adverse reactions
Dexamethasone	Maxidex® (0.1%, 5 mL suspension) Generic (0.1%, 5 mL solution as phosphate)	Maxidex 1–2 drops into conjunctival sac up to 4–6 times/day; may use hourly in severe disease; taper prior to discontinuation Generic 1–2 drops into conjunctival sac every hour during the day and every other hour during the night; gradually reduce dose to 1 drop q4h, and then tid to bid	Hypersensitivity; Burning sensation of eyes, cataract, decreased visual acuity, eye perforation, filtering bleb, glaucoma, secondary ocular infection, stinging of eyes, visual field defect
Fluorometholone	FML® (0.1%, ointment as base) Flarex® (0.1%, 5 mL suspension as acetate) FML Forte® (0.25%, 5 mL and 10 mL suspension as base) FML® Liquifilm® (0.1%, 5 mL and 10 mL suspension as base)	FML ≥2 yr: Apply small amount to conjunctival sac qd to tid; may increase to q4h during initial 24–48 h Flarex, FML Liquifilm ≥2 yr: 1–2 drops into conjunctival sac bid to qid; may instill 2 drops q2h or 1 drop q4h during initial 24–48 h FML Forte ≥2 yr: 1 drop into conjunctival sac bid to qid; may instill 1 drop q4h during initial 24–48 h	Hypersensitivity, viral diseases of the cornea and conjunctiva (i.e., epithelial herpes simplex keratitis, vaccinia, and varicella), mycobacterial or fungal infections of the eye, acute purulent untreated eye infections; Secondary eye infection, blurred vision, burning sensation of eyes, cataract, decreased visual acuity
Loteprednol	Alrex® (0.2%, 5 mL and 10 mL suspension as etabonate) Lotemax® (0.5%, 5 mL, 10 mL and 15 mL suspension as etabonate)	Alrex 1 drop per eye qid Lotemax 1–2 drops into the conjunctival sac of the eye qid; dosing may be increased up to 1 drop q1h during initial 1 week	Hypersensitivity, viral diseases of the cornea and conjunctiva (i.e., epithelial herpes simplex keratitis, vaccinia, and varicella), mycobacterial or fungal infections of the eye, fungal diseases of ocular structures; Anterior chamber inflammation, blurred vision, foreign body sensation, pruritis, chemosis, application site burning, eye discharge, photophobia, visual disturbance, xerophthalmia
Prednisolone			
Prednisolone acetate	Omnipred® (1%, 5 mL and 10 mL suspension) Pred Forte® (1%, 1 mL, 5 mL, 10 mL, and 15 mL suspension) Pred Mild® (0.12%, 5 mL and 10 mL suspension) Generic (1%, 5 mL, 10 mL, and 15 mL suspension)	1–2 drops per eye bid to qid; dosing may be increased during the initial 24–48 h	Hypersensitivity, viral diseases of the cornea and conjunctiva (i.e., epithelial herpes simplex keratitis, vaccinia, and varicella), mycobacterial or fungal infections of the eye, acute purulent untreated eye infections, use after uncomplicated removal of a superficial corneal foreign body (contraindicated for prednisolone sodium phosphate only); Secondary ocular infection, accommodation disturbance, blepharoptosis, conjunctival hyperemia, conjunctivitis
Prednisolone sodium phosphate	Generic (1%, 10 mL solution)	1–2 drops into conjunctival sac q1h during the day and q2h at night; decrease to 1 drop q4h with subsequent reduction to 1 drop tid to qid	

bid twice daily, *h* hour, *ml* millimeter, *qd* daily, *qid* four times daily, *tid* three times daily, *yr* year

conjunctivitis when ocular symptoms of allergic conjunctivitis persist and/or severe. NSAIDs (ketorolac, diclofenac, indomethacin, flurbiprofen) reduce inflammation and pruritus by decreasing thromboxane and prostaglandin formation via inhibition of cyclooxygenase (Masferrer and Kulkarni 1997). NSAIDs also decrease mucus secretion and cellular infiltration.

Topical corticosteroids (Table 8) are reserved for acute flare-ups of severe cases of allergic conjunctivitis, for chronic inflammation refractory to conventional therapies such as AKC, VKC, and GPC (Ackerman et al. 2016). Corticosteroids inhibit phospholipase which is the enzyme involved in the first step of the arachidonic acid pathway, acting on both the cyclooxygenase and lipoxygenase pathway.

Pharmacokinetic properties inherent to the preparation of the topical steroids can dictate the use of a particular steroid for the type of allergic ocular disorder. Ester steroid loteprednol etabonate is effective at reducing the superficial inflammation of the cornea and is used in GPC and contact lens-associated irritation due to its rate of metabolism (Friedlaender and Howes 1997).

Topical corticosteroids are given as pulse doses or short courses no longer than 3 months at a time. The likelihood of adverse effect is dose-dependent, based on the potency of the steroids and the duration of treatment. Adverse effects include delayed wound healing, elevated intraocular pressure, formation of cataracts, and secondary infections. Patients who are on topical corticosteroids are closely monitored by an ophthalmologist for these ocular side effects.

36.2.4.3 Immunotherapy

Topical immunomodulators such as cyclosporine and tacrolimus are indicated for the treatment of ACK and VKC. Both are calcineurin inhibitors with tacrolimus being 100 times more potent than cyclosporine (Erdinest and Solomon 2014). Tacrolimus is indicated in those patients who do not respond to cyclosporine. Cyclosporine may also be used to treat SAC.

While allergen-specific immunotherapy is a potential curative treatment option for allergic rhinitis, further studies are being conducted to validate the use of SCIT and SLIT for allergic conjunctivitis but can be of added benefit in the severe cases of allergic conjunctivitis.

36.3 Conclusion

Treatment for both allergic rhinitis and allergic conjunctivitis begins with avoidance of allergens. Oral or nasal decongestants or topical vasoconstrictors are often used first by patients due to their over-the-counter availability and have a high potential for rebound congestion. Oral and nasal or topical antihistamines are safer and are often the first agents physicians prescribe, with oral antihistamines more effect in the treatment of allergic rhinitis over allergic conjunctivitis. Intranasal corticosteroids are an excellent option as it can be used as monotherapy for allergic rhinitis. Mast cell stabilizers and anticholinergics are also available as adjunct therapy for allergic rhinitis. For allergic conjunctivitis, topical multimodal anti-allergic agents are often the drug of choice as they target various allergic pathways. Topical corticosteroids are used to treat AKC, VKC, and GPC and are reserved for severe allergic conjunctivitis. Immunomodulators are also used for severe AKC and VKC.

Alternative and complementary medicines with herbal agents, acupuncture, or OMT are additional venues for management of allergic rhinitis and conjunctivitis. Finally, allergen-specific immunotherapy with SCIT or SLIT is available as a potential treatment and cures for allergic diseases, including allergic rhinitis, and can offer additional benefits in severe cases of allergic conjunctivitis.

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Bronchodilator Therapy for Asthma

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Abstract

Bronchodilators are essential medications used in the management of asthma. As reversible airway obstruction is a cardinal feature of asthma, bronchodilators play an essential role in reversing airway obstruction and provide "bronchoprotection" against bronchospasm due to exercise and other spasmogenic stimuli. In addition to acting as rescue agents in the treatment of bronchospasm, some bronchodilators, such as long-acting beta-agonists (LABAs) and long-acting anti-muscarinic agents (LAMAs), are used as controller agents when used in combination with inhaled glucocorticoid (GC) therapy. This chapter will provide a comprehensive overview of the three major classes of bronchodilators, beta-adrenergic agonists (β-agonists), anticholinergic agents, and theophylline, followed by a brief discussion of phosphodiesterase inhibitors.

β-Agonists are the most important class of bronchodilators. Short-acting beta-agonists (SABAs) are the most effective medications available in relieving bronchospasm and preventing exercise-induced bronchospasm. LABAs, when used in fixed combination with inhaled GCs, are very effective in improving asthma control and are the preferred controller agents for asthmatics with moderate-to-severe persistent asthma. The anticholinergic ipratropium when used in combination with albuterol in the ED can reduce the number of asthma exacerbations requiring hospitalization. It is less effective than albuterol in relieving bronchospasm in asthma while being as effective as albuterol in patients with chronic obstructive lung disease (COPD). Tiotropium, a LAMA, is now indicated as an add-on agent in patients with asthma inadequately controlled on an inhaled GC alone or in combination with a LABA. Theophylline, although widely used in the past century, is rarely prescribed due to its narrow therapeutic window and the availability of much more effective agents, such as LABAs and inhaled GCs. Phosphodiesterase inhibitors have the potential to be the very effective asthma medications, but problems with toxicity have limited their use.

Keywords

Short-acting beta-agonists (SABAs) · Long-acting beta-agonists (LABAs) · Beta-agonist receptor polymorphisms · Anticholinergic agents · Long-acting anti-muscarinic agents (LAMAs) · Phosphodiesterase inhibitors

37.1 Beta-Adrenergic Agents

37.1.1 Introduction

Inhaled β_2-adrenoceptor agonists (β_2-agonists) are an essential class of asthma medications in that they can be used in both the acute (as rescue agents) and chronic (as controller agents) management of asthma. SABAs are the most effective class of bronchodilators, as airway smooth muscle (ASM) relaxation in both the central and distal airways is solely mediated by β_2-adrenergic receptors (β_2-AR) (Goldie et al. 1984; Nials et al. 1993; Löfdahl and Svedmyr 1982).

β_2-Agonists also act as functional antagonists and inhibit or reverse bronchospasm, irrespective of the constrictor stimuli, such as exercise, allergen exposure, viral infections, and chemical spasminogens such as histamine, methacholine, and adenosine (Torphy et al. 1983, 1985). Regardless of the bronchoconstrictive stimuli, SABAs improve lung function, reduce symptoms, and block exercise-induced asthma.

In contrast, long-acting beta-agonists (LABAs) are considered asthma controller agents when used in combination with inhaled glucocorticoids (iGCs). Despite controversy over their safety, LABAs when combined with an inhaled GC in a single device are among the most effective agents for patients with moderate-to-severe persistent asthma. Combination LABA/iGC therapy is superior to higher-dose iGC, combination iGC/theophylline, or iGC/leukotriene receptor antagonist therapy with respect to improvement in lung function, reduction in symptoms and need for rescue SABA use, improvement in quality of life, and reduction in exacerbations.

37.1.2 History/Pharmacology

Ephedrine, a nonspecific sympathomimetic amine, was used by the Chinese to treat respiratory ailments over 2,000 years ago. It was administered in the form of a tea made from the Chinese medicinal herb called ma huang (*Ephedra equisetina*). Ephedrine was first synthesized in 1885, and by the 1920s, it was a commonly used asthma therapy. In the 1940s a combination theophylline/ephedrine tablet was developed which was widely used for decades. In the early twentieth century, epinephrine, a naturally occurring catecholamine, was synthesized. It was administered subcutaneously to treat episodes of acute bronchospasm (Barger and Dale 1910). Although epinephrine was a potent bronchodilator, it had a very short duration of action (1–2 h), and it was associated with a number of adverse effects such as hypertension, tachycardia, and arrhythmias due to its effects on α_1- and β_1-adrenergic receptors present in the cardiovascular system. In an attempt to lessen its adverse effects profile, an inhaled form of epinephrine was developed in the 1940s using a crude delivery device.

Isoproterenol was the first synthetic catecholamine (Davies 1972). Unlike epinephrine, it was a nonselective β-agonist. Isoproterenol was a very potent bronchodilator, but it too had a short duration of action (2–3 h) due to rapid degradation by the enzyme catechol-*O*-methyltransferase (COMT). In addition, tachycardia and arrhythmias were common adverse effects. The next advance came in the 1960s when metaproterenol, the first non-catecholamine, nonselective β-agonist, was synthesized. Catecholamines have a catechol nucleus (benzene ring with hydroxyl groups at positions 3 and 4) and an amine side chain. Non-catecholamines have modifications of the hydroxyl groups on the catechol nucleus (see Fig. 1a). These changes prevent degradation by COMT resulting in prolonged bronchodilation. By increasing the bulk of the side chains on the ethylamine group, greater selectivity for the β_2-adrenergic receptor was achieved.

In the early 1980s, albuterol was developed. It was the first of what became a whole new class of β_2-selective agents that are now exclusively used to treat asthma (Jack 1991). As it was a β_2-selective agonist, albuterol was largely devoid of cardiovascular adverse effects, and it had a longer duration of action (4–6 h) compared to the 2- to 3-h duration for isoproterenol and epinephrine. Over the next couple of decades, β_2-selective agonists were developed that had much longer durations of action. In the early 1990s, salmeterol (Serevent®) and formoterol (Foradil®), the first LABAs, were developed having a duration of action of at least 12 h. In the past decade, several ultra-long-acting ($\geq$24 h) β_2-selective agonists (ultra-LABAs) have been developed. Many of the ultra-LABAs are available as single agents for the treatment of COPD (indacaterol, Arcapta®, and olodaterol, Striverdi®) (Fig. 1b), while vilanterol is available in combination with either an inhaled steroid (vilanterol/fluticasone furoate, Breo®), a long-acting anti-muscarinic agent (LAMA) (vilanterol/umeclidinium, Anoro®), or a LAMA and an inhaled GC (vilanterol/umeclidinium and fluticasone furoate). Breo® is available for use in both COPD and in adults with asthma. The triple agent combination inhaler has a COPD indication.

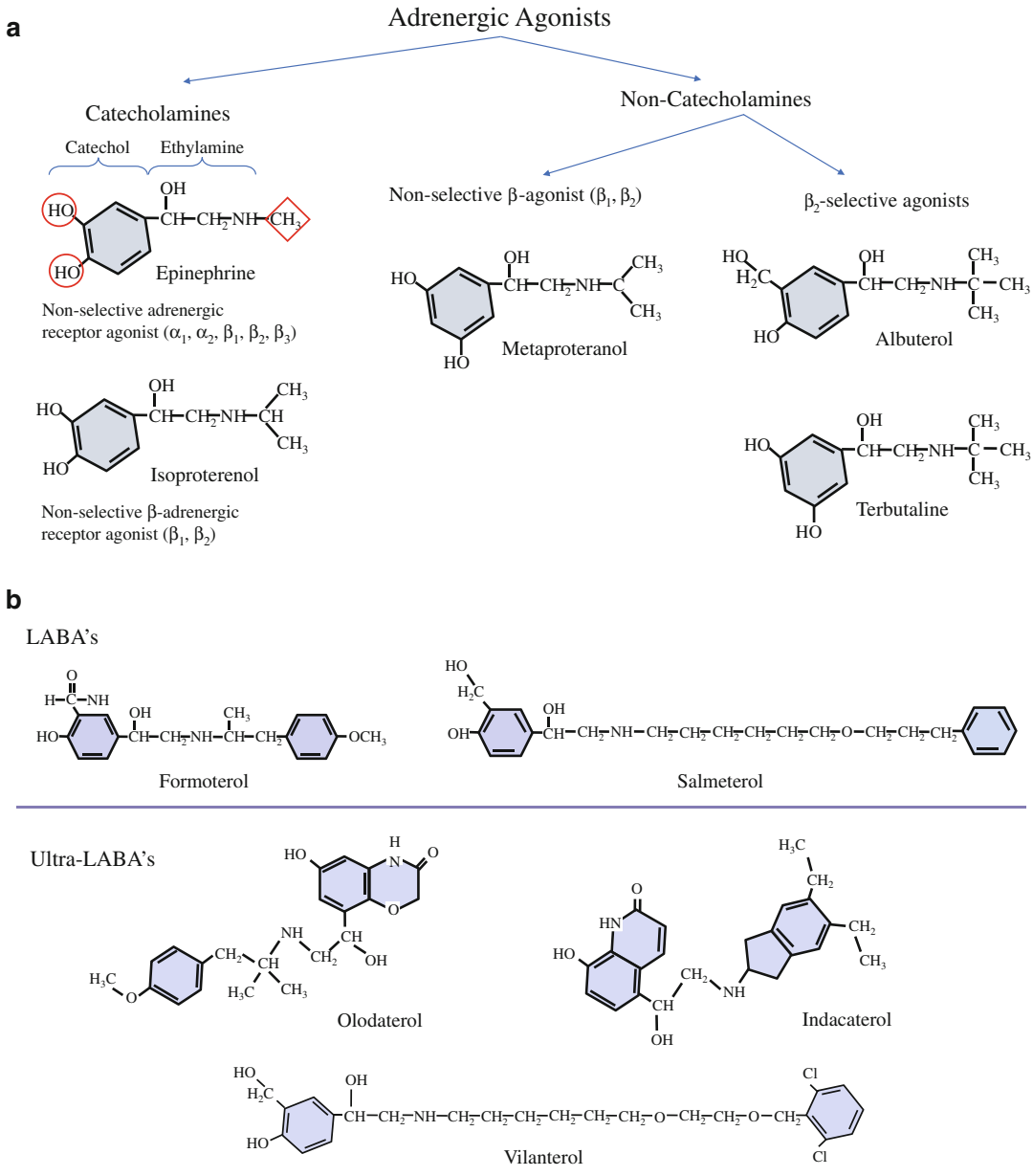

Fig. 1 (**a**) Structure of adrenergic agonists. Epinephrine is a nonselective adrenergic agonist that binds to α- and β-adrenergic receptors. It is a catecholamine, as it is comprised of a catechol ring and ethylamine side chain. Isoproterenol is a catecholamine, but modifications to the R group (represented by the red diamond) on the ethylamine side chain make it bulkier, which enhances its selectivity for β-adrenergic receptors. Non-catecholamine adrenergic agents have had modifications to the hydroxyl groups on the catechol ring (represented by the red circles), making them less susceptible to COMT degradation which prolong their duration of action. Metaproterenol is a non-catecholamine, nonselective, β-adrenergic agent. Albuterol and terbutaline are non-catecholamine β_2-selective adrenergic agents with enhanced β_2-selectivity due to further modifications to the R group on the ethylamine side chain. (**b**) Structure of long-acting β_2-selective adrenergic agonists. Formoterol and salmeterol are the available long-acting beta-agonists or LABAs. These compounds have $\geq$12-h duration of action. Over the past 5 years, three ultra-LABAs have been approved for use in the USA. They have a duration of action of $\geq$24 h. Only vilanterol in a fixed-dose combination with fluticasone furoate is available for use in asthma

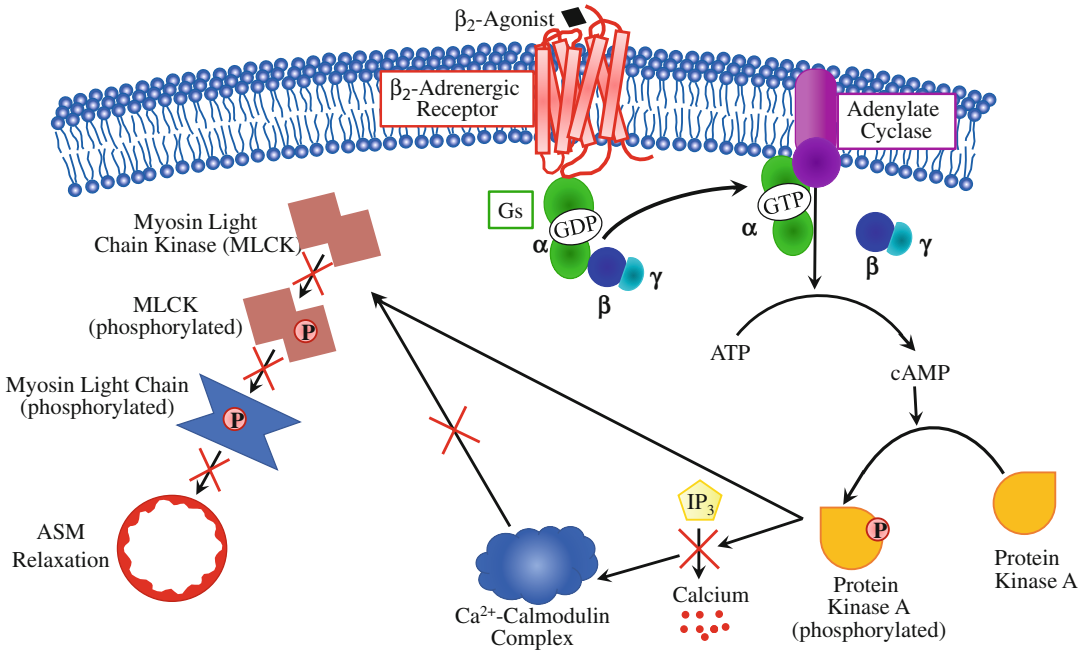

Fig. 2 Signaling pathways involved in β_2-adrenergic agonist-mediated bronchodilation. Beta-agonists such as albuterol bind to the β_2-AR which then activates the G protein-coupled receptor Gs. Gs activation results in activation of adenylate cyclase which converts ATP into the second messenger cAMP. cAMP then phosphorylates protein kinase A (PKA) which interferes with IP3's ability to release intracellular calcium. Without a calcium-calmodulin complex, myosin light-chain kinase is not phosphorylated, which prevents myosin light-chain phosphorylation and ASM constriction. As a result, the ASM relaxes

37.1.3 Mechanism of Action

In 1987, the gene encodingfor the β_2-AR was first cloned (Kobilka et al. 1987). It is a 1242 nucleotide intronless gene coding for a 413-amino acid protein located on the long arm of chromosome 5 (5q31.32). It is a member of the 7-transmembrane receptor superfamily that signal through heterotrimeric G proteins (Gilman 1987). G protein-coupled receptors act as "molecular switches" alternating from an inactive guanosine diphosphate (GDP) to an active guanosine triphosphate (GTP) state, which then regulates downstream cell processes (Neves et al. 2002) (see Fig. 2). Activation of the β_2-AR promotes the binding of a stimulatory G protein (Gs) which consists of α, β, and γ subunits to the receptor. Upon binding of GTP, the Gs protein subunits disassociate into Gα and Gβγ. Gα then stimulates adenylyl cyclase (AC), and the resulting increase in intracellular cyclic 3′, 5′-adenosine monophosphate (cAMP) activates protein kinase (PKA). PKA then inhibits key regulatory molecules involved in the control of airway smooth muscle (ASM) tone resulting in relaxation (Giembycz and Raeburn 1991). The intrinsic GTPase activity of Gα subsequently terminates the process, with reassociation of heterotrimeric protein.

37.1.4 Routes of Administration

37.1.4.1 Oral

Orally administered β-agonists are not recommended due to their greater adverse effects profile which includes tremor (the dose-limiting effect), tachycardia, and palpitations. In addition, much larger doses must be administered to be effective due to poor oral bioavailability and prolonged time to peak dilation (≥2 h). Orally administrated β-agonists should only be considered in children

and adults with cognitive and/or physical impairments that preclude effective inhalation treatment.

37.1.4.2 Subcutaneous or Intramuscular (IM) Administration

Subcutaneous administration of epinephrine or terbutaline can be used to treat severe bronchospasm, but as there is no proven advantage of systemic over aerosol therapy, this form of administration is not recommended (Uden et al. 1985). With that said, intramuscular epinephrine is the bronchodilator of choice if anaphylaxis is the cause of acute bronchospasm (Ayres et al. 2004; Lieberman et al. 2010).

37.1.4.3 Inhalation

Inhalation is the delivery of choice in nearly every situation as the drug is delivered directly to the lungs allowing for higher lung concentrations. Inhaled β_2-agonists can be delivered in aerosolized form in a metered-dose inhaler (MDI), a dry powder inhaler (DPI), in the form of a liquid inhaler, or in an aqueous form delivered via a nebulizer.

Metered-Dose Inhalers (pMDIs)

All SABAs are delivered via MDIs with the exception of ProAir RespiClick® which is delivered via a DPI. In most situations, a spacer is recommended for the administration of all MDI medications in children. They are simple and inexpensive tools that (1) decrease the coordination required to use an MDI, especially in young children; (2) improve the delivery of the inhaled drug to the lower airways; and (3) minimize the risk of drug and propellant-mediated oropharyngeal adverse effects (dysphonia and thrush with inhaled GC therapy) (Toogood et al. 1984; Steckel and Muller 1998). Optimal technique involves a slow (5 sec) inhalation with a 5–10-sec breathhold. No waiting time between puffs of medication is required. Because preschool-aged children cannot perform this inhalation technique, MDI medications are delivered with a spacer and mask, with each puff administered with regular (tidal) breathing for about 30 sec or 5–10 breaths while maintaining a tight seal around the mouth.

Dry Powder Inhalers (DPIs)

Several LABA and ultra-LABAs are available in DPI alone (salmeterol, formoterol, indacaterol, and olodaterol), combined with an iGC (fluticasone propionate/salmeterol [Advair®], fluticasone furoate/vilanterol [Breo]) or combined with a LAMA (vilanterol/umeclidinium [Anoro®], olodaterol/tiotropium [Stiolto®], and indacaterol/glycopyrrolate [Utibron®]). Only the LABA/inhaled GC combination products are indicated for use in asthma, with the single agent and combination LABA/LAMA products indicated for the treatment of COPD. DPI devices are popular because of their simplicity of use. In contrast to the slow inhalation required for adequate delivery of medications delivered via MDIs, a rapid inspiratory flow is required to de-agglomerate drug particles for inhalation in DPI devices (Dunbar et al. 1998). They are breath actuated and do not require the use of spacers.

Nebulizers

There are two types of nebulizers, jet and ultrasonic, that differ in the force used to generate the aerosol from the respective medication. Depending on the model and the manufacturer, nebulizers generate 1–5 μm droplets. Treating infants and toddlers with inhaled medications is a challenge due to a number of factors. First, they have small airways, low tidal volumes, and high respiratory rates, all of which increase the difficulty of inhaled medications to reach the airways. In addition, it is difficult to administer inhaled medications to infants and young children due to their inability/refusal to cooperate. As administration of inhaled medications via nebulizers can deliver large doses and the technique is simple requiring relaxed tidal breathing, nebulized therapy has been the preferred choice of aerosol delivery for infants and young children. Disadvantages of nebulizers include the need for a power source, the expense involved in its use, and the potential for contamination. Furthermore, nebulizers are an inconvenient delivery system as treatments take a minimum of 5 min, a difficult task to perform in an uncooperative young child.

Multidose Liquid Inhalers

The newest delivery system combines the advantages of an MDI with that of a nebulizer. Like an MDI, the Respimat® inhaler is a small, portable, multidose delivery system, and unlike a nebulizer, it does not require electricity and doesn't require loading of each dose of medication. The Respimat® delivers a propellant-free drug solution as a soft mist that decreases oropharyngeal deposition while enhancing the delivery of the drug to both the central and distal airways (Dalby et al. 2011). It is used to deliver formoterol (Foradil®), tiotropium (Spiriva®), and the combination products albuterol/ipratropium (Combivent®) and tiotropium/olodaterol (Stiolto®).

37.1.4.4 MDI Versus Nebulizer

There has been some debate regarding which form of delivery device (MDI or nebulizer) is superior, especially in young children. A study comparing both delivery methods was performed in both preschool- and grade school-aged children (Wildhaber et al. 1999). This was accomplished by evaluating the degree of lung deposition of radiolabeled salbutamol from a nebulizer and from a MDI with spacer. Both delivery devices delivered 5% of the nominal dose to the lower airways, but because larger doses of salbutamol were administered via the nebulizer (2000 mcg) compared to the MDI (400 mcg), a greater amount of salbutamol was delivered to the airways using the nebulizer. Both devices were found to be less efficient in delivering albuterol in preschool-aged compared to grade school-aged children. Another study found no differences in lung function or symptom reduction when albuterol was delivered via a MDI or nebulizer in both children and adults with mild-to-moderate exacerbations presenting to the ED (Parkin et al. 1995). Because nebulized albuterol is associated with a greater adverse effects profile (increased heart rate and tremor) and because MDIs are more cost-effective, the GINA guidelines (GINA 2017) recommend the use of MDIs over nebulizers in the routine management of acute asthma in the ED.

37.1.5 Short-Acting Selective β_2-Agonists (SABAs)

SABAs are considered the first-line treatment for asthma symptoms and for preventing EIB. Improvement in lung function begins within 5 min, peaks within 30 min, and lasts for 4–6 h. SABAs can be used frequently in acute asthma, and if the exacerbation is severe enough, they can even be used continuously. In chronic asthma, regularly administered (four times/day) albuterol does not improve asthma outcomes and results in tachyphylaxis. As a result, SABAs are used exclusively as rescue agents. Frequency of SABA use in a patient with chronic asthma can be used to assess that patient's level of asthma severity or control. The need for albuterol >2 times/week in a controller-naïve patient is indicative of persistent asthma, and institution of a daily controller is recommended. If a patient on a controller agent requires SABA therapy >2 times per week, that asthmatic is considered to have inadequately controlled asthma, and step-up therapy is recommended.

37.1.5.1 Albuterol and Terbutaline

Albuterol (Proventil®, Ventolin®, ProAir®) and terbutaline (Bricanyl®) have equivalent bronchodilator effects with less cardiac stimulation versus short-acting, nonselective β-agonists such as metaproterenol (Alupent®). Albuterol is a hydrophilic molecule with access to the β_2-AR directly from the aqueous, extracellular compartment resulting in bronchodilation within 15 min of inhalation. Due to albuterol's relatively low binding affinity to the β_2-AR, once it dissociates, albuterol quickly enters the microcirculation, which accounts for its relatively short duration of action (4 h). It has negligible α-adrenergic receptor-binding affinity and has >500-fold selectivity for β_2- over β_1-adrenergic receptors.

Terbutaline differs from albuterol in that it has a dihydroxybenzene group at the b-carbon atom instead of a benzene ring, with meta-hydroxymethyl and para-hydroxyl groups (see Fig. 1a). Terbutaline and albuterol are equivalent with respect to maximal bronchodilation and time to maximal bronchodilation, but terbutaline

has a slightly longer duration of action (5 h). Terbutaline when administered intravenously or subcutaneously loses its β_2-selectivity and is associated with a greater increase in heart rate than systemically administered albuterol.

37.1.5.2 Levalbuterol

Albuterol normally exists as a racemic mixture of both R- and S-isomers. Levalbuterol (Xopenex®) contains only the R-isomer (the active isomer). The S-isomer is felt to be inert, as its β_2-AR binding affinity is 100-fold less than that of the R-isomer. Some in vitro and in vivo studies have implicated the S-isomer as being pro-inflammatory and may cause paradoxical bronchospasm. Tachycardia and tremor are less common with levalbuterol as a lower dose is usually required compared to racemic albuterol, although these adverse effects are not mediated by the S-isomer. In stable asthma, lower doses of levalbuterol are needed to produce similar bronchodilation compared to racemic albuterol. A study comparing the effect of levalbuterol versus racemic albuterol in children presenting to the ED with acute asthma found levalbuterol to result in a modest yet significant reduction in hospitalizations compared to racemic albuterol (36% vs. 45%). Levalbuterol was not associated with a shorter hospital stay, nor did it result in less need for β-agonist treatments. Of surprise, there were no differences in adverse effects between the two therapies (Carl et al. 2003). A meta-analysis of 7 studies that included 1625 patients that compared the effectiveness and adverse effects profile of levalbuterol to racemic albuterol in patients presenting to the ED with acute asthma (Jat and Khairwa 2013) found no differences in any efficacy measure including final respiratory rate, change in respiratory rate, change in oxygen saturation, change in lung function (PEF and FEV_1), clinical asthma score, or duration of ED stay between levalbuterol and racemic albuterol. In addition, there are no differences in adverse effects including change in heart rate, tremor, headache, and nausea or change in serum potassium level. Given its increased cost and lack of clear benefit, levalbuterol is not recommended for the routine management of acute asthma.

37.1.6 Long-Acting Beta-Agonists (LABAs)

Salmeterol and formoterol are the two available LABAs as they provide a prolonged duration of action ($\geq$12 h) compared to albuterol.

37.1.6.1 Formoterol

Formoterol is a highly β_2-selective adrenergic agonist with an onset of effect similar to that of albuterol but with a much longer duration of action. In addition, it is 50- to 120-fold more potent than albuterol and 2- to 27-fold more potent than salmeterol in in vitro models of bronchodilation. In vivo studies have confirmed its greater potency in that 36 μg of formoterol delivered via DPI (Turbuhaler®) is as effective as 1600 μg of albuterol administered via MDI in improving FEV_1 in patients with acute asthma (Plamqvist et al. 1997). Formoterol is a phenylethanolamine derivative that is moderately lipophilic (Fig. 1b). Formoterol's prolonged duration of action is thought to result from most of it entering the plasma membrane and serving as a "depot." This allows formoterol to be gradually released into the aqueous phase where it binds to the β_2-AR leading to a duration of action of at least 12 h. This proposed mechanism of action has been termed the "micro-kinetic" hypothesis (Anderson et al. 1994) (Fig. 3a). Unlike albuterol and salmeterol, formoterol is a full β-agonist (Linden et al. 1993). Twice daily formoterol is more effective than albuterol administered four times a day in terms of symptom reduction and the need for rescue bronchodilator (Kesten et al. 1991).

37.1.6.2 Salmeterol

Salmeterol was designed by modifying albuterol such that it would have longer duration of action. This was achieved by attaching a long hydrocarbon "tail" to the albuterol "head" making it very lipophilic (Fig. 1b). The so-called "exo-site" hypothesis describes how the hydrocarbon tail enters and remains in the plasma membrane, while a hinge region allows the hydrophilic albuterol "head" to repeatedly bind to the β_2-AR allowing for a $\geq$12-h duration of action (Johnson et al. 1993) (Fig. 3b). Salmeterol is as β_2-selective as formoterol with an

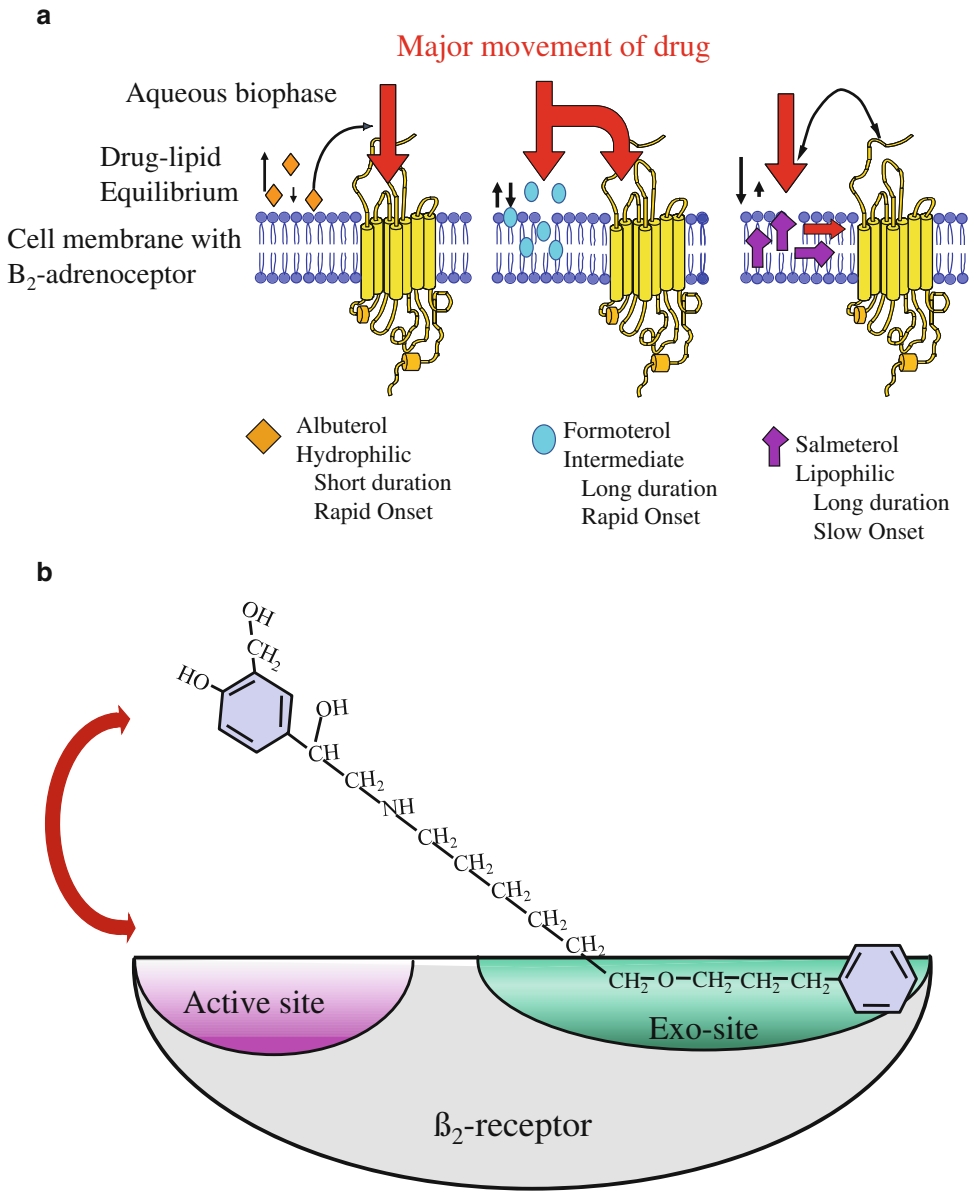

Fig. 3 (**a**) Micro-kinetic diffusion theory explains rapid onset and long duration of action of formoterol. This hypothesis explains the interactions of albuterol (left), formoterol (middle), and salmeterol (right) with the lipid membrane adjacent to the β_2-adrenoceptor. The small arrows at the left of each panel show the drug-lipid equilibrium position. The large red arrows show the major movement of the drug. Due to its high hydrophilicity, albuterol associates with the receptor directly from the aqueous biophase. As a result, albuterol has a rapid onset, but it diffuses from tissues rapidly causing short duration of effect. The association of formoterol with both the receptor and lipid is relatively stable, allowing a rapid onset. Formoterol is retained in the lipid serving as a depot which is released over an extended period, continually activating the β-adrenoceptor. Salmeterol associates predominantly with lipid. As a result, it has a slow onset but long duration of action. (**b**) The exo-site binding hypothesis explains the long duration of action of salmeterol. The long hydrocarbon side chain of salmeterol binds to a structure distinct from the beta$_2$-adrenoceptor (the exo-site), allowing the active albuterol head to angle on and off the active site of the beta$_2$-adrenoceptor (Adapted from Anderson et al. 1994)

equivalent duration of action, but its onset of effect is much longer (median time to reach a ≥15% increase in FEV_1 30 min, time to maximal effect 180 min). Salmeterol, like albuterol, is a partial β-agonist. Salmeterol administered twice daily is more effective than albuterol administered four times daily in decreasing the need for rescue albuterol, decreasing day- and nighttime symptoms, and improvement in both AM and PM PEF (Taylor et al. 1998).

37.1.6.3 Appropriate Use of LABA

LABAs are not to be used for the treatment of acute symptoms or exacerbations. In addition, LABAs should not be used as monotherapy for the treatment of chronic asthma, but this was not always the recommendation. When salmeterol was initially approved for use in asthma in the United States (USA) in 1994, it was considered a major advance in the management of asthma, especially in patients with severe asthma who had frequent nocturnal symptoms. The initial package insert stated that salmeterol was indicated for the "long-term, twice daily administration in the maintenance treatment of asthma and in the prevention of bronchospasm in patients 4 years of age and older with reversible airflow obstructive diseases, including patients with nocturnal asthma, who require regular treatment with inhaled short-acting beta-agonists. It is not recommended for patients whose asthma can be managed by occasional use of inhaled short-acting beta2-agonists." As will be discussed in a subsequent section, there were no initial concerns that LABA monotherapy would be associated with an increased risk of life-threatening asthma exacerbations.

Although formoterol has a rapid onset of effect, similar to that of albuterol, it is not approved as a rescue medication despite the fact that fixed-dose combination formoterol/budesonide is used outside of the USA as both a rescue and controller agent. "Single-inhaler therapy" (SIT) is the term used when combination formoterol/budesonide is used as needed to treat acute symptoms, in addition to its daily use as a controller agent. SIT results in a fewer asthma exacerbations and improved asthma control despite using a lower cumulative inhaled GC dose compared to regularly administered combination therapy plus SABA therapy for symptoms (Rabe et al. 2006; O'Byrne et al. 2005). SIT is unlikely to be adopted in the USA due to the Food and Drug Agency's (FDA's) concerns regarding LABA safety. The 2016 GINA guidelines recommend SIT as one of the two "preferred" regimens of combination iGC/LABA therapy for treatment steps 3 and 4. The 2007 NHLBI guidelines (NHLBI 2007) recommend LABA in combination with an inhaled GC as a preferred controller agent at treatment steps 3 through 6 in patients ≥12 years of age. Add-on LABA is superior to higher-dose inhaled GCs (Greenstone et al. 2005) and montelukast (Nelson et al. 2000; Lemanske et al. 2010) in children and adults who are inadequately controlled on inhaled GC monotherapy.

37.1.6.4 Combination LABA/Inhaled GC Therapy

LABAs should never be used as monotherapy in the treatment of asthma as studies have consistently shown worsening asthma symptoms, increases in airway inflammation, and increased risk of treatment failures, hospitalizations, intubations, and even death (Castle et al., Nelson et al. 2006). Although not entirely elucidated, the mechanism most likely responsible for worsening asthma associated with LABA monotherapy is masking of worsening airway inflammation and deteriorating asthma control due to their potent and long-lasting bronchodilator effects. Of importance, masking of asthma worsening, and in particular increasing inflammation, is unlikely when LABAs are used in combination with inhaled GCs (Tattersfield et al. 1999; Jarjour et al. 2006).

This contention is supported by multiple studies published over the past 15 years demonstrating the effectiveness of combination LABA/inhaled GC therapy as measured by reduction in symptoms, need for rescue SABA, improvement in lung function, and reductions in asthma exacerbations compared with higher-dose inhaled GC therapy. Lastly, studies by Busse and Jarjour have demonstrated that the reduction in inhaled

GC dose that is achievable with the addition of LABA does not result in worsening airway inflammation (Busse et al. 2003; Jarjour et al. 2006). Their first study sought to determine whether the addition of a LABA could allow a reduction in inhaled GC dose without deterioration in asthma control, while their second sought to evaluate whether the reduction in inhaled GC dose following the addition of LABA therapy was associated with worsening airway inflammation. Nearly 1600 asthmatics well controlled on medium-dose inhaled GC therapy had their dose halved (Busse et al. 2003). Those whose asthma worsened ($n = 760$) on lower-dose inhaled GC therapy were then enrolled into the second stage, where they received medium-dose inhaled GC therapy. If asthma control was reestablished ($n = 558$), they entered the third stage. The first two stages were performed to demonstrate that a higher dose of inhaled GC therapy was necessary before the inhaled GC was halved with the addition of a LABA. During the third stage, 281 subjects received low-dose fluticasone (100 mcg) combined with salmeterol (50 mcg), while 277 remained on medium-dose fluticasone (250 mcg) twice daily for 24 weeks. A subset of patients in each group ($n = 88$) underwent bronchoscopy with biopsy at the beginning of the third stage and upon completion of the study (Jarjour et al. 2006). Low-dose fluticasone/salmeterol was as effective as medium-dose fluticasone in reducing symptoms and albuterol use, while it was more effective in improving lung function (FEV_1, AM, and PM PEF) and was not associated with an increase in withdrawals from the study due to asthma worsening. Thus, the addition of salmeterol allowed for a 60% reduction in inhaled GC dose without the loss of asthma control. In the subset of subjects who underwent bronchoscopy with lavage and biopsy, the 60% reduction in fluticasone was not associated with an increase in airway inflammation as measured by the number of airway eosinophils; neutrophils; CD3+, CD4+, CD8+, and CD25+ T cells; or mast cells. In addition, there were no differences in mediators of inflammation (GM-CSF, IL-8, or ECP) in the bronchoalveolar lavage fluid between those who received combination low-dose fluticasone/salmeterol versus medium-dose fluticasone administered twice daily.

Several large studies have demonstrated reductions in asthma exacerbations with combination LABA/inhaled GC therapy compared to higher-dose inhaled GC therapy with the first published over 20 years ago. The *F*ormoterol and *C*orticosteroids *E*stablishing *T*herapy (FACET) study enrolled 852 subjects to receive high (400 μg)- or low-dose (100 μg) budesonide with or without formoterol twice daily for 12 months (Pauwels et al. 1997). Rates of severe and mild exacerbations were reduced by 26% and 40%, respectively, when formoterol was added to low-dose budesonide, whereas combination high-dose budesonide/formoterol therapy resulted in 63% and 62% reductions in severe and mild exacerbations, respectively, compared to high-dose budesonide therapy. Two thirds of the treatment failures related to poor asthma control asthma had been treated with budesonide monotherapy.

Unlike the FACET study where severe asthmatics were studied, *t*he *o*ptimal *t*reatment for *m*ild *a*sthma (OPTIMA) study evaluated subjects with mild-to-moderate persistent asthma (O'Byrne et al. 2001). The cohort consisted of symptomatic inhaled GC-naïve asthmatics (Group A: mild persistent, $n = 698$) or symptomatic asthmatics on low-dose inhaled GC therapy (Group B: moderate persistent, $n = 1272$). Group A subjects received placebo, budesonide 100 μg, or budesonide 100 μg plus formoterol 4.5 μg twice daily, while subjects in Group B received budesonide 100 or 200 μg alone or in combination with formoterol twice daily. The addition of formoterol to budesonide in the inhaled GC-naïve subjects resulted in greater improvement in lung function, but did not further reduce the risk of a severe exacerbation compared with budesonide alone. In contrast, the addition of formoterol to budesonide in patients who were suboptimally controlled on low-dose inhaled GC therapy resulted in a greater reduction in severe exacerbations (43%) and poorly controlled asthma (30%) versus budesonide alone. This study established the recommendation that the addition of a LABA

should be reserved for patients inadequately controlled on inhaled GC therapy.

Matz et al. evaluated the rates of asthma exacerbations in patients receiving low-dose fluticasone plus salmeterol compared to medium-dose fluticasone in 925 symptomatic asthmatics (Matz et al. 2001). Subjects who received combination therapy had fewer exacerbations, and the time to first exacerbation was longer than that of the asthmatics who received higher-dose FP monotherapy.

37.1.7 Non-bronchodilator Effects of β_2-Adrenergic Agents

β_2-Adrenergic agents have many effects on the respiratory system other than bronchodilation, including increased mucociliary clearance due to increased ciliary beat frequency and water secretion, suppression of microvascular permeability, inhibition of cholinergic neurotransmission, and priming of the GC receptor (Eickelberg et al. 1999). The addition of a LABA to airway epithelial cells incubated with fluticasone in vitro results in "priming" of the GC receptor (GCR) resulting in enhanced translocation of the GCR into the nucleus and greater suppression of pro-inflammatory cytokines. In addition, β_2-agonists inhibit mediator release from basophils and mast cells in vitro, although the effect in vivo is small and not clinically meaningful (Baraniuk et al. 1997).

37.1.8 Adverse Effects

The adverse effects of β_2-agonists are the greatest when administered orally, subcutaneously, or intravenously. Tremor, which is caused by direct stimulation of β_2-ARs in skeletal muscle, is the most common adverse effect and is inseparable from the bronchodilator effect. Fortunately, tremor rapidly and substantially decreases due to rapid β_2-AR downregulation on skeletal muscle (Ahrens 1990). Increased heart rate and palpitations are much less common with β_2-selective agonists but can occur due to β_2-adrenergic-mediated relaxation of the skeletal muscle vasculature, leading to diminished peripheral vascular resistance and tachycardia (Teule and Majid 1980). All β_2-adrenergic agonists increase the QTc interval, which can induce arrhythmias in susceptible individuals. Focal myocardial necrosis and ischemia have also rarely been reported. Lastly, multiple metabolic effects such as hyperglycemia, hypokalemia, and hypomagnesemia occur following the institution of β_2-agonist therapy, but they quickly resolve as tolerance develops with continued administration.

37.1.9 V/Q Mismatch

β_2-Agonist administration in patients with acute asthma can cause transient decreases in $Pa0_2$ of $\geq$5 mm Hg in up to 50% of patients. The effect is most pronounced in patients with severe airway obstruction where there is compensatory vasoconstriction of the pulmonary arteries that perfuse the underventilated segments (Wagner et al. 1978). Following the administration of a SABA, β_2-adrenergic-induced dilation of these vessels plus an increase in cardiac output causes increased blood flow through the underventilated areas resulting in V/Q mismatch and a fall in PaO_2. As a result, oxygen should always be administered when intensive β_2-agonist therapy is required.

37.1.10 β_2-Receptor Desensitization or Refractoriness

Associated with β_2-agonist receptor activation within the airway smooth muscle is the autoregulatory process of receptor desensitization, which occurs slowly (days to weeks) in response to downregulation of the β_2-agonist receptor after constant exposure of the receptor with a β_2-agonist (Liggett and Lefkowitz 1993). Desensitization results in the loss of the bronchoprotective, but not the bronchodilator effect of β-agonists (Ramage et al. 1994). This is likely due to the fact that pulmonary mast cells are very sensitive to desensitization, while bronchial smooth muscle cells are relatively resistant. This may

also explain the loss of tremor and tachycardia with ongoing β_2-agonist treatment while still providing bronchodilation.

How important a clinical role desensitization plays remains to be fully elucidated. Although desensitization results in a shortened duration of bronchodilation, there is no effect on peak bronchodilation (Repsher et al. 1984). Loss of bronchoprotection to a variety of stimuli also occurs, including exercise and both indirect (adenosine) and direct (methacholine) spasminogens used to assess airway hyperresponsiveness (Edelman et al. 2000). With that said, once the original reduction in bronchoprotection occurs, the new level of bronchoprotection persists with no further loss (Repsher et al. 1984). Of importance, chronic LABA therapy does not impair the response to albuterol when it is administered during acute asthma exacerbations (Korosec et al. 1999). Just as β-agonists can enhance GC function by "priming" the GC receptor, GCs can reverse β_2-AR downregulation when administered systemically (Davies and Lefkowitz 1983).

37.1.11 β-Agonist Receptor Polymorphisms and Response to β-Agonist Therapy

Whether polymorphisms of the β_2-AR receptor can contribute to poor response to β-agonist therapy and worsening asthma has been extensively studied with conflicting resulted noted. Over time, the polymorphism thought to be harmful changed, and while initial studies suggested worsening asthma control during both SABA and LABA therapy in patients with a specific polymorphism at position 16 of the β_2-AR, subsequent and much larger studies failed to confirm the original observations. The following section provides a brief summary of this evolving story.

Soon after the human β_2-AR was cloned, several single-nucleotide polymorphisms were identified, with two polymorphisms occurring at high allelic frequency: (1) substitution of glycine for arginine at codon 16 (Arg16Gly) and (2) substitution of glutamate for glutamine at codon 27 (Gln27Glu). In vitro studies had demonstrated enhanced isoprenaline-induced β_2-AR downregulation in myocytes from Gly16 homozygotes. Other studies found Gly16 homozygotes to have nocturnal asthma and were more likely to require chronic oral GC therapy. Martinez et al. genotyped the β_2-AR in 269 children. Gly16 homozygotes were found to be less responsive to the bronchodilator effects of albuterol compared to Arg16 homozygotes (Martinez et al. 1997). The authors speculated that Gly16 homozygotes had more airway inflammation/edema and as a result had a poor beta-agonist response. These initial studies suggested that asthmatics homozygous for Gly16 had more severe asthma, perhaps due to enhanced β_2-AR downregulation. At about the same time, Weir et al. genotyped a large cohort of asthmatics with varying levels of asthma severity including 81 near-fatal/fatal asthmatics and 86 mild-to-moderate asthmatics, in addition to 81 non-asthmatic controls. No polymorphisms were associated with near-fatal/fatal asthma suggesting that β_2-AR polymorphisms were unlikely to be a major determinant of near-fatal/fatal asthma (Weir et al. 1998).

Studies from New Zealand found asthmatics homozygous for Arg16 (Hancox et al. 1998; Sears et al. 1990) developed increased airway responsiveness to methacholine with regular fenoterol use. At this point, the focus turned from Gly16 to Arg16 as the genotype associated with worsening asthma control. This observation was reinforced when subjects who had previously participated in a comparative efficacy study of salmeterol and salbutamol were genotyped (Taylor et al. 1998, 2000). Arg16 homozygotes who received salbutamol had >2 times the number of exacerbations compared with Arg16 homozygotes who had received placebo (Taylor et al. 2000). The authors concluded that Arg16 homozygotes were susceptible to clinically important increases in asthma exacerbations during regular treatment with SABAs, but not LABAs.

The next series of studies evaluating β_2-AR polymorphisms came from the Asthma Clinical Research Network (ACRN). Their first study (Israel et al. 2000) genotyped ~75% of subjects

who had previously participated in a study that had allayed fear that regular SABA therapy resulted in worsening asthma (Drazen et al. 1996). Arg16 homozygotes who received regularly administered albuterol experienced a small decline in peak expiratory flow (PEF) during regular albuterol therapy (7 mL/sec). During the 4-week washout period, there was further decline. At the end of the washout period, there was a 30.5 mL/sec difference in morning PEF in the Arg16 subjects who received regularly administered albuterol versus subjects who received placebo. No other differences in asthma outcomes were noted, including asthma exacerbations.

The ACRN investigators then performed a randomized, masked crossover study (Israel et al. 2004) in which inhaled GC-naïve asthmatics who were homozygotes for Arg16 ($n = 37$) or Gly16 ($n = 41$) received regularly administered albuterol or placebo during 16-week treatment periods, with a 6-week run-in period where only ipratropium could be used as a rescue agent. During the run-in period, Arg16 patients had a 23 L/min improvement in their PEF, while no improvement was noted in the Gly16 patients. During regular albuterol treatment, Gly16 patients had a 14 L/min improvement in PEF, whereas the PEF declined 10 L/min in the Arg16 patients, for a genotype-specific difference of 24 L/min. There were no genotype-specific differences with respect to the frequency of asthma exacerbations or treatment failures. The investigators concluded that regularly administered SABA therapy in Arg16 patients resulted in suboptimal asthma control.

The ACRN group then evaluated salmeterol in a retrospective analysis of two previously published studies (Lazarus et al. 2001; Lemanske et al. 2001). In both trials, Arg16 subjects failed to benefit from salmeterol therapy compared with Gly16 subjects. In the first study, the morning PEF was 51.4 L/min lower among Arg16 subjects ($n = 12$) compared with Gly16 subjects, whereas in the second study, the difference in PEF was 36.8 L/min, favoring Gly16 ($n = 22$) over Arg16 ($n = 8$) subjects. The Arg16 subjects also had a lower FEV_1, increased symptom scores, and increased need for rescue albuterol, but neither study demonstrated differences in the frequency of asthma exacerbations or treatment failures based on genotype.

The final ACRN prospectively evaluated whether there were genotype-specific differences in response to treatment with a LABA when used in combination with an inhaled GC (Weschler et al. 2009). Subjects with moderate persistent asthma were matched for lung function, ethnic origin, and genotype [Arg16 ($n = 42$) or Gly16 ($n = 45$)]. They then received, in a randomized crossover manner, salmeterol or placebo plus beclomethasone dipropionate. There were no genotype-specific differences with respect to change in AM PEF, the study's primary endpoint, nor were there differences in rates of exacerbations. This prospective study failed to demonstrate adverse effects of salmeterol when used in combination with an inhaled GC in Arg16 asthmatics.

Large studies from GSK and AstraZeneca (AZ), the makers of the fixed-combination inhaled GC/LABA products fluticasone/salmeterol (Advair®) and budesonide/formoterol (Symbicort®), respectively, failed to demonstrate harmful effects of LABA in Arg16 asthmatics. Similar to many of the ACRN studies, they genotyped asthmatics who had participated in previously published trials. The first study by Bleecker et al. genotyped the β_2-AR of 183 subjects who participated in studies evaluating the comparative efficacy of combination fluticasone/salmeterol and montelukast (Bleecker et al. 2006). Combination fluticasone/salmeterol was superior to montelukast in all measures of asthma control studied with no difference in effect due to genotype. In addition, there were no differences in rates of exacerbation with all subjects having similar decreases in asthma control during the washout period, regardless of genotype.

Bleecker et al. then published the results of two studies evaluating the effectiveness of budesonide/formoterol combination therapy with as-needed budesonide/formoterol or as-needed terbutaline. The first was a double-blind study involving 2250 adult asthmatics, while the second was an open-label study of 405 asthmatics (Bleecker et al. 2007). β-Agonist

polymorphisms were not associated with differences in severe asthma exacerbations, nor were there differences in secondary outcomes including FEV_1, PEF, prn medication use, or nocturnal symptoms. The authors concluded that formoterol in fixed combination with budesonide was safe and effective, regardless of β-agonist polymorphism. Despite these findings, this study was criticized as it excluded patients with severe asthma who were likely to require more frequent use of SABAs and who might have been at greater risk of having adverse effects.

Bleecker et al. performed a prospective study that included an ipratropium run-in period in patients with Arg/Arg, Gly/Gly, or Arg/Gly polymorphisms who were randomized to receive salmeterol alone or in combination with fluticasone (Bleecker et al. 2010). After two 8-week run-in periods (rescue albuterol followed by rescue ipratropium for symptoms), 540 subjects received salmeterol alone or fluticasone/salmeterol combination for 16 weeks, with the primary outcome being changed in morning peak expiratory flow. No significant difference in PEF was seen between treatment groups based on β_2-AR polymorphisms. There were no differences in exacerbations between the Arg/Arg and Gly/Gly subjects during the albuterol or ipratropium run-in periods or during treatment with salmeterol alone or in combination with fluticasone. Lastly, there were no differences in exacerbations among African Americans (AAs) who received salmeterol alone or in combination with fluticasone based on genotype. This was an important observation as AAs are more likely to have the Arg16 genotype (25%) compared to Caucasians (16%) and were more likely to have had fatal asthma attacks in the Salmeterol Multicenter Asthma Research Trial (SMART) as discussed in a subsequent section.

A study that genotyped the β_2-adrenergic receptor children with asthma compared the efficacy of combination low-dose (1x) inhaled GC/LABA, higher-dose (2.5x) inhaled GC, or low-dose (1x) iGC/montelukast in 182 children with uncontrolled asthma on low-dose ICS alone (Lemanske et al. 2010). The study participants received in a triple-crossover, blinded manner 16 weeks each of 2.5x fluticasone, 1x fluticasone/salmeterol, and 1x fluticasone/montelukast. FSC was the most effective therapy, as the children were 1.7 times more likely to respond to FSC than the other therapies. AA children responded equally well to higher-dose inhaled fluticasone or FSC but were less likely to respond to fluticasone/montelukast therapy. In addition, the genotype at position 16 of the β_2-adrenergic receptor did not predict patterns of response.

In summary, the role β_2-AR polymorphisms play in asthma severity and mortality has been extensively studied and largely answered. The genotype at position 16 of the β_2-adrenergic receptor does not predict asthma worsening, nor is it associated with an increased risk of exacerbations with either SABA or LABA therapy. In addition, AAs are at no greater risk of developing worsening asthma when receiving LABA regardless of their genotype. It is difficult to reconcile this with the findings by the ACRN group. It is possible that their findings were the result of a type 1 error as the ACRN studies were limited by small sample sizes, especially compared to the much larger studies by Bleecker et al. Although this issue was of great importance several years ago, with some experts recommending genotyping the β_2-AR of all AA asthmatics and having all Arg16 homozygotes avoid beta-agonists altogether, this recommendation is no longer recommended, nor is it endorsed by any of the asthma guidelines.

37.1.12 Regular Use of Short-Acting β_2-Agonist and Worsening Asthma Control/Asthma Deaths

In the mid-1970s, an epidemic in asthma deaths occurred in New Zealand followingthe introduction and widespread use of a new nonselective β-agonist called fenoterol. Fenoterol had a longer half-life than albuterol, and the dose delivered was approximately twice that of an equivalent dose of albuterol (Pearce et al. 1995). Whether fenoterol-related deaths were due to asthma

worsening or due to a fatal arrhythmia was initially a matter of debate, but evidence suggested the former. Fenoterol was then taken off the market, and the epidemic of asthma deaths ended. Although the increased risk in asthma mortality was thought to be due to a drug (fenoterol), and not a class effect (β-agonists), there were nagging concerns regarding the safety of all SABAs. In order to address whether regularly administered albuterol therapy could lead to worsening asthma control, increased exacerbations, and increased asthma mortality, two large prospective studies involving >1000 asthmatics compared regularly administered albuterol (four times daily) to albuterol administered as needed (Drazen et al. 1996; Dennis et al. 2000) were performed. Both studies found the regular administration of albuterol to have no detrimental effects on the lung function, symptoms, need for rescue albuterol, response to inhaled methacholine, or asthma exacerbations. However, regularly administered albuterol had no beneficial effects. These studies found that regularly administered albuterol use was safe, but because it provided no beneficial effects, SABAs should only be used as needed to treat symptoms.

37.1.13 Regular Use of LABAs and Worsening Asthma Control/Asthma Death

That LABA therapy could result in an increased risk of severe asthma exacerbations and deaths came from a post-marketing study performed in the United Kingdom (UK), called the Serevent Nationwide Surveillance (SNS) study (Castle et al. 1993). It was a 14-week, double-blind, randomized study where 16,787 asthmatics received salmeterol twice daily, while 8,393 received salbutamol four times per day. The salmeterol group had fewer withdrawals from the study due to worsening asthma (2.9% vs. 3.8%; $p = 0.0002$), but there were more asthma deaths in the salmeterol- (12/16,787) versus the salbutamol-treated (2/8,393) group, representing a threefold increase in relative risk (RR) (95% CI 0.7–20; $p = 0.105$). Twelve of the 14 patients who died had used ≥2 SABA canisters/month. An independent consultant concluded that in ten patients, their asthma could possibly have been more appropriately treated by earlier or higher-dose inhaled GC therapy.

Due to concerns raised by the SNS, the FDA requested GSK, the maker of salmeterol (Serevent®) to a perform a post-marketing safety study in the USA. The SMART study was a 7-month placebo-controlled, double-blind study with a target enrollment of 60,000 subjects which began in 1996 (Nelson et al. 2006). The study design was unorthodox in that the study subjects were only seen by the study physician once at study entry, where they received their 7-month supply of study medication (salmeterol or matching placebo). All subsequent contact was by telephone from a central office. Recruitment was difficult, and after 8 years when enrollment had reached approximately 50%, an interim analysis was performed which demonstrated an increase in asthma mortality in subjects who had received salmeterol. There were 13 deaths among 13,176 subjects receiving salmeterol, compared to only 3 deaths among 13,179 subjects who had received placebo (RR 4.37; CI 1.25–15.34). Close examination of the study reveals insight into why salmeterol may have been associated with increased risk of death, while placebo therapy was not. First, AAs who received salmeterol were at greater risk of having a near-fatal or fatal asthma event compared to Caucasians (18% of the cohort were AA, yet AAs accounted for 54% of the asthma deaths). This raised concern that the presence of a particular polymorphism (Arg16) on the β-adrenergic receptor which is more prevalent among AA as discussed previously might be responsible for the observed findings. Second, analysis of the demographics at entry into the study found AAs to have greater asthma severity at study entry, as they were more likely to have been to the ED or hospitalized in the past 12 months and were more than twice as likely to have been intubated compared to Caucasians. In addition, AAs were less likely to have been treated with inhaled GC therapy. Third, less than half of the

study participants were on maintenance of inhaled GC therapy at entry into the study. Although the SMART study wasn't powered or designed to evaluate whether concurrent inhaled GC therapy modified risk of asthma death, there was a striking difference in asthma mortality based on whether a subject was on inhaled GC therapy at entry into the study or not. No differences in asthma deaths were noted among the salmeterol- versus the placebo-treated asthmatics who reported being on inhaled GC therapy (four deaths with salmeterol, three deaths with placebo), while the only deaths in patients not on inhaled GC therapy were those who had received salmeterol ($n = 9$) versus placebo ($n = 0$). This data strongly suggested that LABA monotherapy likely masked worsening inflammation and asthma control which increased the likelihood of having a catastrophic asthma exacerbation. This risk was ameliorated when LABAs were used in combination with an inhaled GC.

A study by Mann et al. supported the notion that the increased risk of life-threatening asthma exacerbations was a class, and not a drug-specific effect (Mann et al. 2003). FDA investigators evaluated three prospective, double-blind, randomized, placebo-controlled studies designed to evaluate the efficacy and safety of low- (12 μg) versus high-dose (24 μg) formoterol therapy. Two of the studies enrolled adults where there were nine hospitalizations, two intubations, and one fatal asthma attack in asthmatics who received high-dose formoterol, while there were two hospitalizations, no intubations, and no asthma-related deaths in subjects who had received placebo. In the third study, 6% of children receiving high-dose formoterol experienced a serious asthma exacerbation, while none of the placebo-treated children had an exacerbation. The authors concluded that the regular use of high-dose formoterol may be associated with an increased risk of serious asthma exacerbations.

A subsequent randomized, placebo-controlled study powered and designed to address the safety of formoterol enrolled 2,085 patients with moderate persistent asthma (Wolfe et al. 2006). They received formoterol 12 or 24 μg twice daily, formoterol 12 μg twice daily plus prn formoterol as needed for symptoms, or placebo for 16 weeks with the primary endpoint being serious asthma exacerbations (hospitalization or life-threatening episodes). Of the nine patients who had a serious asthma exacerbation, two received high-dose formoterol, five received low-dose formoterol, one received low-dose formoterol plus prn formoterol therapy, and one received placebo. Patients on an inhaled GC who received formoterol had fewer withdrawals than patients not treated with inhaled GC therapy. Collectively these studies raised serious concern regarding the risk of serious asthma-related exacerbations with LABA use, especially when used as monotherapy.

In 2003, as a result of these findings, the US FDA placed a "black-box" warning on all products that contained salmeterol or formoterol. This warning was amended in 2004, 2006, and again in 2010 with each warning strengthened. The 2010 black box stated that LABAs should never be used alone in the treatment of asthma. When LABAs are needed, they should be used for the shortest time possible to achieve asthma control. Once asthma control is achieved, LABAs should be discontinued if possible, to limit their long-term use. The changes to the label were based on FDA analyses of studies showing an increased risk of severe worsening of asthma symptoms, leading to hospitalization in pediatric and adult patients as well as death in some patients.

37.1.14 The FDA-Mandated Studies Evaluating the Safety of LABA/Inhaled CG Combination Products

In 2011, the FDA published a "perspective" in the *New England Journal of Medicine* that addressed its concern regarding the safety of combination LABA/inhaled GC therapy in the treatment of asthma (Chowdury et al. 2011). The FDA articulated their position that although it was clear that LABAs increased the risk of serious adverse outcomes when used as

monotherapy, there wasn't sufficient data to determine whether there were similar risks with combination LABA/inhaled GC therapy. They then state that "this question can't be answered through reanalysis of existing data, analyses of spontaneous reports of adverse events, or epidemiologic studies using existing databases; controlled trials are necessary." On April 14, 2011, the FDA issued a requirement for all manufacturers of LABAs to conduct controlled trials to assess the safety of combination LABA/inhaled GC therapy compared to inhaled GC therapy. There would be five trials, four adult and one pediatric (GSK was to perform adult and pediatric studies, while AZ, Merck, and Novartis would perform adult studies). The primary outcome would be a composite of serious asthma outcomes including asthma-related death, intubation, and hospitalization. The studies would be non-inferiority in design with each study enrolling 11,700 adult/adolescents plus 6,200 children which would allow 90% power to rule out a doubling in relative risk. As the endpoint would likely be driven by hospitalizations, all of the studies having similar designs would allow data from all studies to be analyzed for risk of intubations and asthma deaths. The start date would be in 2011 with results delivered in 6 years (2017).

GSK were the first to publish their results in 2016. Their AUSTRI (Stemple et al. 2016a) study randomized 11,679 adolescent and adult asthmatics to receive combination fluticasone/salmeterol (Advair®) or fluticasone alone for 26 weeks with the primary endpoint being time to the first serious asthma-related event (death, endotracheal intubation, or hospitalization). Salmeterol in a fixed-dose combination with fluticasone was found to be non-inferior to fluticasone alone (hazard ratio of 1.03 (95% CI 0.64–1.66), $p = 0.003$). The risk for a serious asthma exacerbation was 21% lower in the inhaled GC/LABA combination than the inhaled GC monotherapy group (8% vs. 10%, $p < 0.001$) with the greatest reduction noted among adolescents. In their VESTRI study (Stemple et al. 2016b), salmeterol/fluticasone combination compared to fluticasone monotherapy was studied in 6208 4- to 11-year-old children with varying levels of asthma severity. The primary endpoints were the same as those of the AUSTRI study. Fluticasone/salmeterol combination was found to be non-inferior to fluticasone alone (hazard ratio, 1.28; 95% CI, 0.73–2.27; $p = 0.0006$). 8.5% of patients in the combination product group versus 10% of patients in the fluticasone-alone group had severe asthma exacerbations (hazard ratio, 0.86; 95% CI, 0.73–1.01).

AZ investigated its combination budesonide/formoterol product (Symbicort®) in 11,693 asthmatics ≥12 years of age (Peters et al. 2016). Combination budesonide/formoterol was found to be non-inferior to budesonide alone with the same endpoints as the GSK studies (hazard ratio, 1.07; 95% CI, 0.70–1.65). In addition, rates of severe asthma exacerbations were found to be 16.5% lower in patients on budesonide/formoterol (hazard ratio, 0.84; 95% CI, 0.74–0.94; $p = 0.002$). There were two deaths in the budesonide/formoterol group with no deaths in the budesonide-alone group (a nonsignificant difference). Merck's study was announced at the American Thoracic Meeting in 2017. 11,729 patients ≥12 years of age were randomized to receive either combination mometasone furoate/formoterol (MF/F) (Dulera®) or mometasone (MF) alone with the same primary and secondary endpoints as GSK and AZ studies. MF/F was found to be non-inferior to MF in the primary endpoint, with a hazard ratio of 1.22 (95% CI, 0.76–1.94; $p = 0.411$). The hazard ratio for severe asthma exacerbations was 0.89 in favor of the combination group (95% CI, 0.80–0.98; $p = 0.021$).

These four large studies involving 6,208 pediatric and 35,101 adult patients demonstrated the safety of LABA when used in combination with an inhaled GC. Combination therapy was not associated with an increase in asthma hospitalization, intubations, or asthma deaths compared to inhaled GC monotherapy. In addition, combination therapy demonstrated a modest, yet significant, effect on decreasing the rates of asthma exacerbations. The two

asthma deaths in all the combined studies were far less than the FDA's estimated 28 deaths. These compelling studies led to the removal of the black-box warning on all LABA/inhaled GC products indicated for use in asthma on December 20, 2017. In their "Drug and Safety Communication," the FDA stated that "Based on our review, the *Boxed Warning*, our most prominent warning, about asthma-related death has been removed from the drug labels of medicines that contain both an ICS and LABA. A description of the four trials is now also included in the *Warnings and Precautions* section of the drug labels. These trials showed that LABAs, when used with ICS, did not significantly increase the risk of asthma-related hospitalizations, the need to insert a breathing tube known as intubation, or asthma-related deaths, compared to ICS alone."

37.2 Anticholinergics

37.2.1 Anticholinergics and the Parasympathetic Nervous System

Airway tone is controlled primarily by parasympathetic nerves carried in the vagus nerve. These nerves provide for a stable and quickly reversible level of airway tone. Unlike other species, humans have no sympathetic (adrenergic) nerves that directly supply the ASM. The sympathetic nervous system affects ASM tone via circulating catecholamines acting on β_2-ARs on ASM cells and on parasympathetic nerve endings (Barnes 1986). Acetylcholine (Ach) when released from parasympathetic nerves binds to muscarinic receptors located on ASM cells, which results in bronchospasm, independent of the inciting trigger (Canning 2006) (Fig. 4). Parasympathetic activation within the airway also results in mucus secretion and vasodilation. As such, increased parasympathetic activity may play a significant role in asthma pathogenesis. Anticholinergic agents such as atropine, ipratropium, and tiotropium which block muscarinic receptors on ASM cells are effective in relieving bronchospasm in asthma, but not to the same extent as in COPD where there is increased basal vagal tone.

37.2.2 Muscarinic Receptors

There are five G protein-coupled muscarinic receptor subtypes (M1–M5), all of which are inhibited by atropine. Binding of M2 and M3 receptors on ASM cells by ACh induces bronchoconstriction (Fig. 4). M3 receptors are primarily responsible for bronchoconstriction but are less dense than M2 receptors (Wess et al. 2007). Inhibitory pre-junctional M2 receptors provide negative feedback to inhibit excessive ACh release. Blocking of these pre-junctional M2 receptors with anticholinergics can result in acetylcholine release and paradoxical bronchoconstriction. In asthma, these inhibitory M2 receptors appear to lose function. As such, they are less able to inhibit ACh release resulting in increased basal ACh levels, greater binding to M3 receptors on ASM cells and enhanced airway tone. In addition, M3 receptor stimulation on AW glands results in increased mucus production and water secretion. M2 and M3 receptor density is greatest in the hilum and decreases distally (Richardson 1979). As a result, anticholinergics have little effect on small airway function.

37.2.3 History of Anticholinergic Agents

Anticholinergic agents were among the first effective asthma medications (Bree 1812). In the early nineteenth century, smoking the leaves of *Atropa belladonna* (atropine) or *Datura stramonium* (an alkaloid anticholinergic) was a common treatment of asthma and other respiratory conditions. Although an effective bronchodilator, atropine is no longer used in asthma due to its significant adverse effects profile which includes dry mouth, urinary retention, and acute atropine poisoning (Gross and Skorodin 1984). In addition, safe, more effective, and longer-

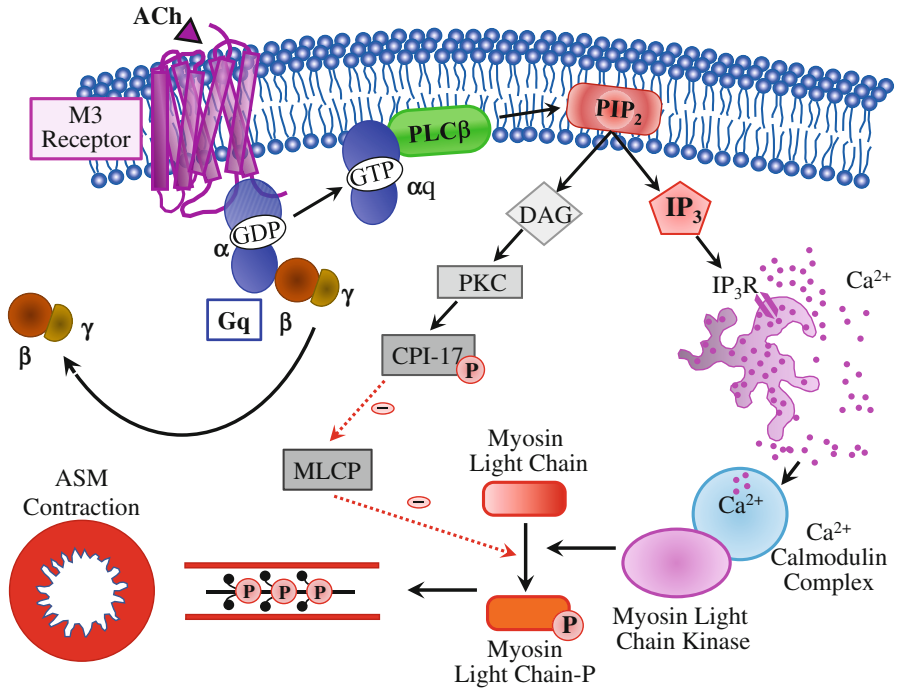

Fig. 4 Signaling pathways involved in parasympathetic nervous system-induced bronchoconstriction. Binding of acetylcholine (ACh) to muscarinic 3 (M3) receptors on airway smooth muscle cells results in the activation of the G protein-coupled receptor Gq which then activates phospholipase C-beta (PLCβ). It hydrolyzes phosphatidylinositol-bisphosphate (PIP_2) to the second messengers inositol trisphosphate (IP_3) and diacylglycerol (DAG). IP_3 binds to its receptor on the sarcoplasmic reticulum (SR) which results in the release of calcium. Calcium then binds to calmodulin, and the calmodulin-myosin light-chain kinase (MLCK) complex then phosphorylates myosin light chain (MLC) which then results in ASM contraction. DAG acting on protein kinase C (PKC) and CPI-17 activate myosin light-chain phosphatase, which by dephosphorylating MLC, terminates bronchoconstriction

acting anticholinergics, such as ipratropium and tiotropium, have been developed and are now widely used (Fig. 5). As these agents don't pass the blood-brain barrier and are poorly absorbed from both the respiratory and GI tracts, they have few adverse effects except for dry mouth.

37.2.4 Ipratropium (Atrovent ®): A Short-Acting Anti-muscarinic Agent

Ipratropium is considered a second-line agent in the treatment of acute asthma. Ipratropium's onset of effect is slower than that of albuterol as its onset of effect is 15–30 min and its peak effect is 90 min, but its duration of 6 h is longer (Scullion 2007). Ipratropium, compared to albuterol, is a less potent bronchodilator and is less effective in blocking exercise-induced asthma. Ipratropium's effectiveness and duration of action is limited because it is a nonselective muscarinic antagonist, binding to M2 and M3 receptors with equal affinity. By binding to M3 receptors on smooth muscle cells, ipratropium prevents ACh-induced bronchoconstriction, but because it binds with equal affinity to inhibitory M2 receptors, paradoxical bronchospasm can result in susceptible individuals (Mann et al. 1984).

37.2.4.1 Ipratropium's Role in Acute Asthma

Studies evaluating repeated administration of ipratropium plus albuterol in children presenting to the ED with acute asthma exacerbations have

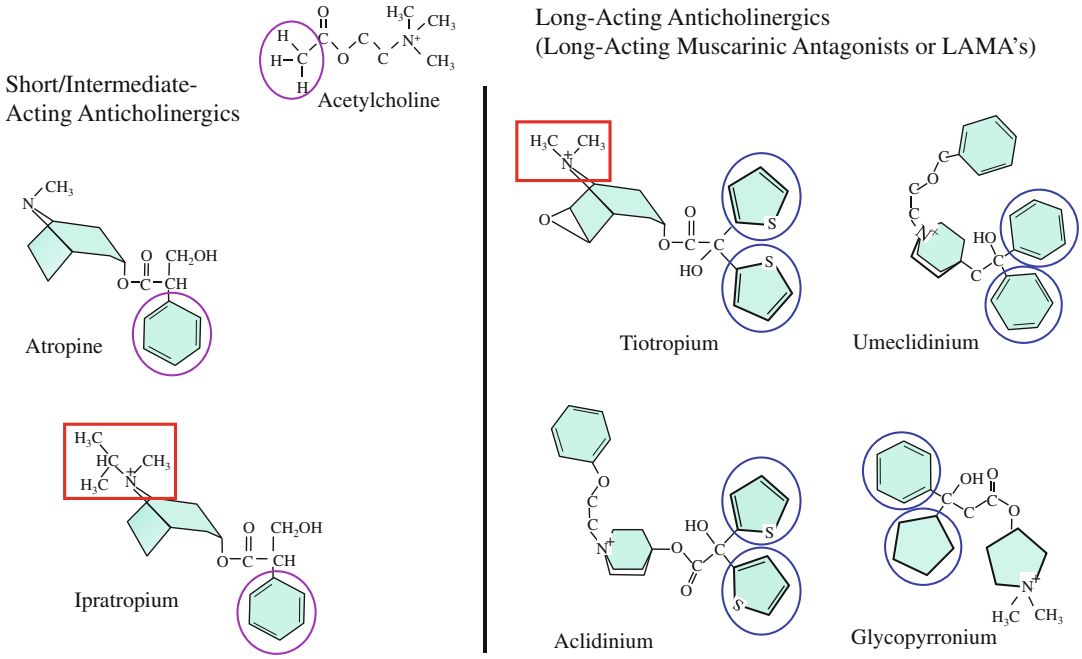

Fig. 5 Structure of anticholinergic agents. Atropine is a naturally occurring anticholinergic. It is similar in structure to acetylcholine except for a bulky substitute (carboxyl group) on the terminal ester carbon (pink circle). Because it is a tertiary amine, it is lipid soluble making it easily absorbed and able to cross the blood-brain barrier, both contributing its systemic and central nervous system adverse effects. Ipratropium and tiotropium are quaternary amines (red box). They are derived by the introduction of an isopropyl group to the N atom of atropine. N-Quaternary congeners of atropine are hydrophilic. As such, they are poorly absorbed from the GI tract and don't easily cross the blood-brain barrier. Other changes to atropine which maximize anticholinergic activity and increase the duration of action are the addition of carbocyclic or heterocyclic rings at R_2 and R_3 of the terminal ester carbon (blue circles). Tiotropium, aclidinium, umeclidinium, and glycopyrronium are examples of anticholinergics with R_2 and R_3 substitutions with heterocyclic rings

uniformly demonstrated improvements in lung function and reductions in the rate hospitalizations compared to the repeated administration of albuterol alone (Schuh et al. 1995; Qureshi et al. 1998). Those who benefited most were children with the greatest degree of airflow limitation upon presentation to the ED. A study that evaluated the additive effect of ipratropium plus albuterol in adult asthmatics presenting to the ED from three separate studies found ipratropium to improve baseline lung function, reduce the need for additional therapies, and reduce hospitalization rates (Lanes et al. 1998). As a result, combination ipratropium/albuterol therapy is recommended in the ED management of acute asthma in both children and adults, with the recommended ipratropium dose being 0.25–0.5 mg added to 2.5–5 mg of albuterol administered every 20 min for three doses. The addition of ipratropium to albuterol in children already hospitalized with acute asthma has not been shown to be more effective than albuterol alone (Goggin et al. 2001).

37.2.5 Long-Acting Anti-muscarinic Agents (LAMAs)

37.2.5.1 Tiotropium (Spiriva®)

Tiotropium was the first LAMA and only LAMA approved for use in asthma. It was initially approved for use in COPD in 2004 and then for severe asthma in 2015. Tiotropium differs from ipratropium in its longer duration of action and enhanced selectivity for M3 receptors. Tiotropium reaches its peak bronchodilator effect between 1 and 3 h with a duration of action of ≥24 h

(Barnes 2000). Although tiotropium binds to M2 and M3 receptors with equal affinity, it dissociates from M2 receptors 10 times faster than M3 receptors while binding to M3 receptors 100 times longer than ipratropium, making it both a longer-acting and a more effective bronchodilator (Restrepro 2007). It is both safe and effective in the long-term management of severe COPD as documented by the UPLIFT study where nearly 6000 patients with poorly controlled COPD on combination inhaled steroid/LABA therapy were treated with tiotropium or placebo for 4 years (Tashkin et al. 2008). Tiotropium was associated with improved lung function and quality of life, reduced symptoms, and fewer exacerbations. There were no serious adverse effects associated with long-term tiotropium, although dry mouth and constipation were more common in the tiotropium- compared to the placebo-treated patients. Tiotropium is available in a soft mist formulation via the Respimat® device.

37.2.5.2 New LAMAs

Three other LAMAs have recently become available. They includeaclidinium (Tudorza®), umeclidinium (Incruse®), and glycopyrrolate (Seebri®). These agents are only approved for use in the treatment of COPD. All LAMAs are devoid of significant adverse effects except for dry mouth which occurs in approximately 15% of patients. The ideal anticholinergic would bind exclusively to M3 receptors. Unfortunately, this may not be achievable as M2 and M3 receptors share 77% sequence homology.

37.2.6 Use of Anticholinergics as Asthma Controller Agents

The latest iteration of the NHLBI asthma guidelines (2007) does not recommend the use of anticholinergics in the long-term control of asthma, while the 2016 GINA guidelines recommend tiotropium as an option for patients at treatment steps 4 and 5. In the decade since the latest NHLBI asthma guidelines were published, a number of studies have found tiotropium to be an effective add-on agent in patients with moderate-to-severe asthma.

37.2.6.1 Tiotropium's Effect on Patients with Moderate-to-Severe Asthma

One of the first studies demonstrating tiotropium's effect on asthma came from a comparative efficacy study for the ACRN group where add-on tiotropium and add-on salmeterol to low-dose inhaled GC were compared to higher-dose inhaled GC therapy in subjects whose asthma was inadequately controlled on low-dose inhaled GC therapy. Combination tiotropium/low-dose inhaled GC therapy was as effective as combination LABA/low-dose inhaled GC therapy, with both combination therapies being more effective than higher-dose inhaled GC monotherapy (Peters et al. 2010). Tiotropium has also been shown to be effective in patients with severe asthma inadequately controlled on combination high-dose inhaled GC plus LABA therapy. A double-blind, placebo-controlled, three-way crossover trial evaluated the effectiveness of tiotropium as add-on therapy in patients whose symptoms were poorly controlled despite high-dose inhaled GC plus LABA. The addition of tiotropium resulted in improvements in FEV_1 and daily PEF measurements and a reduction in the need for rescue medication (Kerstjens et al. 2011). Two replicate, randomized, placebo-controlled trials in 912 adult patients with poorly controlled asthma despite combination high-dose inhaled steroid/LABA therapy evaluated the efficacy of add-on tiotropium (5 μg) or matching placebo for 48 weeks (Kerstjens et al. 2012). Tiotropium improved lung function and increased the time to asthma first severe exacerbation by 56 days which corresponded to a 21% reduction in risk [hazard ratio 0.79; 95% confidence interval (CI) 0.62–1.00; $p < 0.03$]. A post hoc analysis found that the number needed to treat in order to prevent one severe exacerbation was 15. Based on the data from these studies demonstrating its effectiveness in moderate-to-severe asthma,

the FDA approved tiotropium for use in asthmatic patients ≥12 years old at a dose of 2.5 μg/day, while the recommended dose for COPD is 5.0 μg/day.

37.3 Theophylline

37.3.1 Introduction

Theophylline was first used over 100 years ago when the xanthine derivative dimethylxanthine was extracted from tea leaves (Mazza 1982). Although it had been found to have bronchodilator effects in the 1920s, it wasn't widely used to treat asthma until the 1940s, when it was used intravenously to treat acute asthma (Barnes and Pauwels 1994). It was then used orally in combination with ephedrine until the 1970s, when it was then used alone to control chronic asthma. By the 1980s, sustained-release theophylline preparations had been developed that compensated for its rapid absorption and metabolism. In addition, easily performed serum theophylline assays were developed so that therapeutic monitoring could allow patients to achieve and maintain levels that were within its narrow therapeutic level of 10–20 mg/L. Theophylline eventually became the most widely used drug to treat chronic asthma until the late 1980s.

Its popularity began to decline in the early 1990s, when it became clear that airway inflammation played a pivotal role in asthma pathogenesis and when inhaled GCs were demonstrated to be effective in suppressing airway inflammation. Inhaled GCs were also found to improve lung function, reduce symptoms, and significantly reduce asthma exacerbations. As comparative studies demonstrated inhaled GCs to be more effective and were associated with fewer serious adverse effects, the use of theophylline as an asthma controller agent rapidly waned, such that by the end of the twentieth century, it was no longer a preferred agent for the routine management of asthma. In addition, the GINA guidelines no longer recommend theophylline for use in either the acute or chronic management of asthma (GINA 2016), while the 2007 NHLBI asthma guidelines recommend it as a non-preferred alternative add-on agent in both children and adults uncontrolled on low-dose inhaled steroid therapy (NHLBI 2007).

37.3.2 Mechanisms of Action

37.3.2.1 Phosphodiesterase Inhibition

Despite nearly a century of use, theophylline's exact mechanism of action remains uncertain. Theophylline acts as a weak and nonselective phosphodiesterase (PDE) inhibitor. At therapeutic concentrations, theophylline inhibits only 5%–20% of total PDE activity in human lung extracts (Polson et al. 1978). There are at least five PDE isoenzymes that are differentially expressed in different cells and tissues. PDE3 and PDE4 may play a role in asthma pathogenesis, as PDE3 is involved in ASM tone, while PDE4 is present in mast cells, eosinophils, and T lymphocytes (Torphy and Rinard 1983).

37.3.2.2 Adenosine Receptor Antagonism

Theophylline is also a potent adenosine receptor inhibitor at therapeutic concentrations. Adenosine inhalation can cause bronchoconstriction by stimulating histamine release from mast cells (Cushley and Holgate 1985). Thus, theophylline's inhibitory effect on adenosine receptors may contribute to its bronchodilator effects (Mann and Holgate 1985). The life-threatening adverse effects of theophylline toxicity such as seizures and arrhythmias are likely the result of adenosine antagonism (Barnes and Pauwels 1994).

37.3.2.3 Anti-inflammatory effects of Theophylline

Although theophylline was long thought to act as a bronchodilator, studies in the early 1990s found theophylline to have anti-inflammatory effects. Kraft et al. found theophylline to reduce the early AM decrease in lung function and the associated influx of inflammatory cells into

the airways of patients with nocturnal asthma, with the magnitude of improvement dependent upon the patient's theophylline level (Kraft et al. 1996). Theophylline blunted the late-phase asthmatic response (LPR) following allergen challenge when delivered intravenously before an allergen challenge (Pauwels et al. 1985). In contrast, a study evaluating the effect of orally administered theophylline prior to an allergen challenge found no effect of theophylline on the LPR, nor did it attenuate the associated increase in methacholine reactivity following the allergen challenge (Cockroft et al. 1989).

Theophylline has a modest effect on reducing sputum, bronchoalveolar lavage fluid (BALF), and tissue eosinophils at theophylline levels well within the therapeutic range (Lim et al. 2001). Theophylline had no effect on airway CD3- or CD4-positive cells while significantly reducing in CD8-positive cells in patients with moderate-to-severe persistent asthma (Djukanovic et al. 1995). Theophylline has no effect on exhaled nitric oxide levels (Lim et al. 2001), nor does it have an effect on bronchial hyperresponsiveness (BHR) (Dahl et al. 2002). In vitro studies have shown theophylline to upregulate the anti-inflammatory cytokine IL-10 via PDE inhibition (Mascali et al. 1996) and to decrease the translocation of the transcription factor, NFκB into the nucleus, which promotes the downregulation of pro-inflammatory gene transcription (Wymann et al. 2003).

37.3.2.4 Effects of Airway Smooth Muscle

Theophylline causes smooth muscle relaxation, which is likely secondary to PDE3 inhibition, and results in increases in cAMP and cGMP concentrations. This effect is weak at therapeutic concentrations (10–20 mg/L), as maximal bronchodilation only occurs at a serum theophylline concentrations of >67 mg/L (Guillot et al. 1984). Intravenous aminophylline, the ethylene diamine salt of theophylline, has a bronchodilator effect in patients with acute asthma likely due to its relaxant effect on airway smooth muscle (Mitenko and Ogilvie 1973). However, the bronchodilator effect of theophylline in chronic asthma is small in comparison with β-agonists.

37.3.3 Theophylline Pharmacokinetics

Theophylline is rapidly and completely absorbed and metabolized by the cytokine P450 system in the liver, predominantly by CYP1A2. Theophylline's major limitation is its narrow therapeutic window. Theophylline levels below 10 mg/L have little, if any, bronchodilator effects. Higher levels (≥20 mg/ml) result in greater bronchodilation but are associated with greater potential for adverse effects. Because of theophylline's narrow therapeutic window and its susceptibility to significant swings in its metabolism, individualization of theophylline dosing is required. Both trough (pre-dose) and peak (>4 h post-dose) levels should be drawn after achieving a steady state. Based on the level, changes to the theophylline dose are made, and trough and peak levels are rechecked once a steady state is again achieved with the goal to keep theophylline levels between 10 and 20 mg/L.

Theophylline clearance is age dependent. It is slow in infancy, quickly increases during childhood, stabilizes during adulthood, and then slows in the elderly. Thus, the dose of theophylline required to maintain therapeutic levels is based upon the individual's age. Cigarette smoking, concomitant use of drugs that serve as enzyme inducers (phenobarbital, phenytoin, and rifampin), high-protein and low-carbohydrate diets and disease such as cystic fibrosis enhance theophylline clearance which leads to loss of clinical efficacy, if doses aren't increased accordingly. Drugs that serve as enzyme inhibitors such as cimetidine, erythromycin, ciprofloxacin, zileuton, and allopurinol delay theophylline clearance and increase the risk of theophylline toxicity. When these drugs are used concurrently with theophylline, its dose must be adjusted downward by approximately 50%. High-carbohydrate/low-protein diets, congestive heart failure, advanced liver disease, and viral infections associated with high fever are also associated with delayed theophylline clearance. The interaction between certain viral infections and theophylline metabolism was a major issue when theophylline was the preferred controller agent in children with moderate-to-severe asthma.

37.3.4 Efficacy

A meta-analysis of nine studies comparing salmeterol to theophylline found salmeterol to be superior in increasing PEF, decreasing day- and nighttime symptoms, and the need for rescue SABA use. In addition, salmeterol was associated with fewer withdrawals from the studies due to unwanted adverse effects compared to patients treated with theophylline (Davies et al. 1998; Tee et al. 2007). Theophylline is less effective than low-dose inhaled GC therapy in children and adults with mild persistent asthma (Dahl et al. 2002; Reed et al. 1998). A large 1-year study comparing theophylline to beclomethasone dipropionate (BDP) in children and adults with mild-to-moderate asthma found both therapies to improve symptoms and reduce asthma exacerbations, but the magnitude of effect was greater in the BDP-treated compared to the theophylline-treated subjects (Reed et al. 1998). In addition, there were fewer courses of prednisone and a 1.5-fold doubling-dose decrease in methacholine reactivity in BPD-treated patients versus the theophylline-treated patients. Adverse effects (headache, anxiety, insomnia, GI distress) and withdrawals due to adverse effects were more common among theophylline-treated patients, while reductions in plasma cortisol and growth suppression among children were noted in the BDP-treated patients. A smaller study comparing budesonide to theophylline found budesonide to be superior in all outcome measures including improvement in lung function, reduction in symptoms, reduction BHR, and treatment failures due to worsening asthma (Dahl et al. 2002). A trial in children inadequately controlled on inhaled GC therapy found the addition of theophylline to result in a modest improvement in PEF while having no effect on FEV_1 or BHR (Suessmuth et al. 2003). Given its risk of severe toxicity, drug interactions, and need to regularly monitor levels, theophylline is considered by the 2007 NHLBI guidelines to be the least desirable of the four step-up options at treatment step 3 for 5- to 11-year-old children (NHLBI 2007).

Combination theophylline/low-dose budesonide was compared to high-dose budesonide. Low-dose budesonide/theophylline was found to be equally effective as high-dose budesonide in adults with poorly controlled asthma (Evans et al. 1997). Since the two treatments were equally effective and because low-dose budesonide/theophylline was more cost effective than high-dose budesonide therapy, the authors concluded that theophylline/low-dose inhaled GC therapy may be preferable to high-dose inhaled GC therapy. Once LABAs were combined with inhaled GC as add-on agents, this form of therapy was far superior to add-on theophylline therapy. Consequently, add-on theophylline therapy no longer had a place in the management of patients with moderate-to-severe persistent asthma.

Both the 2007 NHLBI guidelines and the 2016 GINA guidelines do not recommend aminophylline for use in patients hospitalized with severe acute asthma as it does not improve lung function or other outcomes in hospitalized adults (Nair et al. 2012) and it is associated with increased toxicity. Its use should only be considered in patients who fail to respond to aggressive β_2-agonist therapy. As its adverse effects can be severe and can lead to death, if used, theophylline levels must be closely followed.

37.3.5 Adverse Effects

Theophylline's adverse effects profile severely limits its use (Tsiu et al. 1990). Adverse effects are associated with increasing serum levels, with toxicity increasing as levels exceed $\geq$25 mg/L. The 2007 NHLBI guidelines recommend steady-state serum theophylline concentrations of only 5–15 mg/L, since lower theophylline concentrations are better tolerated, drug interactions are less likely, and modest anti-inflammatory and immunomodulatory effects have been demonstrated at lower levels. Common adverse effects at therapeutic levels include headaches, nausea and vomiting, insomnia, restlessness, gastric upset, worsening of GERD, and increase in hyperactivity in children. At higher concentrations, life-threatening adverse effects such as seizures and tachyarrhythmias can occur. Since both CNS stimulation and cardiac arrhythmias are mediated

by adenosine receptor antagonism, these potentially life-threatening adverse effects could be eliminated by using pure PDE inhibitors (as discussed below).

37.4 Phosphodiesterase Inhibitors

Since PDE4 plays a key role in the regulation of cyclic nucleotides in inflammatory cells, PDE4 inhibitors could have broad anti-inflammatory effects. It is the predominant PDE in mast cells, eosinophils, neutrophils, T cells, and monocytes/macrophages. PDE4 inhibitors decrease the expression of IL-4 and IL-5 in T cells and have an effect on eosinophilic inflammation. Their effect on neutrophils makes them especially useful in the treatment of COPD and in severe asthma phenotypes where neutrophilic inflammation is predominant. Several PDE4 inhibitors have been tested in asthma. Unfortunately, most PDE4 inhibitors have failed due to a number of adverse effects including headache, insomnia, nausea, and vomiting (Diamant and Spina 2011). Roflumilast is currently the only PDE4 inhibitor available and is approved for use solely in patients with severe COPD (Calverley et al. 2009). With that said, roflumilast has been studied in asthma, and while it has no effect on the immediate phase response, it attenuates the LPR and prevents the subsequent increase in BHR following an allergen challenge (Van Schalkwyk et al. 2005; Louw et al. 2007). Roflumilast is as effective as low-dose inhaled GC therapy in improving lung function in patients with mild asthma (Bousquet et al. 2006). Although PDE4 is present on airway smooth muscle cells, selective PDE4 inhibitors have not been shown to have acute bronchodilator effects (Boswell-Smith et al. 2006). The change in FEV_1 seen after long-term use is thus likely due to the resolution of underlying airway inflammation.

Since these drugs are orally administered, they can reach the peripheral airways. The measurement of changes in small airway function may be larger and more clinically meaningful than changes in the FEV_1 especially in childhood asthma and COPD (Celli 2006). Attempts to develop inhaled forms of PDE4 inhibitors such as roflumilast have failed to demonstrate efficacy (Danto et al. 2007). PDE3 is the primary isoenzyme in the ASM where it has effects on airway tone. Some PDE3 inhibitors have demonstrated acute bronchodilatory effects. Unfortunately, as PDE3 is also found in cardiac and vascular tissue, PDE3 inhibitors are also likely to have unwanted adverse effects. A safe mixed PDE3/PDE4 inhibitor with both bronchodilator and anti-inflammatory effects has undergone phase 2 studies in both asthma and COPD (Cazzola et al. 2012).

37.5 Conclusion

β-Agonists are the most important class of bronchodilators. SABAs are the most effective agents available to relieve bronchospasm. In addition, they have "bronchoprotective" effects in that they block bronchospasm due to exercise and other spasmogenic stimuli. LABAs, when used in fixed combination with inhaled GCs, are the preferred controller agents for asthmatics with moderate-to-severe persistent asthma. Anticholinergic agents are also important agents used to treat asthma. Ipratropium, when used in combination with albuterol in patients presenting to the ED with status asthmaticus, can reduce the rate of hospital admissions. Ipratropium is a less effective bronchodilator in asthma than albuterol while being equally effective in COPD. More recently LAMAs have been demonstrated to be effective step-up agents in the treatment of moderate-to-severe asthma. Tiotropium is now indicated as an add-on agent in asthmatics inadequately controlled on an inhaled GC alone or in combination with a LABA. Theophylline is no longer used due to its narrow therapeutic window and the availability of much more effective agents, such as LABAs and inhaled GCs. Phosphodiesterase inhibitors have the potential to be very effective asthma medications, but unwanted adverse effects have plagued their development and use in diseases such as asthma.

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Inhaled Corticosteroid Therapy for Asthma

38

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Abstract

Inhaled Corticosteroids (ICS) play a significant role in the management of asthma and are the preferred medication for mild, moderate and severe persistent asthma by current asthma management guidelines. Currently, seven ICS are approved for asthma control and maintenance by the United States Food and Drug Administration (U.S. FDA): Beclomethasone dipropionate, budesonide, ciclesonide, flunisolide, fluticasone furoate, fluticasone propionate, and mometasone furoate, with all approved for children under 12 years of age except mometasone furoate and ciclesonide. ICS are effective in improving all asthma outcomes, as demonstrated through multiple rigorous clinical trials. ICS efficacy is dependent upon many factors including but not limited to: pharmacogenetics and pharmacogenomics, ICS delivery device, patient technique and adherence, and ICS pharmacokinetics and pharmacodynamics.

Systemic side effects of ICS are dose-related. Therefore, the lowest effective dose should always be used. Many well-designed studies have examined the effects of FDA-approved ICS doses on HPA axis and growth, but fewer studies with less robust designs have examined their effects on bone mineral density, cataracts, and glaucoma. FDA-approved doses of most ICS suppress the growth of children. FDA-approved doses in highly-susceptible individuals or higher-than-approved doses in any individual can suppress the HPA axis sub-clinically

or clinically and produce life threatening adrenal crisis. Even considering the unexpected growth effect from FDA-approved ICS doses, benefits outweigh risks at FDA-approved ICS doses for most individuals as long as monitoring for systemic side effects is frequent, regular, and accurate. In contrast, benefits may not outweigh risks for those with very mild disease who have the least to gain and most to lose from ICS therapy, or in those using higher-than-approved ICS doses, in which cases even higher levels of monitoring may be warranted.

Keywords
Safety · Efficacy · Inhaled corticosteroids · Growth

38.1 Place in Therapy

Inhaled corticosteroids (ICSs) play a significant role in the management of asthma and are the preferred medication for mild, moderate, and severe persistent asthma by current asthma management guidelines (Global Initiative for Asthma 2018; US Department of Health and Human Services National Institutes of Health 2007). Systemic corticosteroids were first found to be effective in the treatment of acute asthma onset in 1956 with subsequent studies finding the drugs to be effective for both acute and chronic asthma (Raissy et al. 2013). ICSs were first found to have a therapeutic effect in the 1970s with beclomethasone dipropionate (Clark 1972). Currently, seven ICSs are approved for asthma control and maintenance by the US Food and Drug Administration (US FDA): beclomethasone dipropionate, budesonide, ciclesonide, flunisolide, fluticasone furoate, fluticasone propionate, and mometasone furoate (American Academy of Allergy, Asthma, and Immunology 2018).

ICSs are effective in improving all asthma outcomes, as demonstrated through multiple rigorous clinical trials. Both children and adults taking ICS for persistent asthma have a lower risk of developing worsening asthma (Ernst et al. 1992), asthma-related hospitalizations (Donahue et al. 1997), and death (Suissa et al. 2000; The Childhood Asthma Management Program Research Group 2000). Additionally, treatment with ICS improves lung function as characterized by improved forced expiratory volume at 1 s (FEV_1), daytime peak flow values, and nighttime peak flow in adults (Adams et al. 2001; Malmstrom et al. 1999) and in children (The Childhood Asthma Management Program Research Group 2000; Pauwels et al. 2003). Although asthma symptom outcome measurements vary, ICS improves asthma symptoms in both children and adults (Adams et al. 2001) including nighttime awakenings, use of rescue inhaler, activity limitation, and overall daytime symptom frequency (Reddel et al. 2017). ICS use alone and in combination with long-acting beta agonist (LABA) has also shown to significantly improve the quality of life of asthmatic patients, as measured by the Asthma Quality of Life Questionnaire, compared to placebo or LABA alone (Bateman et al. 2015). This proven efficacy provided the support needed for ICS to be the mainstay therapy to treat chronic and acute asthma.

All of the FDA-approved ICSs except mometasone furoate and ciclesonide are approved for children under 12 years of age. Although the lower age limit varies for each ICS, formulation options exist for children as young as 4 years old. In order to achieve approval, each ICS formulation must demonstrate safety and effectiveness in specific pediatric age populations. For instance, Baker et al. demonstrated budesonide's effect for moderate pediatric asthmatics through comparison of four different dosing regimens of budesonide as compared to placebo in children ranging from 6 months to 8 years old (Baker et al. 1999). Each dose produced improvements in some aspect of asthma control. All of the doses showed significant improvements in FEV_1 values, and most doses showed significantly improved peak flow values as compared to placebo (Baker et al. 1999). Kemp et al. conducted similar research with varying doses of budesonide with mild pediatric asthmatics of the same age group (Kemp et al. 1999). All three doses of budesonide significantly improved daytime and nighttime asthma symptoms

and reduced rescue medication use as compared to placebo, and the two highest doses demonstrated significant improvements in FEV_1 values (Kemp et al. 1999). Lastly, Shapiro et al. looked for similar effects with multiple doses of budesonide in severe pediatric asthmatics, ages 4–8 years old. Nighttime and daytime symptoms and peak flow values improved significantly as compared to placebo (Shapiro et al. 1998). No significant differences were noticed between the budesonide doses, and similar safety profiles were exhibited between the budesonide and placebo groups. Thus, budesonide was identified as a safe and effective treatment for mild to severe asthmatic children.

The variability in symptom control that is characteristic of asthma requires careful monitoring and the need to step up and step down ICS doses over time. Current asthma management guidelines provide guidance for both strategies with a goal of maintaining asthma control while using the lowest dose of ICS possible. The initial dose of ICS is chosen based on the patient's asthma severity or intrinsic intensity of the disease process. The patient's asthma control or the degree to which asthma symptoms, impairment, and risk are minimized is then evaluated periodically to determine if a step-up or step-down in ICS dose is warranted. For example, if a patient's asthma remains uncontrolled on the current ICS dose, a step-up in care is initiated which includes either an increase in ICS dose or addition of another class of asthma medication (i.e., LABA). Conversely, if a patient's asthma remains well controlled on the current ICS dose for at least 3 months, the clinician can consider a step down in therapy which includes a decrease in ICS dose and/or elimination of additional asthma medications (Global Initiative for Asthma 2018; US Department of Health and Human Services National Institutes of Health 2007).

Long-acting β_2–adrenergic receptor agonists (LABAs) and long-acting muscarinic antagonists (LAMAs) also serve as additional or alternative controller medications for persistent asthma. LABAs are indicated for use in combination with ICS. LAMAs are prescribed on their own or in addition to ICS/LABA therapy (Melani 2015). The US FDA has approved five ICS/LABA combination formulations for the maintenance of asthma: budesonide and formoterol, fluticasone furoate/vilanterol, fluticasone/salmeterol, fluticasone propionate/salmeterol, and mometasone/formoterol (American Academy of Allergy, Asthma, and Immunology 2018). The US FDA has approved one formulation of LAMA to treat asthma: tiotropium bromide (SPIRIVA RESPIMAT, Boehringer Ingelheim Pharmaceuticals, Inc. 2004).

38.2 Mechanism of Action

ICSs are first-line therapy for persistent asthma, as they effectively suppress the inflammation in the asthmatic airway resulting in reduced airway hyperresponsiveness and improved asthma control. They have a broad action on many components of the asthmatic inflammatory response. On a cellular level, ICSs inhibit the inflammatory response in the airway by (1) reducing the recruitment of inflammatory cells via suppression of chemokines and adhesion molecules and (2) decreasing survival of inflammatory cells (i.e., eosinophils, T-lymphocytes, and mast cells) (Barnes 2010). ICS molecules diffuse through the epithelial membrane of the airway and attach to glucocorticoid receptors in the cytoplasm of the epithelial cells. This steroid-receptor complex then reaches the glucocorticoid response element on steroid sensitive genes in the nucleus of the cell, which switches on or off gene transcription. ICSs activate transcription of anti-inflammatory genes and increase translation of anti-inflammatory proteins (i.e., IL-1 receptor antagonist, IL-10, neutral endopeptidase) (Ye et al. 2017). Perhaps most importantly, ICSs also decrease the expression of inflammatory genes, which reduces the production of cytokines, chemokines, and other inflammatory proteins and receptors (Barnes 2010).

38.3 Factors Influencing ICS Efficacy

ICS efficacy is dependent upon many factors including but not limited to pharmacogenetics and pharmacogenomics, ICS delivery device, patient technique and adherence, and ICS

pharmacokinetics and pharmacodynamics. Although it cannot be controlled, genetic biomarkers can impact a patient's response to ICS. The delivery device is designed to propel each dose of ICS to the patient's lungs where it can have direct contact with the epithelial cells and begin to reduce inflammation locally while minimizing systemic absorption and side effects. In an ideal situation, patient technique will be perfect so that each dose of ICS will be delivered as intended by the device manufacturer, and each patient will be compliant with his or her prescribed regimen. Lastly, the unique pharmacokinetic and pharmacodynamic profile of each ICS as well as the dose-effect response relationship must be considered.

38.3.1 Pharmacogenetics and Pharmacogenomics

We now know that there is inter-individual variation in the response to each class of asthma medications, including ICS. Sequence variants in the genes controlling the pharmacokinetics and pharmacodynamics of corticosteroids have been associated with therapeutic response. For example, variation in corticotropin-releasing hormone receptor 1 (*CRHR1*) has been associated with enhanced response to ICS therapy. Corticotropin-releasing hormone (CRH) binds to CRHR1 in the pituitary gland and sets the hypothalamic-pituitary-adrenal axis in motion, leading to the release of cortisol from the adrenal glands. Researchers believe that alterations in its pathway at the molecular level can impact ICS efficacy. Single-nucleotide polymorphisms in CRHR1 can contribute to the efficacy of ICS. Individuals homozygous for the single-nucleotide polymorphism allele of rs242941 or the GAT haplotype showed significant improvements in FEV_1 values after use of ICS compared to those homozygous for the wild-type allele (Tantisira et al. 2004). The glucocorticoid receptor is another component of the ICS pathway related to individual variability in response in ICS. Multiple single-nucleotide polymorphisms in the SIP1 gene of the glucocorticoid receptor (rs4980524, rs6591838, rs2236647, and rs2236648) were associated with significant improvements in FEV_1 after a treatment with ICS (Hawkins et al. 2009).

On the other hand, certain genetic variations can predict poor asthma outcomes despite ICS treatment. For example, three single-nucleotide polymorphisms in FCER2, a low-affinity receptor gene for IgE, were associated with elevated IgE levels and severe exacerbations despite ICS use (Tantisira et al. 2007). Specifically, the variant T2206C was associated with increased asthma hospitalizations, asthma exacerbations, and uncontrolled asthma (Tantisira et al. 2007; Koster et al. 2011).

When looking at the impact of pharmacogenetics and pharmacogenomics on individual responses to ICS, the variations are not solely related to genetic polymorphism but may be impacted by levels of gene expression. Treatment with ICS suppresses the expression of calcium-activated chloride channel protein 1 (CLCA1), periostin, and serpin family B member 2 (serpinB2), but individuals with high baseline levels of these proteins saw improvements in lung function after 4 weeks of ICS treatment (Woodruff et al. 2007). Additionally, treatment with ICS increases the expression of the protein FK506-binding protein 51(FKBP51), but individuals with high baseline levels of this protein exhibited decreases in lung function after 4 weeks of ICS treatment, with the authors predicting that FKBP51 creates a negative feedback loop (Woodruff et al. 2007).

Lastly, certain individuals may not exhibit the full effect that ICS or the ICS/LABA combination can offer due to corticosteroid resistance. Genetic polymorphisms, vitamin D deficiency, smoking, severe asthma, and obesity may contribute to corticosteroid resistance (Raissy et al. 2013). One such genetic predictor is the NFKB gene, which was highly associated with glucocorticoid resistance (Tse et al. 2011). Additionally, smoking or severe asthmatics often present with corticosteroid resistance, requiring higher doses of ICS. These steroid-resistant patients have a reduction in HDAC2, preventing them from turning off the inflammatory genes (Barnes 2010). For steroid-resistant patients, leukotriene receptor antagonists (LTRA) such as montelukast,

cyclosporine, macrolide therapy, and anti-TNF-α therapy or anti-IgE, anti-IL2, and anti-IL5 therapy may be suggested as an alternative treatment to corticosteroids (Yim and Koumbourlis 2012). Additionally, vitamin D is being studied as an add-on therapy for these patients (Yim and Koumbourlis 2012).

38.3.2 Delivery Devices, Patient Technique, and Adherence

ICSs are delivered via inhalation due to this method's ability to directly reach an individual's airways and act locally at the source of inflammation. The inhalation route, as opposed to oral or parenteral routes, has the potential to cause less systemic side effects. In order for the ICS to reach the airways, the drug particles must first move beyond the mouth and pharynx and deposit directly into the lungs. The more drugs deposited into the mouth or pharynx, the less effective and safe the ICS is. High oropharyngeal deposition can potentially lead to local side effects such as oropharyngeal candidiasis, dysphonia, coughing, bronchospasm, and pharyngitis (Kelly and Nelson 2003). If the oropharyngeal deposition is not rinsed, the individual will swallow this portion of the drug, sending it through the gastrointestinal tract. Absorption in the gastrointestinal tract can lead to a portion of the drug entering systemic circulation.

According to the European Respiratory Society and International Society for Aerosols in Medicine, three aspects must be considered for each delivery device's effective patient use: inhalation coordination, level of inspiratory flow, and clinical conditions (Laube et al. 2011). Furthermore, delivery devices should be assessed for ease of use including coordination from actuation to inspiration and level to which an identical dose is delivered with each actuation. ICSs are delivered via one of four different devices: metered-dosed inhalers (MDIs), dry-powder inhalers (DPIs), Respimat® Soft Mist™ inhalers (SMIs), or nebulizers.

Pressurized MDIs are actuated by pressing down on the canister of medication into the inhaler which aerosolizes the medication. The patient must coordinate a deep breath with the actuation. MDI devices are most often designed to propel medicine by hydrofluoroalkane (HFA) (Ye et al. 2017). Additionally, the drug inside the canister of MDIs is in a solid powder form, requiring shaking the inhaler before actuation. Shaking the inhaler is a commonly missed step in patient actuation. Thus, patient technique to administer MDIs requires accuracy and good coordination. MDIs are similar in function; however, each delivered dose does not have a consistent concentration (Scichilone 2015). Additionally, the emitted particles vary in size between suspended and solution formulations. The suspension formulations produce a larger variety of size in the emitted particles, whereas the solution formulations produce small particles, allowing for deeper penetration into the airways (Scichilone 2015). A valve holding chamber attached to an MDI can increase the number of particles deposited in the lungs rather than the oropharynx (Ye et al. 2017).

DPIs utilize a powdered form of the active drug which the patient inhales quickly (approximately 60 L/min) once the drug is activated (US Department of Health and Human Services National Institutes of Health 2007). This delivery mechanism allows for high lung deposition and low oropharyngeal deposit (Lavorini et al. 2008). Although activation for the medication varies between devices, DPIs do not require any actions between activating the drug and inhaling the particles like the MDI which requires coordination from activation to inhalation (Laube et al. 2011). Another factor to consider with the varying devices is the aerodynamic properties of the device. DPIs require a patient to deeply inhale the activated drug (Laube et al. 2011). Each device has airway resistance to ensure the activated dose is only delivered at the appropriate inspiration. The strength at which the patient can inhale and the support which the device can give to promote the speed of that inhale determines the level of lung deposition the medication will have (Laube et al. 2011). The forceful breath that DPIs require may be difficult for some populations such as the elderly or young children to receive the dose and successfully deposit it into the lungs (Lavorini et al. 2008). Additionally, if the patient exhales into the device, the dose is lost

(US Department of Health and Human Services National Institutes of Health 2007). Due to the powdered nature of the product, humidity can cause the drug to clog the device's delivery system. Some DPIs contain a lactose agent to bind the medication and are contraindications for patients with a milk protein allergy (Robles and Motheral 2014).

SMIs, which use a spring mechanism to produce the drug in an aerosol form, were first introduced in 2007 as an alternative to the pressurized MDI and DPI. The device uses a lower velocity and produces fine particles, which allows for increased lung deposition and decreased oropharyngeal deposition (Bousquet et al. 2002). Each dose is precisely delivered by the energy of the tightly wound spring; little variance exists between delivered doses. A SMI still produces an aerosolized drug "mist" similar to MDI devices, allowing for fine particles to reach the lungs. However, unlike MDI, SMI requires less coordination to deliver the dose. SMI emits the aerosol slowly with one press of a button, with the mist lasting for about 1.2 s as compared to 0.1 s from a pressurized MDI (Lavorini et al. 2014).

Nebulizers are used for the delivery of ICS for patients of any age who are unable to use MDIs, DPIs, and SMIs (US Department of Health and Human Services National Institutes of Health 2007). The nebulizer creates a vapor from a liquid solution that allows a patient to tidal breathe the medication. A face mask can be worn while the dose is being administered, and thus, the medication vapor is cycled through the entire respiratory system, including inhalation and exhalation (Lavorini et al. 2014). A portion of the medication is lost during exhalation; therefore, the delivered dose is not consistent with the intended dose (Lavorini et al. 2014). This device requires less coordination and requires a tight fitting face mask to prevent exposure of the medication to the patient's skin or eyes (Global Initiative for Asthma 2018). The patient's face should be washed after dosing to remove any residue from the medicated vapor, which can create a steroid rash (Global Initiative for Asthma 2018). Although easy to use, nebulized delivery is less convenient and more time-consuming.

38.3.3 Pharmacokinetics and Pharmacodynamics

In addition to an individual's genome and the type of medication delivery device, the efficacy of ICS depends on the individual drug's pharmacokinetic and pharmacodynamics properties including receptor-binding affinity, particle size, bioavailability, activation, pulmonary retention time, lipophilicity, lipid conjugation, protein binding, metabolism, and elimination from the body (Table 1).

38.3.4 Receptor-Binding Affinity

Glucocorticoid receptor binding is crucial for an ICS to be effective; thus, higher binding affinity leads to a higher potency with both positive airway mucosal absorption and negative systemic side effects due to similar mechanisms. Each ICS has varying receptor-binding affinity, represented by relative receptor affinity values. Mometasone furoate, fluticasone propionate, beclomethasone dipropionate's active metabolite, and ciclesonide's active metabolite rank at the highest of ICS for their relative receptor affinity. Even though a high relative receptor affinity is important in the efficacy of ICS, it creates the potential for worse systemic side effects thus not guaranteeing the medication has the best therapeutic index.

38.3.5 Particle Size and Bioavailability

Although delivery devices have been discussed, it is important to look at the individual ICS molecule sizes. These can differ depending on the type of delivery device and drug formulation. Drugs producing particles less than 5 micrometers more easily enter the bronchioles of the lungs. Particles larger than 5 micrometers are often deposited into the mouth and pharynx because they are too large to enter the airways (Derendorf et al. 2006). Some of the ICS on the market produces very small molecules, around 1.1 micrometers. These small particles allow the

Table 1 Key primary growth studies (prospective, randomized, double-blind, placebo-controlled, parallel-group) using *FDA-Approved* ICS doses in children

	Allen et al. 1998	Szefler 2000	Guilbert et al. 2006	Becker et al. 2006	Skoner et al. 2008	Skoner et al. 2011	Bensch et al. 2011	Martinez et al. 2011
Sponsor	Industry	NHLBI	NHLBI	Industry	Industry	Industry	Industry	NHLBI
Number of centers	19	8	5	30	85	30	45	5
Sample size (n)	325 (ICS 181)	1041 (ICS 311)	285 (ICS 143)	360 (ICS 119)	661 (ICS 440)	187 (ICS 142)	218 (ICS 106)	288 (ICS 143)
Age (years)	4–11	5–12	2–3	6–9	5–8.5	4–9	4–10	5–18
Disease severity level	Mild	Mild-moderate	Positive asthma predictive index	Mild persistent	Mild persistent	Mild persistent	Mild persistent	Mild persistent
Controls	Placebo (n = 87)	Nedocromil (n = 312) Placebo (n = 418)	Placebo (n = 142)	Montelukast (n = 120) Placebo (n = 121)	Placebo (n = 221)	Placebo (n = 45)	Placebo (n = 112)	Placebo (n = 74)
Primary study outcome	Growth	Efficacy (not growth)	Efficacy (not growth)	Growth	Growth	Growth	Growth	Efficacy (not growth)
ICS[a] used	FP (Diskhaler DPI)	BUD (Turbuhaler DPI)	FP (MDI with AeroChamber/ mask)	BDP (CFC-MDI)	CIC[b] (HFA-MDI)	MF (DPI)	FLUN (HFA-MDI)	BDP (HFA-MDI)
Daily ICS dose	100 mcg or 200 mcg (50 mcg or 100 mcg bid)	400 mcg (200 mcg bid)	176 mcg (88 mcg bid)	400 mcg (200 mcg bid)	40 mcg and 160 mcg once daily	100 mcg qd and 100 mcg bid and 200 mcg qd	340 mcg (170 mcg bid)	80 mcg (40 mcg bid)
Fixed dose?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Duration of ICS use	1 year	4–6 years	2 years	56 weeks	1 year	1 year	1 year	44 weeks
Adherence method (% adherence)	Objective (90–94)	Self-report (93.6) Objective (60.8)	Objective (69–74)	Self-report (>95) Objective (>95)	Self-report (94–99) Objective (80–82)	Self-report (≥75)	Self-report (>90) Objective (86–88)	Objective (≥75)
Dosing level in NHLBI guideline	Low	Low	Low	Low	Low	Low	Medium	Low
Method used to measure height	Stadiometry	Stadiometry	Stadiometry	Stadiometry	Stadiometry	Stadiometry	Stadiometry	Stadiometry
Frequency of height measurement	Monthly	Every 6 months	Every 4 months	Every 8 weeks	Every 2 months	Every 2–14 weeks	Every 2 months	Every 8 weeks
Analysis method	Analysis of variance	Multiple regression	Linear regression	Linear regression	Linear-regression	Longitudinal random slope	Linear regression	Linear mixed-effects model
Effect size	No significant effect	−1.1 cm ($p = 0.005$ vs. placebo)	−1.1 cm ($p < 0.001$ vs. placebo)	−0.78 cm ($p < 0.001$ vs. placebo)	No significant effect	−0.7 cm ($p = 0.02$ for 200 mcg qd vs. placebo)	No significant effect	−1.1 cm ($p < 0.0001$ vs. placebo)

[a]*BDP* beclomethasone dipropionate, *MF* mometasone furoate, *FP* fluticasone propionate, *BUD* budesonide, *CIC* ciclesonide, *FLUN* flunisolide, *CFC* chlorofluorocarbon, *HFA* hydrofluoroalkane, *MDI* metered dose inhaler, *DPI* dry powder inhaler
[b]FDA-approved for children 12 years of age and older only

medication to deposit deeper into the patient's airways, even reaching the smaller airways that could only be reached with systemic treatment before the introduction of the small molecule ICS, beclomethasone dipropionate and ciclesonide (Gentile and Skoner 2010). Because of these smaller molecules and deeper penetration, these medications require a lower dose to be efficacious (Gentile and Skoner 2010). Even at a lower dose, small particle ICS can have similar or improved effectiveness compared to standard size particle ICS (Van Aalderen et al. 2015).

DPIs generally produce the largest molecules. Fluticasone propionate DPI produces molecules at 6 micrometers in diameter with a lung deposition of 20% (Ye et al. 2017), and budesonide DPI produces molecules at 2.5 micrometers in diameter with a lung deposition of 15–28% (Thorsson et al. 1994; Borgström et al. 1994). MDIs can emit particles of multiple sizes including larger molecules. Two HFA suspension formulas, fluticasone propionate and mometasone furoate produce higher particle size than the three HFA solution formulations. Mometasone furoate HFA has a high oropharyngeal deposition (79%) and a low lung deposition (7.4–24.5%) (Pickering et al. 2000). The three HFA solution formulations emit extra-fine particles: beclomethasone dipropionate, ciclesonide, and flunisolide. Beclomethasone dipropionate and ciclesonide emit the smallest particles of all ICS on the market. Ciclesonide HFA demonstrates a lung deposition of 52% and an oropharyngeal deposition of 33% in a small cohort of twelve mild to moderate asthmatics (Newman et al. 2006) and a lung deposition of 52% and an oropharyngeal deposition of 38% in eight healthy individuals (Leach et al. 2006). Although these are small cohorts, these deposition values are more promising than the other ICS formulations.

Bioavailability of ICS has two sources: oral bioavailability due to oral deposition and pulmonary bioavailability due to lung deposition, ideally with oral bioavailability being low and pulmonary bioavailability being high. A drug's systemic bioavailability is the sum of the pulmonary bioavailability and oral bioavailability of the drug. However, bioavailability is more than just a function of the level of oral deposition versus the level of lung deposition. For instance, ciclesonide HFA has the lowest oral bioavailability and thus the largest pulmonary bioavailability which coincides with the drug's oral deposition (Derendorf 2007). The systemic bioavailability of ICS plays a crucial role in considering the safety of the drug. The lower the bioavailability of the medication, the higher the risk for systemic side effects because more of the drug is being circulated through the body (Derendorf et al. 2006).

38.3.6 Drug Activation

Drug activation is crucial for effective use of the drug. ICSs can be inhaled in their active form (fluticasone propionate and budesonide) or can be converted into their active form upon arrival in the airways, a "prodrug" (ciclesonide and beclomethasone dipropionate). As mentioned earlier, ciclesonide's active metabolite and beclomethasone dipropionates's active metabolite that have high receptor affinity occur after ciclesonide and beclomethasone are converted into this active form by esterases in the airway epithelium. Ninety-seven percent of beclomethasone dipropionate is converted into the active metabolite, allowing for higher potency in the body (Daley-Yates 2015). Less ciclesonide is converted into the active metabolite as compared to beclomethasone dipropionate; however, ciclesonide without being converted into desisobutyryl ciclesonide (des-CIC) is virtually inactive, producing no pharmacological effects (Derendorf et al. 2006). Additionally, almost complete activation of ciclesonide occurs in the lungs and very little in the oropharynx, contributing to its very low oral bioavailability (Derendorf et al. 2006). ICSs that are not prodrugs rely completely on their molecular design upon inhalation for effectiveness (Daley-Yates 2015) and have additional risk for systemic effects because it lacks direct on-site activation of the drug in the lungs (Ye et al. 2017).

38.3.7 Pulmonary Retention

Pulmonary retention time is the length of time the drug is present in the lungs. Quick absorption into the airways and prolonged presence in the cell membranes increase the pulmonary residence time of the drug. High pulmonary residence time can lead to less systemic effects because of a low concentration entering the systemic circulation and a higher potency due to the longer binding of the active drug in the airways. An ICS's pulmonary residence time can be tested by identifying the half-life of the drug after inhalation as compared to the half-life after it is given intravenously. Two characteristics of a drug contribute to pulmonary residence time: lipophilicity and lipid conjugation. Each ICS possesses different levels of lipophilicity and lipid conjugation (Table 1).

38.3.8 Lipophilicity

Lipophilicity is a characteristic of ICS, representing the drug's ability to pass through the phospholipid bilayer of cell membranes and slow the dissolution of the drug into the fluid in the lungs. This passage through the cell membrane allows for quick absorption, leading to a higher volume of drug distributed (Lipworth and Jackson 2000). The molecular structure of an ICS, specifically the lipophilic chains added to the D-ring, allows for the quicker passage through the cell membrane (Derendorf et al. 2006), better specificity for the glucocorticoid receptor (Daley-Yates 2015), and lack of solubility in the bronchial fluid. The higher lipophilicity molecule leads to a higher pulmonary residence time as seen when checking the half-life of the drug as mentioned previously. The lipophilicity of each ICS differs due to the molecular structure. For instance, fluticasone furoate has an ester group which increases lipophilicity, decreases solubility, and increases glucocorticoid receptor binding (Valotis and Högger 2007). Mometasone furoate has the highest lipophilicity, followed by beclomethasone dipropionate, fluticasone furoate, fluticasone propionate, ciclesonide, and budesonide, respectively (Derendorf et al. 2006). Unfortunately, increased lipophilicity has the potential to cause systemic side effects by allowing for the same effects to occur in other organs or parts of the body after the drug is systemically absorbed.

38.3.9 Lipid Conjugation

Lipid conjugation is the process of an ICS creating a chemical bond with fatty acids in the cells of the airway. This esterification of fatty acids forms the ICS and fatty acid complex which stays with the cell membrane and allows for the reversibly bound drug to further bind with glucocorticoid receptors. Lipid conjugation has only reportedly occurred with budesonide (Derendorf et al. 2006), des-CIC (Nave et al. 2005), and triamcinolone acetonide (Hubbard et al. 2003) and can only occur with molecules with a specific molecular structure: steric-hindrance-free hydroxyl group off carbon 21 of the ICS (Tunek et al. 1997). The esterification of ciclesonide and budesonide contributes to a slower release of the active drug, resulting in longer pulmonary retention (Nave et al. 2005; Edsbäcker and Brattsand 2002). This slow release allows for higher pulmonary residency and lower concentration of the drug entering the systemic circulation, resulting in potentially less side effects.

38.3.10 Protein Binding, Metabolism, and Elimination

An ICS's protein-binding affinity affects the amount of free active drug that can enter the systemic circulatory system. This binding can occur intracellularly or extracellularly. Each ICS has a varying affinity in which it binds with circulating proteins, such as albumin. Increased binding affinity reduces the amount of free active drug systemically available, thus decreasing risk of systemic side effects. Both ciclesonide and its active metabolite have high protein-binding affinity, contributing to the drug's low systemic bioavailability (Nave et al. 2004).

The speed of ICS metabolism and elimination affects the concentration and time the active drug

remains in systemic circulation, potentially causing unwanted side effects. Thus, the faster the drug is metabolized and eliminated, the lower the systemically available concentration of drug and thus less systemic side effects. Drugs with higher first-pass metabolism are more quickly metabolized by the body, specifically the liver, significantly impacting the therapeutic effect of the drug (Derendorf et al. 2006). The prodrugs mentioned earlier, ciclesonide and beclomethasone dipropionate, have improved first-pass metabolism resulting in quicker metabolism and elimination of the drug (Daley-Yates 2015).

38.3.11 Drug Dose-Effect Response Relationship

The therapeutic effect of ICS depends upon the delivery and absorption of the drug into the airways and the retention of the drug in the lungs. It might be assumed that medications delivered at higher doses would produce a higher therapeutic effect; however, ICSs have shown a dose-effect response with lower and medium doses and not with a higher dose. Generally, mild to moderate asthmatic patients do not achieve any increased benefit from taking a higher dose of ICS, and few patients require a high dose of ICS to see improvements in lung function (Daley-Yates 2015). Bosquet et al. found in a meta-analysis of 16 studies looking at this dose-response effect that the therapeutic effect ends with the medium dose of ICS (Bousquet et al. 2002) for mild to moderate asthmatics. This dose-effect response relationship also correlates with glucocorticoid receptor affinity. ICSs with higher glucocorticoid receptor-binding affinity require patients to take lower doses to reach the same therapeutic effect (Daley-Yates 2015).

38.4 Dose Frequency

The recommended dose of each ICS varies according to a patient's asthma severity and level of asthma control. Step 2, the lowest step for persistent asthmatics, recommends a low-dose ICS with the next step, Step 3, consisting of a low-dose ICS/LABA combination medication for adults (age 12 years old and older) or a medium-dose ICS for adults or children. Both Step 4 and Step 5 recommend an ICS and LABA combination medication at a medium dose and high dose, respectively. Although alternatives exist, ICS and ICS/LABA combination medications are the preferred medications for patients with persistent asthma.

Just as the recommended dose of ICS varies, the dose frequency of these medications also varies from one puff to two puffs, once daily or twice daily. Historically, ICSs were thought to be most effective in a twice-daily dosing frequency. Additional research is being completed to show that one-daily dosing is effective for some ICS formulations (Kelly 2009). Once-daily mometasone furoate DPI was approved by the US FDA for maintenance treatment of asthma in children and adults. This approval was based on findings that showed once-daily dosing significantly improves lung function and health-related quality of life while reducing rescue medication use and exacerbations despite previous treatment with ICS. Additionally, once-daily dosing may help improve asthma management by addressing issues that inhibit proper adherence (Milgrom 2010). Although the effect was not strong enough to obtain US FDA approval, once-daily ciclesonide demonstrated improvements in baseline FEV_1, decreases in albuterol use, and significant improvements in asthma symptoms over placebo in moderate to severe asthmatic children (Gelfand et al. 2006). Ciclesonide is currently prescribed as once daily in Europe (Stoloff and Kelly 2011). Mallol and Aquirre found similar effects for once-daily and twice-daily dosing of budesonide with asthmatic children. The once-daily group saw a significant improvement in asthma symptoms, a decrease in bronchial hyperresponsiveness, and higher medication compliance than the twice-daily group (Mallol and Aguirre 2007). Once-daily dosing can improve patient adherence and maintain asthma control. Wells et al. found that once-daily dosing had a 20% higher level of adherence compared to twice-daily dosing, further suggesting that once-daily dosing can improve asthma outcomes (Wells et al. 2013).

The safety and efficacy of intermittent ICS therapy have also been studied. This approach addresses ICS safety concerns as well as low compliance with daily ICS therapy. Boushey et al. found that intermittent budesonide guided by a symptom-based treatment plan produced similar effects as daily budesonide and daily leukotriene receptor antagonist (LTRA) in adult patients with mild persistent asthma. Additionally, no difference was exhibited in relation to the morning peak flow assessments, the primary outcome of the study, the number of asthma exacerbations, or post-bronchodilator FEV_1 values among the three arms. However, those in the daily budesonide treatment exhibited a significantly greater number of symptom-free days and asthma control scores. No significant difference was found between the participants assigned to intermittent budesonide or daily LTRA. Thus, this study shows preliminary data that intermittent use of ICS may produce similar outcomes as daily LTRA use (Boushey et al. 2005).

Beclomethasone was used as a daily controller (daily group), rescue medication (rescue group), or both daily controller and rescue medication (combined group) for children and adolescents aged 5–18 years with mild persistent asthma in the Treating Children to Prevent Exacerbations of Asthma study. The frequency of exacerbations in the rescue group was less than in the placebo group but more than the daily group and the combined group. However, there were significant decreases in growth in the daily and combined groups compared to placebo and no evidence of reduced growth velocity in the rescue group. Although these results too reveal that daily ICSs are most efficacious, intermittent ICS might be an effective step-down strategy for children with well-controlled, mild asthma (Martinez et al. 2011).

Intermittent ICS, if effective at reducing asthma outcomes, could prevent unnecessary exposure to medications. In a study performed by Zeiger et al., intermittent budesonide was found to be similar and not significantly different from daily budesonide in children during respiratory tract illness. Mean exposure to budesonide was 104 mg less with the intermittent regimen compared to the daily regimen. Thus, the authors proposed that high-dose intermittent therapy for specific situations should be considered (Zeiger et al. 2011).

A recent study evaluated the self-management concept of having patients quadruple their dose of ICS when asthma control starts to decline. In this pragmatic, unblinded, randomized trial involving adults and adolescents with asthma who were receiving ICS, temporarily quadrupling the ICS dose when asthma control deteriorated resulted in fewer severe asthma exacerbations than when the dose was not increased (McKeever et al. 2018).

38.5 Combining ICS with Long-Acting Beta Agonists (LABA)

Step 3 of the current asthma guidelines recommends the combination of a LABA either with a low-dose ICS or a medium-dose ICS. At Step 4 and higher, the guidelines prefer an ICS/LABA combination. Although there is a safety concern of increased asthma-related deaths with LABA therapy alone in asthma (Castle et al. 1993; Nelson et al. 2006), ICS/LABA combination medications (fluticasone propionate/salmeterol, mometasone/formoterol, fluticasone/salmeterol, budesonide/formoterol, and fluticasone furoate/vilanterol) are considered safe at age-appropriate recommended doses. LABA have been found to produce more beneficial asthma outcomes than adding a LTRA to the existing ICS dose (Ducharme et al. 2006).

The combination medication promotes binding of the glucocorticoid receptor and the glucocorticoid response elements. More rapid binding allows for a quicker anti-inflammatory response. The increase in this molecular binding process was witnessed when comparing the induced sputum of patients taking budesonide/formoterol vs. budesonide alone (Essilfie-Quaye et al. 2011).

The ICS/LABA combination has shown to be more effective at improving asthma outcomes compared to an increased dose of ICS alone. In a study by Grenning et al., salmeterol added to a medium dose of beclomethasone dipropionate resulted in improved asthma outcomes compared to high-dose beclomethasone dipropionate in

429 asthmatic adults who were uncontrolled on a medium dose of beclomethasone dipropionate. The adults were randomized in a double-blind, parallel group trial to either a high dose of beclomethasone dipropionate or a medium dose of beclomethasone dipropionate/salmeterol combination medication for 6 months. Lung function was assessed by morning and nighttime peak flows, and level of asthma control was assessed by participant-reported daytime asthma symptoms and nighttime awakenings. Morning peak flow values increased for both groups within the first week of study treatment, but the combination medication group exhibited significantly higher morning peak flows than the higher-dose group. The combination medication group experienced consistent and greater improvements in symptoms compared to the higher-dose group, and no significant difference in the number of exacerbations or adverse events was noted between the two groups. Thus, the group taking beclomethasone dipropionate/salmeterol witnessed greater improvements in asthma control and lung function, as determined by morning peak flows, and nighttime awakenings and daytime symptoms compared to the group taking high-dose beclomethasone dipropionate (Greening et al. 1994).

Additionally, a meta-analysis performed by Shrewsbury et al. found 9 parallel group trials with a total of 3685 patients with similar criteria existed as the Greening et al. study. Patients 12 years old or older were experiencing symptoms when entering into a study of two arms: a higher dose of ICS or a combination of the same dose of ICS and the addition of salmeterol. The patients taking the combination medication exhibited improved peak flows and FEV_1 values at 3 and 6 months over patients who received higher doses of ICS. Additionally, the combination medication group demonstrated a decrease in daytime and nighttime asthma symptoms and rescue use as compared to the higher-dose group. Additionally, no additional asthma exacerbations were witnessed by the combination medication group (Shrewsbury et al. 2000).

Physicians face two options when a step down in therapy is possible: remove the LABA component or lower the dose of the ICS/LABA combination medication. Due to the safety concerns of LABA creating worsening symptoms, the US FDA suggests removal of the LABA component once the patient's therapy can be safely stepped down (Ye et al. 2017). Mori et al. assessed both options and found that both step-down therapy options produced similar results for the 91 moderate asthmatics taking budesonide/formoterol twice daily. No significant difference was found between the two step-down groups in the incidence of exacerbations, asthma quality of life, or fractional exhaled nitric oxide. The budesonide only group demonstrated lowed FEV_1 values 12 weeks after removal of formoterol; however, these values were not statistically significantly different. Thus, both step-down options produce similar outcomes, but more research may be necessary to look at the relationship of the LABA component with FEV_1 values (Mori et al. 2016).

Moreover, Obase et al. looked at the appropriate time to step down patients from ICS/LABA therapy. Patients that showed improvement in lung function and asthma control in 12 weeks were randomized to receive a step down in treatment or maintain the current treatment. Lung function and asthma symptom scores did not differ between the two groups, but the fractional exhaled nitric oxide increased significantly in the step-down group and decreased significantly in the group continued at the same dose. Thus, inflammation, as demonstrated by exhaled nitric oxide, may not be controlled even if the patient's lung function and symptoms have improved (Obase et al. 2013).

With data supporting the use of ICS/LABA combination medications over increasing the ICS dose, additional studies were conducted to assess the efficacy of the medications at reducing asthma exacerbations. Although there are safety concerns that LABAs can cause worsening asthma, it is believed that the addition of ICS can prevent worsening asthma and exacerbations, allowing the patient to experience the benefit of LABA's anti-inflammatory property (Raissy et al. 2013). In a post-market double-blind randomized safety assessment study, Peters et al. found that

patients aged 12 years of age and older on budesonide/formoterol demonstrated a 16.5% lower risk for experiencing an asthma exacerbation than those on budesonide only (Peters et al. 2016). Stempel et al. conducted a similar study looking at the ability to prevent serious asthma events with fluticasone/salmeterol as compared to fluticasone alone. The randomized double-blind study enrolled patients 12 years of age and older to receive either treatment for 26 weeks. The fluticasone/salmeterol group demonstrated a 21% lower risk for experiencing a severe asthma exacerbation as compared to the group on fluticasone alone (Stempel et al. 2016).

The efficacy of ICS being used intermittently and as needed is being evaluated; likewise, the efficacy of using ICS/LABA combination medications as needed is being evaluated. A double-blind randomized study conducted with children and adults, aged 4–80 years old, evaluated if an ICS/LABA combination medication can be used as needed to improve asthma symptoms for patients on 400–1,000 micrograms per day for adults and 200–500 micrograms per day for children. In this study, O'Byrne et al. discovered that budesonide/formoterol used as a controller and reliever can improve a patient's exacerbation rate, asthma symptoms including nighttime awakenings, and lung function as compared to budesonide/formoterol as only a controller and budesonide only (O'Byrne et al. 2005). Rabe et al. conducted a 6-month randomized double-blind study looking at the efficacy of using budesonide/formoterol as a maintenance medication and as a reliever as compared to a higher dose of budesonide as a maintenance medication and terbutaline as a reliever. The budesonide/formoterol group exhibited significant improvements over the budesonide only group in morning peak flow values and risk of severe asthma exacerbations, which was consistent with previously discussed studies (Rabe et al. 2006). Although the efficacy of use of the budesonide/formoterol as a reliever on its own is unknown, this trial provides additional evidence that using an ICS/LABA combination as both a controller and reliever significantly improves asthma control and lung function.

38.6 Patient Perspective on ICS Safety

From a patient's perspective, knowing the risks and benefits associated with prescribed corticosteroid use is very important in allowing a proper shared decision-making with a healthcare provider (Stiggelbout et al. 2012). When a patient is prescribed a medication, their layperson education in the medical field often limits appropriate discussion with the prescriber at the opportune time. As a result, patients are left with two options: (1) trust the healthcare provider's decision and remain unaware of potential risks associated with medication use, or (2) go home and do an online search of the medication (often sources are questionable in their reliability and accuracy), and this often leads to more questions and consequently doubts of taking the medication.

Assuming patient-directed research is the more likely of the two options, patients need better direction to more reputable online sources. Trustful sources will provide better guidance for learning more about corticosteroids, and a good example of such a website is Macisteams.org. Maci's Teams defines the importance of knowing risks associated with corticosteroid use. As consumers, we patients often find unwanted risks when reading of medication side effects; knowing the accurate prevalence and likelihood of adverse reactions will help determine our level of comfort with taking the medication in question. As demonstrated in Maci's case, this knowledge could allow us to co-manage our health with our physician for possibly safer outcomes. Healthcare providers also need to know how to identify, recognize, and treat corticosteroid side effects when they develop. Patients need and want compassionate, knowledgeable, and responsive healthcare providers who have sufficient time to discuss the benefits and risks of medications.

Surveys have shown that one of the main reasons that people fail to use ICS is a fear of side effects (Canonica 2007). The side effects likely of primary concern to corticosteroid users are ones with long-lasting or permanent effects. The last thing that any patient wants is a permanent side effect from a medication that produces a temporary

benefit; with ICS this could range from effect on final adult height for pediatric users to cataracts and glaucoma for adult users. These potentially permanent health concerns weigh heavy on the mind of the patient and will vary in importance by individual. As a parent of a child using ICS, potentially stunting the natural growth pattern of their developing child can have major consequences. Some studies show that taller adults hold jobs of higher status and, on average, earn more than other workers; investigators have offered a simple explanation – that height is positively associated with cognitive ability, which is rewarded in the labor market (Case and Paxson 2008). As another example, perhaps a patient being asked to take ICS has a pre-existing family history of severe glaucoma. In the mind of this patient, taking corticosteroids will be a very big mental hurdle (possibly insurmountable) if their risk of developing glaucoma increases.

If medication side effects are adequately explained to patients and parents in a shared decision-making process, people might be more agreeable to using ICS on a regular basis as long as they are monitored for side effects by competent healthcare providers.

38.7 Introduction to ICS Safety

ICS doses were FDA-approved only in adults initially. Approval was based on each dose's ability to improve FEV1 and not suppress the HPA axis. Studies of the HPA axis were relatively easy to conduct, since suppression occurs quite quickly after starting ICS and clinical trials could be of relatively short duration (compared to outcomes that require a longer period of ICS use for development, such as bone mineral loss, cataracts, glaucoma, and growth of children).

The same approach for FDA approval was used in children. However, some of the doses that were free of HPA axis suppression in adults did suppress the axis of children and were not FDA-approved for children (e.g., FP-MDI 110 mcg and 220 mcg). It was widely assumed that ICS doses that were FDA-approved and free of HPA axis suppression would also be free of growth suppression in children. However, the FDA did require a commitment from the pharmaceutical manufacturer to conduct a future Phase 4 growth study as a contingency for approval. When those growth studies were finally conducted, it was surprising to learn that many of the FDA-approved ICS doses did indeed suppress the growth of children.

Originally, based on the results of studies conducted using non-robust designs, it appeared that the small short-term growth suppression of ICS would not result in an impact on final adult height. However, a more robust study design proved that childhood use of FDA-approved ICS doses suppressed final adult height.

The key to detecting systemic side effects of ICS is to design studies with sufficient sensitivity and duration to detect small effects that may take a significant amount of time to develop on ICS. Many well-designed studies have examined the effects of FDA-approved ICS doses on HPA axis and growth, but fewer studies with less robust designs have examined their effects on bone mineral density, cataracts, and glaucoma and when used at doses higher than those approved by the FDA and in combination with INCS.

38.8 Historical Perspective on ICS Efficacy and Safety

ICSs were developed to replace OCS, which were efficacious and a mainstay of asthma therapy at the time, but which were also associated with significant systemic side effects (Covar et al. 2000). When introduced, ICS seemed like the perfect asthma therapy, delivering the benefit of a corticosteroid, but with a much lower tendency to produce systemic side effects than OCS. The degree of side effect risk reduction afforded by the change from OCS to ICS only became evident over a long period of time.

During their development, ICS underwent extensive controlled clinical trials to obtain FDA approval. Approvals were sought for adults first and then subsequently for children. Determination of the effectiveness of a dose was generally based

on its ability to improve the FEV_1 and safety of a dose was generally based on its inability to suppress the HPA axis. FDA-approved doses in adults and children weren't always the same, because doses that were determined to be safe for adults were not always safe for children. For example, fluticasone propionate (FP-MDI) was FDA-approved in three strengths for adults (44, 110, and 220 mcg/puff), but only the lowest strength (44 mcg/puff, two puffs bid) was approved for children because the higher strengths suppressed the HPA axis.

It was assumed that HPA axis suppression served as a surrogate for another very important clinical outcome in children, i.e., growth suppression. The operating assumption was that if an FDA-approved dose did not suppress the HPA axis of children (e.g., 44 mcg/puff, two puffs bid), it would likewise not suppress their growth. But, even though that was commonly believed, no one was sure it was true. Therefore, the initial FDA approval of an ICS dose for children was contingent on a commitment by the pharmaceutical company to conduct a future Phase 4 study to examine its effect on childhood growth. Investigators viewed the FDA-required Phase 4 commitment studies on growth as necessary, but useless exercises, and had absolutely no expectation of a positive result based on lack of suppression of HPA axis and their clinical experience.

The early growth studies that were conducted by industry under those circumstances produced variable results, with some studies detecting ICS growth effects and others finding no effect. However, one such seminal study used a high-quality study design and detected no growth suppression from FP doses up to 200 mcg/day (Allen et al. 1998), supporting the operating assumption that doses free of HPA axis suppression are also free of growth suppression.

Collectively, these early industry-sponsored studies were viewed by the FDA as "flawed," prompting a critical review of ICS growth studies by the FDA in 1998. This review concluded that ICSs do affect the growth of children and prompted significant label changes related to growth suppression and the publication of a guidance for industry to follow when designing future ICS growth studies (Food and Drug Administration – "draft" guidance issued in 2001, final guidance published in 2007). The design elements recommended in the guidance served to increase the sensitivity of studies in detecting small growth effects of ICS and INCS (Fig. 1). The recommendation included the enrolment of children who were prepubertal and had mild, persistent asthma to avoid or minimize confounding by the pubertal growth spurt, the suppressive effect that severe disease has on growth, and the use of systemic corticosteroids.

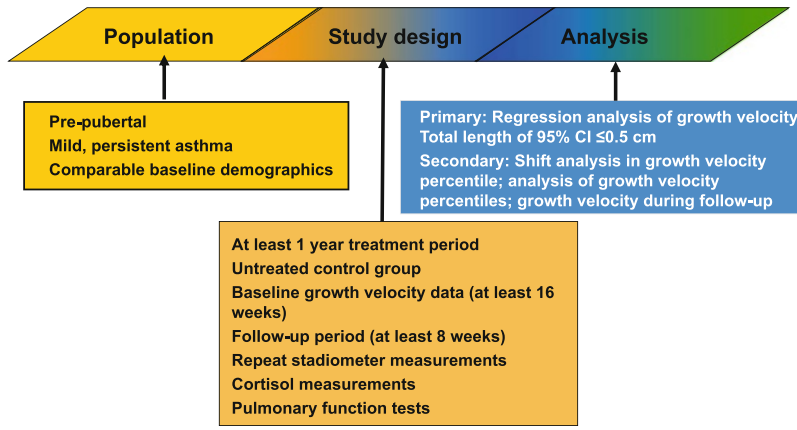

Fig. 1 FDA 2001 guidelines for evaluation of the effects of inhaled corticosteroids on growth. (www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071968.pdf. Accessed 7/24/13 FaDAOiaiceoteogiccAAf)

Using design elements recommended in the industry guidance and, in some cases, funding by NIH instead of industry, investigators surprisingly began to show more consistent results, i.e., small (~1 cm/year), statistically significant growth suppression by most ICS. This included the FDA-approved dose of FP for children (44 mcg/puff, 2 puffs bid) (Guilbert et al. 2006). The Guilbert study contradicted the result of the Allen study, showed that an ICS dose that did not suppress the HPA axis could suppress the growth of children, and proved that the earlier operating assumption was wrong.

So, how did the studies by Allen and Guilbert differ, and why did they produce different results? There were differences in the age groups of the two studies, but the most notable difference was that the Allen study used a delivery device (Rotadisk) with low lung deposition and systemic bioavailability and the Guilbert study employed a more commonly used delivery device (MDI), which has higher lung deposition and systemic bioavailability.

The early growth studies and their level of compliance with the FDA guidance, along with the changing landscape with regard to the effects of ICS on childhood growth, were reviewed in previous publications (Bartholow et al. 2013; Skoner 2016b).

Since the early days when the conversion was made from OCS to ICS and there were no childhood growth data for ICS, much has been learned. Indeed, growth can serve as a process to help compare the level of systemic corticosteroid bioavailability for different doses of a given ICS or to compare those of various ICSs. Growth suppression is now considered a more sensitive indicator of systemic bioavailability than HPA axis suppression, as shown in a number of publications (Skoner 2000a; Skoner et al. 2015; Skoner et al. 2011), as stated by the FDA in package labels, and as recently demonstrated eloquently by others (Chawes et al. 2017). Therefore, much of the rest of this review will focus on the growth of children, reviewing the results of 1-year studies using FDA-approved ICS doses and the results of studies examining the impact of ICS use during childhood on final adult height.

38.9 Short-Term Effect of ICS on Childhood Growth

The early unexpectedly positive growth studies, the critical FDA review, and the publication of a guidance for industry to follow raised the scientific bar for quality of design and conduct of every subsequent growth study, including those sponsored by the industry and NIH.

Table 1 shows the key primary growth studies using FDA-approved ICS doses in children. All are high-quality studies scientifically, whether designed and conducted by industry after the FDA guidance or by the NIH. These studies show that potent ICSs, such as FP, MF, and BDP, clearly suppressed the growth of children, even when FDA-approved doses were used. The effect is dose-related (Verberne et al. 1998) and small (~1 cm), and variability in individual susceptibility to the effect is evident. Children with mild disease may be more susceptible to the growth effect than those with more severe disease because of greater airway patency, lung deposition, and systemic absorption (Skoner 2000b).

Only two clinical trials designed using the FDA guidance and FDA-approved ICS doses produced negative results for growth effects, one employing ciclesonide (Skoner et al. 2008) and the other flunisolide (Bensch et al. 2011). Lower potency and other unique pharmacokinetic features may explain the negative results and the difference in results compared to other ICSs. Amazingly, both are generally unavailable in the United States because of lack of insurance coverage.

Finnish researchers recently used a novel study design to examine the effects of ICS exposure before age 24 months on linear growth. Instead of the usual prospective controlled clinical trial comparing the growth effects of placebo and ICS, they performed a retrospective study. ICS use was determined on the basis of information from the drug purchase register covering all prescribed and reimbursed drug purchases in Finland. The study population

was also unique, including large numbers of infants (n = 12,482) who were exposed and unexposed to ICS. At 25 months of age, the exposed population was significantly shorter than the unexposed population based on two growth parameters, height for age Z score and deviation from target height based on parental heights. They showed that ICS exposure during infancy is independently associated with poor linear growth at or after age 24 months. Young children who were exposed to daily low-dose ICS therapy for more than 6 months had significant reduction in height compared to unexposed children. However, neither daily minimal dose nor short-term (<3 months) use of ICS even at a medium/high dose was associated with attenuated growth. More studies are needed in this vulnerable population (Saari et al. 2018).

38.10 Long-Term Effect of Childhood ICS Use on Final Adult Height

Table 2 shows the two key studies assessing effects of childhood ICS use for asthma on final adult height. The first study (Agertoft and Pedersen 2000) used a study design that was too insensitive to detect the small but statistically significant effect identified in the later study (Kelly et al. 2012), which used a much more rigorous study design.

38.11 Use of Higher-Than-FDA-Approved ICS Doses

The effect of ICS on systemic side effects is clearly dose-related (Szefler et al. 2002; Skoner et al. 2010; Martin et al. 2002; Verberne et al. 1998; Carr and Szefler 2016; Israel et al. 2001). Therefore, adverse outcomes can be expected when using higher-than-approved doses compared to doses which have been approved by the FDA (Table 3).

A recently published abstract showed that US HCPs are deficient in knowledge about FDA-approved FP-MDI doses and side effects and therefore unknowingly use higher-than-FDA-approved doses and place children at risk for developing serious systemic side effects (Sforza et al. 2018). Based on the methods used in the FDA approval process (Table 3), it would be expected that high, unapproved doses would suppress the HPA axis and even produce adrenal crisis. Most HCPs are unaware of the age dependence of the FP-MDI FDA indication and use the higher unapproved doses "off-label." The study also showed that FP-MDI is the ICS with which HCPs are most familiar. Surprisingly then, it was also the ICS most commonly associated with "off-label" prescribing and adrenal crisis in children in many countries (Todd et al. 2002; Eid et al. 2002; Thomas et al. 2006; Goldbloom et al. 2017; Choi et al. 2017), for reasons that are unknown.

"Off-label" prescribing in children is common (Palmaro et al. 2015), legal, often unknown by the prescribing physician, and unregulated by the FDA (Stafford 2008). Some of the most commonly prescribed "off-label" medications for children are used for allergy and asthma. HCPs must be reeducated about FDA-approved ICS doses and side effects for children, and better systems must be put into place to protect children from the well-known and expected consequences of off-label prescribing of high ICS doses, including at the levels of the FDA, pharmaceutical company, pharmacy, and electronic medical record systems.

The FDA approval process for ICS is long and complex (Table 4), potentially leading to confusion about the doses which were approved by the FDA for children and contributing to off-label prescribing. The asthma guidelines further complicate the picture for off-label ICS prescribing in children. Using the ICS FP-MDI as an example (Table 5), low, medium, and high doses align with the three FDA-approved doses for adults (44, 110, and 220 mcg, respectively). However, for children, there is no such alignment. The 110 and 220 mcg doses are both

Table 2 Key studies assessing effects of childhood ICS use for asthma on final adult height

	Agertoft et al. (NEJM 2000)	Kelly et al. (NEJM 2012)
Sponsor	Vejle County hospitals Kolding, Denmark	NHLBI United States
Number of centers	1	8
Years of enrolment	1986–1999	1993–1995
Prospective?	Yes	Yes
Randomized?	No	Yes
Double-blind?	No	Yes
Placebo-controlled?	No	Yes
Sample size (n)	211 (142 on ICS)	943 (281 on ICS)
Disease severity level	Mild	Mild-moderate
Controls	ICS-naïve children with asthma (n = 18) and healthy siblings of asthmatic children receiving ICS (n = 51)	Nedocromil (n = 285) Placebo (n = 377)
Primary outcome of the study	Efficacy (not growth)	Efficacy (not growth)
ICS used	Budesonide	Budesonide (Turbuhaler DPI)
Daily ICS dose	412 mcg	400 mcg (200 mcg bid)
Fixed ICS dose?	No	Yes
Adherence method (% adherence)	Self-report (68, range 49–90)	Self-report (93.6) Objective (60.8)
FDA-approved dose for children?	Yes	Yes
Dosing level in NHLBI asthma guideline	Low	Low
Duration of ICS use during childhood	9.2 years	4–6 years
Method used to measure height	Stadiometry	Stadiometry
Frequency of height measurement	Every 6 months	Every 6 months
Age range during which ICS therapy was started	3–13 years	5–13 years
Age of measurement of final Adult height	16–24 years[a]	24.9 years
Analysis method	Difference between measured and target adult height	Adjusted multiple linear regression
Effect size	+0.3 cm	−1.2 cm (p = 0.001 vs. placebo)

[a]Measured adult height was the height measured when the height of a child over 15 years of age had increased by less than 0.5 cm for two consecutive years

considered high doses in the guidelines, and neither is FDA-approved for children. Likewise, for MF, the DPI, but not the HFA-MDI, is FDA-approved for children 4–11 years of age. In contrast, both MF formulations are FDA-approved for adults. As yet another example, CIC HFA-MDI is FDA-approved for adults (12+ years), but not for children less than 12 years of age. Collectively, this could potentially lead to confusion and contribute to off-label prescribing of high ICS doses for children.

38.12 Effect of ICS on Bone Mineral Density

Compared to HPA axis and growth studies, which were required as part of the FDA approval process, relatively few studies have addressed the short-term or long-term effects of ICS on bone mineral density.

38.12.1 Pathogenesis

Osteoporosis, traditionally defined as reduced bone mass and/or abnormal bony architecture leading to increased risk of fracture, is a known side effect of excess corticosteroid presence as first described in 1932 (Cushing 1932; Kanis et al. 1994). Exogenous systemic corticosteroids have long been associated with negative impacts on the bone, and this, as is the case with hormone-secreting tumors, is thought to be due to the development of secondary hyperparathyroidism as well as direct inhibition of bone-building osteoblasts, particularly in trabecular bone due to its rapid turnover (i.e., vertebrae) (Allen et al. 2003; Dahl 2006; Kapadia et al. 2016; Van Staa et al. 2002). Bone mineral density (BMD) directly correlates with bone health and inversely with fracture risk and is often measured by dual-energy x-ray absorptiometry (DEXA) or quantitative computed tomography (QCT) (Allen et al. 2003).

Further complicating our understanding of BMD is that it is greatly affected by age, sex, hormonal status (pre−/postmenopausal), diet, exercise, BMI, medication use, substance use, and overall health (Allen et al. 2003). BMD tends to increase steadily throughout childhood and into young adulthood prior to peaking in the third or fourth decade of life. This is followed by a steady decline which accelerates in postmenopausal women (Tattersfield et al. 2001).

Table 3 What to expect when prescribing ICS doses that are approved and unapproved by the FDA

	Adult	Child HPA Axis	Child Growth
Approved doses	No HPA axis suppression[a]	No HPA axis suppression[a]	Suppression of growth and final adult height
Higher-than-approved doses	Dose-dependent subclinical or clinically-evident HPA axis suppression; adrenal crisis with higher doses	Dose-dependent subclinical or clinically-evident HPA axis suppression; adrenal crisis with higher doses	Dose-dependent suppression of growth and final adult height

[a]Except in highly-susceptible individuals

38.12.2 Clinical Studies

While systemic corticosteroids have demonstrated a clear association with reduced BMD, the role of inhaled corticosteroids (ICS) on BMD is less clear. Numerous retrospective and prospective studies on BMD in adults with a history of ICS use have been conducted with somewhat conflicting results. Wong et al. found that not only was ICS use associated with reduced BMD but that after 7 years of consistent use, for every 2000 mcg of ICS used per day, BMD was lowered one standard deviation, which subsequently doubled fracture risk in older women (Wong et al. 2000). Bonala et al. found reduced BMD with ICS

Table 4 Overview of FDA-approval process and systemic side effects for ICS (exemplified by FP-MDI)

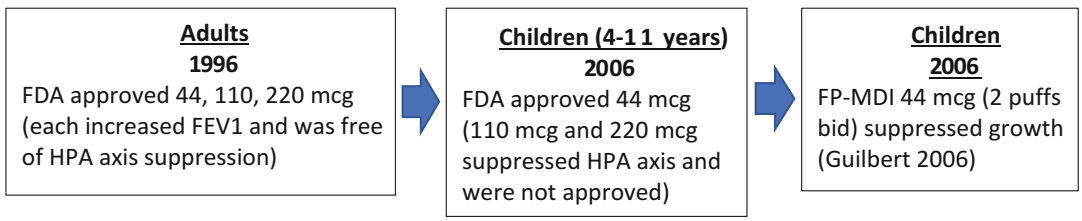

Table 5 NHLBI asthma guideline FP-MDI ICS dose levels for adults and children

Dose (MCG/PUFF)	Ideal	Actual[a] (Adult)	Actual[a] (Child)
44	Low	Low	Low
110	Medium	Medium	High[b]
220	High	High	High[b]

[a]2 puffs bid
[b]Not FDA-approved for children, but dose is listed in the asthma guideline and defined as "high"

use and emphasized the risk to postmenopausal women (Bonala et al. 2000). Monadi et al. found that ICS did negatively impact BMD but only in adults younger than age 50 and after more than 6 years of ICS use (Monadi et al. 2015). A study of 32 women found reduced BMD at the lumber spine and femur after only 3 months of beclomethasone dipropionate use, while Tattersfield et al. found no change in BMD for 239 adults on ICS for over 2 years (Sivri and Çöplü 2001; Tattersfield et al. 2001). Kemp et al. found no difference in BMD in a randomized trial of 160 adults following 6 months of low or moderate ICS dosing (Kemp et al. 2004). In a population cohort study, Langhammer et al. found reduced BMD with ICS use that was not dose-dependent in a sample of 2,113 adults (Langhammer et al. 2004).

In a meta-analysis by Richy et al. in 2003, the authors concluded that high-quality studies indicated a significant inverse relationship between ICS use and BMD that was particularly impactful when the ICS was triamcinolone (Israel et al. 2001), which is no longer on the market (Richy et al. 2003). Sharma et al., however, determined via a meta-analysis that while BMD was reduced in individuals on ICS, this was not a statistically significant reduction (Sharma et al. 2003). Sutter reviewed eight prospective studies in patients with asthma and four in patients with COPD and found that while there seems to be an association between ICS use and BMD, the relationship is not entirely clear (Sutter and Stein 2016). Halpern et al. conducted a meta-analysis looking at studies following BMD in ICS users for at least a year and found no association with reduced BMD (Halpern et al. 2004).

In a summary by Mortimer et al., the authors argued that there is sufficient evidence for an ICS dose-related reduction in BMD (Mortimer et al. 2005). A 2006 summary by Bielory et al. and a 2003 review by Allen came to the same conclusion (Allen et al. 2003; Bielory et al. 2006). These summary articles as well as the works of Bonala, Richy, Sidoroff, and Wong recommended using the lowest effective dose as the majority of studies have found a dose relationship (Bonala et al. 2000; Wong et al. 2000; Richy et al. 2003; Sidoroff et al. 2015).

In pediatric patients, research is further complicated by the variable bone density associated with pubertal linear growth (Kapadia et al. 2016). Few short-term studies have shown a significant reduction in BMD; however, it has been proposed that chronic use in childhood and young adulthood can significantly impact adult BMD (Sidoroff et al. 2015; Skoner 2016a). Allen et al. did find a negative impact in under 2 years in 48 asthmatic children on beclomethasone dipropionate or budesonide as did the Helsinki Early Intervention Childhood Asthma Study with children on budesonide (Allen et al. 2000; Turpeinen et al. 2010). Of note, van Staa et al. made the case that asthma itself may be associated with a slowing of bone mineral accretion as asthmatic children are more likely to be overweight and have reduced tolerance for physical activity, particularly weight-bearing exercise, which reduce BMD (Van Staa et al. 2004). Numerous prospective studies have shown no difference in BMD when using low to medium doses of ICS in children (The Childhood Asthma Management Program Research Group 2000; Paoli de Valeri et al. 2000; Baraldi et al. 1994; Hopp et al. 1995; Martinati et al. 1998; Roux et al. 2003; Griffiths 2004; Visser et al. 2004). Notably, the CAMP study of 2000 did show a significant reduction in bone mineral accretion in boys on ICS in follow-up analysis (Kelly et al. 2008).

A summary of pediatric literature in 2016 concluded that ICSs seem to negatively impact BMD only at high doses and children may be at higher fracture risk as adults after years of high-dose ICS use. For this reason, regular monitoring of BMD in high-dose ICS-treated children may be appropriate (Skoner 2016a).

38.13 Effect of ICS on Cataracts and Glaucoma of the Eyes

Compared to HPA axis and growth studies, which were required as part of the FDA approval process, relatively few studies have addressed the short-term or long-term effects of ICS on the eyes.

38.13.1 Cataract Pathogenesis

Cataracts, opacities in the lens of the eye, are a leading cause of blindness, particularly in developing countries. Not all cataracts are the same; clinical classification is dependent on the location within the lens (anterior/posterior, capsular/subcapsular, cortical, or nuclear) or the nature of development (congenital, traumatic, metabolic, toxic, etc.) (Robb 1994). The most common cataract morphologies associated with ICS use (toxic in nature) are posterior subcapsular (PSC) and nuclear; they can range from mild visual significance to severe visual impairment (Gupta et al. 2014). These morphological types often require surgical removal because their location in the center of the lens can be highly visually disruptive. Beyond ICS is outside the scope of this chapter; however many other risk factors are associated with the development of cataracts including age, smoking, diabetes, refractive error, and many more (Cumming and Mitchell 1999).

38.13.2 Cataract Risk Modification by Corticosteroid

At the time of this writing, the etiology of PSC and nuclear cataract secondary to steroid use is unclear; however it is well documented that corticosteroid use is a leading risk factor for secondary cataract development. The mechanism of development has been proposed to include oxidative stress, metabolic disruption, osmotic stress, and related protein modification (Jobling and Augusteyn 2002). In addition, it is difficult to determine if there is steroid dose dependence and individual-based susceptibility related to cataract development.

In regard to osmotic stress and protein modification, it has been proposed that corticosteroids inhibit sodium-potassium pumps in the lens which allows for water to collect within lens fibers. This accumulation in the fibers is associated with changes in protein agglutination leading to opacification (Urban and Cotlier 1986; Karim et al. 1989). It has also been proposed that gene activation by corticosteroids leads to increased cellular proliferation with suppressed differentiation and effects on apoptosis and increased susceptibility to oxygen radicals (James 2007), causing oxidative damage to the lens fibers.

38.13.3 Cataract Clinical Studies

Systemic corticosteroids were first linked to the development of cataracts by Black et al. in 1960. While the association between systemic corticosteroid use and cataract development is well defined, the potential relationship with inhaled corticosteroids (ICS) is more controversial. Inhaled corticosteroids were first linked to cataracts via a case report by Kewley in 1980 wherein a 9-year-old girl developed posterior subcapsular cataracts on inhaled beclomethasone with minimal additional systemic steroids.

Several small population studies in the 1990s (Toogood et al. 1993; Simons et al. 1993; Abuekteish et al. 1995) suggested no correlation between ICS use and cataract formation in adult patients; however, works by Cumming and Garbe did show a dose and duration association with increased cataract prevalence (Cumming et al. 1997; Garbe et al. 1998). Cumming's retrospective Blue Mountains Eye Study looked at the prevalence of cataracts based on ICS use in 3,654 Australians and found that a cumulative lifetime dose of beclomethasone >2000 mg correlated with the highest prevalence of cataracts – particularly subcapsular cataracts (Cumming et al. 1997). It is notable that 2000 mg of beclomethasone is equivalent to just over eight and a half years of the maximum FDA-approved dose of inhaled beclomethasone. Garbe et al. retrospectively studied 3,677 patients seeking cataract extraction surgery and found that ICS

use for >3 years was associated with more than a threefold risk of requiring cataract surgery compared to the general population and also found that this risk was closer to 3.5-fold when patients used >1000 mcg/day of inhaled budesonide or beclomethasone for >2 years (Garbe et al. 1998). Notably this amount is in excess of the maximum FDA-approved dose.

There are numerous limitations to these studies including lack of prospective research, potential for recall bias in use of oral corticosteroids in conjunction with ICS, and the ages of the populations studied. Numerous meta-analyses have been attempted to better quantify this association. Gartlehner looked at both Cumming and Garbe's work as well as that of Jick et al., who retrospectively studied patients in the UK general practice database, and found that all ICS users had a small increase in lifetime cataract risk (RR = 1.3) compared to the general population but that age (40+ years) and the number of prescriptions for ICS increased this risk (Gartlehner et al. 2006; Jick 2001). Weatherall et al. conducted a similar meta-analysis in 2009 using several of the same datasets and found a dose-associated risk of cataracts following ICS use (approximately 25% per 1000 mcg/day) (Weatherall et al. 2009). A 2016 Inhaled Corticosteroids Safety Panel concluded that currently available research suggests an increased risk in lifetime development of posterior subcapsular cataracts, though it is unclear how specific ICS, dose, and treatment duration modulate this risk. They recommend routine monitoring for cataracts in adults on long-term or on short-term high-dose courses (Carr and Szefler 2016).

As cataracts are typically a disease of older adults, studies about potential impacts of ICS use in children are difficult to interpret. Numerous short-term (≤6 years) prospective studies on children have shown no association with cataract development (Nassif et al. 1987; Pelkonen et al. 2008; Simons et al. 1993; Szefler et al. 2000). The most well known of these is the Childhood Asthma Management Program Research Group (CAMP) study which followed 1,041 children aged 5–12 with mild to moderate asthma randomized to inhaled budesonide, nedocromil, or placebo and found that budesonide treatment leads to improved symptom control and found no statistical association with ICS use and cataract development over 4–6 years of monitoring (Szefler et al. 2000).

Further study, particularly long-term longitudinal research, is necessary to better determine if childhood use of ICS conveys increased risk for cataract development in adulthood or if only use in adulthood is associated with this risk. Routine cataract screening is not recommended for the pediatric population on ICS.

There is clear evidence that systemic corticosteroid use is associated with cataract formation, and numerous studies do link dose and duration of ICS use with increased risk for cataracts in the adult population. It is not known if there is a "threshold" dose or duration that predisposes patients or if there are differences based on which ICS is used. Even less is known for the pediatric population where long-term prospective study is warranted to better elucidate potential long-term risk.

38.13.4 Glaucoma Pathogenesis

Glaucoma is a major cause of irreversible blindness characterized by progressive optic neuropathy, typically (though not always) associated with increased intraocular pressure (IOP). The optic nerve is composed of over one million retinal ganglion nerve fibers, and damage that IOP or other factors create on retinal nerve axons translates to visual field defects and eventual blindness from complete loss of visual field. The increase in IOP is associated with the volume of the aqueous humor and its subsequent resorption via the trabecular meshwork (Wiggs et al. 1998). Increased IOP without abnormal examination findings (normal optic disk, visual field) is classified as ocular hypertension. In contrast, glaucoma does have changes to the optic disk and/or visual field and, in non-low-tension, the IOP can be >21 mm Hg (Nuyen et al. 2017). Risk factors for glaucoma include race, ethnicity, age, family history, and elevated IOP. Of these, IOP is the only modifiable risk factor for glaucoma. There is research

currently being done to understand the link between blood pressure, IOP and glaucoma. Growing evidence suggests blood pressure and its associated ocular perfusion pressure are key glaucoma risk factors. There is a positive correlation between blood pressure and IOP, furthermore low ocular perfusion pressure seems significantly correlated with glaucoma development (Leske 2009).

38.13.5 Glaucoma Risk Modification by Corticosteroids

As in the case of cataracts, it is unclear exactly how corticosteroid use interferes with normal ocular anatomical function. However, it is well-documented that corticosteroid use can cause secondary IOP spikes. It has been proposed that corticosteroids lead to changes in the trabecular meshwork system via cell enlargement and increases in glycoprotein in a way that limits outflow of the aqueous humor, and mimics changes seen in primary open-angle glaucoma (Johnson et al. 2012). A gene on chromosome one, trabecular meshwork-induced glucocorticoid response protein (TIGR/Myocilin), has been implicated (Stone et al. 1997; Wiggs et al. 1998).

38.13.6 Glaucoma Clinical Studies

The first reports of open-angle glaucoma or increased IOP thought to be associated with systemic (or topical) corticosteroids were published in the 1950s (Stern 1953; François 1954; Covell 1958). Studies in the 1960s suggested that some individuals have significant elevations in IOP (15+ mmHg) in response to topical use of betamethasone or dexamethasone, and those with more significant responses frequently had diabetes, high myopia, and prior diagnoses of open-angle glaucoma (Becker 1965; Marcus et al. 2012).

While the connection between systemic corticosteroids and ocular hypertension/glaucoma is frequently documented, any potential causative effect from ICS is controversial. Due to the potential genetic link, it is not surprising that some of the data linking ICS use with increased ocular hypertension and glaucoma found a strong association with family history of glaucoma. Mitchell et al. studied 3,654 Australians aged 49–97 in the retrospective Blue Mountains Eye Study and noted that positive family history is strongly correlated with glaucoma risk (2.6-fold) and that this risk increases in an ICS dose-dependent fashion (Mitchell et al. 1999). Garbe et al. found a moderately increased risk of developing glaucoma or increased IOP in a case-control study using high-dose ICS for at least 3 months, further underscoring the dose-dependent relationship, but was not able to determine potential familial associations and notably may have confounding risk associated with systemic steroid use (Garbe et al. 1997).

Several other studies found no relationship. Johnson et al. followed 42 ICS users for over 3 years and found no association with glaucoma development (Johnson et al. 2012). In the Rotterdam study, Marcus et al. prospectively followed 3,939 individuals aged 55+ years on various forms of corticosteroids an average of 9.8 years and found no association between any form of corticosteroid and glaucoma risk, and accounted for family history, but not dose. The authors do note that there may be an association with increased IOP that did not meet criteria for glaucoma (Marcus et al. 2012).

Several summary articles emphasize the importance of screening for increased IOP given the potential association with glaucoma in adults, particularly those with a family history and/or those on high doses (Bielory et al. 2006; Carr and Szefler 2016; Gartlehner et al. 2006; Irwin and Richardson 2006; Ye et al. 2017). However, there is no evidence of the association between ICS and glaucoma in children. Duh et al. studied 1255 individuals from age 6 years through age 70 for 20 weeks and found no increased risk of glaucoma (Duh et al. 2000). Alsaadi et al. studied 69 Saudi Arabian children aged 5–15 years old on fluticasone 250 mcg daily for at least 6 months and found no association with increased IOP (Alsaadi et al. 2012). Chang et al. followed 1,232 children aged 6 years or younger who used

ICS for just over 3 years and found a lower rate of glaucoma in the ICS-using population (Chang et al. 2017).

The relationship between ICS and glaucoma remains unclear, but there is enough data to suggest that routine IOP screening in adults with a family history and/or on a high-dose ICS is appropriate. There is no evidence to suggest that children are at increased risk of glaucoma from ICS and routine screening is not recommended. More research is needed to fully understand this association and to better define the most at-risk groups.

38.14 Short-Term Effect of INCS on Childhood Growth

The FDA approval process for INCS had similarities to that of ICS, including Phase 4 commitments for growth studies. For example, the FDA approved doses of the INCS-BDP (Vancenase AQ) for use in children in June 1996 based on lack of effect on HPA axis. The approval was contingent on Schering Plough's commitment to conduct a future Phase 4 study to evaluate the effect of INCS-BDP on the growth of children. Certainly, none was expected given the lack of HPA axis suppression and delivery into the nose, which produces much less systemic bioavailability than lung delivery (Daley-Yates et al. 2001). The results of that study were presented at the FDA meeting in 1998 and published in the year 2000 (Skoner 2000a) and were unexpectedly positive (a significant growth effect was detected).

Most of the currently available INCS have been tested for growth effects in industry-sponsored studies (Table 6), but only two (fluticasone furoate and triamcinolone acetonide) were tested using the rigorous design elements recommended in the FDA guidance for industry. Both studies detected small but statistically significant effects (Lee et al. 2014; Skoner et al. 2015). The latter study showed that the effect was detectable quite early and was evident within 2 months of initiating treatment (Skoner et al. 2015).

Curiously, INCS are now sold OTC in pharmacies despite opposition from national organizations (Friedlander et al. 2013). In particular, TAA is now available OTC to treat children and had a positive growth study when used at a dose of 1 spray per nostril qd. This was a clear indication that INCS-TAA had sufficient systemic bioavailability and activity to affect the growth process, but the same dose did not affect the HPA axis of children (Georges et al. 2014). The FDA decision to transition TAA from prescription to OTC sales was surprising in light of the growth effect, especially the decision to allow the indication down to the age of 2 years (only country in the world).

38.15 Use of Combination ICS and INCS

The FDA has not required pharmaceutical companies to conduct such studies because there are no "combination" products on the market (i.e., one device that would simultaneously deliver INCS to the nose and ICS to the lung). However, combination ICS and INCS therapy using separate devices is quite common in clinical practice and likely to produce bigger systemic side effects than the use of either ICS or INCS alone. One high-quality study has shed light on this issue using HPA axis suppression as the primary outcome (Zollner et al. 2012). A scatter plot of post-metyrapone ACTH versus the combined daily ICS and INCS doses showed a significant inverse relationship ($r = -29$, $p < 0.001$) in 143 asthmatic children. Dose dependency of the effect was evident. The authors concluded that two-thirds of children using ICS/INCS may have HPA axis dysfunction, that suppression may occur at low doses and especially with concomitant ICS and INCS use, and that children with poor adherence or obesity may be less prone to adrenal crisis.

38.16 Balancing Benefit and Risk

Studies have clearly shown that caution in the use of ICS in children is warranted and expected benefit must always be weighed against the risk of growth suppression when using FDA-approved doses and HPA axis suppression when using

Table 6 Key primary growth studies (prospective, randomized, double-blind, placebo-controlled, parallel-group) using *FDA-Approved* INCS doses in children with perennial allergic rhinitis

	Skoner 2000a	Schenkel et al. 2000	Allen et al. 2002	Murphy et al. 2006	Lee et al. 2014	Skoner et al. 2015
Sponsor	Industry	Industry	Industry	Industry	Industry	Industry
Number of centers	8	10	Multiple	28	77	81
Sample size (n)	100 (INCS 51)	98 (INCS 49)	150 (INCS 74)	229 (INCS 155)	373 (INCS 186)	299 (INCS 151)
Age (years)	6–9	3–9	3.5–9	4–8	5–8.5	3–9
Controls	Placebo (n = 49)	Placebo (n = 49)	Placebo (n = 76)	Placebo (n = 74)	Placebo (n = 187)	Placebo (n = 148)
Primary study outcome	Growth	Growth	Growth	Growth	Growth	Growth
INCS[a] used	BDP	MF	FP	BUD	FF	TAA
Daily INCS dose	168 mcg bid	100 mcg qd	200 mcg qd	110 mcg qd	110 mcg qd	110 mcg qd
Fixed INCS dose?	Yes	Yes	Yes	Yes	Yes	Yes
Duration of INCS use	1 year	1 year	1 year	76	1 year	1 year
Adherence method (% adherence)	Self-report (>80)	Self-report and Objective (≥80)	Self-report (>80)	Self-report (95–96)	Self-report and Objective (82–83)	Self-report (76–77)
Method used to measure height	Stadiometry	Stadiometry	Stadiometry	Stadiometry	Stadiometry	Stadiometry
Frequency of height measurement	Every 2 months	Every 4–13 weeks	Every 30 days	Every 3 months	Every 4 weeks	Every 2 months
Analysis method	Linear regression	Linear regression	Linear regression	Linear regression	Adjusted ANCOVA	Linear regression
Effect size	−0.9 cm ($p < 0.01$ vs. placebo)	No significant effect	No significant effect	No significant effect	−0.27 cm (statistically-significant)	−0.45 cm ($p = 0.01$ vs. placebo)

[a]*BDP* beclomethasone dipropionate aqueous, *MF* mometasone furoate aqueous, *FP* fluticasone propionate aqueous, *BUD* budesonide aqueous, *FF* fluticasone furoate aqueous, *TAA* triamcinolone acetonide aqueous

higher-than-FDA-approved doses. For example, the risk of growth suppression may not be acceptable in the mildest patients that have the least to gain from ICS therapy. Alternatively, the benefit-risk analysis is likely weighted much differently for children with more severe asthma who have more to gain from therapy.

Systemic side effects of ICS are dose-related. Therefore, the lowest effective dose should always be used. Doses should be reduced when possible, but the step-down dosing recommended in the asthma guidelines is not routinely performed in clinical practice (Rank et al. 2013). The methods for balancing the benefits and risks of ICS and optimizing steroid-sparing strategies have been reviewed (Skoner 2002).

For children and the elderly, the best approach is to start low and go slow, i.e., start with FDA-approved doses (Table 7) and increase the dose if necessary. The young and old are unique populations with unique susceptibilities to side effects. Children are not just young or little adults (Kearns et al. 2003), and elderly are not just old adults. Active and aggressive monitoring for systemic side effects, including changes in behavior, appearance (e.g., cushingoid), and growth

Table 7 FDA-approved ICS Doses[a]

ICS formulation	FDA approved inhaled Corticosteroid doses	
	Adult	Pediatric
BDP HFA-MDI	**Ages 12+ years** Initial dose 40–80 mcg BID Max dose 320 mcg BID	**Ages 4–11 years** Initial dose 40 mcg BID Max dose 80 mcg BID
BUD DPI	**Ages 18+ years** Initial dose 180–360 mcg BID Max dose 720 mcg BID	**Ages 6–17 years** Initial dose 180–360 mcg BID Max dose 360 mcg BID
BUD NEB INH	**Ages 9+ years** [b]initial dose 0.5–1 mg BID Max dose 1–2 mg BID	**Ages 1–8 years** [b]initial dose 0.25–0.5 mg BID Max dose 0.5–1 mg BID
CIC HFA-MDI	**Ages 12+ years** Initial dose 80–320 mcg BID Max dose 160–320 mcg BID	N/A
FLUN HFA-MDI	**Ages 12+ years** Initial dose 160 mcg BID Max dose 320 mcg BID	**Ages 6–11 years** Initial dose 80 mcg BID Max dose 160 mcg BID
FP HFA-MDI	**Ages 12+ years** Initial dose 88–440 mcg BID Max dose 440–880 mcg BID	**Ages 4–11 years** Initial dose 88 mcg BID Max dose 88 mcg BID
MF DPI	**Ages 12+ years** Initial dose 220–440 mcg qPM Max dose 440–880 mcg qPM	**Ages 4–11 years** Initial dose 110 mcg qPM Max dose 110 mcg qPM
MF HFA-MDI	**Ages 12+ years** Initial dose 100–200 mcg BID Max dose 200 mcg BID	N/A

[a]Based on information in Package Labels: *BDP* beclomethasone dipropionate, *BUD* budesonide, *CIC* ciclesonide, *FLUN* flunisolide, *FP* fluticasone propionate, *MF* momentasone furoate, *HFA* hydrofluoroalkane propellant, *MDI* metered dose inhaler, *DPI* dry powder inhaler, *NEB INH* nebulized inhalation suspension, *ICS* inhaled corticosteroid, *N/A* not approved

[b]During initial period of severe symptoms, may start with maximum dose and then reduce to initial dose for maintenance

percentiles (decreased height, increased weight), is clearly warranted when treating children with ICS and INCS.

38.17 Summary

FDA-approved doses of most ICS suppress the growth of children. Childhood ICS use produces an effect on final adult height.

FDA-approved doses in highly susceptible individuals or higher-than-approved doses in any individual can suppress the HPA axis subclinically or clinically and produce life-threatening adrenal crisis.

38.17.1 Systemic Side Effects of ICS Are Dose-Related

Even considering the unexpected growth effect from FDA-approved ICS doses, benefits outweigh risks at FDA-approved ICS doses for most individuals as long as monitoring for systemic side effects is frequent, regular, and accurate. In contrast, benefits may not outweigh risks for those with very mild disease who have the least to gain and most to lose from ICS therapy or in those using higher-than-approved ICS doses, in which cases even higher levels of monitoring may be warranted.

38.17.2 ICS Also Have Systemic Effects on Bone Mineral Density and the Eyes

The FDA approval process is very expensive for the pharmaceutical industry and produced valuable information about the efficacy and safety of ICS doses. Healthcare providers and educators need to become more familiar with the process and the results and use ICS and INCS carefully and wisely to assure the safety and well-being of children and adults.

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Subcutaneous Immunotherapy for Allergic Rhinitis and Asthma

39

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Abstract

Subcutaneous immunotherapy, a type of allergen immunotherapy, is an effective and disease-modifying treatment in patients who have suffered from allergic rhinitis with or without conjunctivitis and/or asthma and who demonstrate specific IgE antibodies to the relevant allergens. Indications of subcutaneous immunotherapy for respiratory allergies include patients who are poorly responsive to pharmacotherapies, not tolerable to medications because of side effects, and sometimes even considered for primary allergy prevention. Subcutaneous immunotherapy requires a buildup phase as the allergen content is increased until a therapeutic "desensitization" level is achieved and usually continues for 3 to 5 years. Randomized, double-blind, placebo-controlled studies have shown that subcutaneous immunotherapy is an effective treatment for allergic rhinitis and/or asthma. Even with newer therapies on the horizon, subcutaneous immunotherapy will continue to have an important role in the management of allergic diseases.

Keywords

Allergy · Allergic rhinitis · Asthma · Allergen immunotherapy · Immunotherapy · Subcutaneous immunotherapy

39.1 Introduction

Ever since hay fever, aka allergic rhinitis (AR), was first described by John Bostock in 1819, allergen sensitization has become recognized as a major role in rhinitis, conjunctivitis, asthma, atopic dermatitis, and other allergies including stinging insects (Hymenoptera), drug, and food (Ramachandran and Aronson 2011; Lin et al. 2016). These allergic diseases represent a substantial health problem in both developed and developing countries and have increased in prevalence over the past decades. Either of the two most common allergic diseases, AR or asthma, has affected approximately 8% of each pediatric and adult population in the 2015 US National Health Interview Survey (Summary Health Statistics for Hay Fever 2015; Summary Health Statistics for Asthma 2015). AR and asthma are frequent clinical diagnoses, but they may not be well controlled by standard management. Allergen immunotherapy (AIT), among all other available treatments for allergic diseases, is a unique remedy. AIT is composed of a series of allergen administration to an allergic individual over a defined period which results in decreased sensitization or even induced tolerance to the disease-causing allergens. At present, it is the only therapy known to not only modify the underlying allergic immune cascades but also lead to symptom mitigation, quality of life improvement, and overall medication reduction. The term allergen extract has also been replaced by allergen vaccine by the World Health Organization (WHO) to reflect that AIT is an immune modifier with proved long-term benefits (Bousquet et al. 1998).

This chapter reviews inhalant allergen subcutaneous immunotherapy (SCIT), a type of AIT, utilized to treat AR and asthma. Each following section covers a different SCIT aspect including,

but not limited to, indications, allergen and allergen vaccine characteristics, mechanisms, and management of adverse events. Sublingual immunotherapy (SLIT) on inhalant allergens and other specific immunotherapies for food or stinging insect hypersensitivity are covered in depth in other chapters throughout this book.

39.2 Allergen, Aeroallergen, and Atopy

The term "allergen" was previously used to define an antigenic substance that induces the production of specific IgE antibodies (Blumenthal and Fine 2014). However, this may generate two misunderstandings with such definition. First, not all individuals having specific IgE antibodies develop clinical symptoms. Second, an allergen response may not be limited only to IgE as it can be cell-mediated or other antibodies such as IgG-mediated. The more tailored definition of "allergen" is a type of antigen that causes an immunological hypersensitivity in which the immune system reacts to a harmless substance. Such immunological hypersensitivity is named as "allergy." While historically all the allergens are known to be proteins, there is a new allergen, galactose-alpha-1,3-galactose (often abbreviated as "alpha-gal" in the medical literature), which comes from a mammalian carbohydrate which can cause a delayed IgE-mediated allergy (Carter et al. 2017). This new finding suggests that medical terms in the allergy and immunology field may need to be adjusted to keep up with the times.

Inhalant allergens, i.e., aeroallergens, are all the allergens that precipitate respiratory allergies through inhalation. Common aeroallergens include pollens, mold spores, arthropod body parts and feces, and animals' dander, saliva, secretions, and excretions. Depending on different original sources, way of dispersal, and size of the particles, individual aeroallergen has its own distinct features. Their originating sources could be from visible plants or animals to a microscopic level such as house dust mites (HDM) or fungi. Aeroallergens are required to be sufficiently ample in the ambient air to trigger a sensitization and/or provoke a respiratory allergy (Sporik et al. 1990). Once the aeroallergens encounter with related body regions on a susceptible individual, they can trigger a variety of allergic diseases including allergic conjunctivitis, rhinitis, and asthma.

Another common term used in the allergy and immunology field is atopy. The word "atopy" was coined first to describe a specific type of sensitization state. Over the years, atopy has been defined as a personal and/or familial tendency to allergy according to the revised nomenclature of allergy by the World Allergy Organization (WAO) on the previous European Academy of Allergy and Clinical Immunology (EAACI) position statement (Johansson et al. 2004). Furthermore, atopy should be reserved to describe the genetic predisposition to common IgE-mediated allergic diseases, e.g., allergic conjunctivitis, rhinitis, asthma, and atopic dermatitis, and not be used until an IgE sensitization has been demonstrated by serum-specific IgE antibodies testing in vitro or by positive skin testing in vivo. Less common allergens such as drug or Hymenoptera are not considered to be atopy although genetic susceptibility may exist in the spectrum (Kim et al. 2010).

39.3 Indications

AIT should be considered for any patient who has demonstrated allergic symptoms along with specific IgE antibodies to clinically relevant allergens (Cox et al. 2011). It has been used in the treatment of allergic conjunctivitis, rhinitis, asthma, atopic dermatitis, Hymenoptera allergy, and, recently, food allergy. For Hymenoptera allergy, venom immunotherapy (VIT) is the treatment of choice other than insect prevention and as-needed epinephrine auto-injector (EAI) to dramatically decrease the risk of future systemic allergic reaction (SAR). Candidates for VIT include patients with moderate to severe SAR to Hymenoptera stings (Golden et al. 2017). On the other hand, an emerging success on food AIT trials has shed

light on future management as there are few treatment choices, same with Hymenoptera allergy, such as triggering food avoidance and EAI prescription (Sampath et al. 2018). Compared to Hymenoptera and food allergy in which the medical managements are limited, there is no absolute indication for SCIT in respiratory allergies. Allergen avoidance, patient education, pharmacotherapy, and device technique for sprays and inhalers all constitute the basic management for AR and asthma. SCIT for aeroallergen, when appropriate, should be utilized adjunctively with continuous environmental control and medical treatment.

Numerous randomized, prospective, single- or double-blinded, placebo-controlled clinical trials have demonstrated the effectiveness of SCIT for respiratory allergies (Cox et al. 2011). However, due to active allergen ingredients that are contained in the SCIT vial, there is as small but existing risk during SCIT to develop an immunotherapy-related SAR (IR-SAR). SCIT, therefore, always have to be balanced on a risk-benefit ratio. The relative indication of prescribing SCIT for respiratory allergies depends on the degree to which patient symptoms can be minimized by allergen avoidance, pharmacologic treatments, education, and adherence. The decision of initiating SCIT may also be influenced by patient's preference, adverse events to previous medications, and socioeconomic status (Cox et al. 2011). Symptomatic patients with AR and asthma may benefit from SCIT including those who are poorly responsive to pharmacotherapies, not tolerable to medications because of side effects, and sometimes even considered for primary allergy prevention. SCIT for AR has been shown to have persistent benefits after SCIT discontinuation and possible prevention of future asthma development (Cox et al. 2011).

In contrast, there is no absolute contraindication for using SCIT in respiratory allergies either. The relative contraindications proposed before considering aeroallergen SCIT include (1) uncontrolled or severe asthma, (2) past severe IR-SAR, (3) poor adherence to SCIT, (4) significant cardiovascular or pulmonary diseases, (5) pregnancy, and (6) status of mentally or physically unable to communicate clearly with the physician (Cox et al. 2011). These medical conditions may add more risk and reduce patient's ability to survive in the setting of a severe or life-threatening IR-SAR. Precautions to some of the special groups and other details are discussed in subsequent sections.

Herein lie the important step-by-step considerations for SCIT:

1. Allergic versus non-allergic condition.

The concept of AIT is to administer a certain amount of allergen content in order to desensitize a patient who is known to have allergic disease caused from the responsible allergen. It is a precise and individualized medicine designated for allergic diseases. For AR and/or asthma, physicians have to first determine whether patient's disease is an allergic versus non-allergic type or, in a real-world situation, that there is often an overlap in between, a predominant allergic versus non-allergic nature before implementing SCIT. In the advent of precision medicine, prior disease classes have been categorized into specific phenotypes and endotypes. Instead of debating the definition between phenotypes and endotypes, it is better to bond phenotype/endotype together as clinical disease characteristics almost always link to distinct pathological mechanisms. For the purpose of this chapter, a simplified way to separate disease patterns and justify which one will be more beneficial from SCIT is illustrated in Fig. 1. In order to maximize the treatment effect of SCIT, it is pivotal for physicians to determine the proportion of allergy component in each disease and select the right patient with an allergic dominance. The stratification may not be easy, but most allergic patients could be carefully identified based on a good history and physical examination supported by appropriate procedures and laboratory and radiology findings.

2. Relevant versus irrelevant sensitization.

Once a patient's disease was considered to have an underlying allergy in nature, physicians need to clarify what are the causative allergens for SCIT to be prescribed. This evaluation is

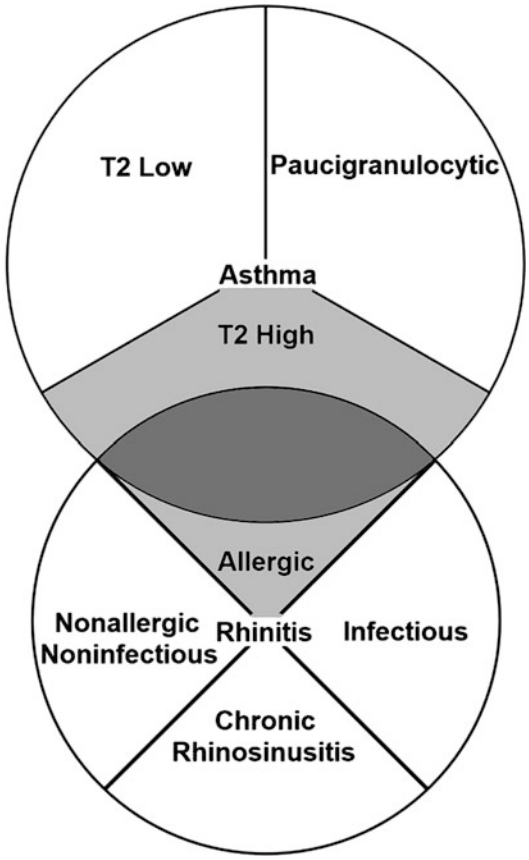


Fig. 1 A brief categorization of different types of allergic rhinitis and asthma. Gray areas denote a potential indication for aeroallergen immunotherapies which include subcutaneous and sublingual immunotherapy. In a real-world situation, patient may have an overlap pattern

usually done by an allergist/immunologist who performs a series of skin and/or serum testing to figure out the culprit inhalant allergen(s). Patient's age, influence by concomitant medications, and improper techniques or materials can all cause significant false positive or negative results (Bernstein et al. 2008). An allergist/immunologist is a physician specially trained to diagnose, manage, and treat allergies, asthma, and immunologic disorders including primary immunodeficiencies and, therefore, is experienced with performing the testing, interpreting the results, and treating any adverse events that may happen during the testing. As noted previously, SCIT can only be considered for a symptomatic patient who has done either skin or serum testing with demonstrated specific IgE antibodies to a clinically relevant allergen.

The hallmark of allergic diseases is the production of specific IgE antibodies, which is dependent on the allergen exposure and a collaboration between innate and adaptive immune systems. The typical sequence of events in allergy consists of an exposure to a low-dose allergen, activation of T and B cells specific for the allergen, production of specific IgE antibodies, and binding of the IgE antibodies to the mast cells, followed by repeated allergen exposure to trigger the activation of the mast cells. The stimulation of mast cells will result in release of various mediators and cytokines and cause immediate and/or delayed hypersensitivity reactions.

Percutaneous or intracutaneous skin testing is able to elicit an in vivo allergic response by applying a small amount of allergen on a picked or injected skin where mast cells are abundant in the dermis, respectively. Serum testing is a direct in vitro measurement of total and specific IgE antibodies. By using standard allergen extracts, there is a general agreement about 85–95% between skin and serum testing. Skin testing is more sensitive but less specific than in vitro serum testing (Heinzerling et al. 2013).

Despite a positive result in either a skin or serum testing confirming the presence of specific IgE antibodies, i.e., allergen sensitization, it does not always guarantee the presence of allergic symptoms or diseases. Allergen sensitization without correlative allergic symptoms or diseases is quite common and found to be in 8–30% of the population when performing a skin testing for aeroallergen (Bodtger 2004). Whether a positive result for an asymptomatic individual is a false alarm or herald sign of the future onset of allergy is a continuing debate. However, with appropriate history correlation, one study has shown that skin or serum testing can increase the predictive value to 97–99% compared with 82–85% of history alone for seasonal aeroallergens (Crobach et al. 1998). Physicians should always correlate the testing results to the pertinent clinical history which is the best way to verify a relevant or irrelevant allergen sensitization.

3. Responsive versus unresponsive to traditional therapy.

Many patients with allergic diseases receive pharmacological and/or non-pharmacological therapies, including, but not limited to, antihistamines, glucocorticosteroids, leukotriene modifiers, anticholinergics, bronchodilators, environmental control, nasal irrigation, and novel biologics. These therapies have all been shown to be effective in treating allergic diseases. Because of easy access to over-the-counter medications, oftentimes physicians have to manage patients who do not respond to conventional allergy therapies and feel strongly toward commencing SCIT. Nonetheless, SCIT is not considered a first-line therapy. Two major routes of administering aeroallergen AIT, SCIT and SLIT, are listed as add-on therapies in AR and asthma treatment guidelines in step 2, 3, or above, meaning in the moderate or severe disease category, due to their potential severe adverse effects (Bousquet et al. 2008; GINA Report 2018). Before SCIT is initiated, a failure control of symptoms with medical therapies should be documented unless primary allergy prevention is a concern (Craig et al. 1998). A physician should diligently assess a patient to make sure all other treatments are optimized.

For respiratory allergies, considerations to optimize treatment response are listed as the following:

(a) Have allergen avoidance and environmental control been evaluated and improved? Have skin and/or serum testing been done to identify possible trigger(s)?
(b) What are the characteristics (phenotype/endotype) of the patients' disease? Do current managements cover the whole disease spectrum especially if the patient has overlap pattern such as mixed rhinitis or asthma-COPD overlap syndrome?
(c) Is there any comorbidity of the disease that makes it refractory to management?
(d) Have the patient education and counseling been optimized including medication adherence, device technique, and allergen and/or irritant avoidance?
(e) Without creating a medical or economic burden for the patient, have all other alternative therapies been tried? For each patient having a different pharmacokinetic profile, is the medication dosage sufficient for the patient?

4. Adherence, cost, and preference.

Other important aspects to be incorporated into SCIT consideration include adherence, cost, and preference. AIT, whether SCIT or SLIT, is a series of allergen vaccine administration which at least have to be 2 years and at best to be extended to a total duration of 3–5 years in order to have long-term benefits (Cox et al. 2011). Both SCIT and SLIT are proven cost-effective. An analysis of SCIT in a US Medicaid population found a 12% reduction in direct costs following such therapy. SLIT similarly decreases healthcare expenditures (Hankin et al. 2008). While AIT is economically advantageous, adherence to both SCIT and SLIT is similar with equal percentages of patients remaining on AIT for a similar duration. A total of 11–77% of patients prematurely discontinue SCIT, whereas 22–93% do similarly with SLIT (Cox et al. n.d.). Patient preference should also be taken into account.

A brief summary for abovementioned SCIT considerations is shown in Table 1. The advantages of SCIT include reduction of medication burden, more flexible schedule than traditional therapy, and long-term vaccination benefit, while the disadvantages are potential adverse reactions, prolonged treatment time, and increased time and resources for the health facility. These once again highlight the importance of involving both patients and doctors in the decision of SCIT.

39.4 Allergen Characteristics and Vaccines

An allergen vaccine (AV) is a solution of extractable substances derived from source materials. Each vaccine is a complex mixture of natural biomaterials containing proteins, enzymes, glycoproteins,

Table 1 A summary for subcutaneous immunotherapy consideration and its relative indication and contraindications

Principle questions for subcutaneous immunotherapy (SCIT) initiation	
1. Is the disease allergic or allergy dominant? 2. Is the sensitization relevant to the disease? 3. Are conventional therapies optimized? 4. Does the patient prefer SCIT after a detailed discussion including benefits/risks, adherence, and cost?	
Relative indication	**Relative contraindications**
1. A diagnosis with allergic rhinitis with or without conjunctivitis and/or asthma **Plus** 2. Specific IgE antibodies to clinically relevant allergens demonstrated by skin and/or serum allergen testing	1. Uncontrolled or severe asthma 2. Past severe immunotherapy-related systemic allergic reaction 3. Poor adherence to SCIT 4. Significant cardiovascular or pulmonary diseases 5. Pregnancy 6. Status of being mentally or physically unable to communicate clearly with the physician

carbohydrates, and pigments. Real allergens, presumably the active components, may only contribute a small portion in an AV. The major difference between AVs and other pharmaceutical medications is that most AVs are made from natural products instead of being refined and synthesized in the laboratory. In terms of inhalant AVs, the sources may include, but are not limited to, pollens, fungi, and animal parts derived from their dander, saliva, secretions, and excretions. The AV variability in potency and product composition inconsistency could cause major consequences since both allergen skin testing and AIT depend on the quality of AVs. In the United States, the manufacturing and quality surveillance are regulated by the Center for Biologics Evaluation and Research, Division of Allergenic Products and Parasitology under the Food and Drug Administration. Some of the common AVs are available as standardized products including cat hair/pelt, short ragweed, HDM (*D. pteronyssinus* and *D. farinae*), grass species (Bermuda, Kentucky blue, perennial rye, orchard, timothy, meadow fescue, red top, and sweet vernal), and Hymenoptera venoms (yellow jacket, honeybee, wasp, yellow hornet, and white-faced hornet) (Cox et al. 2011). Standardization means that AVs, when provided by commercial manufactures, meet standards that ensure the same consistency of their biological activity, i.e., appropriate amount of allergen, in a given vial. The utilization of standard AVs has greatly increased the regularity of skin testing results andAIT effect. Therefore, when possible, standardized AVs should be used for preparation of both allergen skin testing and AIT (Cox et al. 2011).

To date, many AVs derived from natural sources are not yet standardized. It is probably not economically feasible or practical to standardize all available AVs (Fox and Lockey 2007). Nonstandardized AVs are labeled on the basis of relative concentration either by weight in grams per volume in milliliters or protein nitrogen units per milliliter. Neither parameters reflect the underlying and comparative information of the vaccine biologic potency, so lot-to-lot variations in allergen contents could be substantive. As for standardized AVs, they are often labeled as bioequivalent allergy unit which is based on a quantitative intradermal test method and/or the estimate amount of major allergen. In the following sections, a short overview for the production of each AV category is discussed. This is pertinent to not only allergists/immunologists but also general physicians as often the patients will inquire how the AVs are extracted from and processed. Newer AIT, such as recombinant, purified major allergen, and peptides are more modified products and will be discussed within the "Future trends" section.

39.4.1 Pollens

Pollens are a natural, biologically active substance of many plants. Transport of the male gamete, the pollen, to the female gamete, the ovary, accomplishes plant's reproduction. There are two routes for pollen dispersal. Wind pollinated plants are called anemophilous whereas insect pollinated ones are named entomophilous. Some plants may use both mechanisms. "Hay fever" or seasonal respiratory allergies are mostly caused by anemophilous plants with few exceptions.

Depending on the variety of plant orders, families, genera, and species, there are substantial pollen diversities. In order to cause allergy for a particular pollen, it has to fulfill certain requirements which was originally described by August A. Thommen: a. the pollen must contain an excitant of hay fever; b. the pollen must be anemophilous, or wind-borne; c. the pollen must be produced in sufficiently large quantities; d. the pollen must be sufficiently buoyant to be carried considerable distances; and e. the plant producing the pollen must be widely and abundantly distributed (Thommen 1931). While these principles continue to be the correct postulations, few terms may need further explanation and modification. The sentence "the pollen must contain an excitant of hay fever" may be adjusted as "the pollen must be easily eluted its substance on contact with water, or coated on respirable cytoplasmic particles" (Weber 2013). The other sentence "the pollen must be anemophilous, or wind-borne" should be replaced as "the pollen has to be dominantly anemophilous, or wind-borne."

Because of the size of the North America continent, the plant species in each biogeographic area vary dramatically. In total, there are ten major floristic zones defined in the United States (Weber 2014). Different environmental aspects, such as geography, climate, and human activities, significantly impact on botanical biodiversity and allergenicity as well as the quality of AVs. It is a difficult and complicated task to assure the consistency of not only the major allergens but the non-allergic ingredients in each vial as they may also modulate the pollen allergenicity. However, allergen manufacturing companies should keep consistency of each vial at their best. This is done through highly specialized activities ranging from pollen collection, storage, elution, extraction, and stabilization with commonly used glycerin, phenol, and/or human serum albumin (Codina and Lockey 2017). Additional validation is prerequisite for standardized AVs. It is a collaborative effort by botanical, engineering, and scientific professionals to produce a high-quality pollen AV without contamination and microorganism growth (Codina and Lockey 2017).

39.4.2 Fungi

Fungi are unicellular or multicellular heterotrophic, non-chlorophyll-containing eukaryotic organisms including molds, yeast, mushrooms, polypores, rusts, and smuts (Esch and Codina 2017). They exist as saprophytes or as parasites of animals and plants. The kingdom fungi is estimated to constitute more than 90% of the biomass on earth. Without fungi, life would not long remain possible. Fungi have developed a complex but unique ecology to inhabit the world by secreting digestive enzymes directly into their surrounding environment and absorbing the breakdown substrates. Their presence in the environment depends on climate, vegetation, and animal activities. Although fungi can be unicellular like yeast, most fungal spores typically germinate and grow thread- or tubelike filaments called hyphae. Hyphae often continue to grow by lengthening and branching into a network mass, known as mycelium, when food source and water moisture are abundant. Fungi can reproduce by generating spores either from meiosis or mitosis. Asexual mitotic spores are spawn from differentiated hyphae or conidiophores (anamorphic stage), while sexual meiotic spores are produced in various and species-specific structures such as ascus and basidium (teleomorphic stage). Then their spores are released into the environment mostly through airborne dispersal. Formerly, fungi classification was based on the sexual stage morphology, so lots of fungi which lack a clear sexual stage were assigned into an arbitrary category labeled as Deuteromycetes or Fungi Imperfecti. Over the last 20 years, fungi taxonomy has tremendously improved with DNA sequencing technique. This genetically determined taxonomy is paramount because it solves the issue with the category Deuteromycetes, clarifies other fungi-like but not fungi organisms such as slime molds (myxomycetes) and water molds (oomycetes), and predicts the allergenic tendency for fungi with close phylogenetic relationships (Levetin et al. 2016; Soeria-Atmadja et al. 2010). Three phyla, including Ascomycota, Basidiomycota, and Zygomycota, are major genera of fungi relevant

to respiratory allergies and known to disperse airborne allergenic spores.

Fungi could grow on almost any material if appropriate nutrition, moisture, and temperature suffice. Therefore, they are ubiquitous, and the spore number in the ambient air is far exceeding the pollen by hundred- to thousandfold. Airborne spores are present in outdoor air throughout the year. Many indoor fungi are comprised of outdoor fungi that have entered, and those grow and reproduce indoors (Baxi et al. 2016). The outdoor and indoor fungal flora may differ in species and colonies based on various environments and activities of building residents including pets. Indoor fungi are usually overlooked or unnoticeable unless there is water intrusion or plumbing leakage resulting in exaggerated fungi overgrowth. In terms of health impacts from fungi, there have been a lot of controversies in different aspects over the years. However, there is clear clinical evidence that exposure to molds and other dampness-related microbial agents increases the risks of developing respiratory and other diseases including, but not limited to, rhinoconjunctivitis, asthma, hypersensitivity pneumonitis, bronchopulmonary mycoses, fungal rhinosinusitis, atopic dermatitis, and local and invasive fungal infections (WHO Guidelines 2009). One of the most important messages is that although atopic individuals are more susceptible to fungi exposure, fungi-related adverse health effect can affect nonatopic population as well (WHO Guidelines 2009). Thus, fungi avoidance and mitigation should always be considered the first step before AIT due to health effect from fungi may not be limited to allergy. When fungi extracts are made, pure fungal seeds have to be cultured using specific and consistent media to minimize occurrence of natural mutation and validated with purity and identity tests. Once fungi strains can be harvested, multiple processes containing inactivation, filtration, centrifugation, and extraction are conducted to produce pure fungal extracts (Esch and Codina 2017). Compared to other AVs, quality of fungi vaccines is the most variable because of batch-to-batch material and metabolite discrepancy and research scarcity for major allergen identification (Esch 2004; Vailes et al. 2001). As yet, no fungal AVs have been standardized in the United States.

39.4.3 House Dust Mites

The term "HDM" has been applied to a large number of mites that are found indoors throughout the world. Mites are eight-legged and sightless tiny creatures related to ticks and spiders that live mostly in beddings, mattress, upholstered sofas, carpets, and any other porous material. They measure between 0.1 and 0.5 mm, so ones are visible with the aid of a microscope. Their primary food source is skin scales shed from humans and pets, but they could feed on other organic debris. The main species of HDM, i.e., *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, and *Euroglyphus maynei*, are under the family Pyroglyphidae. Other clinical relevant mites are the storage mites. For example, *Blomia tropicalis*, belonging to the family Echimyopodidae, are revealed in agricultural and household environments in tropical and subtropical areas such as Florida (Fernández-Caldas et al. 1990; Stanaland et al. 1996). HDM are not capable of biting and stinging humans nor considered to be parasitic, although recent evidence have shown that they are found infested on the skin of atopic dermatitis patients (Teplitsky et al. 2008). Their significance as whether they are on the skin or inside the house is due to the strong allergenicity contained in the mite bodies and parts, egg cases, skin casts, and fecal pellets. HDM are considered one of the major allergenic components in household dust that contribute to perennial allergic diseases. More than 80 mite allergens has been identified so far and classified into a total of 36 mite allergen groups (Carnés et al. 2017).

HDM prevention and avoidance measures are frequently emphasized on commercial. This is likely due to several distinctive characteristics of HDM. First, mites do not have the ability of searching and drinking liquid water, and they are entirely depending on the moisture of the surrounding environment. HDM numbers can be decreased significantly if the relative humidity is below 50% (Portnoy et al. 2013). Second, HDM have a fairly tight temperature range for appropriate growth. Either below 65 or above 80 F will limit their activity (Platts-Mills 2013). Third,

HDM are photophobic and they will burrow into fabric to escape from light. Therefore, it is possible to have tight fabric encasements to block both the physical infiltration of HDM and release of other allergenic components especially when HDM could not live on the surface of encasements because of their photophobic feature. It may look like there are multiple ways to decrease the HDM load indoors including dehumidification, freezing and heating, washing, covering, removing fabrics, high-efficiency particulate air (HEPA) filter vacuuming, and using acaricides; however, the cumulative scientific evidence for HDM prevention and avoidance is equivocal and controversial (Portnoy et al. 2013). There is probably not a simple method nor a cost-effective and practical way in HDM environmental control, which should be only considered as an add-on therapy. That being said, one of the most effective ways to treat HDM allergy is utilizing HDM AIT. Due to HDM AVs are standardized vaccines and made directly from live mites, they require more operations to ensure the vaccine quality. It is somewhat similar to fungal vaccine manufacturing that involves two major steps: the original culture of raw material followed by processing to final mite AVs. The final product needs not only delicate control of the culture environment and raw material extraction but further validation testing because it is a standardized vaccine (Carnés et al. 2017). HDM AVs in the United States are standardized based on $ID_{50}EAL$ (intradermal dilution for 50 mm sum of erythema) testing biologically and IgE enzyme-linked immunosorbent inhibition assay for reference comparison (Carnés et al. 2017).

39.4.4 Mammalian Animals

Household mammalian animals are one of the important indoor aeroallergens worldwide. It is estimated around 70% of the families in the United States to have at least one or more pets in which cats and dogs are the most common ones (American Pet Products 2017). Common mammalian animals known to contribute to sensitization and respiratory allergies are cats, cattle, dogs, horses, pigs, rabbits, and rodents. Occupational sensitization and allergies are also a well-known problem among laboratory employees. It is not unusual to consistently detect mammalian animal aeroallergens, especially cats and dogs, in homes with no household pets and public facilities (Zahradnik and Raulf 2014). This identification not only confirms the known fact that allergens from cats and dogs are sticky enough to adhere to clothing but suggests that exposure to mammalian animal allergens may come from indirect contact. Notably, sensitization to rodents can occur in different situations. It can happen in home as an increasingly popular household pet, inner-city residence as pests, and laboratories as experimental animals. Asthma severity is associated with mouse sensitization in inner-city children (Pongracic et al. 2008; Grant et al. 2017). The exposure routes are the same with other aeroallergens that include respiratory tract, conjunctiva, and skin contact.

Unlike pollens and fungi, it may be more practical to implement allergen avoidance in HDM and pet allergies. However, the efficacy of allergen reduction in either HDM or mammalian animals is limited and should only be considered only as an adjunctive therapy. There are multiple ways in terms of lowering indoor mammalian animal allergens that involve pest control for rodents, frequent pet washing and cleaning, area restriction for pet animals, and the usage of HEPA filters (Portnoy et al. 2012; Phipatanakul et al. 2012). Compared with HDM, removal of the pet animal is a possible, curative, and ultimate resort to solve the issue although oftentimes this is not realistic. Even after removal of a pet animal in residence, it could take up to 4 to 6 months for animal allergens to decrease at clinically insignificant levels as these allergens can attach to fabrics by electrostatic charges and become resistant to usual cleaning methods (Wood et al. 1989). It is also worth to mention that hypoallergenic animals, despite often appearing on commercials, do not exist (Lockey 2012). Among a variety of sources for mammalian animal allergens, the major ones are derived from animal dander, which by definition is shed skin flakes that may contain hair, feathers, and fur. More importantly,

skin is an essential organ across all mammalian animals. While it is possible for commercial breeders to claim certain breed produces less allergens due to small body size, long hair cycle, and low tendency to shed and thus is entitled "hypoallergenic," there is no proven evidence showing that any relative lower level of allergen exposure is significantly enough to be transformed into a lower rate of allergy development. Paradoxically, allergen amount may be even higher in so-called "hypoallergenic" animals, and high levels of animal contact may introduce to clinically allergen-specific tolerance (Vredegoor et al. 2012; Woodfolk 2005; Renand et al. 2015).

Mammalian animal AVs may be a good alternative to household members who are allergic to their pets if removal is not possible. Most manufacture companies in the United States use dander, pelt, and epithelia from diverse animals as raw materials followed by individual species-specific process to the final product. Special precautions for the raw material must be taken to avoid any potential harm to human health. Other than usual prevention for bacterial and fungal contamination, certain peculiar infections such as external parasites and transmissible spongiform encephalopathies, also known as prion diseases, have to be examined vigilantly by a certified veterinarian before collection (Fernández-Caldas et al. 2017). Currently, there are no standardized mammalian animal AVs except cats. Dog extracts are not well standardized owing to lack of vaccine potency and dog allergen diversity. Besides allergen avoidance, pharmacological intervention, and AIT, surfacing evidence has demonstrated that early exposure from farm animals to urban pests could be related to a lower risk of developing allergy (Konradsen et al. 2015; O'connor et al. 2018). However, a real sensible way to actualize this "hygiene hypothesis" remains to be elucidated.

39.5 Pathophysiology

The definition of vaccine is a product that stimulates a person's immune system to produce immunity to a specific disease and protects the person from that disease. Similarly, AIT has the immune modification effect for each individual extract corresponding to specific allergen and is recognized as a vaccine by WHO in 1998 (Bousquet et al. 1998). Nonetheless, there are differences among allergen versus conventional vaccines. The primary goal for conventional vaccines is to stimulate and/or boost immune response to a pathogen as in antibody production and immunological memory, whereas AVs aim to transform and/or suppress immune reaction to an allergen by modulating specific IgE antibodies and allergen-specific T cells. Both allergen and traditional vaccines are antigen specific.

For respiratory allergies, airway mucosa is exposed to allergens through inhalation. Upon contact and infiltrate through the mucosa, allergens bound to allergen-specific IgE antibodies which cross-link with sensitized mast cells and basophils. Once mast cells and basophils are activated, they release various preformed and newly synthesized mediators and cytokines that provoke symptoms and trigger further allergic immune cascades. The features for allergy symptom are pruritus, vasodilation, increased vascular permeability, mucus secretion, and for lower airway prominently, smooth muscle contraction. These responses, especially immediate reactions, may be considered as an original self-defense system to protect individual from potential exposure to hazardous substance; therefore, the body threshold for stimulation is set at a relative low antigen level. However, this safety net may turn into pathologically allergic when having exaggerated responses to a harmless molecule. In many patients, the early response could be followed by a late-phase response characterized by multiple cell attraction including eosinophils, neutrophils, activated T cells, and macrophages. The recruitment and content release from these cells are responsible for prolonged inflammation and tissue damage.

Dosage of SCIT, in contrast, is approximately 100 times of the estimated maximal annual exposure to a natural allergen (Larsen et al. 2016). This quantitative difference will elicit intense immune effect through immune deviation and tolerance. An important observation is that the decrease of mast cell and basophil sensitivity and tendency for

degranulation could take place in early SCIT stage and lead to the inhibition of both the immediate and delayed responses in the conjunctiva, skin, nose, and lungs. In other words, a reduction in mediators and cytokine release from mast cells and basophils can prevent further inflammation and cell recruitment. Following initial desensitization of end organs with SCIT administration, changes in the cellular and humoral responses ensue (Blumenthal and Fine 2014; Cox et al. 2011).

Allergic patients have increased numbers of allergen-specific CD4+ helper type 2 T (Th2) cells in the serum, but normal levels of antigen-specific CD4+ helper type 1 T (Th1) cells and CD4+ CD25+ regulatory T cells (Frew and Smith 2016). Commonly recognized major alternations for both humoral and cellular immunity following a successful SCIT are listed as below:

- **Cellular immunity.**
  1. An increase of regulatory T cell numbers and their inhibitory cytokines.
  2. A reduction of Th2 cell responsiveness to specific allergen and an immune deviation toward Th1 cell subset.
- **Humoral immunity.**
  1. An elevation of allergen-specific IgA and IgG levels, particularly IgG4 isotype.
  2. An initial rise of allergen-specific IgE level followed by a gradual decline.

There are several points to be noted. First, the abovementioned immunologic changes do not happen in sequence but rather overlap and interact with each other simultaneously. Second, the immune modification is complex, and therefore, the exact mechanism is difficult to be put together and fully depicted as a whole picture by discrete observational studies. However, the succinct concepts are immune deviation and tolerance (Cox et al. 2011). Immune deviation is a term indicating a modification of immune response to an antigen exposure in contrast to immune tolerance which is a state of unresponsiveness of the immune system to previous reaction-eliciting antigen. In both situations, regulatory T cells appear to be the pivot. SCIT has been shown to induce regulatory T cell releasing key cytokines including interleukin (IL)-10 and transforming growth factor-β (Jutel et al. 2003). The presence of such regulatory cytokines has been described to decrease B cell antigen-specific IgE but increase in antigen-specific IgA and IgG4 production, induce expression of Th1 cell response (producing interferon-γ) while suppressing Th2 cell cytokines (producing IL-4, IL-5, and IL-13), and prevent long-term inflammation and inflammatory cell recruitment such as eosinophils (Akdis and Akdis 2015). A simplified cell-to-cell interaction during SCIT is represented in Fig. 2. Despite being implemented for over a century, the exact SCIT pathophysiology for its clinical efficacy is continually being elucidated.

Even with observed correlation between post-SCIT immune alterations and clinical improvement, no distinctive immunological biomarkers have been proven useful for prediction of responsiveness, risk of adverse events, and periodic monitoring. Likewise, the immune deviation and tolerance induced by SCIT should not be considered as a complete immunological transformation, nor a total elimination of allergies either symptomatically or histologically. Besides the risks for having IR-SAR from direct allergen injection, SCIT seems to be safe in terms of their immunological amendment. To date, there is no definite cause-and-effect relationship established between SCIT and its theoretical probability of precipitating autoimmune diseases from circulating IgG4 immune complex, immunosuppression from regulatory T cells, and helminth infections from Th2 cell deviation. If indeed there is a cause-and-effect relationship, as noted in anecdotally reported cases, the occurrence of such immune complications caused by SCIT administration is extremely rare (Cox et al. 2011; Randhawa et al. 2007; Sánchez-morillas et al. 2005; Branco-ferreira et al. 1998; Phanuphak and Kohler 1980; Bunnag and Dhorranintra 1989).

Immunological effects for both SCIT and SLIT are similar, but the site for allergen uptake is in the skin or oral mucosa, respectively. There are also other routes of giving AIT such as intralymphatic and oral immunotherapy. The above section is

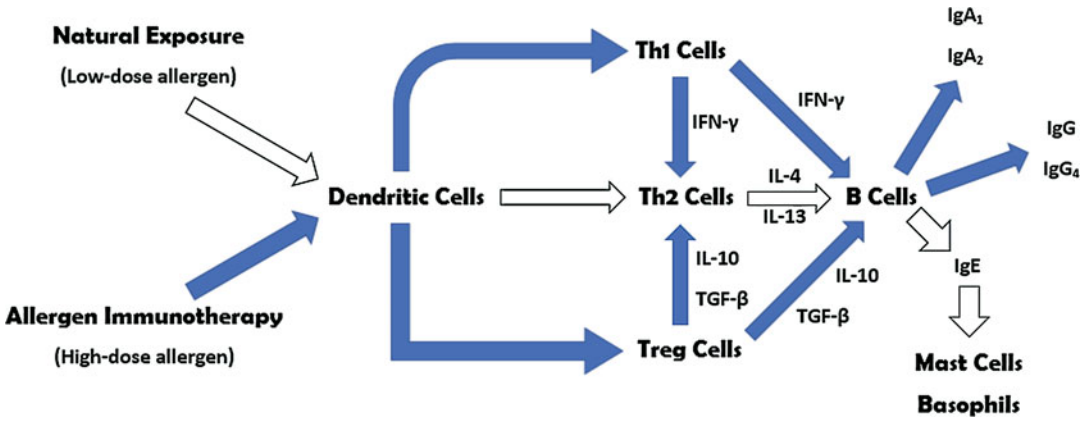


Fig. 2 A simplified cell-to-cell interaction in allergy versus allergen immunotherapy. White and blue arrows denote allergy- and immunotherapy-related immune pathway, respectively. Abbreviations: Th1 cells, helper type 1 T cells; Th2 cells, helper type 2 T cells; Treg cells, regulatory T cells; IL, interleukin; TGF-β, transforming growth factor-β

focused on SCIT as a fundamental example. Differences and details among other routes of AIT are discussed elsewhere in a latter section or chapter.

39.6 Efficacy

Many well-designed studies, systemic reviews, meta-analyses, and written guidelines have attested AIT as an effective treatment for allergic airway diseases. In this section, the efficacy of SCIT in two major allergic airway diseases, AR with or without conjunctivitis and asthma, is discussed. It is worth to remind that both SCIT and SLIT have been demonstrated to be equally beneficial in AR and asthma, yet SCIT is more studied than SLIT. There is insufficient evidence to conclude which one is more efficacious.

39.6.1 Allergic Rhinitis

SCIT can achieve multiple clinical improvements in AR with or without conjunctivitis such as in reducing nasal and ocular symptoms, decreasing total medications, enhancing quality of life, delaying disease progression, and even preventing new sensitizations (Ross et al. 2000; Jutel et al. 2015; Burks et al. 2013). However, not all categories in SCIT, e.g., fungi, could provide sufficient data to support their efficacy, and the degree of improvement should not be considered to be universal in all treated patients (Helbling and Reimers 2003). Depending on the different research populations, method designs, and primary outcomes, there may be substantial heterogeneity among studies, further affecting the systemic reviews and meta-analyses. Different AVs may also lead to various clinical outcomes due to quality and quantity of particular allergens. Standardized AVs are less differing compared to nonstandardized ones. Each specific category of AVs is discussed separately in the following sections.

39.6.2 Allergic Asthma

Compared to AR, data supporting SCIT in asthmatics are less robust. According to the Global Initiative for Asthma (GINA) report updated in 2018, the efficacy of AIT, including both SCIT and SLIT, in asthmatics is demonstrated but limited (GINA Report 2018). The reasons are that the efficacy data are extrapolated from many studies conducted primarily for AR and not asthma, other primary asthma studies but only involving mild asthmatics, and scant studies compared AIT with pharmacotherapies and/or used standard outcomes such as asthma exacerbations. It is

concluded that the potential benefit of SCIT usage in an asthma individual who has prominent allergy and allergen sensitization(s) must be weighed against the risk of adverse events, adherence, and cost to the patient and health system (GINA Report 2018). The other systemic review and meta-analysis has demonstrated that AIT may reduce short-term symptoms and medication scores and improve quality of life and allergen-specific airway hyperreactivity with modest increased risk of systemic and local adverse events in allergic asthmatics (Dhami et al. 2017). A report from the Agency for Healthcare Research and Quality also endorses that SCIT may reduce quick-relief and long-term control medications, improve lung function and quality of life, and have glucocorticosteroid-sparing effect. Local and systemic allergic reactions are frequent but infrequently required a change in treatment with rarely reported life-threatening adverse events including anaphylaxis (Lin et al. 2018).

39.6.3 Pollens

Patients with seasonal AR typically have symptoms in specific season corresponding to pollination of different plants which they are allergic to. However, there are exceptions in subtropical or tropical areas where pollination from a single plant may be year around. The allergic culprits are commonly identified from detailed clinical history and confirmed by skin or serum testing with rarely utilized nasal or bronchial provocation challenge for AR and asthma, respectively. Many patients have coexisting AR and asthma. In terms of efficacy, the best evidence for SCIT is in pollen allergy including ragweed, grasses, mountain cedar, *Parietaria*, and birch (Nelson 2013). Compared to year-round SCIT, it deserves to mention that, for patients with clear seasonal symptoms, there are threeSLIT tablets approved by FDA for preseasonal treatment 3–4 months prior to the pollen allergy season. They are Oralair® (Stallergenes), which has five northern grass pollen; Grastek® (Merck), which has timothy grass pollen; and Ragwitek® (Merck), which is for the short ragweed (Oralair 2014; Grastek 2016; Ragwitek 2016). In the GRASS randomized clinical trial, both timothy grass SCIT and SLIT were shown to have short-term benefit when compared to placebo, but the long-term benefit was not observed due to short-term treatment, which may indicate at least more than 2 years of either SCIT or SLIT treatment to see a prolonged protection. In the same study, comparison between SCIT and SLIT cannot be concluded because of insufficient power (Scadding et al. 2017).

39.6.4 Fungi

Fungal spores in the air were known to cause asthma exacerbations and epidemic asthma outbreaks (Pulimood et al. 2007; Grinn-gofroń and Strzelczak 2013). Unfortunately, there are substantial obstacles and controversies in assessing efficacy in fungal SCIT with the substantial problem coming from the quality of nonstandardized fungal AVs. Despite the difficulties, there are double-blinded, placebo-controlled SCIT studies with relatively stable fungi extracts such as *Cladosporium herbarum* and *Alternaria alternata* that have reported to have some efficacy in treating AR and/or asthma (Malling et al. 1986; Horst et al. 1990). There is essentially scant or no double-blind, placebo-controlled study in evaluating for other fungal extracts so the presumptive advantage of administrating fungal SCIT is mainly extrapolated from *Cladosporium* and *Alternaria* studies. Another often overlooked concern is that fungi are well-known to induce toxic, nonatopic, and mixed diseases like organic dust toxic syndrome, hypersensitivity pneumonitis, and allergic bronchopulmonary aspergillosis, respectively. It is prudent to rule out other diseases caused by fungi and avoid worsening outcomes by immune deviation before initiation of fungal SCIT.

39.6.5 House Dust Mites

HDM sensitivity has become prevalent because of considerable time that people stay indoors nowadays and been implicated as a risk factor for developing AR and asthma. However, unlike

seasonal allergies, the relevance or importance of HDM sensitization in a continually symptomatic patient is sometimes hard to be determined as other perennial allergens often coincide, including rodent, cockroach, fungus, and even mammalian animal if there is a pet animal. Fortunately, HDM extract is a standardized AV, and convincing results from clinical efficacy trials of HDM SCIT in both AR and asthma have been demonstrated. Patients receiving HDM SCIT are found to have a response reduction in HDM nasal and bronchial challenge, decrease in symptoms, and amelioration of late-phase reaction following bronchial challenge (Malling and Bousquet 2014). One study also reported inhaled glucocorticosteroid-sparing effect in HDM SCIT treating patients compared to placebo group (Blumberga et al. 2006). Besides AR and asthma, HDM SCIT has shown additional benefit in treating atopic dermatitis with reducing dermatitis scoring and medication use (Werfel et al. 2006).

In March 2017, there is an alternative way for HDM SCIT, a SLIT tablet, ODACTRA™, approved by FDA as a once daily tablet for HDM-induced allergic rhinoconjunctivitis in adults (Odactra 2017).

39.6.6 Mammalian Animals

Sensitizations to domestic pets are associated with respiratory allergies, and affected patients can often be confirmed based on clinical history. Several controlled studies have demonstrated that cat SCIT for dander-allergic asthmatics who do not have cats at home is effective in increasing the threshold for bronchial challenge and reducing symptoms after cat dander exposure in a challenge room. More data are needed for nonstandardized dog SCIT (Haugaard and Dahl 1992; Varney et al. 1997). Additionally, clinical efficacy of cat and dog SCIT for pet owners remain to be confirmed.

39.6.7 Mono- Versus Multi-Allergen

From an immunology point of view, it is possible to give multiple traditional vaccines simultaneously and achieve each disease protection, and, theoretically, the similar effect should apply to SCIT as well. Nonetheless, efficacy for multi-allergen SCIT is controversial. Most of the double-blind, placebo-controlled studies that have demonstrated efficacy of SCIT in AR and asthma were conducted with single AV, while few studies investigated multi-allergen SCIT. Among those few studies, both the heterogeneity of the trials and the negative outcomes in some studies have made it difficult to convincingly document the advantage or disadvantage to use multi-allergen SCIT (Cox et al. 2011). The deep discussion with the potential methodological pitfalls or bias into the positive and negative studies is beyond the scope of this chapter, but there are several important factors to be considered. First, comparing to traditional vaccination that gives individual vaccine at different sites, the trait of multi-allergen SCIT is to mix several AVs into a single vial which is to be drawn to give a single injection at each time, and therefore, there may be a diluting effect by mixing the extracts and lowering the dose of each allergen below the optimal threshold. Second, AVs with enzymatic activities, especially insects and fungi, should be separated from other AVs because of mutual degradation. Because of the difficulties interpreting the results, there are nationwide practice variations in the usage of multi-allergen SCIT. The typical SCIT prescription in the United States is multi-allergen based in which the Allergen Immunotherapy: A Practice Parameter Third Update (AIPP), prepared by a joint task force from the American Academy of Allergy, Asthma, and Immunology (AAAAI); American College of Allergy, Asthma, and Immunology (ACAAI); and Joint Council of Allergy, Asthma, and Immunology, has not recommended against multi-allergen SCIT (Cox et al. 2011), whereas in Europe, mono- or oligo-allergen SCIT is a more common practice of both the Guideline on Allergen Products: Production and Quality Issues from European Medicines Agency and Allergen Immunotherapy Guideline from EAACI that have recommended only homologous allergens that are taxonomically related, for example, a mixture of grass AVs, can be mixed (European Medicines Agency 2008; Roberts et al. 2017).

39.6.8 Disease Prevention

Although AR and asthma control can be achieved in most patients, there is no known cure. Primary prevention of any disease, including AR and asthma, is ideal. Both SCIT and SLIT have demonstrated to be successful therapies in respiratory allergy modification. As a result, they have been studied for potential prevention of new sensitization and asthma development. From a 2017 systemic review and meta-analysis, there are total of six and two randomized controlled trials for short- and long-term prevention of new sensitization identified, respectively (Halken et al. n.d.). The studies comprise three low (Zolkipli et al. 2015; Garcia et al. 2010; Szepfalusi et al. 2014), one moderate (Pifferi et al. 2002), and two high (Marogna et al. 2004; Moller et al. 2002) risks of bias clinical trials for short-term sensitization prevention in contrast to one moderate (Limb et al. 2006) and one high (Dominicus 2012) risk of bias trials for long-term sensitization prevention. Due to varied study quality, allergens, and vaccine formulation, these randomized controlled trials have shown inconsistent results. Even though the meta-analysis demonstrated benefit in short-term risk reduction of new sensitization, the overall risk reduction becomes negative excluding the two high risks of bias studies (Halken et al. n.d.). Nevertheless, data in preventing development of asthma in AR patients have shown good outcomes. Within a total of six randomized controlled trials studying asthma prevention effect up to 2 years post AIT, the systemic review and meta-analysis have demonstrated a significant asthma prevention effect in AR patients. Additionally, a subgroup analysis of utilizing either SCIT or SLIT favors more in pediatric versus adult population (Halken et al. n.d.). Long-term asthma preventive effect could not be seen but this may due to strict diagnostic criteria for primary outcome (Valovirta et al. 2011, 2017). In summary, there is no good evidence to conclude the usage of SCIT for both short- and long-term new sensitization prevention as immune deviation and tolerance might be more allergen-specific, but some positive data, even though in high risk of bias, suggest that a small group may attain benefit and the consideration should be a case-by-case scenario. There may be good evidence of implementing AIT in pediatric AR group for asthma prevention but multiple facets, including risks, adherence, and cost, need to be evaluated to reach an agreement between patients and physicians.

39.7 Beginning of Immunotherapy

In view of the decision-making as who will be beneficial from SCIT (previously discussed in Sect. 3), along with the complexity of appropriate dosage range and preparing and mixing for each relevant AVs, it is clear that the prescription of AITshould be made under physicians with special training in allergy and immunology. The AIPP states that the physician prescribing AIT should be trained and experienced in prescribing and administrating AIT, which is based from patient's clinical and allergen exposure history and the results of either in vitro or in vivo testing for specific IgE antibodies (Cox et al. 2011). Instead of going deeply through how to write AIT prescription, mix proper extracts, and make a tailored schedule, for the purpose of this section, the aim is to convey important issues of what should be concerned for a patient before and during SCIT offered by an allergist/immunologist.

1. What is the indication?

As mentioned earlier, it is noteworthy to emphasize again the necessity of a clear indication to initiate SCIT. The risk of having a SAR or even potential life-threatening anaphylaxis is existing across SCIT although it can be minimized. A detailed consultation between both a patient and physician and an informed consent should be conducted and obtained. All the other aspects of AIT such as preference, adherence, and cost should be co-evaluated and achieved mutually at best.

2. Which route is chosen?

Currently there are FDA-approved SCIT liquid extracts and four SLIT tablets. Both SCIT and SLIT have demonstrated efficacy as a single-allergen therapy. However, multi-allergen immunotherapy may only be reasonable and limited with SCIT injections. While it may be commonly seen in some practice to use multi-allergen SLIT drops, which is to use mixed SCIT liquid extracts through sublingual route, this is not a FDA approved treatment. The data on multi-allergen SLIT drops are scant and the results are mixed (Marogna et al. 2007; Moreno-Ancillo et al. 2007; Swamy et al. 2012; Amar et al. 2009). Hence, both SLIT drops and tablets are considered to be single- or at best oligo-allergen-based immunotherapy. Therapeutic effect and proper dosage of SLIT drops and tablets for multi-allergen remain to be explored (Maloney et al. 2016; Greenhawt et al. 2017).

3. What is the schedule?

There are two phases in SCIT: the initial buildup and maintenance phase. During the buildup phase, patients get incremental dosage and/or concentration of the AV at each injection. Once patients reach the effective dosage target, they are switched to the maintenance phase which mostly is one injection per month and stay on the same dosage over a period of time. Generally speaking, patients need to be on the maintenance therapy for at least 3 to 5 years in order to have a long-term protection benefit (Cox et al. 2011). In terms of the buildup phase, there are three types of injection schedules, including conventional, cluster, and rush immunotherapies. The conventional schedule contains injection one to three times a week. This is consistent with the AV package insert in which it indicates a weekly schedule and patients usually reach their maintenance dose within 3 to 6 months depending on the initial starting dose and adverse events during the buildup phase that may need schedule adjustment. Alternatively, the cluster and rush schedule can be used to accelerate the buildup phase. A cluster immunotherapy schedule begins with SCIT administration one or two times a week with each time two or more injections are given at a 30-minute interval to achieve maintenance dose as brief as within 4 weeks. For a rush or even a faster ultra-rush immunotherapy schedule, patients are given SCIT at a regular interval but intense schedule to reach the therapeutic maintenance dose within from hours to days. The advantage of fastened schedules is that they permit patients to complete the buildup phase more rapidly than a conventional protocol, but either cluster or rush SCIT has more risk of causing a SAR (Cox et al. 2011). Patients should be fully explained with the risks and benefits of accelerated schedules, premedicated before injections, and monitored closely during the buildup phase. Antihistamines, leukotriene modifiers, and other drugs have been reported to be useful as premedications (Nielsen et al. 1996a; Hejjaoui et al. 1992; Portnoy et al. 1994). Management for adverse events during both buildup and maintenance phase will be discussed subsequently in this chapter.

4. What allergen vaccine(s) is prescribed?

While allergists/immunologists are usually the physicians who select and prescribe the SCIT, it is also important for general physicians to know the rationale of how allergists/immunologists or other doctors who are specially trained and experienced in SCIT choose the allergen extracts. First, a prescribing physician must obtain a detailed clinical history, confirm with the appropriate testing, and identify the correct patient to receive SCIT. The corresponding allergens contributing to seasonal or perennial allergies may vary substantially depending on regions of different climate, geography, and indoor environment. For instance, in a patient who has typical seasonal allergies, his/her testing results should correlate with particular season such as tree for spring, grass for summer, and weed pollens for fall. Similarly, inner-city subjects with perennial allergies should be evaluated for cockroach and/or rodent allergies. Second, when possible, standardized AVs should be utilized to prepare the AIT regime, which include a number of grass pollens, short ragweed, HDM, cat

hair and pelt, and Hymenoptera venoms. The advantage of choosing standardized extracts is that their allergen content and activity are much more consistent, and therefore both retaining of therapeutic effect and reduction of adverse events could be accomplished. Third, cross-reactivity and enzyme activity have to be considered when multiple AVs are mixed for SCIT. Allergen cross-reactivity is the elicitation of same or similar patient's immunologic response to a single or multiple allergen(s) which share the overlapped or similar biochemical structure. It is not advisable nor necessary to include the AVs that share significant cross-reactivity due to undesirable dilution of other allergen extracts and unwanted risks of SAR from too much of the same/similar allergen constituents. Manufacturing companies may offer mix of the compatible pollen species that belong to the same or different genera and, ideally, prepare extracts based on cross-reactivity to further assist physicians in selecting the most appropriate AVs for diagnosis and treatment. Likewise, AVs for respiratory allergies including cockroaches and fungi should be separated from others due to their proteolytic enzyme that can degrade other allergenic proteins (Grier et al. 2007). Other studies have shown that pollens, HDM, and cat allergens could be mixed together (Esch 2008). If high proteolytic AVs are required, it is necessary to prepare two or more vials and give separate injections to assure the therapeutic dose of each allergen and avoid extract-to-extract interactions. Allergen cross-reactivity and mixing compatibility among different species are represented in Table 2.

39.8 Precautions

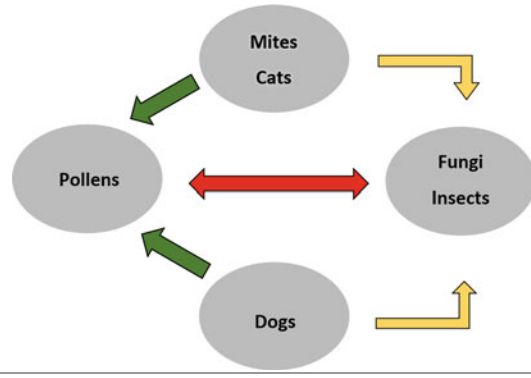
Since no single AV is considered completely safe for an allergic individual, a general layer of precaution should be applied to every patient on AIT. SCIT should be administered only by a trained personnel who is sophisticated in administrating injections, adjusting dose, and managing adverse events appropriately. An established protocol at the office or hospital clinic for managing different kinds of adverse event is prerequisite, especially in case of anaphylaxis, a life-threatening situation, which needs to be treated promptly with epinephrine. Early recognition and immediate response to a SAR is imperative to prevent further damage. It is prudent to identify and recognize patients on SCIT who are at higher risks for IR-SAR (Cox et al. 2011; Fox and Lockey 2007):

1. Uncontrolled and/or currently symptomatic asthma.
2. Significant seasonal or nonseasonal exacerbation of allergic symptoms, particularly asthma (e.g., severe asthma symptoms during springtime or exposure to pet animals).
3. Other serious comorbidities or specific function decline, primarily with cardiac and pulmonary diseases and/or cardiopulmonary functional impairments.
4. Previously demonstrated a high degree of hypersensitivity on either skin or serum aeroallergen testing or even having a SAR from skin testing.
5. On certain medications that may interfere with the treatment of an adverse event from SCIT. Examples would be β-blockers or angiotensin converting enzyme inhibitors.
6. An accelerated SCIT schedule such as cluster, rush, or ultra-rush immunotherapy.
7. SCIT administration from new vials, particularly to nonstandardized AVs or their mix due to inconsistent allergen quality and quantity.
8. Special populations including children under 5 years of age, during pregnancy, and systemic mastocytosis.

Notably, although there is no absolute contraindication in SCIT, the aforementioned groups at risk may be considered as relatively contraindicated for SCIT administration depending on the risk and benefit ratio, and this is often a case-by-case scenario. The same precaution rule is also true for an elderly patient due to there is no absolute upper age limit for SCIT initiation. Elderly patients are not included in the special populations because the comorbidities may be present on younger subjects as well, albeit they occur more frequently in older

Table 2 Patterns of allergen cross-reactivity and vaccine compatibility. Allergen cross-reactivity: plant species between the same or different families in each cell listed share strong cross-reactivity. Using one member of the group for subcutaneous immunotherapy may be adequate. Vaccine compatibility: red, yellow, and green arrows denote unsuitable, probable, and favorable compatibilities when allergen vaccines are mixed

Allergen cross-reactivity			
Trees	**Grasses**	**Weeds**	**Indoor**
Cedar Cypress Juniper	Bahia Johnson	Mugworts Sages Wormwood	**Dust mites** D. pteronyssinus D. Farinae
Alder Beech Birch Chestnut Hazel Hophornbeam Hornbeam Oak	Kentucky blue Meadow fescue Orchard Red top Rye Timothy	Amaranth Burning bush Lambs quarter Pigweed Red root Russian thistle	**Cockroach** American cockroach German cockroach
Ash European olive Privet		False ragweed Giant ragweed Short ragweed Western ragweed	
Aspen Cottonwood Poplar		Saltbush Wingscale	
Allergen vaccine compatibility			



subjects (Cox et al. 2011). Other obstacles or illnesses that may complicate SCIT including poor adherence or severe psychological disorders should be carefully reviewed as whether such patients are suitable for immunotherapy. A further detailed precaution regarding certain risky populations is discussed below.

39.8.1 SCIT during Pregnancy

A SCIT-prescribing physician must know the risks and benefits of continuing immunotherapy among pregnant females. There are two concerning major risks that may occur for SCIT during pregnancy: uterine smooth muscle contraction and fetal injury from rescue medication usage during an adverse allergic reaction. Because of the small but serious risk concern on the fetus, mother, or both, including spontaneous abortion, preterm labor, and fetal hypoxia, SCIT is usually not initiated for pregnant patients unless a life-threatening situation exists, such as moderate to severe Hymenoptera hypersensitivity (Metzger et al. 1978). Discontinuation of SCIT should be considered for any schedule during the buildup

phase because of the non-therapeutic dosage and increased risk of having a reaction while updosing. For pregnant women who are on the maintenance phase of immunotherapy, SCIT could be continued, given that there is no past significant SAR from SCIT. As for questions regarding the changes in fetal development and immune function, despite there is no single large prospective study investigating the safety of SCIT during pregnancy, several retrospective studies have found that there is no greater risk of prematurity, toxemia, abortion, congenital malformation, neonatal death, or other adverse outcomes in women who receive SCIT during pregnancy and there might be potential prevention effect of allergen sensitization in newborns (Metzger et al. 1978; Shaikh 1993; Schwartz et al. 1990; Glovsky et al. 1991; Flicker et al. 2009). Whether the maternal SCIT will truly benefit the unborn children remains unanswered, and this is unlikely to be formally and prospectively studied owing to possible but clear risk of having SAR from SCIT administration. There is no evidence to suggest an increased risk of commencing or continuing SCIT for a breastfeeding mother and her breastfed child.

39.8.2 SCIT in Children

SCIT in the pediatric population has been shown to be effective for both AR and asthma. The clinical indication of SCIT is similar for both adults and children except there may be more focus on the prevention of new sensitization and/or asthma development, despite not all the preventive studies have shown strong evidence as discussed earlier. Experience suggests that SCIT injections may be stressful in young children, and therefore SLIT might be a good and preferred alternative if they have single- or oligo-allergies (Roberts et al. 2017). Aside from moderate to severe Hymenoptera hypersensitivity, SCIT is usually not considered for infants and toddlers in view of the fact that repeated injections are traumatic to younger children and there is difficulty in communication if an allergic adverse event occurs. SCIT is suggested to be avoided in children who are younger than 5 years of age; however, there are researches that have reported efficacy in this particular age group (Roberts et al. 2006; Rodriguez Perez and Ambriz Moreno Mde 2006). This is not an absolute contraindication to be restrained from receiving immunotherapy nor there is definitely more risk of having SAR from SCIT (Finegold 2007). Consequently, the AIPP clearly states that SCIT can be considered as a disease-modifying treatment for patients at all ages, and the risk and benefit assessment along with detailed clinical history and diagnostic testing results must be evaluated in every situation (Cox et al. 2011).

39.9 Follow-Up and Duration of Immunotherapy

For widely distributed effective dose range for each AV and each patient that has his/her own biological therapeutic level, it is hard to predict when will a patient notice or report a clinical response despite immunological changes that may already take place within weeks after initiating AIT injections. Routine follow-up is critical, since there is no good immunological biomarker that can well correspond with clinical improvement. Studies have demonstrated that physiological and clinical response can often be observed when patients are close to or reach their maintenance dosage (Varney et al. 1997; Frew et al. 2006; Kohno et al. 1998). It is appropriate to follow up with patients shortly after achieving their maintenance phase for conventional SCIT schedule which is one to two injections per week and 3–6 months to reach therapeutic dose. Similar rule applies to cluster and rush SCIT schedules, yet a shorter follow-up is needed. Patients who are on active SCIT should be evaluated at least every 6–12 months on a regular basis (Cox et al. 2011). The purpose of a follow-up is not only to assess the clinical efficacy but also to monitor adverse events, reinforce good adherence, and determine whether the dosage should be adjusted. Other aspects, such as severity of disease, level of clinical improvement and medication reduction, patient adherence, time, cost,

and convenience, should all be considered for the continuation or discontinuation of SCIT.

Once the patient has allergic symptom amelioration from SCIT, clinical trials and observations suggest that SCIT should be continued at least for 3–5 years in order to see a long-term protection (Cox et al. 2011; Jutel et al. 2015). Vice versa, this also indicates that SCIT can be stopped after 3–5 years of successful immunotherapy treatment. There are both groups of patients that have demonstrated prolonged symptom remission or disease relapse after SCIT discontinuation. At present, no specific clinical and laboratory markers can distinguish between both groups, and therefore, the continuation of SCIT after 3–5 years is an agreement between physicians and patients after a full explanation and discussion. Experience suggests that when symptom relapses after SCIT is discontinued, a response to restarting such immunotherapy happens more rapidly than the original course of SCIT (Fox and Lockey 2007).

39.10 Unresponsiveness from Immunotherapy

As a result of the great heterogeneity of patient status, allergen characteristics, and AVs, individual response to SCIT is different. A general rate of successful SCIT treatment among the trials and studies should not be extracted and implemented to a single patient. However, this does not preclude a physician to investigate a patient who has no improvement from SCIT administration and simply claim the patient as unresponsive to immunotherapy treatment. If there is no obvious clinical improvement after 1 year of maintenance immunotherapy, possible reason(s) explaining the SCIT unresponsiveness should be pursued (Cox et al. 2011). Such reason(s) of lack of efficacy might include, but not limit to, (1) failure to reduce significant allergenic exposure or continuous exposure to high levels of allergen (e.g., receiving cat SCIT but there are cats in the house), (2) inappropriate treatment due to dominant non-allergy-mediated diseases (e.g., vasomotor rhinitis or neutrophilic asthma), (3) continued exposure to non-allergen triggers or irritants (e.g., tobacco smoke), (4) incomplete identification and treatment of clinically relevant allergens, (5) failure to treat with adequate doses of each allergen because of low-potency AVs or low-dosage immunotherapy prescription, or (6) a coexisting condition which accounts for patient's symptoms (e.g., chronic rhinosinusitis or nasal polyps). If none is found, discontinuation of SCIT should be considered and discussed with patients, and other alternatives may be sought.

39.11 Safety and Adverse Events

39.11.1 Local Reactions

Adverse events associated with AIT can be either local or systemic. Local reactions, including one or more symptoms of pruritus, burning sensation, erythema, and injection-site swelling, are quite common with SCIT. The frequency can range from 26 up to 82% in all patients receiving SCIT and 0.7 to 4% per injection (Nelson et al. 1986; Prigal 1972; Tankersley et al. 2000a). Of one survey conducted in patients having SCIT, over 80% of patients who have local reactions did not perceive local reactions to be bothersome, and 96% of the local reactors continue on their treatment of SCIT (Coop and Tankersley 2008). From a safety perspective, published studies have demonstrated that a single local reaction does not predict subsequent local or systemic reaction (Kelso 2004; Tankersley et al. 2000b); however, with more frequency of having local reactions, there may be more risk of having future systemic reactions (Roy et al. 2007). Some of the local reactions, specifically pain or burning sensation, are attributed from the glycerin content in AVs. Higher concentration of the glycerin is associated with higher chance of pain at the injection site (Van Metre et al. 1996). Other local reactions or the sizes of local reaction are not particularly associated with glycerin even when the glycerin concentration is elevated up to 50% (Calabria et al. 2008). The comparable local reaction rates between aeroallergen and Hymenoptera SCIT, for which the Hymenoptera extracts lack glycerin

component, have indicated that allergen content in the AV plays a bigger role in local reactions (Calabria et al. 2008).

39.11.2 Systemic Reactions

Severity of a SAR related to SCIT can range from mild generalized pruritus and/or rhinitis symptoms to severe or even life-threatening anaphylaxis. There is a 5 graded classification system developed by WAO based on the severity of reactions and number of organs involved (Cox et al. 2010). The prevalence of conventional schedule SCIT-related SAR has been reported to be 0.1 to 0.2% per injections and 2 to 5% of all patients receiving SCIT (Epstein et al. 2014). As for the rate of fatal and near-fatal reaction, for which a near-fatal reaction is defined as respiratory compromise, hypotension, or both, evaluated by survey studies from AAAAI physician members, it is estimated to be once in every 2 to 2.5 million injections for fatal reactions versus 1 to 5.4 events in every one million injections for confirmed or plus unconfirmed near-fatal reactions, respectively, between the year from 1990 to 2001 (Lockey et al. 1987; Reid et al. 1993; Amin et al. 2006; Bernstein et al. 2004). In the recent report from the AAAAI/ACAAI national surveillance study in the year of 2008–2013, there have been a few SCIT-related fatalities in which two out of four deaths occurred under the care of allergists (Epstein et al. 2016). The rate of having systemic reactions remained stable, including 1.9% of all SCIT-treated patients and 0.08% and 0.02% for grade 3 and 4 SAR, respectively. Precaution of not giving SCIT to uncontrolled asthma patients has significantly reduced the grade 3 and 4 systemic reactions. In accordance, reduced SCIT dosage during corresponding pollen season in patients with highly positive skin testing has experienced fewer systemic reactions (Epstein et al. 2016). Appropriate preinjection evaluation should be taken to minimize the risk of IR-SAR. Recently, the WAO SCIT grading system has been reviewed and updated (Cox et al. 2017). The new grading system along with incorporated anaphylaxis symptom prevalence and diagnostic criteria is listed in Fig. 3.

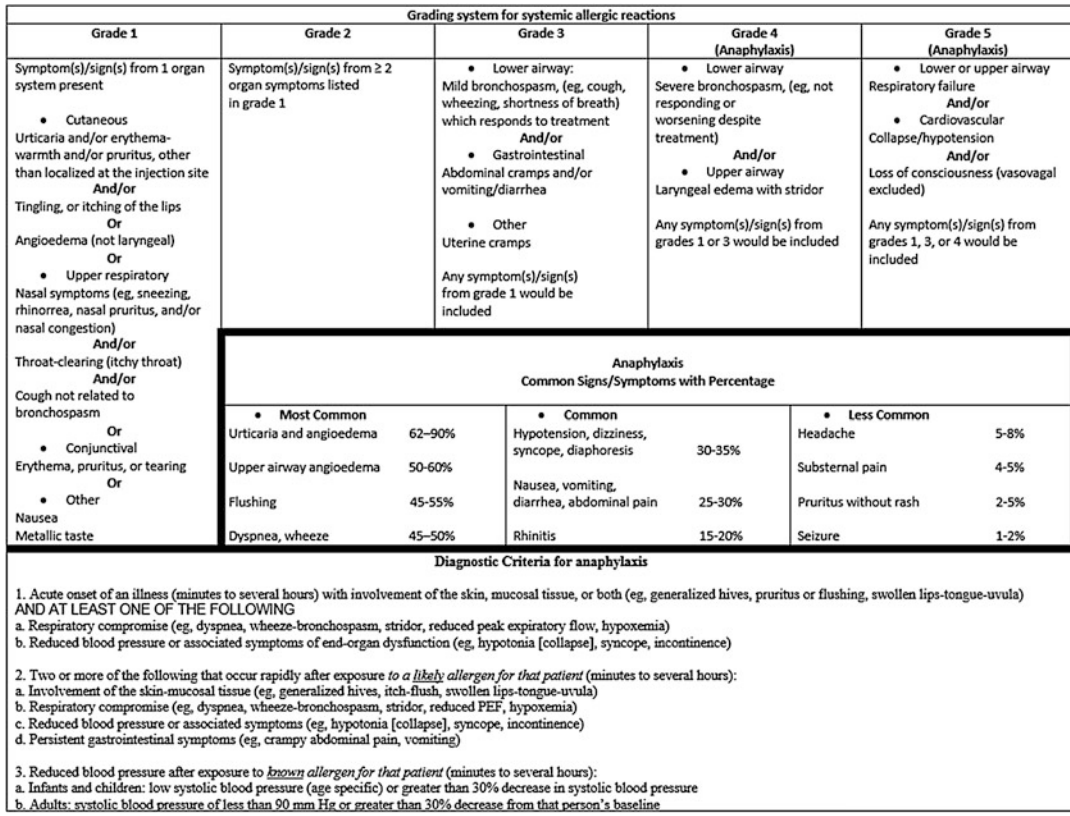
39.11.3 Preinjection Assessment

The risk of developing IR-SAR and fatal anaphylaxis should be avoided or minimized whenever possible, and it may be achieved by preinjection assessment. The preinjection assessment consists of inquiries regarding asthma and/or rhinoconjunctivitis symptom control, change in health condition such as pregnancy, previous skin testing sensitivity and SCIT-related systemic reactions, and concurrent medication use like β-blockers. Additional peak flow measurement may be included to concur that asthma is in a good control. Patients with any active systemic illness and/or prior adverse events from SCIT should be evaluated by an allergist/immunologist before the next SCIT injection.

39.12 Treatment of Adverse Events

39.12.1 Local Reactions

There is no comprehensive study evaluating the treatment for local reactions during conventional buildup and maintenance phase although medications such as H1 and H2 antihistamines and leukotriene receptor antagonists are commonly used in clinical practice. The potential benefit of using premedications for local reactions is mostly extrapolated from rushVIT studies for Hymenoptera allergy except one double-blind, placebo-controlled study showing the benefit of loratadine premedication for cluster aeroallergen SCIT (Nielsen et al. 1996b; Berchtold et al. 1992; Reimers et al. 2000; Brockow et al. 1997; Wohrl et al. 2007). Oral H1 antihistamines have been demonstrated to decrease local reactions, while H2 antihistamines were not found to have any additional benefit if added to fexofenadine, an H1 antihistamine, as a premedication during rush VIT (Berchtold et al. 1992; Reimers et al. 2000; Brockow et al. 1997). In another double-blind, placebo-controlled rush VIT study, montelukast premedication was found to delay and decrease the size of local reaction when compared to placebo group; however, in the



Grading system for systemic allergic reactions

Grade 1	Grade 2	Grade 3	Grade 4 (Anaphylaxis)	Grade 5 (Anaphylaxis)
Symptom(s)/sign(s) from 1 organ system present • Cutaneous Urticaria and/or erythema-warmth and/or pruritus, other than localized at the injection site **And/or** Tingling, or itching of the lips **Or** Angioedema (not laryngeal) **Or** • Upper respiratory Nasal symptoms (eg, sneezing, rhinorrea, nasal pruritus, and/or nasal congestion) **And/or** Throat-clearing (itchy throat) **And/or** Cough not related to bronchospasm **Or** • Conjunctival Erythema, pruritus, or tearing **Or** • Other Nausea Metallic taste	Symptom(s)/sign(s) from ≥ 2 organ symptoms listed in grade 1	• Lower airway: Mild bronchospasm, (eg, cough, wheezing, shortness of breath) which responds to treatment **And/or** • Gastrointestinal Abdominal cramps and/or vomiting/diarrhea • Other Uterine cramps Any symptom(s)/sign(s) from grade 1 would be included	• Lower airway Severe bronchospasm, (eg, not responding or worsening despite treatment) **And/or** • Upper airway Laryngeal edema with stridor Any symptom(s)/sign(s) from grades 1 or 3 would be included	• Lower or upper airway Respiratory failure **And/or** • Cardiovascular Collapse/hypotension **And/or** Loss of consciousness (vasovagal excluded) Any symptom(s)/sign(s) from grades 1, 3, or 4 would be included

Anaphylaxis
Common Signs/Symptoms with Percentage

• Most Common		• Common		• Less Common	
Urticaria and angioedema	62–90%	Hypotension, dizziness, syncope, diaphoresis	30-35%	Headache	5-8%
Upper airway angioedema	50-60%	Nausea, vomiting, diarrhea, abdominal pain	25-30%	Substernal pain	4-5%
Flushing	45-55%	Rhinitis	15-20%	Pruritus without rash	2-5%
Dyspnea, wheeze	45–50%			Seizure	1-2%

Diagnostic Criteria for anaphylaxis

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula)
AND AT LEAST ONE OF THE FOLLOWING
a. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)
b. Reduced blood pressure or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)

2. Two or more of the following that occur rapidly after exposure *to a likely allergen for that patient* (minutes to several hours):
a. Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)
b. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
c. Reduced blood pressure or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)
d. Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)

3. Reduced blood pressure after exposure to *known allergen for that patient* (minutes to several hours):
a. Infants and children: low systolic blood pressure (age specific) or greater than 30% decrease in systolic blood pressure
b. Adults: systolic blood pressure of less than 90 mm Hg or greater than 30% decrease from that person's baseline

Fig. 3 The updated grading system for subcutaneous immunotherapy-associated systemic allergic reactions (upper part) along with incorporated anaphylaxis signs/symptom prevalence (middle part) and anaphylaxis diagnostic criteria (bottom part) are separated from each other with thicker solid lines. (Adapted from references Cox et al. (2017), Sampson et al. (2006) and Lieberman et al. (2015))

same study, there is no difference between the desloratadine premedication and placebo group (Wohrl et al. 2007).

39.12.2 Systemic Reactions

The majority of IR-SAR, particularly most of the severe reactions, begin within 30 minutes after a SCIT injection (Cox et al. 2010, 2011). Any healthcare provider who administers SCIT regardless of subspecialty should keep the patient under monitoring in the physician's office for at least 30 minutes following an injection. A longer time may be necessary for high-risk patients. In accordance, most of the extract manufacture's package inserts suggest a monitoring period of either 20–30 or 30 minutes after a SCIT injection. It must be acknowledged that a delayed SAR may occur after the 30-minute monitoring period up to 50% of all IR-SAR (Lin et al. 1993; Rank et al. 2008; DaVeiga et al. 2008). Furthermore, there may be a biphasic reaction, defined as symptom recurrence after complete clinical symptom resolution of the initial reaction, reported up to 20% of all IR-SAR, which usually happen within 24 hours after the initial injection (Scranton et al. 2009). There is no specific symptom from the initial reaction that can predict ensuing delayed and/or biphasic reactions, but fortunately, delayed and biphasic reactions are typically less severe than the original reactions (Cox et al. 2011). Patient should be counseled on the chance of developing these reactions and an appropriate management plan with instructions especially on when to seek medical attention.

Importantly, physicians who are prescribing and/or administering SCIT must be aware of the potential risks of IR-SAR, promptly recognize the early signs and symptoms, and institute proper managements, if necessary. Assessing and maintaining of airway, breathing, circulation, and adequacy of mentation are critical. Epinephrine is the first-line therapy for anaphylaxis, and there is no contraindication to give an epinephrine injection in an anaphylactic patient. It is paramount to administer epinephrine injection early in the management of anaphylaxis. Delayed epinephrine injection has been linked to fatalities resulting from severe respiratory and/or cardiovascular complications and biphasic reactions (Cox et al. 2011). The preferable treatment recommendation for epinephrine injection is 0.2 to 0.5 ml intramuscular in the mid-outer thigh (1:1000 dilution; 0.01 mg/kg in children and maximum 0.3 mg per dose) and should be repeated every 5 minutes, as necessary, to relieve and control symptoms. If the clinical situation deems appropriate, the 5-minute interval may be shortened to permit more frequent injections (Cox et al. 2011). Physicians should know the pharmacologic kinetics and interactions, as well as the potential lack of response to an epinephrine injection especially when a patient is on a β-blocker. In such case, glucagon could be used to bypass the β-adrenergic receptor and reverse refractory bronchoconstriction and hypotension by directly activating adenyl cyclase during an anaphylaxis.

Indeed, the advocacy of epinephrine injection has brought more questions which need to be answered: how to define anaphylaxis? When to administer epinephrine if there is an IR-SAR? In 2006, the National Institute of Allergy and Infectious Diseases, Food Allergy and Anaphylaxis Network, and Food Allergy Research and Education assembled experts from different specialties and proposed the diagnostic criteria for anaphylaxis which is listed in Fig. 3 (Sampson et al. 2006). It should be noted that the proposed criteria is a balance between trying to include all patients with anaphylaxis and avoiding unacceptably high number of mild to moderate SAR to be labeled as "anaphylaxis." Thus, the criteria suggest at least two system involvements or major organ compromise including pulmonary and/or cardiovascular system with a known allergen exposure. In the same report, a caveat was added: "there undoubtedly will be patients who present with symptoms not yet fulfilling the criteria of anaphylaxis yet in whom it would be appropriate to initiate therapy with epinephrine." This statement remains true, particularly with patients who are on SCIT which contains known allergens. Likewise, the 2015 anaphylaxis practice parameter update states that observational studies and analysis of near-fatal and fatal reactions have shown early treatment of any systemic reaction, even mild in severity, with epinephrine injection may prevent progression to more severe or life-threatening SAR (Lieberman et al. 2015). In one study, the rapid administration of a single dose of epinephrine for mild SAR from SCIT was able to cease further symptom development with no extra epinephrine injection needed (Scranton et al. 2009). Realizing this, physician and other healthcare professionals should not wait a systemic reaction to evolve into anaphylaxis to justify an epinephrine injection given the fact that the benefit from such treatment outweighs the potential risk. Although there will be likely no consensus on determining which symptom(s) would be the perfect herald or threshold for ensuing anaphylaxis, any symptom listed in the WAO SCIT grading system should be considered for potential indication of epinephrine injection to prevent deleterious outcomes.

There are other second-line therapies that have been implemented in the treatment of SAR consisting of oxygen administration, recumbent position with elevated lower extremities, intravenous fluid replacement, and intubation if clinically necessary for laryngeal edema. Ancillary medications such as nebulized β2 agonist for respiratory symptoms, H1 and H2 antihistamines, and glucocorticosteroid can be given as an adjunctive therapy (Lieberman et al. 2015). The detailed discussion regarding efficacy of each management or medication is beyond the scope of this chapter, but the concept is to provide optional therapies in addition to epinephrine administration. Clinicians who perform and administer SCIT should have the appropriate medications and equipment available to treat any IR-SAR.

Patients should also be instructed as when to seek for medical assistance if there is a delayed or biphasic reaction once they have been stabilized and discharged from the physician's office for an initial systemic reaction. If auto-injectable epinephrine is justified and prescribed, a patient must be educated on the use of portable epinephrine. The risks and benefits of continuing SCIT in patients who have had a severe SAR should be carefully discussed and evaluated before the next shot.

39.13 Future Trends

Even though SCIT and SLIT could benefit many allergic diseases, they have caveats, including general low adherence in both immunotherapies (likely due to the numbers of administration and duration of treatment course), the threat of significant adverse events (SCIT is more risky than SLIT), and not all patients responding to such therapies. There is a need for safer, more convenient, and effective AIT. Several novel immunotherapies have been designed to improve SCIT and may involve adding adjunctive therapy to the traditional SCIT, altering the allergens, or basically changing the route of delivery of the AVs. These advances may result in a new, safer, and substantially more effective method of modifying the allergic immune responses.

One of the options is the addition of omalizumab, an anti-IgE recombinant humanized monoclonal antibody approved for usage in allergic asthma uncontrolled with inhaled corticosteroids and chronic spontaneous urticaria uncontrolled by antihistamine treatment, to SCIT. Omalizumab pretreatment has been shown to improve safety and tolerability of SCIT, especially in high-risk cluster and rush schedule for patients having AR and asthma (Casale et al. 2006; Massanari et al. 2010; Tsabouri et al. 2017). The underlying pathophysiology is that omalizumab can decrease serum-free IgE antibodies and FcεR1 receptors on dendritic cells, mast cells, and basophils. Additionally, omalizumab-combined SCIT has demonstrated symptom score improvement compared to SCIT alone, albeit this may be an adjunctive rather than a synergic effect (Kuehr et al. 2002; Kopp et al. 2002). Similar successfulness of reducing SAR by add-on omalizumab is seen with other types of AIT including VIT and oral immunotherapy (Galera et al. 2009; Schulze et al. 2007; Takahashi et al. 2017). However, cost-effectiveness of supplemental omalizumab has to be considered as part of the standard treatment.

Allergoids are allergens modified by either glutaraldehyde or formaldehyde, which theoretically results in reduced IgE epitopes (allergenicity) while preserving T cell epitopes (immunogenicity). These products allow faster AIT updosing without increasing the risk of a systemic reaction (Ricketti et al. 2017). Allergoids are commonly used in European SCIT, whereas there is no FDA-approved product in the United States. Although the major concern is that low allergenicity may be associated with low immunogenicity, allergoids remain to be an appealing alternative to traditional SCIT given their improved safety and shorter dosing schedule.

A recombinant AV is a novel approach to reproduce purified allergen by using the recombinant DNA technology to mimic allergen's known molecular, immunologic, and biologic characteristics. It can be made as a natural or an allergenicity reduced, immunogenicity increased, or both types of allergen. In addition, recombinant AV can be hybrid molecules constituting relevant epitopes of multiple allergens. The less contamination and inconsistency compared to general allergen extracts are also the key features. To date, recombinant allergens that have been investigated include birch, timothy grass, ragweed, dust mite, and cat (Casale and Stokes 2011). Modified birch major allergen, recombinant Bet v 1 fragments or trimers, and timothy grass have been the most extensively studied vaccines in clinical trials (Casale and Stokes 2011). Recombinant DNA technology offers the possibility of improving the allergen standardization and safety; however, it is not clear if recombinant AVs result in better clinical outcomes versus wild-type allergens (Ricketti et al. 2017). Even with similar clinical efficacy plus additional benefits seen in recombinant-type compared to wild-type

vaccines, two main aspects such as authority regulations and vaccine quality hurdles still need to overcome before putting into clinical practice.

Toll-like receptors (TLRs) are innate immune receptors expressed on the cell surface or, intracellularly, within the endosomal compartments. These receptors recognize molecular patterns broadly shared by pathogens. Once TLRs are stimulated by their inducers, activation of the cell will lead to not only innate but also adaptive immune systems including both Th1 and regulatory T cell responses (Racila and Kline 2005). There are ten TLRs identified in humans, and four (TLR-4, TLR-7, TLR-8, and TLR-9) have been studied in conjunction with SCIT to help treating allergic diseases. Monophosphoryl lipid A, derived from lipopolysaccharides of a specific *Salmonella bacterium* and a TLR-4 agonist, has been successfully added to chemically modified pollen and HDM extracts (Gawchik and Saccar 2009; Baldrick et al. 2001). Pollen SCIT with attached TLR-4 agonist has been approved and used in Europe and Canada as a preseasonal, ultrashort SCIT schedule consisting of three to four weekly injections (Drachenberg et al. 2001; Mccormack and Wagstaff 2006). Of other interest are TLR-9 agonists. TLR-9 is typically activated by unmethylated cytosine-phosphate-guanine oligonucleotides that are commonly expressed in bacterial DNA. Once cells are stimulated by TLR-9 agonists, they release cytokines that trigger both Th1 and regulatory T cell immune responses (Nelson 2016). However, several large multicenter trials for TLR-9 agonist mixed with AV did not demonstrate efficacy (Stokes and Casale 2014; Casale et al. 2015).

Another strategy is based on the concept that when a SCIT injection is given, the injected allergens have to be processed into small peptides and presented to allergen-specific T cells to initiate the immune deviation and tolerance. It is possible to use synthetic peptide fragments directly targeting to their corresponding T cells without the allergenicity and risk of IgE-mediated allergic reactions. Peptide fragments have fewer chances to cross-link with allergen-specific IgE on mast cells and basophils due to their small size (Larché 2007). The candidate peptide fragments are identified by their ability to induce lymphocyte proliferation in patients with the same specific allergy. Despite initial promising results being presented or published for grass, HDM, and cats with a well-tolerated and favorable safety profile, in a large field study scale, there was no proven benefit with both cat and HDM peptides versus placebo. As a result of significant placebo response, the peptide AV treatment in both cat and HDM trials did not meet the phase 3 and 2b study's primary endpoint, respectively (Ellis et al. 2017; Circassia Announces n.d.-a; Circassia Announces n.d.-b).

Last but not least, different routes of AV administration have been researched, such as nasal, sublingual, oral, bronchial, epicutaneous, intradermal, and intralymphatic (Greenhawt et al. 2017; Passalacqua et al. 1995; Taudorf et al. 1987; Tari et al. 1992; Senti et al. 2008, 2009). Nasal and bronchial immunotherapy is not currently used because of unacceptable local side symptoms (Passalacqua et al. 1995; Tari et al. 1992). Sublingual form of immunotherapy has been shown to be safe and effective (Greenhawt et al. 2017). Both oral and epicutaneous immunotherapy trial results are much more promising in terms of food allergy and considered to be the transformative therapy for food than inhalant allergy (DBV Technologies Announces n.d.; Aimmune Therapeutics' Pivotal n.d.). Intralymphatic immunotherapy remains experimental, but there are few studies reporting their efficacy and safety (Senti et al. 2012; Hylander et al. 2013; Witten et al. 2013).

39.14 Summary

AR and asthma represents a significant and expanding health problem worldwide. While environmental control, allergen avoidance, and pharmacotherapy are still valuable managements, only AIT is considered to have the capacity to modify the natural course of disease by inducing long-term immunological deviation and tolerance. SCIT, as the first effective AIT, has been practiced in treating both diseases for the past 100 years. The risks of SCIT can be minimized when immunotherapy is given to carefully

selected patients in an appropriate setting. As exploring new technology and advancing knowledge in the basic mechanisms and pathophysiology of SCIT in allergic diseases, there will be even more ways to take advantage of that technology and knowledge and completely change SCIT in the future.

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Sublingual Immunotherapy for Allergic Rhinitis and Asthma

40

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Abstract

Allergic rhinitis, atopic eczema, and asthma, which affect a large proportion of the population, have adverse effects on work and quality of life, and have the propensity to worsen with time. Allergen immunotherapy (AIT) has been around for over 100 years and is the only treatment that can change the natural history of disease and can reverse the natural progression of allergic rhinitis, asthma, and atopic eczema. This chapter reviews subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT) and compares and contrasts in vitro mechanisms of the two treatment modalities highlighting immune changes through time, and potential biomarkers associated with treatment response. This chapter then focusses on patient clinical changes through time, safety, and cost effectiveness. This chapter concludes with information on current FDA-approved treatments Odactra®, Grazax/Grastek®, Oralair®, Ragwitek® and include information on patient populations approved for these therapies, dosing regimens, when to initiate treatment, and standard doses.

Keywords

SLIT · Immunotherapy · Sublingual immunotherapy · Treatment of allergic rhinitis

Abbreviations

AEs	Adverse events
AR	Allergic rhinitis
AIT	Allergen immunotherapy
EET	Environmental exposure chambers
HDM	House dust mite
SCIT	Subcutaneous immunotherapy
SLIT	Sublingual immunotherapy

40.1 Allergen Immunotherapy

Allergic disorders affect a large proportion of the global population (Lombardi et al. 2017). Allergy is thought to be affected by genes and environment. Environmental climate change, increasing atmospheric carbon dioxide concentrations, profoundly impact geographic vegetation growth and distribution (Ziska and Beggs 2012). Allergens such as ragweed can bind diesel exhaust particles, creating a more potent allergic response in allergic subjects (Ziska and Beggs 2012). Alterations in weather patterns such as thunderstorms alter aeroallergen distribution with increase in emergency room presentations for asthma flares (Katelaris and Beggs 2018; Cockcroft et al. 2018).

Allergic responses can range in severity from mild to moderate symptoms such as oral pruritus and nasal congestion to severe reactions including asthma and anaphylaxis, which can be fatal. Furthermore, a phenomenon called the atopic march often develops and is characterized by the spreading of allergic symptoms over time. Symptoms typically affect one anatomic location such as the skin and then spread to affect other organ systems such as the nose and lungs, thereby leading to a combination of eczema, allergic rhinitis, and asthma. Allergic rhinitis (AR), often referred to as hay fever, is common affecting 17–29% of Europeans (Demoly et al. 2016). Symptoms associated with AR significantly impact quality of life causing physical, emotional, social, occupational, and financial problems and typically worsen over time (Chivato et al. 2017). Sick leave due to AR

costs in the billions of dollars (Aasbjerg et al. 2014). Allergy treatment includes antihistamines and corticosteroids; however, these interventions do not change the natural history of the disease. Through the repeated administration of a specific allergen to an allergic sensitized individual, allergen immunotherapy (AIT) can induce a state of sustained unresponsiveness leading to symptom reduction during subsequent allergen exposure and can alter the natural history of the disease (Klimek et al. 2016). Disease-modifying effects from AIT can be sustained for years beyond treatment (Durham et al. 2012). Allergen can be administered subcutaneously via injection or sublingually using tablets or drops placed under the tongue.

40.1.1 History

In 1911, Leonard Noon was the first physician to use allergen immunotherapy (AIT) in clinical practice at St. Mary's Hospital in London, England. Noon administered AIT subcutaneously, inoculating patients suffering from hay fever with a vaccine composed of grass pollen extracts. Noon noticed that if he gradually increased the dose of grass pollen extracts, patients' symptoms improved. Sadly, Noon died of tuberculosis 2 years after making this discovery.

Noon's colleague John Freeman continued to treat patients with subcutaneous immunotherapy (SCIT), publishing "the first rush immunotherapy protocol" in 1930. In 1954, William Frankland, a colleague of Noon and Freeman, performed the first randomized controlled clinical trial with grass pollen immunotherapy establishing "... a firm scientific foundation for the practice of allergen immunotherapy (Durham and Nelson 2011)." The empirical use of SCIT in medical practice continued, and in 1965, a glimpse into the mechanism underlying the basis of allergy occurred when IgE was discovered (Passalacqua and Canonica 2016).

One year later, Douglas Johnstone and Arthur Dutton published the findings of their 14-year pediatric study which suggested that treatment with immunotherapy might provide protection from the development of asthma in children (Johnstone and Dutton 1968). In 1978, the first of many trials supported the safety and efficacy of venom immunotherapy (VIT), which shares many of the same mechanisms of aeroallergen AIT. The year 1986 was a pivotal time in the history of allergen immunotherapy. At this time, the UK Committee on Safety Medicine concluded that SCIT involving respiratory allergens posed serious risk of severe or fatal adverse events (AEs). This prompted researchers to explore safer alternatives to allergen immunotherapy administration. Numerous trials, with small sample sizes, were conducted and demonstrated the efficacy of sublingual immunotherapy (SLIT). In 1998, the World Health Organization (WHO) named SLIT as a possible alternative to SCIT leading to the first uses of SLIT in clinical practice in Europe. Over the next decade, studies with significantly larger sample sizes were conducted. In 2006, the Timothy grass SLIT medication Grazax® (*Phleum pretense* 75,000 SQ-T/2,00 BAU, ALK-Abelló, Hørsholm, Denmark) was approved for use in Germany (Reiber et al. 2015). That same year, SLIT drops with *Dermatophagoides farinae* (*Der. f*) extracts were approved by the Chinese Food and Drug Administration to treat house dust mite allergy (Tang et al. 2018).

In 2009, the WHO officially endorsed SLIT. In 2014, the FDA approved three SLIT tablets for use in the United States: Oralair®, Grazax®, and Ragwitek®. By August 2015, 11 European countries approved SQ-HDM SLIT tablet to treat house dust mite allergy (Klimek et al. 2016). In September 2015, Japan approved SQ-HDM SLIT tablet (Klimek et al. 2016). While the use of allergen immunotherapy began over a century ago, there has been a proliferation of research and advancement over the last 30 years leading to the global use of this disease-modifying treatment (Passalacqua and Canonica 2016). In 2017, Odactra® received FDA approval becoming the fourth and most recent SLIT medication to be approved for use in the United States.

While SLIT is an emerging treatment in the United States, it is a commonly used method of treatment outside the United States (Chivato et al. 2017). Since 2007, a survey of American College of Allergy, Asthma and Immunology (ACAAI) members reported that 5.9% of those surveyed actively prescribed SLIT, which increased to 11.4% in 2011. The biggest deterrent reported was a lack of FDA approval at the time (Cox 2017).

40.2 How Does It Work?

Allergen immunotherapy (AIT) is the only disease-modifying therapy for immediate hypersensitivity reactions (which mechanistically share the underlying basis of AR, asthma, and anaphylaxis). AIT is effective in the treatment of allergic rhinitis, asthma, eczema, and stinging insect allergy (Rael 2016a).

Treatment, historically, has been best studied with subcutaneous immunotherapy (SCIT), which involves incremental weekly up doses, starting with a dilute dose, either at 1:1000 or 1:10,000 of the final dose, usually with weekly dose escalations until the highest dose (maintenance immunotherapy) is reached, typically at about 6 months. Treatments are typically conducted in the allergy office, with a 30-min post-treatment observation period because of the side effect risk of anaphylaxis. Treatment typically is administered for 3–5 years.

SLIT is thought to carry a lower risk for anaphylaxis and involves administration of allergens in drops or as a lower dose tablet. SLIT is administered as a fixed dose underneath the tongue. The first dose is typically given in the allergy office and subsequent daily doses are administered at home. Since dosing is given at home, contraindication to treatment includes severe unstable or uncontrolled asthma, history of any severe systemic allergic reaction or any severe local reaction to SLIT, history of eosinophilic esophagitis, or hypersensitivity to any of the inactive ingredients contained in the SLIT tablet.

Following exposure to an allergen, allergic hypersensitivity usually involves a sensitization phase and an effector phase. During the sensitization phase, the immune system becomes primed via the innate immune system and acquires the ability to detect an allergen. Areas of the body with direct interface with the environment, such as in the skin, the nose, and the lungs include sensor cells within the innate immune system that detect and process the allergen by cells such as dendritic cells. Dendritic cells have the capacity to migrate to T cell locations, such as in the lymph node to send signals to polarize the T cell into more specialized subsets. T helper cells originate from common precursors, and in response to signals from dendritic cells, mature into Th1, Th2, and Th3 regulatory subsets. T helper subsets have the capacity to produce different cytokine profile responses that, in essence, modulate and direct immune responses by other cells such as B cells which have the capacity to generate antibody responses. Th1 cells are associated with immune responses to infections from mycobacteria and intracellular infections. Th2 cells are associated with allergic responses and with the production of cytokine signals that propagate allergic responses such as interleukin (IL)-4, IL-5, and IL-13. IL-4 is a cytokine associated with B cell class switching to produce IgE allergic antibodies. Th3 cells are associated with immune regulatory effects including the potential to turn off Th2 allergic responses.

In an allergic response, a dendritic cell can present a piece, also known as an epitope, of the processed antigen to T cells within regional lymph nodes. In the lymph node, the Th2 polarized cell will send signals to B cells, which then trigger them to start making allergen-specific IgE antibodies that can circulate throughout the bloodstream.

During the effector phase, the adaptive immune system has already established memory. On subsequent encounter with the same allergen, a more advanced response including an immediate and a delayed response occurs, and these responses vary across anatomic locations and involve recruitment of allergen effector cells. Hallmark allergic symptoms often include itch, mucus production, local neurogenic

activation, and vasodilation. In the skin, symptoms can manifest as eczema. In the nose, symptoms can manifest as rhinorrhea, sneezing, postnasal drip, and nasal congestion. In the lungs, symptoms can manifest as coughing, wheezing, shortness of breath, and chest tightness.

On subsequent exposure to an allergen, after immunologic memory has been established, the mucosal surface interface is primed to respond to allergen challenge. Mucosal surfaces become involved in a complex cascade of events, activating neighboring cells such as dendritic cells leading to recruitment of allergy effector cells such as mast cells and basophils. The cross-linking of preformed allergen-specific IgE antibodies with allergen creates complexes that can bind receptors on effector cells leading to activation. Activation triggers the release of mediators such as histamine and tryptase from preformed granules, within the activated effector cells, leading to the induction of the early allergic response within 60 min.

A late response, 2–10 h after challenge, includes infiltration of eosinophils into the tissue, leading to propagation of allergy symptoms which can persist for days or weeks after a single allergen challenge (Shamji et al. 2017).

Over the course of many years, immune recognition often expands. Early in life, the immune system commonly recognizes only a few allergens. Later in life, allergen recognition diversifies resulting in the detection of multiple allergens leading to increased sensitization. It is thought that the B cells can generate a broader spectrum of IgE antibodies over time, with the ability to recognize different epitopes on different allergens, a phenomenon called epitope spreading.

40.2.1 In Vitro Mechanisms of SLIT and SCIT

Naïve B cells make IgM antibody. Upon B cell activation, the cell can class switch their genes to enable them to generate IgG, A, and E, which are antibodies that are more specific for their target. Both SLIT and SCIT are associated with short-term increases in serum allergen-specific IgE, which is subsequently followed by an increase in IgG_4. IL-10 is a cytokine that induces IgG_4 production. IgG_4 can compete with IgE for allergen (Rispens et al. 2011). IgG_4 antibodies have the ability to swap parts of their structural components such as their heavy-light chain component with other IgG_4 antibodies which theoretically can make the antibody more potent and can create more variable immune recognition. As an example, IgG_4 can compete for allergen with IgE and can block binding by IgE antibodies, thereby preventing cross-linking of IgE antibodies with mast cells and basophils. IgG_4 can also competitively inhibit IgE allergen complexes from binding low-affinity B cell receptors such as the FcγRIIb, preventing B cell antigen presentation to T cells (Burton et al. 2018). Hence, IgG_4 can blunt many steps in the process important in allergic responses.

Both SCIT and SLIT appear to follow similar patterns of in vitro immunologic changes. Typically with AIT treatment, IgE levels transiently increase (Fig. 1). IgG_4 levels subsequently increase. Time studies suggest that immunologic changes occur more rapidly with SCIT versus SLIT. Both SCIT and SLIT are associated with an increase in IgG_4 levels; IgE levels decline with SCIT versus placebo, but stay the same with SLIT versus placebo after 2 years of treatment and 1 year post 2 years of treatment (Scadding et al. 2017).

In weeks 4–12 comparing SCIT with SLIT, the change in log10 IgG_4 level is twice that in SCIT versus SLIT (Fig. 2). This pattern persists through 15 months of treatment with a similar pattern noted with attenuation of basophil activation (Aasbjerg et al. 2014). Recall, basophils are involved with degranulation of allergic mediators such as histamine upon allergen challenge. There is more competitive IgE inhibition with SCIT than SLIT in weeks 4–12 of treatment, due to the faster and higher levels of IgG_4 production from SCIT. However, this contrast fades by month 10 of treatment (Aasbjerg et al. 2014).

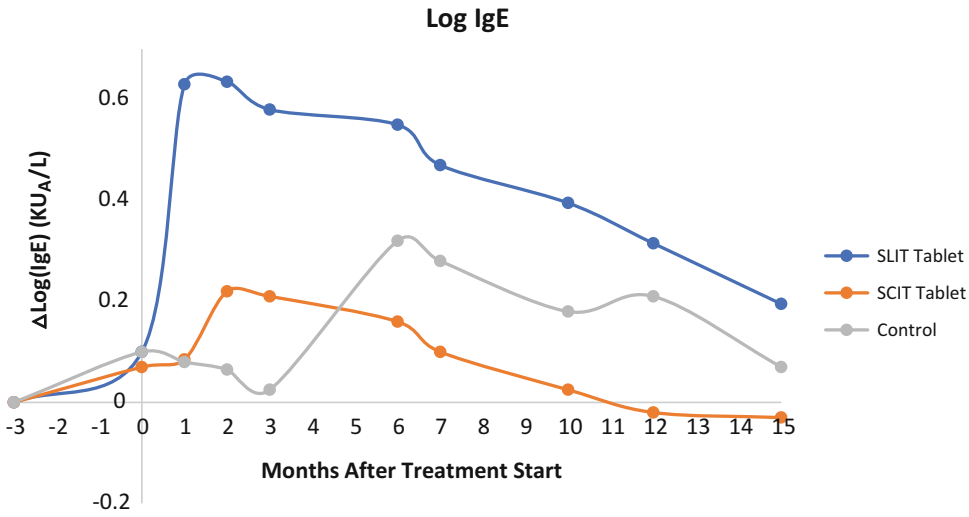

Fig. 1 Changes in Log IgE over 15 months of Timothy grass AIT. (Modified from Aasbjerg et al. 2014)

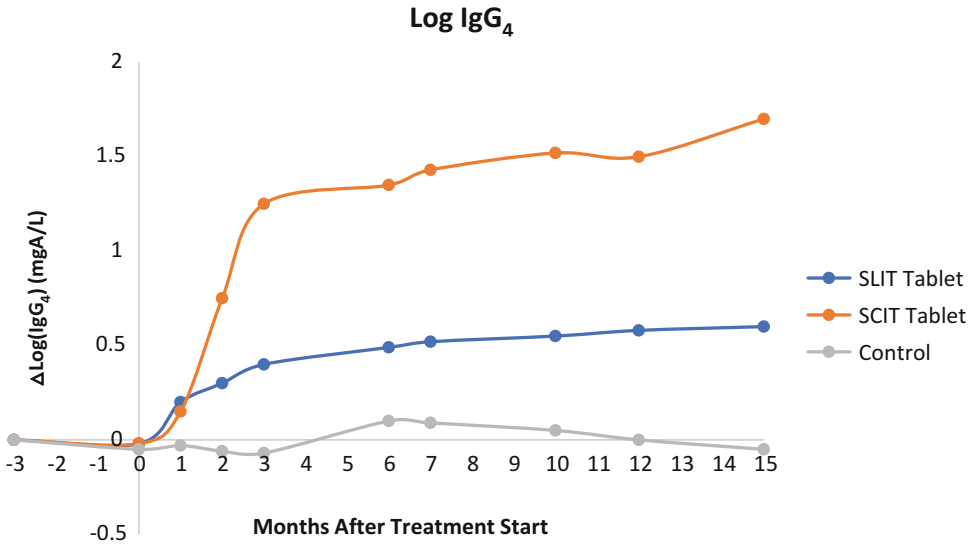

Fig. 2 Changes in Log IgG$_4$ over 15 months of Timothy grass AIT. (Modified from Aasbjerg et al. 2014)

Upon discontinuation of SCIT, within 1 year, IgG$_4$ levels decrease by 80–90%. This suggests that lower levels of antibodies might be associated with more functional affinity or avidity to the allergen as well as the possibility for long-lived B cell memory (James et al. 2011).

In general, cell-signaling changes appear to be modulated in the first 3 years of AIT treatment; however, these changes appear to be unstable and lost if AIT is discontinued prior to 3 years of either SCIT and SLIT treatment. Polarization and regulation of adaptive immune responses associated with tolerance or sustained unresponsiveness appear to take at least 3 years to generate. The effects are more durable and longer lasting (Rael 2016b).

After 2 years of treatment, IL-4, IL-5, and IL-13 cytokines decrease versus placebo in the

SCIT and SLIT groups 10 h after allergen challenge with nasal provocation. An additional study found a decline in Th2 cell subsets with the phenotype CRTH2+CCR4+CD27-CD4+ TH2 cell. As will be mentioned later on in the chapter, the CD27+ cell surface marker might be a potential biomarker for successful AIT treatment (Lawrence et al. 2016). There was no statistical difference in cytokine levels 1 year after completion of 2 years of SCIT or SLIT (Renand et al. 2017), further suggesting that 3 years of treatment is required to develop more durable and long-lasting sustained unresponsiveness to allergen.

In summary, AIT modifies T and B lymphocyte populations, thereby increasing local regulatory pathways, which upregulates the production of cytokines that inhibit allergic inflammation (Lawrence et al. 2016; Pelaia et al. 2017; Gunawardana et al. 2018).

40.3 Overall Concept of SLIT

SLIT involves placement of the allergen in the sublingual tissue for 3–5 years, the allergen is processed by myeloid dendritic cells (mDC) and Langerhan cells (LCs) which produce the cytokines IL-10, IL-12, and TGF-β. IL-12 facilitates Th1 polarization, and TGF-β and IL-10 facilitate Th3 immunity. TGF-β helps with B cell class switching to generate IgA-mediated responses.

A hypothesis suggests that there are a limited number of sublingual dendritic cells available to process the orally administered allergen, which raises the possibility for dendritic cell saturation (Lawrence et al. 2016). Because SLIT involves administration of a lower dose of allergen in a highly vascularized region, if the dendritic cell does not take up the allergen and process it, the allergen can leave the region via the bloodstream and potentially lose the ability to induce an immune response. In contrast, SCIT is administered into the subcutaneous tissue and can stay in the regional location longer, giving the dendritic cells more time to process the allergen and mount a more potent immune response. This mechanism might explain why SLIT has a better safety profile than SCIT. SLIT has been linked to more benign adverse events (AE) than those associated with SCIT injections (Creticos et al. 2013). The SLIT saturation effect is best demonstrated by one study in which multiple non-grass allergens were administered with a fixed concentration of timothy grass. The combination of allergens resulted in reduced treatment benefits further supporting the saturation mechanism previously mentioned. Amar SM Response to sublingual immunotherapy (Amar et al. 2009).

Although there are no biomarkers associated with sustained unresponsiveness, following long-term treatment with SLIT, a pattern involving oral CD 103-CD11b+ classical dendritic cell presentation to Foxp3+Th3 cells has been reported (Tanaka et al. 2017).

40.3.1 SLIT Timeline

Temporal patterns associated with SLIT have been published. Specifically, IgG_4 increases at weeks 8 and 12 after initiation of treatment with house dust mite (HDM) SLIT. After 10 months of treatment, increased IL-10 levels have been detected which are thought to be CD4+ Th1-associated responses (Schulten et al. 2016).

Six months of HDM and Timothy grass SLIT were associated with a decrease in serum IgE in SLIT versus the placebo group (Aasbjerg et al. 2014; Wang et al. 2016). The Timothy grass SLIT IgE levels continued to decrease with time through 15 months of treatment and reciprocally IgE inhibition reached 17.2% after 15 months of treatment (Aasbjerg et al. 2014). The HDM study also showed a reduction in Th2 cytokines IL-4, IL-5, and IL-13 and an increase in Th1 IFN-γ production and regulatory TGF-β at 6 months. Increases in serum Th1 cytokine IL-12 as well as the regulatory cytokine IL-10 occurred at 12 months (Wang et al. 2016).

At 10 or 24 months following continuous Timothy grass SLIT treatment, there was no T cell reduction in IL-5, an important cytokine for

eosinophil proliferation. Another paper further confirmed these findings in that there was no change in mucosal IL-5, IL-13, or eosinophil-associated gene expression by week 12 of SLIT treatment (Gunawardana et al. 2018).

Fifteen months of continuous treatment with Timothy grass SLIT resulted in decreased basophil activation by a factor of −1.4 and −0.71 with SLIT after 15 months (Schulten et al. 2016).

40.4 Overall Concept of SCIT

After subcutaneous injection of allergen, there are three potential levels of lymphoid organs, primary, secondary, and tertiary, where an immune response can be generated. The spleen is considered a primary lymphoid organ, the axillary lymph nodes are considered secondary organs, and the local lymphoid regions are considered tertiary lymphoid organ. Although the exact mechanism of cell homing changes associated with AIT are incompletely understood, it is thought that only a small proportion of allergen reach secondary lymphoid organs (Senti and Kundig 2015; Senti et al. 2012). Theoretically, allergen can access the circulatory system where the allergen can elicit immune responses at any lymphoid organ (Lawrence et al. 2016). This might explain why SCIT, in contrast to SLIT, can induce sustained unresponsiveness to multiple allergens. Treatment with SCIT can result in multiple depths of stimulation of the immune response; whereas SLIT might induce local responses that can be saturated.

40.4.1 SCIT Timeline

Likewise, temporal patterns associated with SCIT have been published. IL-10 production occurs earlier than SLIT, within 1–4 weeks during dose escalation and continues through 10 months, and is associated with suppressed late phase allergic responses and is thought to be a CD4+ Th1 response (Lawrence et al. 2016; Schulten et al. 2016; Francis et al. 2008). IL-10 production can occur from multiple sources. One study identified Tregs as the IL-10 source, generating IL-10 within 7 days of SCIT initiation (Lawrence et al. 2016). Subsequent work in a human SCIT model suggests that IL-10 production may be from T follicular regulatory (Tfr) cells compared with T follicular helper (Tfh) cells. The authors speculate that repeated treatment with SCIT leads to increased IL-2 production, a regulatory cytokine and shifts the balance from Tfh to Tfr cells, contributing to tolerance induction (Schulten et al. 2017). Subjects in this study were on SCIT at least 6 months and were on maintenance IT. Given that there were different technologies deployed at the time of the two studies previously mentioned, it is unclear if the Tregs mentioned initially were at a more naïve developmental stage versus the later study noting Tfr cells at a later time point in treatment. IL-10 producing T cells with Th1 characteristics co-expressed CD27+ in contrast to Th2 characteristic cells that were CD27−, with the hypothesis that CD27+ might be a marker for successful IT (Lawrence et al. 2016).

With SCIT, IgG_4 levels logarithmically increase earlier than SLIT, at around 4–12 weeks following treatment initiation (Aasbjerg et al. 2014). IgG_4 levels progressively increased at week 6–8 and peaked at week 16 with immediate skin test suppression. In contrast to SLIT where there is no attenuation of IL-5 production by T cells, with SCIT, T cell IL-5 reduction occurs at 10 months following Timothy grass treatment and is further reduced at 24 months of treatment. As previously mentioned, IL-5 is a proliferation cytokine for eosinophils, important in the last phase allergic response.

Six months of Timothy grass SCIT was associated with lower IgE production than SLIT, by a log10 factor of 2, but paralleled SLIT and was associated with a decrease in serum IgE in SCIT versus the placebo group (Aasbjerg et al. 2014). Following initiation of Timothy grass SCIT, IgE inhibition was 22.5% after 3 months, whereas SLIT IgE inhibition reached 17.2% after 15 months of treatment, suggesting that IgE inhibition occurred more rapidly in SCIT in relationship to SLIT (Aasbjerg et al. 2014).

40.4.2 Clinical Changes

SLIT and SCIT are both associatedwith attenuated early and late phase skin responses (Scadding et al. 2017). Clinical symptom scores with the visual analog scale (VAS) and with the mini rhinoconjunctivitis quality of life questionnaire (MiniRQLQ) scores improved with both SCIT and SLIT for 2 years, but returned to placebo levels in the year following completion of 2 years of AIT (Scadding et al. 2017). In a real-world retrospective study in a German cohort, grass SLIT resulted in slower progression of allergic rhinitis (AR), a lower frequency of asthma onset and slower progression of asthma (Zielen et al. 2018). Similar results have been demonstrated with SCIT from the prevent asthma trial (PAT) study demonstrating a disease-modifying effect with SCIT (Zielen et al. 2018; Passalacqua et al. 2016; Brunton et al. 2017).

The PAT study demonstrated decreased risk of asthma with up to 10 years of protection after 3 years of SCIT (Jacobsen et al. 2007). Two other studies showed similar findings (Novembre et al. 2004; Marogna et al. 2008). With regard to SLIT, a clinical trial comparing 35 HDM subjects versus 25 placebo subjects among the SLIT group, there was a reduction in incident asthma that reached clinical significance $p < 0.01$ (Di Rienzo et al. 2003). Another study compared 3 years of SLIT, where subjects could receive adjunctive medication plus SLIT versus adjunctive medication treatment without SLIT. The study showed a reduction in mild persistent asthma versus the medication treatment group with an odds ratio (OR) 0.04% with a 95% confidence interval of 0.01 to 0.17, as well as a reduction in the number of pediatric subjects with a positive methacholine challenge in the treatment group (Marogna et al. 2008). Methacholine is a bronchoconstrictor and is used as a provocative test to diagnose asthma.

To determine if SLIT could temporally prevent development of asthma, the Grazax asthma prevention (GAP) trial was conducted with a cohort of 812 children aged 5–12 years comparing Grazax to placebo with 3 years of SLIT treatment and 2 years of follow-up. The study was conducted at 101 sites across 11 European countries, with 398 subjects in the treatment arm versus 414 subjects in the placebo arm. While the study did not demonstrate asthma prevention, the treatment group experienced reduced risk of asthma symptoms and need for asthma medication at 2 years, post 3 years of treatment $OR = 0.66, p < 0.036$. Furthermore, there was a rhinoconjunctivitis symptom reduction between 22% and 30% for all 5 years $p < 0.005$ and rhinoconjunctivitis medication reduction by 27% at 5 years, $p < 0.001$ (Valovirta et al. 2018).

A similar study was conducted in adults aged 18–65 utilizing 3 years of 5-grass pollen SLIT versus placebo with 2 years follow-up post treatment with a cohort of 238 subjects. The study was conducted at 51 sites across 8 European countries. The study demonstrated overall mean symptom score reductions. The rhinoconjunctivitis symptom score decreased between 25% and 36% ($p \leq 0.004$) versus placebo over the 5-year period. Furthermore, the medication score was reduced between 20% and 45% over the 5-year period. The strongest statistical reductions occurred while on treatment in years 1 through 3. While season 4 reached statistical significance ($p \leq 0.022$) with a 29% reduction in medication score, year 5 demonstrated a 20% reduction in medication score which did not reach statistical significance ($p = 0.114$). The weighted combined score decreased by 27% to 41% ($p \leq 0.003$) over the 5 years (Durham et al. 2012).

Early on in immunotherapy treatment, there is the greatest potential for development of adverse events (AEs). In a German multicenter open-label, observational study conducted over 3 months with both adults and pediatric subjects, there was no increase in adverse events or changes in safety or tolerability profiles when SQ grass SLIT tablet was administered simultaneously with SCIT or additional SLIT (Reiber et al. 2017).

40.4.3 Use and Implications of SLIT

SLIT is used to treat environmental allergies, asthma, and eczema. Currently there are four SLIT medications (Odactra®, Grastek®, Oralair®,

and Ragwitek®) that have received FDA approval and are used in clinical practice in the United States today.

40.5 Odactra Dust Mite® House Dust Mite (*Dermatophagoides farinae* and *Dermatophagoides pteronyssinus*) Allergen Extract

It is estimated that 1–2% of the global population is allergic to house dust mites, one of the most common inhalant allergens whose symptoms negatively impact quality of life (Klimek et al. 2016). In China, from 2001 to 2010, AR in children increased from 9.1% to 15.4% (Tang et al. 2018).

If taken daily for 1 year, Odactra® has been shown to reduce and prevent symptoms of rhinitis induced by house dust mite allergy. It may take up to 14 weeks following initiation of treatment for symptoms to improve, and an optimal duration of treatment with Odactra® has yet to be determined (The Medical Letter 2018). Continuous treatment for 3 years is more effective and confers long-lasting results than continuous treatment for 1 or 2 years (Guo et al. 2017). SLIT medication in tablet form has been shown to reduce allergic rhinitis symptoms more effectively than aqueous SLIT drops (Novakova et al. 2017).

The effects of Odactra® SLIT are dose-dependent (Klimek et al. 2016). While efficacy has been demonstrated for both 6 and 12 SQ-HDM doses, the 12 SQ-HDM dose yields more effective results (Figs. 3 and 4) (Demoly et al. 2016).

The 12 SQ-HDM SLIT tablet was associated with more frequent adverse events; however, the symptoms usually resolve within hours or days of onset making it a tolerated and effective treatment in adults and adolescents (Virchow et al. 2016). A 2016 study used environmental exposure chambers (EECs) to prove the efficacy of 12 SQ-HDM SLIT tablet. One year after a 24-week treatment period with 12 SQ-HDM SLIT tablet, when exposed to EECs, subjects had decreased symptoms (Zieglmayer et al. 2016).

A pediatric study in China concluded that after 6 months of *Dermatophagoides farinae* drop SLIT treatment, AR symptoms significantly decreased in children aged 2–13. There was no notable difference in efficacy between 1- and 2-year treatment durations (Tang et al. 2018). Odactra® is currently FDA approved for use by patients over 18 years old in the United States (Table 1).

In a study published in 2016, there were no systemic allergic reactions reported among adults aged 18–65 treated with HDM SLIT. The most common side effects with HDM SLIT in adults include oral pruritus (20%), throat irritation (14%), and mouth edema (8%) (Demoly et al. 2016).

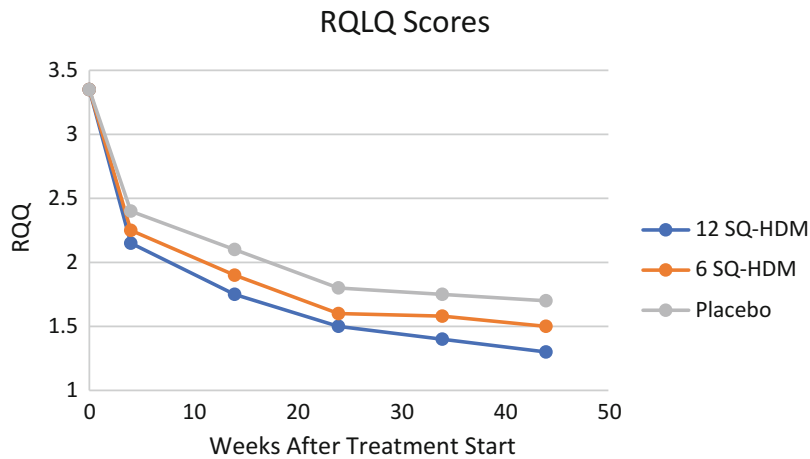

Fig. 3 Changes in Rhinoconjunctivitis Quality of Life Questionnaire Scores over time with varying doses of HDM SLIT versus Placebo. (Modified from Demoly et al. 2016)

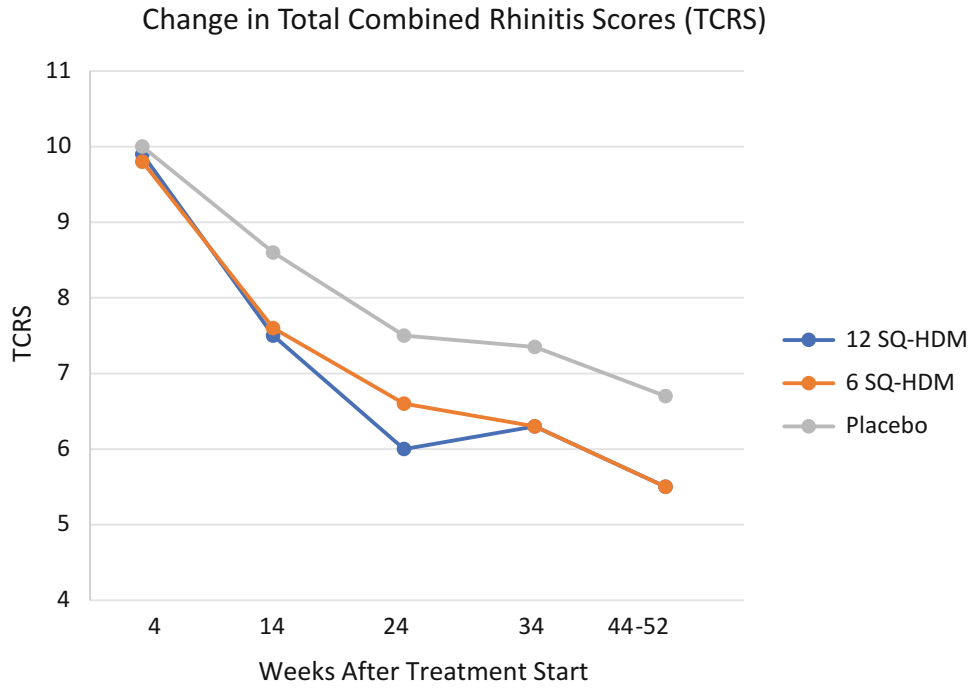

Fig. 4 Changes in combined medication and symptom scores over time with varying doses of HDM SLIT versus Placebo. (Modified from Demoly et al. 2016)

While there are limited studies involving subjects over age 65, one study suggested improvement in symptoms and demonstrated that with 3 years of continuous treatment with Odactra®, symptoms decreased and persisted for 3 years following treatment cessation. Additionally, serum IgE levels decreased and serum IgG_4 levels increased and remained at the same level for 3 years after treatment was stopped (Bozek et al. 2017).

40.5.1 Quality of Life

House dust mite-induced allergic rhinitis (AR) has been linked to an increased risk of developing asthma (Novakova et al. 2017). HDM SLIT is associated with reduced asthma symptoms, exacerbations, and medication use (Mosbech et al. 2014; Nolte et al. 2015). Studies have shown significant improvement of quality of life after 24 weeks of treatment with 12 SQ-HDM tablet including improved sleep and decrease in total nasal symptom scores (TNSS) by 48.6% as well as in the RQLQ score (Fig. 5) (Klimek et al. 2016; Novakova et al. 2017).

40.5.2 Safety and Cost Effectiveness

In addition to having a better safety profile than SCIT, SLIT provides a convenient alternative for those patients who cannot afford the time commitment SCIT treatment requires. Provided that initial administration of SQ HDM SLIT-tablet is performed under medical supervision, the safety and tolerability profiles for SQ-HDM SLIT-tablets supports subsequent at-home administration of doses up to 12 SQ-HDM (Klimek et al. 2016). SLIT is more cost-effective than SCIT because it can be administered at home and thus patients do not have to incur the costs associated with the office visits and injections that SCIT administration requires (Lombardi et al. 2017). SLIT

Table 1 Comparison of FDA-approved SLIT medications. (Modified from The Medical Letter 2018)

FDA-approved sublingual immunotherapy medications						
Medication	Allergen (s)	Formulations	Standard dosage	Cost/ month[a]	Adverse events (AEs)[d]	Contraindications
Oralair® (Stallergenes S.A./Greer)	Sweet vernal, orchard, perennial rye, timothy, and Kentucky blue grass pollen	100 IR (~3000 BAUs) tablets 300 IR (~9000 BAUs) tablets	10–17 years: 100 IR SL on day 1 200 IR on day 2 300 IR once/day 18–65 years: 300 IR SL once/day (Start 4 months before grass season and continue through the season)	~$440	Reported in ≥5%: Oral/ear itch, throat irritation, ear itch, mouth edema, tongue itch, cough, and oropharyngeal pain	1. Severe, unstable or uncontrolled asthma 2. History of any severe systemic allergic reaction or any severe local reaction to sublingual allergen immunotherapy 3. History of eosinophilic esophagitis 4. Hypersensitivity to any of the inactive ingredients contained in this product
Grastek® (ALK)	Timothy grass pollen	2800 BAUs tablets	5–65 years: 1 tab SL once/ day[b]	~$295	Reported in ≥5% of patients: Oral itch, throat irritation, ear itch, mouth edema, oral paraesthesia, tongue itch	
Ragwitek® (ALK)	Short ragweed pollen	12 Amb a 1-unit tablets	18–65 years: 1 tab SL once/ day[b]	~$295	Reported in ≥5% of patients: throat irritation, oral itch, ear itch, oral paresthesia, mouth edema, and tongue itch	
Odactra® (ALK)	House dust mites (HDM)[c]	12 SQ-HDM tablets	18–65 years: 1 tab SL once/ day	~$295	Reported in ≥10% of patients: Mouth itch, throat tickle, ear itch, mouth/ uvula edema, lip edema, tongue edema, nausea, tongue pain, tongue ulcer, stomach pain, mouth ulcer, taste alterations	

BAUs bioequivalent allergy units, *IR* index of reactivity, *SQ* biological potency dose unit standardization, SL sublingually
[a]Wellrx.com, Accessed on June 19, 2018
[b]Start treatment at least 12 weeks before the start of allergy season and continue for the duration of the season. Treatment can continue for 3 consecutive years
[c]Contains extracts from *Dermatophagoides farina* and *Dermatophagoides pteronyssinus*. Prescribe epinephrine auto-injector, observe patient for 30 min after the initial clinic dose administration
[d]Adverse events in order of frequency

treatments with *D. farinae* drops are safe and effective in pre-school and school age children as young as 2 years old who suffer from HDM-induced AR; but FDA approval for this age group has not been attained to date (Tang et al. 2018). However, according to *The Medical*

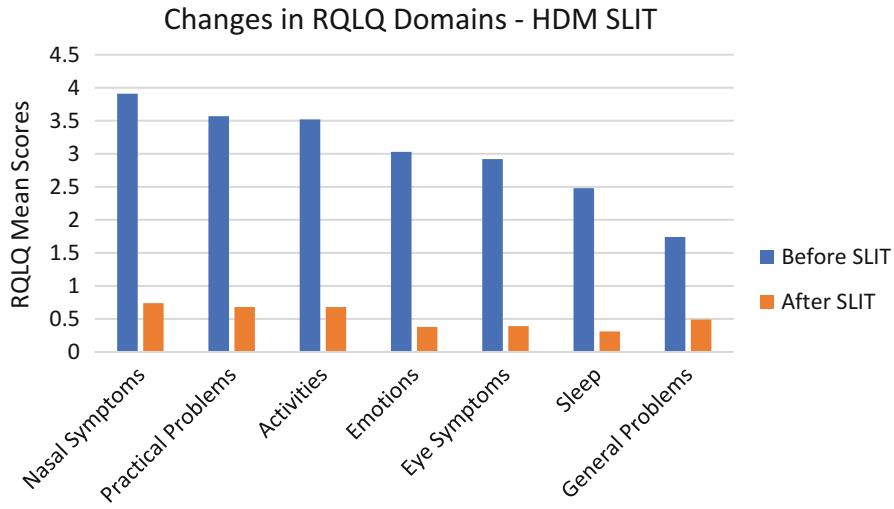

Fig. 5 Changes in RQLQ Domains with HDM SLIT. (Modified from Novakova et al. 2017)

Letter, h_1-antihistamines and intranasal corticosteroids are safer protocols for allergy symptom management and they are less expensive than SLIT (The Medical Letter 2018). One notable challenge in treatment with antihistamines is that they tend to lose their beneficial effect over time through a concept known as the allergy priming phenomenon.

40.6 Grastek®(Timothy Grass Pollen Allergen Extract): From Package Insert on www.fda.gov

Grass pollen is the main cause of pollen allergy responsible for the rise of allergic rhinitis, conjunctivitis, and asthma around the world. Grastek® and Oralair® are the two grass pollen SLIT products currently on the market in the European Union and the United States used to treat grass pollen allergy. Grastek® is a single allergen SLIT medication that contains Timothy grass (*P. pratense* L.) pollen extract (Devillier et al. 2017). Timothy grass has significant commercial use as it is widely cultivated for hay and is indigenous throughout the Northeast and Southeast United States (Larenas-Linnemann 2016).

40.6.1 Effect

Treatment with Grastek® has been shown to be similarly effective in both children and adults. It induces similar immunologic changes, namely an increase in IgG_4 and IgE-blocking factor. Furthermore, it decreases AR symptoms as demonstrated by improvements in total combined symptom and medication scores of 21% (children) and 20% (adults) (Kaur et al. 2017). Year-round treatment for 3 years results in paralleled increases in serum grass pollen allergen-specific IgG_4 antibodies, serum IgE-blocking factor, and serum inhibitory activity for the binding of allergen-IgE complexes to B cells. These changes were sustained for 2 years post treatment, confirming the long-term efficacy of Grastek. In contrast, after treatment with SCIT, IgG_4 levels returned 80% toward baseline levels (Durham et al. 2012). When placed under the tongue, Grastek® dissolves faster than Oralair® because it contains fish gelatin (Larenas-Linnemann 2016).

40.6.2 Adherence

Adherence to treatment is higher in children, yet in both children and adults, adherence diminishes

as length of treatment increases. The main reason cited for noncompliance was treatment-related adverse effects. However, having regular contact with one's health care provider has been shown to increase a patient's adherence to treatment (Kiotseridis et al. 2018). Patient satisfaction and compliance might be linked to the amount of information and time the patient receives from the physician explaining the disease and treatments; therefore, improved communication between patient and physician may increase patient knowledge (Chivato et al. 2017).

40.6.3 Quality of Life

79.2% of patients suffering fromal lergic rhinitis report their symptoms interfere with their professional lives and 91.8% claim their symptoms negatively affect their daily lives (Kiotseridis et al. 2018). Grastek® significantly improves quality of life in children and adults by slowing the progression of allergic rhinitis, reducing the risk of asthma onset in nonasthmatic patients and slowing asthma progression in asthmatic patients (Devillier et al. 2017).

40.6.4 Safety

Of the sublingual immunotherapies available, Grastek® has the most safety and efficacy data (Chivato et al. 2017). Both mono- and polysensitized patients experience significant symptom reductions (Larenas-Linnemann 2016). No safety issues were detected during lung function assessments, physical exams, and vital signs (Durham et al. 2012).

40.7 Oralair®(Sweet Vernal, Orchard, Perennial Rye, Timothy, and Kentucky Blue Grass Mixed Pollens Allergen Extract): From Package Insert on www.fda.gov

Approved by the FDA in 2014, Oralair®, a 5-grass pollen SLIT tablet, was the first allergen immunotherapy tablet to be approved in the United States and it is currently approved for use in 30 other countries (Didier et al. 2015). Oralair® contains pollen extracts from five cross-reacting grasses including cock's-foot or orchard grass (*Dactylis glomerata* L.), sweet vernal grass (*Anthoxanthum odoratum* L.), rye-grass (*Lolium perenne* L.), Kentucky blue-grass or meadow-grass (*Poa pratensis* L.), and Timothy grass (*P. pretense* L.). The FDA set the age limit of Oralair between 10 and 65 years; however, in Europe, Oralair® is used to treat adults and children as young as 5 years old (Larenas-Linnemann 2016).

40.7.1 Safety

At the onset of treatment, mild to moderate local adverse events have been frequently reported but usually resolve within the first 1–2 weeks. Adverse events are less common and less severe when treatment is restarted before the following pollen season. Both mono- and polysensitized patients experience symptom reductions following treatment with Oralair®(Larenas-Linnemann 2016).

40.7.2 Effect

Similarly to Grastek®, treatment with 5-grass SLIT tablets has yielded comparable effects on pediatric and adult populations, reporting a reduction in rhinoconjunctivitis symptom scores by 31% and 29%, respectively (Kaur et al. 2017). Onset of action is detected only 1 month after treatment initiation with Oralair®. Initiating treatment with Oralair® either 2- or 4-months prior to the start of pollen season has been demonstrated to be equally effective at reducing AR symptoms during pollen season. However, long-term (2 years) post-treatment effects are best accomplished when Oralair® is administered using a 4-month coseasonal schedule for 6 months a year for 3 consecutive years (Larenas-Linnemann 2016). Treatment with 5-grass-pollen SLIT tablet led to a 26.4% decrease in asthma medication prescriptions. Overall,

Oralair® has similar efficacy to Grastek® in its ability to delay the progression of AR, reduce the risk of asthma onset in nonasthmatic patients, and slow asthma progression in asthmatic patients (Fig. 6) (Devillier et al. 2017).

40.7.3 Cost Effectiveness

Although Oralair is the most expensive of the four sublingual immunotherapy treatments marketed in the United States, it still presents a cost-effective alternative to AR symptom treatment and management. The average annual cost per patient due to AR, including direct (i.e., office visits, drug treatment) and indirect (i.e., reduced work productivity, sick leave from work or school, sleep disorders, and overall lower quality of life) costs, is $657. In 2005, total cost of treating AR was $11.2 billion. A study in the Czech Republic showed that over a 3-year course of treatment, SCIT costs an average of €1004 ($1242.22) per patient and SLIT costs an average of €684 ($846.29) per patient. Before starting SLIT, the average yearly cost to treat allergies was €2672 ($3305.99) per patient, and during SLIT treatment, yearly costs were reduced to €629 ($778.24) per patient (Fig. 7) (Lombardi et al. 2017).

40.8 Ragwitek®(Short Ragweed Pollen Allergen Extract): From Package Insert on www.fda.gov

Short ragweed is a common seasonal aeroallergen in most of North America (Creticos et al. 2014) affecting roughly 26% of the US population, causing allergic rhinoconjunctivitis (ARC) and significant morbidity. Short ragweed cross-reacts with other ragweed species including European mugwort (Creticos et al. 2013).

40.8.1 Efficacy

Ragwitek is dose-dependent and can be self-administered. A daily dose of 12 Amb a 1-U reduces symptoms and rescue medication use most significantly. To a lesser extent, a 6 Amb a 1-U dose reduces total combined scores (TCS) and daily medication scores (DMS) and a 1.5 Amb a 1-U dose is ineffective (Creticos et al. 2013). Studies show that doses of 3, 6, and 12 result in significant increases in IgE and IgG_4 with the 12 dose producing in the highest increases in IgE and IgG_4 (Nayak et al. 2012). In addition to SLIT tablets, aqueous SLIT drops are effective and well tolerated in patients suffering from ragweed allergies (Creticos et al. 2014).

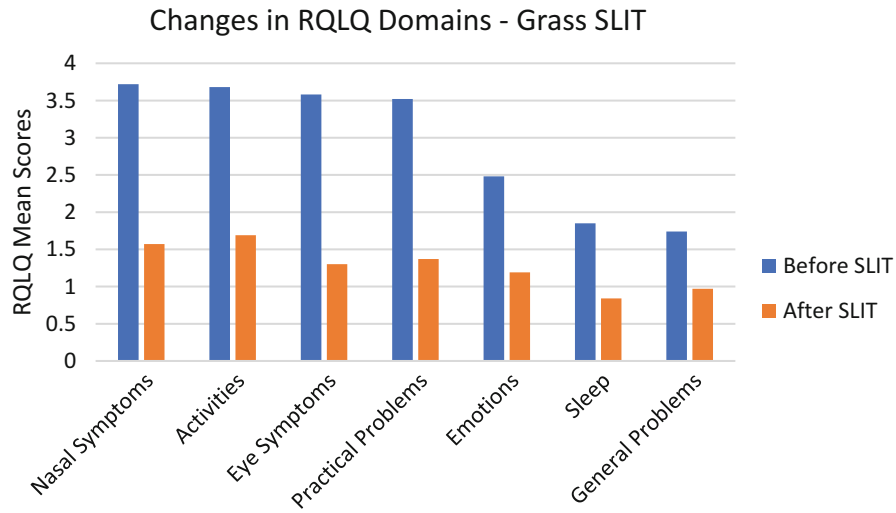

Fig. 6 Changes in RQLQ domains on Grass SLIT. (Modified from Novakova et al. 2017)

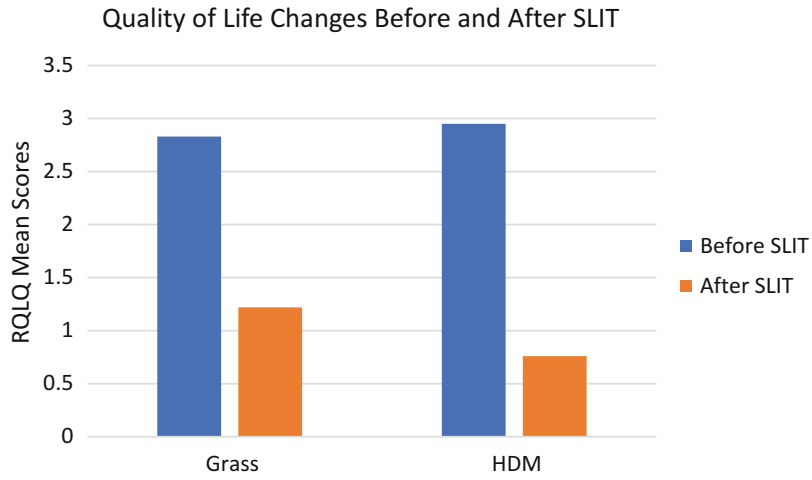

Fig. 7 Comparison of RQLQ changes before and after Grass and HDM SLIT. (Modified from Novakova et al. 2017)

40.9 Conclusion

Allergen immunotherapy has an interesting history spanning over 100 years of research across the globe. The atopic march, whereby allergy symptoms spread across the body through time, leading to eczema, followed by allergic rhinitis and asthma, has been well reported in the literature. Furthermore, the phenomenon of epitope spreading, whereby the immune system expands its ability to recognize new allergens over time, has given insight into the natural history of the disease.

Allergen immunotherapy is the only treatment option that can change the underlying natural history of immediate hypersensitivity reactions to inhaled allergens and alter the course of the atopic march, while blocking the progression of allergic recognition of more inhalational allergens through time. Treatment is safe, well-tolerated, and cost effective. As we develop an understanding into the natural history of the disease with and without treatment, further progress can be made into advancing the goal toward personalized medicine.

Research efforts have provided insight into molecular signaling pathways associated with allergy. Clinical trials looking at blocking allergic pathways, when used in conjunction with allergen immunotherapy, may further increase safety and efficacy of allergen immunotherapy. Splitting allergens into component parts or supplementing treatments with adjuvants, may more closely target mechanisms aimed at generating immune tolerance. Time will tell.

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Biologic and Emerging Therapies for Allergic Disease

41

Christina G. Kwong and Jeffrey R. Stokes

Contents

Abstract

Biologic therapies can be used to treat allergic diseases, which is when the body overreacts or inappropriately responds to normally harmless substances. Several biologic therapies have been successfully developed to treat severe and recalcitrant allergic diseases. Currently approved biologics for the treatment of allergic diseases are omalizumab, benralizumab, mepolizumab, reslizumab, and dupilumab. The majority of these approved biologics are for asthma, but treatment for chronic idiopathic urticaria and atopic dermatitis is also available. Additional research is ongoing for the use of other biologic therapies in a variety of allergic disorders. Approved and investigational biologic therapies for allergic diseases are reviewed in this chapter.

Keywords

Asthma · Allergic disease · Omalizumab · Mepolizumab · Benralizumab · Reslizumab · Dupilumab

Abbreviations

CIU	Chronic idiopathic urticaria
EASI	Eczema Area and Severity Index
EASI-50	Proportion of patients who reach 50% improvement as based on the EASI score

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EASI-75	Proportion of patients who reach 75% improvement as based on the EASI score
FcεRI	High-affinity IgE receptor
FDA	Food and Drug Administration
FeNO	Fractional exhaled nitric oxide
FEV1	Forced expiratory volume in 1 second
ICS	Inhaled corticosteroid
IGA	Investigator's Global Assessment
IgE	Immunoglobulin E
IL	Interleukin
IL-4R	Interleukin-4 receptor
ILC-2	Type 2 innate lymphoid cells
LABA	Long-acting beta-adrenoceptor agonist
LTRA	Leukotriene receptor antagonist
PGD2 receptor	Prostaglandin D2 receptor
SCORAD	Scoring Atopic Dermatitis
T_H-2	T-helper lymphocyte type 2
TSLP	Thymic stromal lymphopoietin

41.1 Introduction

Biologic therapies are any form of therapy that uses the body's immune system to combat disease. They generally contain a component of a living system, such as an antibody. In the past few decades, biologic therapies have emerged as effective treatments for severe and uncontrolled allergic diseases. Allergic diseases are caused by reacting to normally harmless substances or hypersensitivity of the immune system. This includes conditions such as asthma, allergic rhinitis, atopic dermatitis, and food allergy. In this chapter, we will review biologic treatments for allergic diseases with a focus on currently approved therapies.

Two key players in the allergic pathway are the lymphocyte T-helper type 2 (T_H-2) cells and a subtype of nonspecific lymphoid cells called type 2 innate lymphoid cells (ILC-2). Both of these cells produce type 2 cytokines, which are small secreted proteins involved in cell-to-cell signaling and include interleukins 4, 5, and 13 (IL-4, IL-5, IL-13) (Polk and Rosenwasser 2017). Immunoglobulin E (IgE) plays a vital role in the pathogenesis of allergic diseases, especially mast cell/basophil activation, and in antigen presentation. It is necessary for the immediate allergic reaction. Production of IgE requires IL-4 and IL-13 (Steinke et al. 2014). IL-5 is the most important activator of eosinophils, which stimulate allergic inflammation and lead to clinical symptoms. As a result of their effects on the allergic response, these are areas targeted by biologics (Fig. 1).

The efficacy of biologics targeting IgE, IL-4, IL-5, and IL-13 has predominantly been studied in asthma. The response of asthmatics to these biologics has helped us to better characterize asthma endotypes, which are based on pathophysiologic mechanisms. The two major endotypes are T_H2-high and T_H2-low (Table 1) (Barnes 2015; Woodruff et al. 2009). T_H2-high endotypes are characterized by increased eosinophils in the sputum and airways. T_H2-high cells produce the cytokines IL-4, IL-5, and IL-13. Patients with this endotype exhibit a greater response to biologic therapies with these targets. Conversely, T_H2-low endotypes have increased neutrophils or a pauci-granulocytic profile, with normal eosinophil and neutrophil levels (Stokes and Casale 2016). They are less likely to respond to biologics targeting IgE, IL-4, IL-5, and IL-13.

41.2 Biologics

41.2.1 Anti-IgE: Omalizumab

41.2.1.1 Introduction

Omalizumab or Xolair® is a recombinant humanized monoclonal anti-IgE antibody which was approved by the Food and Drug Administration (FDA) in 2003 as the first commercially available biologic treatment for allergic diseases. It is approved for children and adults 6 years of age and older with moderate to severe persistent asthma of an allergic phenotype and 12 years of age and older with chronic idiopathic urticaria, also known as chronic spontaneous urticaria ("Full Prescribing Information, XOLAIR," 2017; Genentech 2003). It is administered

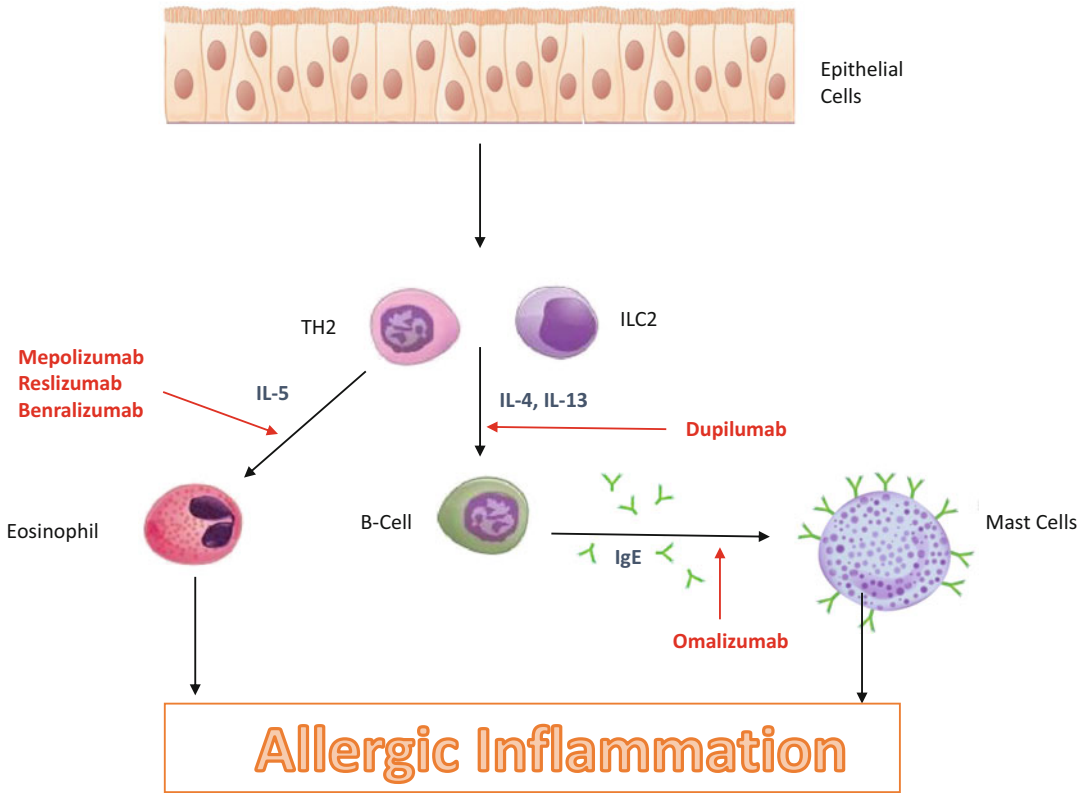

Fig. 1 Target areas for current biologics to treat allergic disease

Table 1 TH2-high and TH2-low asthma

Asthma endotype	Predominant cell type[a]	Primary cytokines	Unique therapeutic targets
T_H2-high	Eosinophils	IL-4, IL-5, IL-13	Eosinophils IgE PGD2
T_H2-low	Neutrophils or Paucigranulocytic[b]	IL-8, IL-17, IL-23	Muscarinic receptors Neutrophils

[a]In sputum and airways
[b]Paucigranulocytic: normal eosinophil and neutrophil levels in the sputum and airways

subcutaneously, and dosing for asthma is adjusted based on weight and IgE.

Atopic individuals secrete IgE antibodies directed at typically harmless substances (allergens). These antibodies circulate and bind to mast cells and basophils at the high-affinity IgE receptor (FcεRI). When these substances are then reintroduced to the bound IgE, cross-linking occurs, stimulating mediator release and allergic inflammation (Fig. 2). Omalizumab functions by decreasing the amount of free IgE that is available to bind aeroallergens and inflammatory cells. It binds to free IgE in a trimer formation, with two omalizumab molecules and one IgE antibody. These complexes are then cleared by the reticuloendothelial system (Brownell and Casale 2004). Since omalizumab binds to IgE at the same site that IgE binds to the high-affinity receptor, omalizumab cannot bind to IgE receptors or to IgE already attached to the mast cell or basophil. Therefore, it does not interact with cell-bound IgE or activate mast cells or basophils. Omalizumab lowers IgE levels and down-regulates the high-affinity IgE receptors ("Full Prescribing Information, XOLAIR," 2017). This limits the release of mediators that can lead to an allergic response.

In chronic idiopathic urticaria (CIU), 80–90% of patients have no known allergic or other

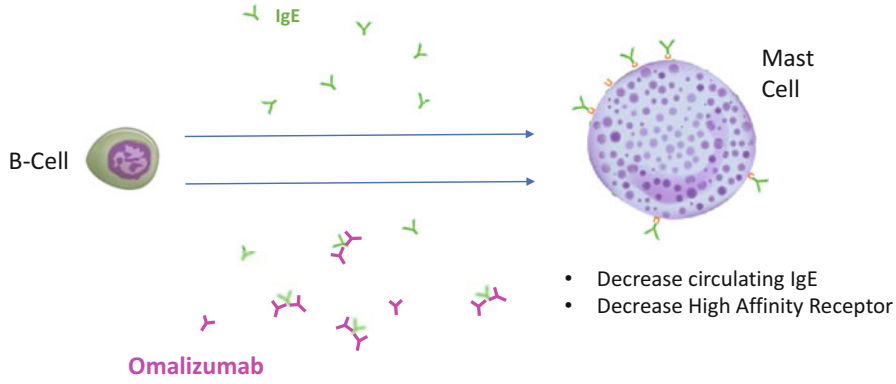

Fig. 2 Mechanism of omalizumab in allergic disease

identifiable cause of their symptoms, and omalizumab's mechanism in reducing urticaria symptoms is not fully known (Sheikh 2005). However, 40–45% of patients with CIU do have an autoimmune component, with the presence of an IgG autoantibody against the high-affinity IgE receptor (Kaplan et al. 2008). Omalizumab may function by preventing binding of the autoantibody with IgE.

41.2.1.2 Clinical Studies

Asthma

Of all of the approved biologics for allergic disease, omalizumab for the treatment of allergic asthma has been the most extensively studied. Early studies found that omalizumab, initially called rhuMAb-E25 which was an abbreviation for "recombinant humanized monoclonal antibody," had potential as a treatment for asthma. It inhibited the binding of IgE to mast cells, caused a significant and immediate reduction of free IgE, and decreased early- and late-phase responses to environmental allergens (Boulet et al. 1997; Fahy et al. 1997). A subsequent phase II study assessed 317 adolescents and adults with allergic asthma who were randomized to receive high- or low-dose omalizumab or placebo (Milgrom et al. 1999). Those receiving omalizumab at either dose had reduced asthma symptom scores and were more likely to successfully decrease or discontinue maintenance inhaled corticosteroid (ICS) treatment.

Several phase III trials confirmed the effectiveness of omalizumab as add-on maintenance treatment for moderate to severe allergic asthma. An early phase III double-blinded, placebo-controlled randomized trial included 525 adolescent and adult patients aged 12–75 years old with uncontrolled symptoms despite ICS treatment. They were treated with either subcutaneous omalizumab or placebo at varying doses every 2–4 weeks (Busse et al. 2001). Concomitant ICS doses were kept stable for 16 weeks and then tapered as tolerated over the next 12 weeks. The omalizumab group experienced a decreased rate of asthma exacerbations (14.6% compared with 23.3% in placebo). Additionally, 75% of patients receiving omalizumab were able to reduce their ICS dose, half of which were weaned off completely, compared with a 50% reduction rate in the placebo group and 19.5% cessation rate. A similar study assessed outcomes of 546 patients during a 16-week steroid-stable phase, followed by an 8-week steroid-reduction phase (Solèr et al. 2001). Comparable results were found, with a lower exacerbation rate and higher success rate of steroid reduction and elimination in the omalizumab treatment group. In a third study, 334 children ages 6–12 and adults with well-controlled asthma were treated with either omalizumab or placebo (Milgrom et al. 2001). In this study, a greater proportion of participants were able to achieve steroid reduction or discontinuation when compared to placebo. However, no significant differences in asthma symptom scores

between groups were found. A pooled analysis of participants in all three studies, which included 1071 adolescents and adults, was performed, confirming that omalizumab subcutaneous treatment decreased the rate of asthma exacerbations, unscheduled outpatient visits, emergency room visits, and hospitalizations related to asthma (Corren et al. 2003).

Further analysis of the phase III trials on 254 higher-risk patients (history of intubation, or a history within the last year of requiring emergency room visit, hospitalization, or intensive care unit) showed that omalizumab therapy resulted in a 56% reduction of asthma exacerbations, decreased symptoms, and increased quality of life scores (Holgate et al. 2001). A pooled analysis of 1070 adolescents and adults from 2 of the phase III trials showed that the greatest improvement from omalizumab was seen in patients with more severe disease (Bousquet et al. 2004). History of emergency room visit within the past year was the most predictive factor of response to omalizumab. Patients also benefited more if their baseline forced expiratory volume in 1 second (FEV1) was at or less than 65% of predicted or if they were on high doses of ICS prior to omalizumab initiation.

Regarding younger children ages 6–12, additional large-scale studies have confirmed omalizumab's efficacy. A randomized, double-blind, placebo-controlled trial of 627 children ages 6–12 with uncontrolled asthma assessed omalizumab versus placebo in a 52-week study (Lanier et al. 2009). Asthma exacerbation rate was reduced by 43% in the omalizumab group when compared with placebo although a significant reduction in maintenance ICS dose was not achieved. In the Inner-City Anti-IgE Therapy for Asthma (ICATA) study, 419 participants aged 6–20 participated in a 60-week trial (Busse et al. 2011). All patients were required to have persistent, uncontrolled allergic asthma. The primary outcome was the number of days with asthma symptoms. In the omalizumab group, the mean number of symptomatic days per 2-week interval was reduced by 24.5%, and hospitalizations were also reduced. The asthma exacerbation rate was also improved, with a rate of 30.3% in the omalizumab group compared with 48.8% in the placebo group.

Multiple meta-analyses have confirmed omalizumab's efficacy in treating allergic asthma. A 2014 Cochrane Report included 25 trials of 6382 adults and children (Normansell et al. 2014). The majority of the studies involved subcutaneous administration, with four of the older studies assessing intravenous or inhalational delivery. Study durations ranged between 8 and 60 weeks. Overall, omalizumab was associated with improvement in asthma symptoms and quality of life, decreased asthma exacerbation rates, and a reduction in the daily required ICS dose. A review of 8 trials with 3429 patients found that those receiving omalizumab as add-on therapy experienced decreased asthma exacerbations (risk ratio of 0.57) and hospitalizations (risk ratio of 0.44) and were more likely to successfully discontinue maintenance ICS treatment (Rodrigo et al. 2011). These effects seemed to be independent of age, duration of treatment, and asthma severity.

Multiple studies have assessed the "real-world" effects of omalizumab, in that it is added to the medical regimen of patients who have poorly controlled asthma despite maximal medical therapy. In the INNOVATE trial, 419 adolescents and adults with uncontrolled severe persistent asthma despite combination of high-dose ICS and long-acting bronchodilator agonist therapy received omalizumab or placebo as an add-on therapy for 28 weeks (Humbert et al. 2005). Those receiving omalizumab experienced reduced rates of severe asthma exacerbation compared to placebo (0.24 vs 0.48) and a similar decrease in emergency room visits. Patients also reported improved quality of life. Another similar but longer study with 312 patients receiving omalizumab or placebo for 1 year also reported similar results (Ayres et al. 2004). Those omalizumab-treated patients experienced decreased asthma exacerbation rates (2.86 vs 1.12 in placebo), symptoms, and rescue bronchodilator use, as well as improved lung function. Recently, the eXpeRience registry assessed 943 patients from 14 countries who had uncontrolled persistent asthma on omalizumab

therapy for 2 years (Braunstahl et al. 2013). This was a single-arm, open-label, observational registry. They found that 69.9% of patients responded to omalizumab after 16 weeks with a reduction in symptoms, rescue medication use, and asthma exacerbation rates. In 2017, a meta-analysis of "real-life" effectiveness studies included 25 trials assessing omalizumab in uncontrolled asthma as add-on therapy to ICS with or without long-acting beta-adrenoceptor agonist (LABA) therapy (Alhossan et al. 2017). Omalizumab therapy was found to reduce symptoms, ICS and oral corticosteroid use, asthma exacerbations, and hospitalizations and improve FEV1 and quality of life.

A few biomarkers have been identified as potential predictors and markers of response. A high blood eosinophil count has been shown to be predictive of an improved response to omalizumab, with an increased reduction in asthma exacerbations in the high eosinophil group (>300 cells/μL) (Busse et al. 2013). Blood and sputum eosinophil counts also decrease from baseline during omalizumab therapy (Fahy et al. 1997; Noga et al. 2003). An analysis of biomarkers from patients from the EXTRA study showed that a greater response to omalizumab was found in patients with higher fractional exhaled nitric oxide (FeNO), blood eosinophil, or blood periostin levels (Hanania et al. 2013). The FeNO levels were significantly reduced from baseline with omalizumab use, even when maintenance ICS doses were also reduced (Silkoff et al. 2004).

The duration of post-withdrawal effectiveness of omalizumab has not yet been clearly defined. Evaluating the Xolair Persistency of Response After Long-Term Therapy (XPORT) was a randomized, double-blind, placebo-controlled trial which aimed to assess the persistence of response to omalizumab (Ledford et al. 2017). Study participants were between 17 and 70 years of age and had moderate or severe persistent asthma, with stable disease and a treatment regimen including omalizumab for at least several years. Most patients were from the EXCELS study, which was a post-marketing observational study to assess safety. A total of 176 subjects were randomized to continuation of therapy with omalizumab or placebo for 52 weeks. Patients who continued to receive omalizumab had better asthma control and were more likely to have no exacerbations during the study period (67% vs 47.7% in the placebo group, which is a 40.1% relative difference). Time to first exacerbation was longer in the omalizumab group. The Spanish Omalizumab Registry assessed the persistence of response after stopping long-term omalizumab. Forty-nine patients discontinued treatment after 6 years of omalizumab therapy and were followed for at least 4 years. Asthma exacerbations requiring oral corticosteroids occurred in 12 patients within the first 12 months and in 7 additional patients in the next 36 months. Based on these observations, the effects of 6 years of omalizumab therapy were estimated to persist for over 4 years in at least 60% of patients.

In addition to its established use as maintenance therapy, research is also being performed regarding its use as a targeted approach for reducing peak asthma exacerbations. Asthma is known to have seasonal variability, with peaks during the fall and lower rates during the summer (Gergen et al. 2002; Johnston et al. 2005). Omalizumab reduces asthma exacerbation rates during all seasons, with seasonal exacerbation rates compared with placebo as follows: 4.3% versus 9.0% in the fall, 4.2% versus 8.1% in the spring, and 3.3% versus 4.6% in the summer (Busse et al. 2011). Since asthma exacerbations are highest in the fall, the Preventative Omalizumab or Step-up Therapy for Fall Exacerbations (PROSE) study assessed the effect of preseasonal treatment with 4 months of omalizumab or an ICS boost compared with placebo, initiated 4–6 weeks prior to the first day of school on 513 children ages 6–17 with uncontrolled allergic asthma (Teach et al. 2015). Those receiving omalizumab were found to have a significantly lower fall exacerbation rate when compared with placebo (11.3% vs 21.0% odds ratio (OR) 0.48), but not when compared with the ICS boost (8.4% vs 11.1%, OR 0.73). It is likely that omalizumab may be differentially effective in certain subgroups.

Urticaria

Early research studies have also demonstrated the efficacy of omalizumab in the treatment of chronic idiopathic urticaria. The three key phase III trials were ASTERIA I, ASTERIA II, and GLACIAL. ASTERIA I and II were both multicenter trials which enrolled adolescents and adults with uncontrolled chronic idiopathic urticaria despite antihistamine use (Maurer et al. 2013; Saini et al. 2015). Patients were randomized to three different doses of omalizumab (75, 150, and 300 mg) or placebo given subcutaneously every 4 weeks. ASTERIA I enrolled 318 participants for a 24-week treatment period (Saini et al. 2015). In ASTERIA I, all doses of omalizumab resulted in a decrease in baseline itching. In the high-dose 300 mg group, symptom improvement was seen by the first week of therapy. By week 12, 52% had well-controlled urticaria, and 36% experienced complete control. ASTERIA II enrolled 323 similar participants for a shorter 12-week treatment period with a 16-week observation period (Maurer et al. 2013). The two higher omalizumab doses (150 mg and 300 mg) correlated with a clinically significant improvement in weekly itch severity scores. By week 12, those in the 300 mg omalizumab group had significantly higher rates of being hive-free (53% vs 10% in placebo), and both hive- and itch-free (44% vs 5% in placebo). The GLACIAL study was unique in that participants failed high-dose antihistamine therapy, up to four times the approved dose, as well as either H2 antihistamines, leukotriene receptor antagonists (LTRA), or both (Kaplan et al. 2013). Even in this group, omalizumab reduced the weekly itch severity score. Pooled data from all three studies showed that treatment with omalizumab 300 mg given subcutaneously every 4 weeks was similarly efficacious regardless of the background therapy (Casale et al. 2015).

Other Conditions

Omalizumab use has been described in other atopic diseases in small trials and case reports. Multiple research studies have demonstrated that omalizumab treatment is associated with symptomatic improvement in perennial and seasonal allergic rhinitis (Ädelroth et al. 2000; Casale et al. 2001; Chervinsky et al. 2003; Tsabouri et al. 2014). In patients with food allergies, omalizumab pretreatment can increase the likelihood of achieving oral food desensitization to prespecified doses and decrease adverse reactions (Andorf et al. 2018; Nadeau et al. 2011; Wood et al. 2016). A few small studies have suggested symptomatic improvement in patients with nasal polyps and comorbid asthma treated with omalizumab (Gevaert et al. 2013; Penn and Mikula 2007; Pinto et al. 2010).

41.2.1.3 Safety

Omalizumab has been extensively studied for several decades and has been shown to be well tolerated in the majority of patients. In asthma studies, injection site reactions were the most common, occurring with similar frequency in both omalizumab and placebo groups (45% vs 43%) ("Full Prescribing Information, XOLAIR," 2017). Other relatively frequent adverse events were also observed at similar rates in the treatment and placebo groups and included viral infections (23%), upper respiratory tract infections (20%), sinusitis (15%), headache (15%), and pharyngitis (11%).

Omalizumab has a black box warning for anaphylaxis. Anaphylaxis was reported at an estimated frequency of approximately 0.1–0.2%, based on exposure reports of approximately 57,300 patients during a 3-year period ("Full Prescribing Information, XOLAIR," 2017). Most of these reactions occur during the first three doses (Lieberman et al. 2016). Due to the potential risk of anaphylaxis, the Omalizumab Joint Task Force recommends that all patients have an epinephrine auto-injector available during and after omalizumab treatment. They should be monitored in a medical setting for 2 h after the first three injections and for 30 min for each subsequent injection (Cox et al. 2007).

Potential malignancies had been a concern with omalizumab treatment. In the initial studies, neoplasms were seen in 0.5% of those treated with omalizumab, compared with 0.2% treated with placebo ("Full Prescribing Information, XOLAIR," 2017). There was no predominance of a particular type of malignancy. Most patients

were only assessed for 1 year. Subsequently, a multicenter prospective cohort study was performed to assess long-term safety (Long et al. 2014). The Epidemiologic Study of Xolair (omalizumab): Evaluating Clinical Effectiveness and Long-term Safety in Patients with Moderate-to-Severe Asthma (EXCELS) was a phase IV post-marketing long-term safety study of 7836 adolescents and adults, comparing those treated with omalizumab with those who had not. The omalizumab cohort had a higher proportion of patients with severe asthma compared with the non-omalizumab cohort (50.0% vs 23.0%). During the 5-year follow-up period, no difference in malignancy rate was noted. Of note, a small increase in cardiovascular and cerebrovascular events was noted in this cohort (13.4 events per 1000 years in the omalizumab group compared with 8.1 in those not treated with omalizumab) (Iribarren et al. 2017).

41.2.2 IL-5 Inhibitors: Mepolizumab

41.2.2.1 Introduction

Mepolizumab, or Nucala®, is a humanized IgG1 kappa monoclonal anti-IL-5 antibody. It was approved in November 2015 for maintenance treatment of severe, eosinophilic-phenotype asthma in patients 12 years of age and older ("FDA approves Nucala to treat severe asthma," 2015). It is administered subcutaneously every 4 weeks. Mepolizumab binds to IL-5 which inhibits it from binding to the IL-5 receptor complex on the eosinophil (Fig. 3) ("Full Prescribing Information, NUCALA," 2017). This reduces eosinophil production and survival. Eosinophils are known to be involved in inflammation, which contributes to asthma pathogenesis.

41.2.2.2 Clinical Studies

Asthma

After two proof-of-concept trials showed a correlation between mepolizumab treatment and reduction of asthma exacerbations, the large-scale trials DREAM and MENSA were performed (Haldar et al. 2009; Nair et al. 2009; Ortega et al. 2014; Pavord et al. 2012). The Dosing Ranging Efficacy and Safety with Mepolizumab (DREAM) study was a multicenter, double-blind, placebo-controlled trial of 621 patients 12–74 years of age with uncontrolled severe persistent asthma (Pavord et al. 2012). Patients had to have evidence of eosinophilic inflammation, which means that they had an elevated sputum eosinophil count (3% or greater) or blood eosinophil count (at least 300 cells/μL), elevated exhaled nitric oxide concentration, or worsening symptoms after decreasing maintenance steroid doses by 25% or less. Participants were randomized to one of three doses of intravenous mepolizumab (75 mg, 250 mg, or 750 mg) or placebo, given every 4 weeks for a total of 52 weeks. A significant 48–52% decrease in asthma exacerbations was found in all mepolizumab treatment groups when compared to placebo. Mepolizumab treatment also reduced the levels of sputum and blood eosinophils. Despite this no effect was seen on FEV1 scores during pulmonary function testing. No change in asthma control or quality of life scores was observed. The Mepolizumab as Adjunctive Therapy in Patients with Severe Asthma (MENSA) study compared intravenous and subcutaneous mepolizumab formulations with placebo in a similar population (Ortega et al. 2014). The rate of clinically significant asthma exacerbations was decreased by a similar amount in the intravenous and subcutaneous groups (47% vs 53%), when compared with placebo. Mepolizumab treatments were also associated with an improvement in FEV1. A post hoc analysis of the DREAM and MENSA studies confirmed that mepolizumab treatment reduced the rate of asthma exacerbations (Ortega et al. 2016). Additionally, increased baseline blood eosinophil count was associated with a greater response to mepolizumab. The exacerbation rate reduction was 52% in patients with a baseline blood eosinophil count of at least 150 cells/μL, which increased to 70% in those with eosinophil levels of at least 500 cells/μL.

A meta-analysis published further assessed the effect of mepolizumab on the frequency of asthma

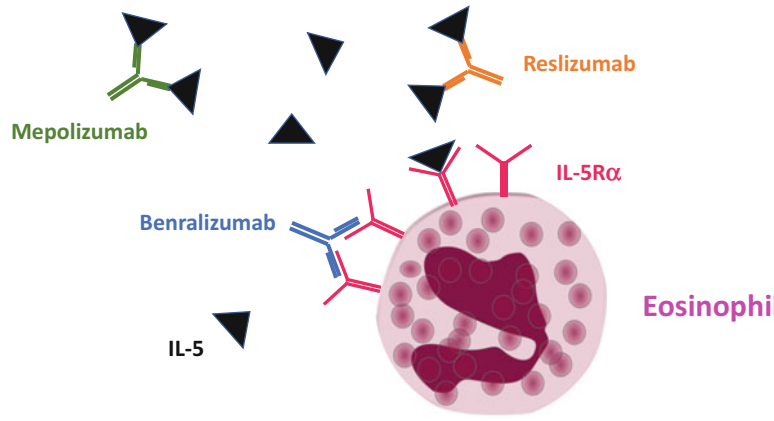

Fig. 3 Mechanism of current anti-IL 5 therapies

exacerbations (Yancey et al. 2017). It included four studies with a total of 1388 severe asthmatics in the final analysis. Mepolizumab treatment resulted in a significant reduction in asthma exacerbations requiring hospitalization (relative rate 0.49). The frequency of hospitalizations or emergency room visits was also decreased by approximately 50%.

The MUSCA (Mepolizumab adjUnctive therapy in subjects with Severe eosinophiliC Asthma) study assessed 551 participants in a randomized, double-blind, placebo-controlled, parallel-group trial in 146 centers in 19 countries for 24 weeks (Chupp et al. 2017). This was the first trial with the primary aim of assessing the impact of mepolizumab on disease-specific quality of life, based on questionnaire assessments. Mepolizumab treatment was significantly associated with early and sustained improvements in quality of life scores.

Additionally, mepolizumab is associated with a successful reduction of maintenance oral corticosteroid requirements. A pilot study found that patients receiving intravenous mepolizumab experienced a 84% decrease in daily oral corticosteroid requirements compared with placebo (Nair et al. 2009). The Steroid Reduction with Mepolizumab Study (SIRIUS) was a larger, randomized, double-blinded, placebo-controlled trial of severe asthmatics with an eosinophilic phenotype (Bel et al. 2014). In the prior MENSA study, only 25% of participants were taking daily oral corticosteroids, whereas in SIRIUS all participants were on the equivalent of 5–35 mg of prednisone per day. The primary outcome was the degree of reduction in the oral corticosteroid dose at week 24, 4 weeks after completing 20 weeks of subcutaneous mepolizumab administered every 4 weeks. Those receiving mepolizumab had a 50% median reduction in steroid dose from baseline, while there was 0% reduction in the placebo group. Additionally, the treatment group also experienced a 32% relative reduction in the rate of asthma exacerbations.

There have been no direct comparisons between mepolizumab and omalizumab. One study performed an indirect comparison by performing a systematic literature review and analysis of 7 mepolizumab and 29 omalizumab studies (Cockle et al. 2017). In the "overlap" population of patients who were eligible for both treatments, no differences in the rate of total asthma exacerbations and those requiring hospitalization were found between the two treatments. Another study performed a post hoc analysis of patients with severe eosinophilic asthma who first received omalizumab and later mepolizumab, using data from the MENSA and SIRIUS trials (Magnan et al. 2016). The response to mepolizumab was similar irrespective of whether or not the patient had previously been on omalizumab. Patients who previously received omalizumab experienced similar asthma exacerbation reductions, maintenance corticosteroid dose reductions, and improvements in quality of life scores when compared with omalizumab naive patients.

The optimal duration of mepolizumab is not known. One 12-month posttreatment analysis observed a significant increase in blood eosinophil levels, asthma symptoms, and exacerbation rates after stopping therapy (Haldar et al. 2014).

Other Conditions

Mepolizumab is not approved for any other atopic diseases. Research studies have suggested a potential role of mepolizumab in eosinophilic esophagitis (Assa'ad et al. 2011; Otani et al. 2013; Stein et al. 2006; Straumann et al. 2010) and chronic sinusitis with nasal polyps (Gevaert et al. 2011).

41.2.2.3 Safety

Mepolizumab has been shown in research studies to be generally well tolerated ("Full Prescribing Information, NUCALA," 2017; Lugogo et al. 2016). Hypersensitivity reactions are a potential risk, but in research trials, the reaction rate in the treatment groups was less than in placebo ("Full Prescribing Information, NUCALA," 2017). Injection site reactions such as pain, erythema, itching, a burning sensation, or swelling were reported in 8% of mepolizumab-treated patients, compared with 2% in the placebo group. Notably, herpes zoster was reported in two patients in the mepolizumab group compared with 0 in the placebo group.

41.2.3 IL-5 Inhibitors: Reslizumab

41.2.3.1 Introduction

Reslizumab or Cinqair® is a humanized monoclonal IgG4 kappa antibody directed against IL-5. It was approved in March 2016 for maintenance treatment of severe persistent eosinophilic asthma in patients aged 18 and older ("Full Prescribing Information, CINQAIR," 2016). Similar to mepolizumab, reslizumab blocks IL-5 from binding to the IL-5 receptor on the surface of eosinophils, preventing eosinophil maturation and survival (Fig. 3). It is administered in healthcare settings only as a weight-based intravenous infusion given every four weeks.

41.2.3.2 Clinical Studies

Asthma

One of the earlier studies assessed the impact of intravenous reslizumab in adults with severe persistent asthma (Castro et al. 2011). Those receiving reslizumab had improved lung function, but only patients with nasal polyps had improved asthma control scores. Later studies that stratified patients by blood eosinophil counts or only included patients with higher baseline eosinophil levels found that reslizumab had greater efficacy. Likewise, when another cohort of adults with moderate or severe persistent asthma and unselected for eosinophil counts were randomized to reslizumab or placebo, no improvement in lung function was detected (Corren et al. 2016). But the subgroup of patients with blood eosinophil counts 400 cells/μL or greater did show a significant improvement in lung function and degree of asthma control. Two additional parallel-group, placebo-controlled, double-blind trials randomized 953 adolescents and adults with poorly controlled moderate or severe persistent eosinophilic asthma to receive intravenous reslizumab or placebo (Castro et al. 2015). Compared to placebo, the rate of asthma exacerbations per year was reduced by 50–59% in the treatment group. Additionally, they had significant improvements in FEV1 and quality of life scores.

Regarding dosing, two dose regimens of reslizumab (0.3 mg/kg, 3.0 mg/kg) were compared with placebo, and only the higher dose was associated with improvements in lung function, asthma symptoms, asthma control, and quality of life (Bjermer et al. 2016).

A 2017 meta-analysis of the above 5 studies, with a total of 1366 patients, further confirmed that reslizumab treatment resulted in a decrease in blood eosinophil levels and frequency of asthma exacerbations (Li et al. 2017). It also improves asthma symptoms and quality of life.

Other Conditions

Reslizumab is not approved for any other atopic conditions. It has been studied in children and adolescents with symptomatic eosinophilic esophagitis (Spergel et al. 2012). Although

eosinophil counts were reduced in the esophagus, no improvement in clinical symptoms was observed.

41.2.3.3 Safety

Reslizumab has a black box warning for risk of anaphylaxis, which was seen in 0.3% of patients in clinical trials (three patients compared to zero on placebo) ("Full Prescribing Information, CINQAIR," 2016). Malignancy was observed more frequently in the reslizumab group (0.6% compared with 0.3% in placebo). There was no association with a particular type of malignancy. Other adverse events more commonly observed in the reslizumab group compared to placebo included oropharyngeal pain (2.6% vs 2.2%), transient elevated creatine phosphokinase levels (0.8% vs 0.4%), and myalgia (1% vs 0.5%).

41.2.4 IL–5 Inhibitors: Benralizumab

41.2.4.1 Introduction

Benralizumab or Fasenra® is a humanized monoclonal IgG1 kappa antibody directed against IL-5. Unlike the other IL-5 inhibitor biologic therapies, benralizumab binds to the IL-5 receptor alpha subunit, preventing IL-5 binding and the downstream effects associated with eosinophilic activation, maturation, and survival (Fig. 3) ("Full Prescribing Information, FASENRA," 2017). It was approved in November 2017 as maintenance therapy for treatment of severe persistent eosinophilic asthma in patients 12 years of age and older. It is administered as a subcutaneous injection, given every 4 weeks for the first three doses and subsequently every 8 weeks.

41.2.4.2 Clinical Studies

Asthma

The safety and efficacy of benralizumab therapy as an addition to high-dose ICS maintenance therapy were demonstrated in the CALIMA and SIROCCO studies (Bleecker et al. 2016; FitzGerald et al. 2016). The CALIMA study was a randomized, double-blinded, parallel-group, placebo-controlled phase III study which included 1306 patients ages 12 and older with uncontrolled moderate or severe persistent eosinophilic asthma (FitzGerald et al. 2016). They were randomized into either benralizumab subcutaneous therapy given every 4 or 8 weeks or placebo. Those receiving benralizumab had reduced rates of asthma exacerbations compared with placebo and improved lung function. The greatest improvement in exacerbation rates was observed in patients with elevated blood eosinophil levels of 300 cells/μL or greater. The other large phase III study, SIROCCO, enrolled a similar population as CALIMA, with the exception that all participants had to be on high-dose ICS/LABA combination therapy (Bleecker et al. 2016). CALIMA allowed only for medium-dose ICS/LABA controller therapy (FitzGerald et al. 2016). Benralizumab treatment dosing was the same as in CALIMA. The primary endpoint, a decrease in annual asthma exacerbations during the 48-week study period, was demonstrated in both treatment dosing regimens, with a greater improvement noted in patients with blood eosinophil counts of 300 cells/μL or greater. Lung function was also improved. Interestingly, similar to the CALIMA findings, asthma symptoms only improved with every 8-week benralizumab dosing and not with every 4-week regimen, for reasons that are unclear. A pooled analysis of the SIROCCO and CALIMA studies showed that higher rates of asthma exacerbation reduction correlated with higher baseline blood eosinophil counts (FitzGerald et al. 2017).

In a third large randomized control trial, ZONDA, benralizumab was found to have an oral glucocorticoid-sparing effect in 220 adults with severe asthma (Nair et al. 2017). Both every 4- and 8-week dosing of benralizumab resulted in a reduction in the median final steroid dose by 75% versus 25% for placebo. Interestingly, the responders and nonresponders had similar baseline blood eosinophil counts in a preliminary analysis. Benralizumab treatment did deplete blood and sputum eosinophil levels. Annual exacerbation rates were also reduced, but no significant change in lung function was demonstrated. In these three studies, benralizumab was demonstrated to decrease the rate of asthma

exacerbations, while improvements in lung function were less consistent.

Benralizumab treatment for patients with uncontrolled mild to moderate asthma was assessed in the BISE trial, but efficacy was not demonstrated when evaluating improvement in FEV1 (Ferguson et al. 2017).

Regarding all IL-5 inhibitors, a 2017 Cochrane review by Farne et al. reviewed studies assessing a total of 6000 patients who received mepolizumab, reslizumab, or benralizumab. Overall, anti-IL 5 therapy led to improved FEV1, reduced asthma exacerbations, and improved quality of life (Farne et al. 2017).

41.2.4.3 Safety

In research studies, the most common adverse effects were asthma exacerbations and nasopharyngitis, with no difference found in the rates between treatment and placebo groups ("Full Prescribing Information, FASENRA," 2017). Side effects with an incidence of 5% or greater were headache and pharyngitis. Similar to recommendations for reslizumab and mepolizumab, the package insert recommends when on benralizumab therapy, maintenance corticosteroid dosing should be reduced gradually, not abruptly ("Full Prescribing Information, CINQAIR," 2016, "Full Prescribing Information, NUCALA," 2017).

41.2.5 IL–4 and IL–13 Inhibitors: Dupilumab

41.2.5.1 Introduction

Dupilumab, also called Dupixent®, is a humanized monoclonal IgG4 antibody directed against the IL-4 receptor (IL-4R) which was approved in March 2017 for the treatment of atopic dermatitis in adult patients 18 years of age and older with uncontrolled moderate or severe atopic dermatitis ("Full Prescribing Information, DUPIXENT," 2017). It is given as a subcutaneous injection every other week. Dupilumab binds to the IL-4R alpha subunit, which inhibits both IL-4 and IL-13 signaling. While the precise mechanism of dupilumab in atopic dermatitis is not fully known, recent studies suggest that the mechanism may be related to improvement in skin barrier function, RNA transcriptome alterations, and reduction in epidermal hyperplasia in lesional sites (Beck et al. 2014).

41.2.5.2 Clinical Trials

Atopic Dermatitis

After initial studies demonstrated that dupilumab had a potential role in treating asthma, Beck et al. conducted four studies of dupilumab in adult patients with uncontrolled moderate to severe atopic dermatitis (Beck et al. 2014). All were double-blind, placebo-controlled, randomized trials. Three were monotherapy studies, including two 4-week studies (phase 1) and one 12-week study (phase 2a), while one was a combination therapy study (Beck et al. 2014). Multiple doses of dupilumab given as weekly subcutaneous injections were assessed. Three of the studies had a primary end point of safety, but all four studies included clinical endpoints. Across the 4 studies, a total of 127 patients completed the trial on the varying dupilumab doses compared with 80 on placebo treatment, due to a high placebo study discontinuation rate. In all studies, dupilumab resulted in a rapid, significant, and dose-dependent improvement in all measured markers. In the 4-week monotherapy trials, 59% of all dupilumab-treated patients reported at least a 50% improvement in their Eczema Area and Severity Index score (EASI-50) compared with 19% in the placebo group. The greatest improvement was seen in the highest dose group, 300 mg dupilumab once weekly, of which over 70% achieved EASI-50. Improvements in pruritus and affected body surface area were also observed. Similar results were reported in both the 12-week monotherapy and 4-week combination studies.

Two subsequent phase III trials, SOLO 1 and SOLO 2, were performed in parallel to assess dupilumab's efficacy and safety (Simpson et al. 2016). They each enrolled approximately 700 patients and were 16-week monotherapy studies which included adult patients with uncontrolled moderate to severe atopic dermatitis.

Participants received subcutaneous injections of weekly or every-other-week dupilumab, or weekly placebo. The primary end point was the proportion of participants with an Investigator's global assessment (IGA) score of 0 or 1 (interpreted as clear or almost clear), and a key secondary endpoint was the achievement of EASI-75 during the study, as well as other markers of symptomatic improvement (mean percent change in EASI score, SCORing atopic dermatitis (SCORAD) score, and global individual signs score). Significant improvements in IGA and EASI-75 scores were found in both dupilumab regimens in both trials. Notably, every other week dosing of dupilumab was found to be fairly comparable to weekly dosing.

Asthma

Although dupilumab is not currently approved for the treatment of asthma, multiple studies indicate a potential therapeutic role, and phase III studies are ongoing. Early studies of adding dupilumab subcutaneous therapy to the treatment regimens of patients with moderate or severe persistent eosinophilic asthma have led to significant decreases in asthma exacerbations and improvements in lung function. In one 12-week study of weekly dupilumab, the asthma exacerbation rate decreased by 87% in the treatment group (6% with dupilumab compared to 44% with placebo) (Wenzel et al. 2013). Lung function, as assessed by improvement in FEV1 from baseline, and asthma symptom scores were all significantly improved in the dupilumab group.

A subsequent research trial assessed the effectiveness of dupilumab in 769 participants from 174 study sites (Wenzel et al. 2016). Similarly, eligibility requirements were adult patients with moderate to severe persistent asthma. However, baseline eosinophil counts were measured but not used for determining study entry. This trial compared multiple dupilumab dosing and interval regimens for 24 weeks, followed by a 16-week follow-up period. All dupilumab treatment regimens were associated with a decreased rate of severe asthma exacerbations and FeNO levels, with significant improvements in lung function. In general, the results were more significant in the subgroup with serum eosinophil levels of 300 cells/μL or greater.

Phase III trials are ongoing to assess dupilumab's efficacy and safety for the treatment of asthma. Two studies evaluating the efficacy and safety of dupilumab are the phase III Liberty asthma quest study for adolescents and adults and VOYAGE for children 6 to <12 years of age (Sanofi 2017a, 2018a). VENTURE is another phase III trial assessing dupilumab's efficacy in reducing maintenance oral corticosteroid doses (Sanofi 2017b), while Liberty asthma traverse is assessing long-term safety (Sanofi 2018b). Lastly, there is a Dupilumab compassionate use study for patients with extremely severe asthma (Wenzel 2017). Regarding dupilumab's mechanism, EXPEDITION is a phase II randomized trial assessing the effect of dupilumab on inflammatory cells in the bronchial submucosa (Sanofi 2018c).

Other Conditions

Dupilumab is not approved for any other atopic conditions aside from atopic dermatitis. Phase III studies for nasal polyposis, atopic dermatitis, and eosinophilic esophagitis are under development. Dupilumab also has a potential role in treating patients with comorbid asthma and chronic sinusitis with nasal polyps, but additional studies are needed (Bachert et al. 2016; Barranco et al. 2017).

41.2.5.3 Safety

Hypersensitivity was reported in less than 1% of treated patients and included conditions such as serum sickness and generalized urticaria ("Full Prescribing Information, DUPIXENT," 2017). Conjunctivitis in particular and keratitis were both reported more frequently in the dupilumab group compared to placebo in research studies. Of note, no increased rate of eczema herpeticum or herpes zoster was noted in the treatment group when compared to placebo.

Table 2 summarizes the current FDA-approved biologics for the treatment of allergic disease.

Table 2 Approved biologic therapies by indication

Disease condition	Approved biologics
Moderate or severe atopic dermatitis	Dupilumab
Chronic idiopathic urticaria	Omalizumab
Moderate-severe persistent allergic asthma	Omalizumab
Severe persistent eosinophilic asthma	Benralizumab Mepolizumab Reslizumab

41.2.6 Other Potential Therapies

Additional investigational biologic therapies are currently being evaluated for efficacy in allergic diseases.

41.2.6.1 IL–2 Receptor Inhibitor, Daclizumab

Daclizumab is a humanized monoclonal antibody that binds to the alpha subunit of the IL-2 receptor, consequently inhibiting IL-2 binding (Busse et al. 2008). It is currently on the market under the trade name Zinbryta and is approved for multiple sclerosis ("Full Prescribing Information, ZINBRYTA," 2016). It is not approved for any allergic disorders. IL-2 is involved in T-cell activation and expansion, and it is hypothesized that a T-cell targeted therapy may have a yet unexplored role in the treatment of asthma (Steinke et al. 2014). A proof-of-concept, randomized, placebo-controlled, double-blind, parallel-group study of 115 adult patients with moderate to severe persistent asthma has been performed (Busse et al. 2008). Participants received intravenous daclizumab for 12 weeks, and then the maintenance ICS dose was tapered over 8 weeks. Treatment with daclizumab was found to improve lung function and asthma control and prolonged time to first asthma exacerbation. Regarding safety, three patients in the daclizumab group reported severe adverse events considered to be related to the study drug, compared to zero in the placebo group. These severe adverse events were an anaphylactoid reaction requiring epinephrine and intubation, varicella zoster viral meningitis, and breast cancer.

41.2.6.2 IL–13 Inhibitor, Tralokinumab

Tralokinumab is a humanized monoclonal antibody against IL-13. After initial studies suggested a potential role of its use in the treatment of asthma, a phase II trial found that in adult patients with uncontrolled, moderate to severe persistent asthma, treatment with subcutaneous tralokinumab led to improvements in lung function, but not in quality of life scores (Piper et al. 2013). A subsequent phase IIb trial of 452 adults with uncontrolled, severe persistent asthma found that tralokinumab treatment did not reduce asthma exacerbations (Brightling et al. 2015). However, post hoc analyses found that a greater improvement in lung function was associated with certain characteristics: elevated biomarker levels, the presence of bronchodilator reversibility on pulmonary function testing, and the absence of chronic oral corticosteroid maintenance therapy. Two phase III trials, STRATOS2 and TROPOS, are currently ongoing to assess its efficacy and safety in the treatment of asthma, with a focus on subgroups that may derive the greatest benefit (AstraZeneca 2017).

41.2.6.3 Thymic Stromal lymphopoietin Antibody (Anti-TSLP), Tezepelumab (AMG–157)

Tezepelumab is a humanized monoclonal IgG2 antibody which binds to TSLP and prevents it from binding to the TSLP receptor complex. TSLP contributes to deviation toward a T_H-2 phenotype and is hypothesized to have a role in amplifying T_H-2 responses in allergic inflammation (Adkinson Jr. et al., 2014). The PATHWAY trial was a randomized, placebo-controlled, double-blind, phase II trial involving adults with uncontrolled moderate or severe persistent asthma (Corren et al. 2017). They were treated with subcutaneous tezepelumab or placebo for 52 weeks. Those in the tezepelumab group had decreased asthma exacerbation rates, regardless of baseline blood eosinophil levels. Studies are also ongoing to assess tezepelumab's efficacy in atopic

dermatitis (Paller et al. 2017). Regarding safety, tezepelumab was generally well tolerated. A few serious adverse events occurred, including pneumonia and stroke in the same patient and Guillain-Barre syndrome in another patient.

41.2.6.4 Prostaglandin D2 Receptor (PGD2) Antagonist, Fevipiprant

Fevipiprant (QAW039) is an antagonist to thePGD2 receptor. A unique feature is that it is an oral drug. It is thought to have a potential role in allergic disease because the PGD2 receptor mediates T_H-2 migration, delaying apoptosis and stimulating production of IL-4, IL-5, and IL-13 (Hirai et al. 2001; Xue et al. 2005, 2009). The first study assessing fevipiprant's efficacy in moderate to severe persistent asthma recruited 61 adult patients to receive 12 weeks of oral, twice daily fevipiprant or placebo (Gonem et al. 2016). Treatment with fevipiprant was associated with a reduced mean sputum eosinophil percentage. It is currently being evaluated in two phase III trials in patients with severe asthma (Knutsen 2017). Regarding safety, it was well tolerated with no serious adverse events reported.

41.2.6.5 Tyrosine Kinase Inhibitor, Imatinib

Imatinib is an inhibitor of the tyrosine kinase activity of KIT, a proto-oncogene receptor tyrosine kinase (Cahill et al. 2017). KIT and its ligand, stem cell factor, are crucial for mast cell development and survival. Tryptase levels have been found to be higher in patients with difficult-to-control asthma compared to those with well-controlled asthma, so it is hypothesized that mast cells may play a role in uncontrolled asthma (Kraft et al. 2003). A proof-of-principle, randomized, double-blind, placebo-controlled trial recruited 62 adult patients with severe, refractory asthma and assigned them to receive once daily oral imatinib versus placebo for 24 weeks (Cahill et al. 2017). Imatinib was found to reduce airway hyperresponsiveness and reduce serum tryptase levels compared to placebo. Regarding safety, muscle cramps and hypophosphatemia were found to be more common in the imatinib group.

41.2.6.6 GATA3 DNAzyme, SB010

SB010 is a DNA enzyme which can cleave GATA3, a transcription factor in the T_H-2 pathway (Krug et al. 2015). A randomized, double-blind, placebo-controlled trial assessed adult patients with mild persistent asthma who were treated with once daily nebulized SB010 for 28 days. Patients were then assessed for allergen-triggered early- and late-phase asthmatic responses through pulmonary function testing. Both measures were significantly reduced. Another similar trial also found that SB010 treatment attenuated early- and late-phase asthmatic responses, and patients who had higher levels of blood eosinophils had a greater response (Krug et al. 2017). Regarding safety, SB010 was well tolerated with similar adverse event rates between treatment and placebo groups and no severe adverse events.

41.2.6.7 Glucocorticoid Receptor Agonist, AZD5423

AZD5423 is a nonsteroidal glucocorticosteroid receptor antagonist. This therapy is currently in phase II trials for chronic obstructive pulmonary disease (Kuna et al. 2017). One clinical trial of 20 patients with mild allergic asthma receiving either nebulizer AZD5423 once daily, budesonide or placebo showed that those receiving AZD5423 had reduced allergen-induced responses (Gauvreau et al. 2015). Regarding safety, it was well tolerated in that small clinical trial.

41.3 Conclusion

In summary, multiple effective biologic treatments for allergic disease have emerged in the past few decades (Tables 2 and 3). The majority of biologics are being used to treat asthma, but ongoing research is also evaluating their role in atopic dermatitis, urticaria, eosinophilic esophagitis, chronic sinusitis with nasal polyps, and

Table 3 Summary of approved biologic therapies[a]

Biologic	Mechanism	Approved conditions	Indicated age group	Dosing and frequency	Route of administration
Omalizumab	Anti-IgE	Moderate or severe persistent allergic asthma	6 years and older	150–375 mg every 2–4 weeks[b]	Subcutaneous
		Chronic idiopathic urticaria	12 years and older	150 or 300 mg every 4 weeks	Subcutaneous
Mepolizumab	Anti-IL-5	Severe persistent eosinophilic asthma	12 years and older	100 mg every 4 weeks	Subcutaneous
Reslizumab	Anti-IL-5	Severe persistent eosinophilic asthma	18 years and older	3 mg/kg every 4 weeks	Intravenous
Benralizumab	Anti-IL-5 receptor	Severe persistent eosinophilic asthma	12 years and older	30 mg every 4 weeks for first 3 doses, then every 8 weeks	Subcutaneous
Dupilumab	Anti-IL-4 receptor	Atopic dermatitis	18 years and older	Initial dose of 600 mg, then 300 mg every other week	Subcutaneous

[a]Listed in the order they are discussed in this chapter
[b]Based on weight and serum IgE

other diseases. These biologic agents offer physicians treating allergic diseases an expanded and more individualized selection of therapeutics for patients with uncontrolled disease.

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