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GOLDMAN'S
CECIL
MEDICINE

西氏内科学

第24版

免疫与风湿疾病分册

LEE GOLDMAN
ANDREW I. SCHAFER

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北京大学医学出版社

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PREFACE

The 24TH Edition of *Goldman's Cecil Medicine* symbolizes a time of extraordinary advances in medicine and in technological innovations for the dissemination of information. This textbook and its associated electronic products incorporate the latest medical knowledge in formats that are designed to appeal to learners who prefer to access information in a variety of ways.

The contents of *Cecil* have remained true to the tradition of a comprehensive textbook of medicine that carefully explains the *why* (the underlying normal physiology and pathophysiology of disease, now at the cellular and molecular as well as the organ level) and the *how* (now frequently based on Grade A evidence from randomized controlled trials). Descriptions of physiology and pathophysiology include the latest genetic advances in a practical format that strives to be useful to the nonexpert. Medicine has entered an era when the acuity of illness and the limited time available to evaluate a patient have diminished the ability of physicians to satisfy their intellectual curiosity. As a result, the acquisition of information, quite easily achieved in this era, is often confused with knowledge. We have attempted to counteract this tendency with a textbook that not only informs but also stimulates new questions and gives a glimpse of the future path to new knowledge. Grade A evidence is specifically highlighted in the text and referenced at the end of each chapter. In addition to the information provided in the textbook, the Cecil website supplies expanded content and functionality. In many cases, the full articles referenced in each chapter can be accessed from the Cecil website. The website is also continuously updated to incorporate subsequent Grade A information, other evidence, and new discoveries.

The sections for each organ system begin with a chapter that summarizes an approach to patients with key symptoms, signs, or laboratory abnormalities associated with dysfunction of that organ system. As summarized in Table 1-1, the text specifically provides clear, concise information regarding how a physician should approach more than 100 common symptoms, signs, and laboratory abnormalities, usually with a flow diagram, a table, or both for easy reference. In this way, *Cecil* remains a comprehensive text to guide diagnosis and therapy, not only for patients with suspected or known diseases but also for patients who may have undiagnosed abnormalities that require an initial evaluation.

Just as each edition brings new authors, it also reminds us of our gratitude to past editors and authors. Previous editors of *Cecil Medicine* include a short but remarkably distinguished group of leaders of American medicine: Russell Cecil, Paul Beeson, Walsh McDermott, James Wyngaarden, Lloyd H. Smith, Jr., Fred Plum, J. Claude Bennett, and Dennis Ausiello. As we welcome new associate editors—Wendy Levinson, Donald W. Landry, Anil Rustgi, and W. Michael Scheld—we also express our appreciation to Nicholas LaRusso and other associate editors from the previous editions on whose foundation we have built. Our returning associate editors—William P. Arend, James O. Armitage, David Clemmons, Jeffrey M. Drazen, and Robert C. Griggs—continue to make critical contributions to the selection of authors and the review and approval of all manuscripts. The editors, however, are fully responsible for the book as well as the integration among chapters.

The tradition of *Cecil Medicine* is that all chapters are written by distinguished experts in each field. We are also most grateful for the editorial assistance in New York of Theresa Considine and Silva Sergenian. These individuals and others in our offices have shown extraordinary dedication and equanimity in working with authors and editors to manage the unending flow of manuscripts, figures, and permissions. We also thank Faten Aberra, Reza Akari, Robert C. Brunham, Ivan Ciric, Seema Daulat, Gregory F. Erikson, Kevin Ghassemi, Jason H. Huang, Caron Jacobson, Lisa Kachnic, Bryan T. Kelly, Karen Krok, Heather Lehman, Keiron Leslie, Luis Marcos, Michael Overman, Eric Padron, Bianca Maria Piraccini, Don W. Powell, Katy Ralston, James M. Swain, Tania Thomas, Kirsten Tillisch, Ali Turabi, Mark Whiteford, and Y. Joseph Woo, who contributed to various chapters. At Elsevier, we are most indebted to Dolores Meloni and Linda McKinley, and also thank Cathy Carroll, Taylor Ball, Virginia Wilson, Linda Van Pelt, Suzanne Fannin, and Steve Stave, who have been critical to the planning and production process under the direction of Mary Gatsch. Many of the clinical photographs were supplied by Charles D. Forbes and William F. Jackson, authors of *Color Atlas and Text of Clinical Medicine*, Third Edition, published in 2003 by Elsevier Science Ltd. We thank them for graciously permitting us to include their pictures in our book. We have been exposed to remarkable physicians in our lifetimes and would like to acknowledge the mentorship and support of several of those who exemplify this paradigm—Robert H. Gifford, Lloyd H. Smith, Jr., Frank Gardner, and William Castle. Finally, we would like to thank the Goldman family—Jill, Jeff, Abigail, Mira, Daniel, and Robyn Goldman—and the Schafer family—Pauline, Eric, Pam, John, Evan, and Kate—for their understanding of the time and focus required to edit a book that attempts to sustain the tradition of our predecessors and to meet the needs of today's physician.

LEE GOLDMAN, MD
ANDREW I. SCHAFER, MD

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XXI

DISEASES OF ALLERGY AND CLINICAL IMMUNOLOGY

257 APPROACH TO THE PATIENT WITH ALLERGIC OR IMMUNOLOGIC DISEASE

STEPHEN I. WASSERMAN

Allergic diseases and disorders of the immune system affect multiple organ systems and may arise in a variety of manners. The reader is directed to Section VII for a detailed discussion of the immune system and specific autoimmune and acquired immune disorders. This chapter addresses allergic disorders, the most common manifestation of immune system dysfunction, and primary immune deficiencies, which are uncommon manifestations of immune dysfunction. For clarity, these two issues are treated separately.

ALLERGIC DISEASE

DEFINITION

Allergic disorders are common, and their prevalence is increasing, particularly in urbanized, Western societies. It is said that allergic diseases are the most common disorders seen by primary care physicians. Moreover, even in nonallergic patients, consideration of allergy frequently enters the differential diagnosis of a problem under consideration. Therefore, an appreciation of how to approach the diagnosis and treatment of allergic patients is of major importance to the practice of internal medicine. Allergic disorders are those caused by the interaction of a sensitized host (one who has made immunoglobulin E [IgE] antibody recognizing a specific antigen) with a specific allergen. Not all patients possessing specific IgE antibody react adversely on interaction with the allergen, and such individuals are termed *sensitized* but not *allergic*. The primary allergic conditions are seasonal allergic rhinoconjunctivitis (hay fever), perennial allergic rhinitis or sinusitis, asthma, anaphylaxis (especially secondary to foods, medications, and hymenopteran stings), urticaria or angioedema, atopic dermatitis (eczema), and food allergy.

EPIDEMIOLOGY

It is currently estimated that more than 50% of the population is atopic (i.e., able to mount an IgE immune response and to exhibit an immediate positive prick-puncture hypersensitivity response to common aeroallergens). Clinically, 10 to 20% of the general population will develop allergic rhinoconjunctivitis, 5 to 7% will have active asthma, and 20% will experience urticaria at some time.

The increase in allergic diseases noted in the past 2 decades is thought to result from better hygienic conditions, decreases in infant and childhood infections, and an increasingly sedentary and indoor lifestyle. These changes appear to be associated with a less effective activation of the innate immune system, thereby altering the protective maturation of the acquired immune system. The immune bias in utero and in infancy is toward a type 2 helper T-lymphocyte (T_H2)–directed immune response, which is the immune pathway required for the expression of allergic disease. Ineffective generation of regulatory T lymphocytes underlies the genesis and persistence of allergy. It is therefore postulated that without sufficient early childhood infection to induce a switch to an effective and protective T_H1 immune response, allergic disease is more likely to emerge during childhood. Substantial epidemiologic evidence has been gathered to support this concept, now termed the *hygiene hypothesis*. Thus, allergy is more prevalent in individuals of higher socioeconomic status, among those living in urban areas, in less polluted communities (e.g., western Germany), in first-born children compared with later siblings, in multiply immunized individuals, and in those free of mycobacterial disease. Conversely, children living on farms, in rural communities, and in more highly polluted areas (e.g., eastern Germany), as well as children with mycobacterial infection and those who have experienced multiple early childhood infections, are less likely to develop allergic disorders. A concentration-effect relationship appears to exist between exposure to endotoxin (as a marker for hygiene) and the incidence of allergic sensitization. Low and very high levels of exposure to endotoxin are associated with abnormal immune maturation and allergic expression, whereas moderate levels of exposure predispose to a nonallergic phenotype.

PATHOBIOLOGY

The persistence or aberrant activation of T_H2 lymphocytes leads to the generation of cytokines (e.g., interleukins-4, -5, -13), which stimulate B-lymphocyte synthesis of IgE antibody and the production of eosinophilic polymorphonuclear leukocytes. The expression of allergic disorders results from the interaction of a specific allergen with allergen-reactive IgE bound to high-affinity receptors on mast cells and basophils. This interaction leads to activation of these target cells and to their release of preformed, granule-associated mediators (exemplified by histamine); the synthesis of lipid mediators from membrane lipids (sulfidopeptide leukotrienes); and the transcription and secretion of cytokines, including tumor necrosis factor-α and interleukins-4, -5, and -13. These mediators directly induce smooth muscle contraction, vascular dilation, and endothelial leakage; they also cause vascular adhesion molecule expression, and they attract and activate inflammatory leukocytes, particularly $CD4^+$ T lymphocytes, basophils, and eosinophils. These and other IgE-dependent mediators are thought to be responsible for stimulating smooth muscle proliferation and tissue remodeling.

DIAGNOSIS

Allergy is a systemic immune disorder, so its expression can be multifocal. It is essential to remember this fact when examining a patient with suspected allergic problems because a focus on only the major presenting symptom may be insufficient to identify all the pertinent medical issues in a given patient.

History

Allergic disease has a high degree of heritability, with a great degree of concordance in identical twins. The risk of expressing allergic disease is highest if both parents are atopic. The inheritance of specific manifestations of allergy and of the specific allergen to which a patient is sensitized is less simple. Quite often, the diagnosis of allergic disorders is straightforward and can be made by asking about the nature of the patient's complaints, when and where reactions occur, and what exposures the patient believes are relevant to symptom induction or exacerbation (Table 257-1).

Seasonal and Perennial Rhinitis

Patients with seasonal and perennial rhinitis (Chapter 259) commonly present with complaints of itchy nose and palate; sneezing; watery rhinorrhea; itching, watery, and burning eyes; and nasal obstruction, which, when severe, may cause anosmia. In the evaluation of possible causes of seasonal rhinoconjunctivitis or sinusitis, the time of the year when symptoms occur is pertinent. Symptoms may be associated with the pollination of trees (early spring), grasses (late spring and summer), or weeds (fall). In some patients with perennial symptoms, the multiple overlapping pollen seasons are responsible for their symptoms. Indoor exposures at home, school, work, or

TABLE 257-1 SYMPTOMS, SIGNS, AND TREATMENT OF ALLERGIC DISEASE

SYMPTOMS AND SIGNS	APPROACH TO TREATMENT
SYMPTOMS	
Cutaneous: itch, rash	H_1-antihistamine
Ocular: gritty sensation, itch	Topical H_1-antihistamine or mast cell stabilizing agent
Upper respiratory: palatal pruritus, clear rhinorrhea, sneeze, nasal obstruction	Topical corticosteroid, oral H_1-antihistamine, leukotriene receptor antagonist, topical nasal H_1-antihistamine
Lower respiratory: wheeze, cough, dyspnea	β_2-agonist, inhaled corticosteroid, inhaled β_2-agonist, leukotriene receptor antagonist, oral methylxanthine, parenteral corticosteroid, parenteral anti-IgE
Gastrointestinal: nausea, vomiting, cramping pain	Epinephrine (if caused by anaphylaxis), oral corticosteroid, oral cromolyn
SIGNS	
Cutaneous: flushing, urticaria, angioedema, eczema	
Ocular: conjunctival erythema, chemosis	
Upper respiratory: pallor, edema, clear rhinorrhea, polyps	
Lower respiratory: wheeze	

recreational sites to furred animals, dust mites or insects, and mold should be addressed in the search for additional causes of perennial symptoms. Mold and mites are to be expected in humid environments, and mites are nearly ubiquitous in bedding and in homes with pets, carpeting, and overstuffed furnishings. Additional occupational or recreational exposures may be pertinent in selected situations (e.g., bakers, health care workers, food handlers, horse fanciers, laboratory animal handlers) in which specific inciting allergens may be identified. Because many patients with rhinitis have concomitant asthma, it is important to obtain information about the presence of this disease in patients with rhinitis.

Asthma

Patients with asthma (Chapter 87) may present with cough or wheeze with dyspnea, which is reversible spontaneously or with treatment. In addition to the association with rhinitis, the influence of exercise, exposure to tobacco smoke, effect of respiratory infection (particularly viral), occupational exposures (e.g., ≤30% of atopic animal handlers develop asthma), and medication use (e.g., β-adrenergic blocking drugs) are pertinent. Because most patients with asthma have concurrent rhinitis, it is essential that the physician evaluate this issue in all asthmatic patients. Wheezing may accompany other disorders, including pulmonary edema in congestive heart failure.

Urticaria and Angioedema

Patients with urticaria (Chapter 260) describe pruritic, erythematous cutaneous lesions with regular or irregular borders occurring anywhere on the body; they may vary in size from small (1 × 1 mm) to extremely large. Skin lesions are often preceded by intense intertriginous pruritus. Individual urticarial lesions generally persist for a few hours and rarely last for more than 24 hours. However, many disorders can cause a sensation of itching; skin and systemic diseases associated with pruritus are listed in Table 443-1 in Chapter 443. Angioedema (Chapter 260) is most frequently appreciated in the face, hands, and other soft tissues and is generally accompanied by symptoms of stretching, tingling, and tightness of the skin rather than pruritus. Lesions, especially in the face, typically last 24 to 36 hours. Although most cases of urticaria or angioedema are not IgE mediated, it is important to identify foods and medications used by patients with acute urticaria or angioedema, particularly those substances ingested within 2 to 4 hours of the development of lesions, and to inquire about insect stings. Chronic urticaria is less often IgE mediated; questions about medications, especially nonsteroidal anti-inflammatory drugs, recent infection (especially with Epstein-Barr virus), and the presence of autoantibodies to the IgE receptor must be addressed. Approximately one half to two thirds of patients with such autoantibodies also have antibodies to thyroid antigens. In angioedema, the use of angiotensin-converting enzyme inhibitors must be sought. Atopic dermatitis is another allergic cutaneous disorder in which patients complain of intense pruritus, especially in flexural surfaces. In adults, foods (IgE mediated) and cutaneous infection with *Staphylococcus aureus* (superantigen mediated) are the most commonly identified precipitating events for atopic dermatitis.

Anaphylaxis

Anaphylaxis (Chapter 261) is the most important allergic emergency and is potentially fatal. It is an acute allergic response associated with cutaneous (urticaria, angioedema, flushing), respiratory (laryngeal edema, asthma), cardiovascular (arrhythmia, hypotension, extravascular fluid loss), gastrointestinal (nausea, vomiting, abdominal pain, diarrhea), and nonspecific symptoms (metallic taste, sense of impending doom) that may occur singly or together. Historical information of note includes all medications, foods, and other encounters occurring within 2 hours of the reaction. Epidemiologic data suggest that foods (especially peanuts, tree nuts, shellfish, milk, and eggs), hymenoptera stings, and medications (antibiotics, muscle relaxants, radiocontrast media) are the most frequently identified causes of this important problem.

Food Allergy

Patients presenting with food allergy often complain of oral pruritus and nausea, vomiting, diarrhea, and abdominal pain. Eczema, urticaria, and anaphylaxis, as noted previously, may also be consequences of food allergy. In general, allergic symptoms consequent to foods occur within minutes to 2 hours of ingestion of the causative food; delayed symptoms are unlikely to be mediated by an IgE-allergen interaction. Other symptoms attributable to foods are less easily explained by allergic mechanisms and are termed *food intolerance*.

Physical Examination

The physical examination of a patient with suspected allergic disease should emphasize the organ systems pertinent to the patient's complaints. The skin should be examined for the presence of urticarial or angioedematous lesions and for signs of atopic dermatitis, including flexural papules, excoriations, and lichenification. Keratosis pilaris, particularly on the outer aspect of the upper arm, commonly accompanies atopic dermatitis. Urticaria typically consists of small, pink, irregular lesions that blanch on pressure and then clear, leaving normal skin. In a patient with urticaria, a simple test for dermatographism should be undertaken. Angioedematous lesions are larger, more diffuse, and pale, and they are found most often on the face and in acral areas.

The eyes, ears, nose, and throat should be examined in all patients suspected of having allergic disease, particularly those whose symptoms suggest seasonal or perennial allergic rhinoconjunctivitis-sinusitis or asthma. In allergic disease, the conjunctivae are often injected and may be edematous. "Cobblestoning" of the epithelium may be present. The periorbital tissues may be swollen and darkened. Examination of the nares may show pale and edematous nasal mucous membranes and swollen turbinates, and polyps may be seen. Secretions, generally clear, may be seen in the nasal passages or in the posterior pharynx. Such secretions generally contain copious numbers of eosinophils (see later), and their absence is a point against an allergic cause. Fever and discolored secretions, particularly those that are thick and yellow or green, in the presence of neutrophilic polymorphonuclear leukocytes suggest infection. Percussion over the maxillary or frontal sinuses may elicit tenderness in acute sinusitis, and in this case, transillumination of the sinus (albeit a test of low sensitivity) may be impaired. In chronic sinusitis, the physical examination may be unrevealing. In acute otitis media, patients may have erythema and bulging or perforation of the tympanic membrane, with fluid in the canal; in chronic cases the drum may be scarred and retracted. Alteration in airborne conduction may be noted as well.

Patients with acute asthma may display tachypnea and auditory wheezes, and they may be unable to speak in full sentences because of shortness of breath. Use of accessory muscles of respiration and evidence of cyanosis should be sought. Examination of the chest includes inspection for evidence of chronic hyperinflation and auscultation for wheezing (which, if unilateral, may suggest a foreign body or tumor). In mild asthma, the examination may be normal, or the only physical finding may be wheezing on forced expiration and a slight prolongation of the expiratory phase.

Patients experiencing acute anaphylaxis usually demonstrate flushing, and concomitant urticaria and angioedema are often present. Assessment of vital signs may disclose hypotension and tachycardia. In some situations, hoarseness or stridor related to laryngeal edema or wheezing secondary to asthma can be identified. Hyperactive bowel sounds may be noted. Progressive hypoxia and cyanosis may ensue. In severe anaphylaxis, cardiovascular collapse secondary to hypoxia and hypotension may result in death.

Laboratory Evaluation

In the evaluation of patients with allergic disorders, the laboratory may be of assistance in both the identification and the quantification of specific organ dysfunction, as well as in the assessment of the presence and specificity of IgE antibody.

Assessment of Total and Allergen-Specific Immunoglobulin E

Essentially all (>95%) IgE antibody is bound to specific high-affinity receptors on tissue mast cells and circulating peripheral blood basophils. The small amount of free serum IgE antibody circulates in nanogram quantities and can be identified only with techniques of sufficient sensitivity. A large proportion of IgE in a given individual may be directed toward a single antigen, so total IgE levels may be normal in the presence of allergic disease. Therefore, the measurement of total serum IgE is rarely of help in making a diagnosis. In a few situations, such as adult atopic dermatitis or allergic bronchopulmonary aspergillosis, measurement of total serum IgE levels may provide insight into disease severity or risk of disease exacerbation.

Of more importance is the identification of allergen-specific IgE in a patient with suspected allergic disease (Table 257-2). Such specific IgE may be identified in vitro or in vivo. A search for allergen-specific IgE is particularly useful in the evaluation of patients with suspected allergic rhinitis, asthma, eczema, food reactions, and anaphylaxis. In vitro assessment is similar to the quantification of total IgE, except the initial capture reagent bound to a solid phase is a specific pollen, mold, insect, venom, food, or other allergen. Development of the assay is identical to that used to quantify total

TABLE 257-2

METHOD	PATIENT SELECTION	CLINICAL ADVANTAGES	CLINICAL DISADVANTAGES
Skin testing	Clinical indication suggesting allergic disease	Rapid (15-30 min) turnaround Sensitive and specific; prick-puncture for aeroallergens, prick-puncture followed by intradermal testing for drugs, sera, and venoms	Patient must not be taking H_1-antihistamine agents for 5-7 days Not interpretable in the presence of dermatographism Requires sufficient normal skin to enable testing
In vitro testing	Clinical indication suggesting allergic disease	Antihistamine therapy not contraindicated Dermatographism not a problem Sensitive and specific; equal to prick-puncture skin testing	Requires blood drawn Slow turnaround (7-14 days)

IgE, and results are generally reported in a semiquantitative manner. The magnitude of the reaction is weakly correlated with the degree of sensitization and expression of allergy, although for certain foods, more precise correlative data exist on the risk of allergy and the amount of allergen-specific IgE detected. To assess allergen-specific IgE in vivo, a minute quantity of the allergen in question is introduced into the skin by a prick-puncture technique, and the cutaneous response is assessed 15 to 30 minutes thereafter. A positive response is one in which a wheal and flare at least 2 mm larger than those caused by a saline control occur at the injection site. In vivo tests are rapid and inexpensive; their use requires the absence of dermatographism, that patients not be taking antihistamine medications, and that patients exhibit a positive response to a control using histamine. In some situations (e.g., penicillin allergy or hymenopteran sting), a more diluted allergen is injected intradermally, and wheal and flare responses are assessed similarly. The presence of allergen-specific IgE antibody and a clear temporal correlation between exposure to allergen and genesis of symptoms are required to conclude that a patient is allergic to a specific allergen. In the absence of symptoms, a patient with allergen-specific IgE is termed *sensitized* but not allergic.

Specific in vivo challenge tests can also be used to identify allergen responsiveness. Such tests in the presence of specific IgE antibody may be useful in research settings, or they may be used clinically to clarify the exact relationship between exposure and symptoms. Such tests can be dangerous, however, because they introduce the allergen to which the patient is presumed allergic. In the case of food allergy, such challenges are best done in a double-blind and placebo-controlled manner; they may be useful to distinguish allergy from sensitization or to eliminate a suspect food from consideration. However, food challenge tests are unnecessary in the case of anaphylaxis and a positive test for IgE antibody to the putative allergen. Because many patients falsely believe that foods are responsible for their symptoms, such double-blind challenges may be useful in directing patients' concerns to more productive areas. Inhalation tests employing specific allergens or chemicals have been helpful in elucidating some cases of occupational allergy or asthma.

Other Laboratory Aids in Allergic Disease

In a patient with acute asthma, chest radiographs generally demonstrate hyperinflation. In some instances, evidence of bronchiectasis may be present, a finding that raises the specter of allergic bronchopulmonary aspergillosis. The presence of a tumor or radiopaque foreign body may be noted on a chest radiograph and should be sought in a patient with unilateral localized wheezing. In the examination of a patient with asthma, assessment of both airflow and volumes can provide a clear picture of the severity of asthma and its response to treatment. Flow-volume loops can also identify the presence of vocal cord dysfunction. When patients with airway obstruction are evaluated, their response to an inhaled β_2-adrenergic agonist medication can be helpful in elucidating the reversible nature of their disorder. Essentially all asthmatic patients exhibiting bronchoconstriction display a bronchodilatory response to the inhalation of such agents. In suspected cases of asthma in which pulmonary function is normal, a histamine or methacholine challenge can be performed. These agents take advantage of the nonspecific bronchial hyperresponsiveness that is characteristic of patients with asthma. Failure to develop bronchoconstriction on inhalation of either of these agents strongly argues against the diagnosis of asthma.

Other laboratory tools may be of clinical benefit in the identification and classification of allergic disorders. Audiometry may clarify the degree of hearing loss caused by otitis media in a patient with allergic rhinitis. When sinusitis is suspected, computed tomography of the sinuses provides the most complete image and has the highest degree of sensitivity for the identification of mucosal thickening, opacification of air spaces, and presence of polyps and bone erosions. Computed tomography is particularly useful in the examination of the ethmoid and sphenoid sinuses, which are often affected in chronic allergic disease and are difficult to assess on physical examination or with plain radiographs.

The quantification of blood, sputum, nasal mucus, or tissue eosinophilia and the response to corticosteroid therapy are useful correlates in the identification and management of allergic disease. The quantification of tryptase, a mast cell–specific protease with a serum half-life of 2 hours, can assist in the diagnosis of anaphylaxis if performed on serum or plasma obtained within hours of a systemic response with associated hypotension.

IMMUNOLOGIC DISEASE

EPIDEMIOLOGY

Diseases related to disordered immune function (immunodeficiency) are far less common than allergic disorders. The most frequent is IgA deficiency, which occurs in approximately 1 in 1000 individuals and is often asymptomatic. Next most frequent are disorders of B and T lymphocytes, such as common variable hypogammaglobulinemia, and other disorders, including DiGeorge syndrome and severe combined immunodeficiency (Chapter 258). Much less common are defects in neutrophil function or complement.

DIAGNOSIS

The clinical expression of immunodeficiency disorders is primarily infection, related to impaired host defense. Thus, the diagnosis of suspected immunodeficiency involves the evaluation of recurrent, persistent, severe, and otherwise unexplained infections. Many, but not all, immune disorders arise in early childhood, and with improved management, many patients presenting in childhood live into adulthood. It is important for the general internist and internal medicine subspecialist to be cognizant of the presentation of these disorders.

History

The most important historical information includes the following: age at onset of the problem in question; family history of frequent infection or death at an early age from infection; number, site, and type of infections; and presence of other physical abnormalities (Table 257-3). The earlier the onset of infections, the more severe the immune defect is likely to be. T-lymphocytic defects, with or without B-cell deficiencies, usually arise in the first 3 to 5 months of life, whereas B-cell function is supported by maternal antibody until after 6 months of age. Many of the immune disorders are X-linked, and a careful family history is critical in such situations. Infection-related death of a patient's male sibling or the patient's mother should lead to the search for such an X-linked disorder.

In a patient with a T-cell disorder, viral, fungal, mycobacterial, and other opportunistic infections (*Pneumocystis jirovecii, Toxoplasma gondii*) are most commonly noted, and live virus vaccination may be associated with disseminated and progressive viral disease. Persistent thrush, diarrhea, malabsorption, and failure to thrive occurring in early childhood may suggest the presence of T-cell abnormalities.

In B-cell or antibody deficiency, pyogenic bacterial infections predominate, particularly infections involving encapsulated microorganisms. Usually such infections affect the upper and lower respiratory tract and the skin and are severe and persistent. Infections with unusual organisms, with unexpected complications, or involving multiple sites (lung, sinus, joint, bone, or

TABLE 257-3

ANTIBODY DEFICIENCY DISORDERS
Onset after 6 mo of age
Recurrent respiratory infection
Infection with bacteria, especially encapsulated organisms
Absence of isohemagglutinins
Evaluation of B-cell function, not numbers
CELLULAR IMMUNE DEFECTS
Onset before 6 mo of age
Recurrent viral, fungal, or parasitic (opportunistic) infection
Defective delayed hypersensitivity skin responses
Malabsorption or diarrhea
COMPLEMENT DEFICIENCIES
Recurrent bacterial infection
Recurrent neisserial infection (deficiency of late components)
Associated rheumatic disorder (especially systemic lupus erythematosus)
FACTORS SUGGESTING NEUTROPHIL DYSFUNCTION
Late separation of umbilical cord
Persistent neutrophilic leukocytosis
Recurrent or persistent gingivitis or periodontitis
Recurrent bacterial infection with granuloma formation

meninges, with abscess formation or sepsis) should raise the index of suspicion. In adults, the most common disorder in this class is termed *common variable immunodeficiency.*

As in any patient with infection, information should be sought about exposure to ill individuals or to irritants such as tobacco smoke, the hygiene of the environment to which the patient has been exposed, and the presence of an anatomic abnormality or allergy that could predispose to infection.

Physical Examination

Physical examination beyond that necessary to assess the extent and severity of a particular infection should focus on immune organs. Assessment of tonsillar tissue and determination of the presence and size of lymph nodes, spleen, and liver are important. Patients with common variable immunodeficiency often present with hepatosplenomegaly and lymph node hyperplasia, whereas in X-linked hypogammaglobulinemia, lymph tissue is absent. Telangiectasia (ataxia-telangiectasia), cardiac defects (DiGeorge syndrome), chronic eczema (Wiskott-Aldrich syndrome), and chronic periodontitis (neutrophil defects) all suggest immunodeficiency syndromes.

Laboratory Evaluation

The proper use of the laboratory is essential to elucidate a suspected immunodeficiency disorder. Screening tests appropriate to the generalist's initial approach include complete blood count, total neutrophil and lymphocyte enumeration, quantitative immunoglobulin levels, and assessment of isohemagglutinins (especially when common variable immunodeficiency is suspected). In some situations, quantification of IgG subclasses may be warranted to identify a specific subclass deficiency. When considering T-lymphocyte defects, it is important to enumerate total T cells and specific T-cell subsets. Delayed hypersensitivity skin testing to recall antigens is also helpful in assessing cellular immunity. When neutrophil defects are suspected, a nitroblue tetrazolium test or measurement of phagocytic potency can be performed. Complement defects are best addressed by obtaining a CH_{50} level. CH_{50} is the amount of patient serum required to cause lysis of 50% of test erythrocytes. It is compared with the amount of pooled normal serum required to cause the same degree of lysis. Tests for specific individual components of complement, or of complement regulatory proteins, can also be obtained under special circumstances.

Additional tests of antibody production in response to defined stimuli, including vaccinations, may be helpful when selective antibody deficiency is suspected or when borderline immunoglobulin levels are encountered in the presence of frequent infection. In some situations, assessment of T-cell proliferation to mitogens or antigen may be of benefit. Further testing might include the assessment of natural killer–cell function and the production of cytokines by activated lymphocytes. In general, such additional laboratory tests should be performed in consultation with an expert in immune disorders.

SUGGESTED READINGS

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258 PRIMARY IMMUNODEFICIENCY DISEASES

MARK BALLOW

DEFINITION

Although immunodeficiency diseases are relatively uncommon, more than 165 primary immunodeficiency diseases have been described. Immunodeficiencies are generally divided into several categories: B-cell or antibody immunodeficiencies (55% of all immune deficiencies), T-cell or cellular immunodeficiencies (20%), immunodeficiencies associated with the phagocytic system (20%), immune defects of the innate immune system, and immune abnormalities associated with the complement system (5%). Although many primary immunodeficiencies are first noticed in infants and young children, the most frequent B-cell (humoral) immunodeficiencies become evident later in life, especially in young adults; the characteristic presentations of these diseases should be recognized by the physician so diagnosis and treatment can be initiated. The purpose of this chapter is not to present an encyclopedic list of all the known immunodeficiencies but to identify the most common presenting clinical characteristics, define the initial laboratory evaluation, and briefly discuss the approach to treatment.

PATHOBIOLOGY

Genetics

Many of these disorders are caused by mutations of genes required for the development of T cells or B cells or genes needed for the development of precursor cell lineages that differentiate into various types of immune cells. Other genetic abnormalities are widely expressed in many tissues, resulting in complex multisystem disorders along with the immunodeficiency. Some gene mutations that occur in the same immunologic pathway (e.g., cytokine receptor and signaling pathway) result in similar clinical phenotypes and laboratory findings. Conversely, depending on the nature and location of the mutation, defects in other genes may result in immune defects associated with compound heterozygous mutations with complex variable (hypomorphic) clinical phenotypes.

CLINICAL MANIFESTATIONS

This chapter presents the important details of the history and physical examination and the common clinical signs when evaluating a patient with recurrent infections. The association of particular sites of infection and specific pathogens with certain immunodeficiencies is also helpful in directing the physician toward a differential diagnosis and the appropriate screening laboratory tests.

Clues from the Infecting Pathogen and the Organ System Involved

The organ systems affected by infection and the identity of the isolated pathogens provide clues to the nature of the possible defect. A patient presenting with lymphadenitis or recurrent abscesses caused by low-virulence gram-negative organisms such as *Escherichia coli, Serratia,* or *Klebsiella* may have an abnormality in phagocyte function (Chapter 172). Infections with unusual pathogens such as *Staphylococcus epidermidis* or *Pseudomonas* species, especially *Burkholderia cepacia,* also suggest a phagocytic disorder. Another characteristic presentation of patients with a phagocyte defect is a history of recurrent skin infections with catalase-positive *Staphylococcus aureus,* a finding underscoring the importance of effective phagocytosis and intracellular superoxide-mediated killing in controlling these infections. A history of delayed separation of the umbilical cord exceeding 6 to 8 weeks or poor wound healing suggests the diagnosis of a leukocyte adhesion defect. Suppurative adenitis is common in patients with chronic granulomatous disease, and it can be an important clue in the diagnosis when gram-negative bacteria are recovered from the tissues. Gingivostomatitis and dental erosions are characteristic of patients with a phagocytic cell defect such as leukocyte adhesion deficiency (Chapter 172). Recurrent oral ulcers are characteristic of patients with cyclic neutropenia (Chapter 170). Defects in the late complement components C5 through C9 (Chapter 49) are associated with infections caused by *Neisseria* species, such as meningitis caused by *Neisseria meningitidis* or septic arthritis caused by *Neisseria gonorrhoeae.* Patients with C3 deficiency can present with overwhelming septicemia, especially with gram-negative organisms; this finding is consistent with the important role of complement, particularly C3b, in opsonization and the facilitation of phagocytosis.

B-cell abnormalities most commonly lead to recurrent sinopulmonary infections that are frequently caused by encapsulated bacteria such as *Streptococcus pneumoniae* or *Haemophilus influenzae.* Examination of the pharynx and nasal cavities for signs of sinusitis, including posterior pharyngeal cobblestoning, postnasal drainage, or purulent nasal discharge, is important. Tympanic membranes can appear scarred and disfigured as a result of recurrent or chronic infection of the middle ear. Rales on auscultation of the chest may suggest bronchiectasis as a complication of recurrent lung infections. Digital clubbing points to significant lung disease. A characteristic feature of patients with X-linked agammaglobulinemia (XLA) is an unusual susceptibility to a viral meningoencephalitis caused by enteroviruses (e.g., coxsackievirus, echovirus). Chronic gastrointestinal symptoms caused by *Giardia lamblia* are likely related to impaired mucosal immunity and lack of secretory immunoglobulin (Ig) A. Small bowel bacterial overgrowth and infections with *Yersinia* and *Campylobacter* can lead to chronic gastrointestinal symptoms; diarrhea and occasionally malabsorption may be presenting symptoms in patients with common variable immunodeficiency (CVID).

T cells are essential not only in controlling viral, fungal, mycobacterial, and protozoal infections but also in providing crucial signals to help B cells produce immunoglobulins. Extensive mucous membrane candidiasis suggests a T-cell defect. Patients with cellular immune defects often present with opportunistic infections such as *Mycobacterium avium-intracellulare* and *Pneumocystis jirovecii.*

Lymphatic System in Patients with Immunodeficiency

Assessing the lymphatic system for hepatosplenomegaly and for the presence or absence of lymphoid tissue is an important aspect of the physical examination in a patient suspected of immunodeficiency (Chapter 171). Patients with severe combined immunodeficiency disease (SCID) or infantile XLA do not have palpable lymphoid tissue or visible tonsils. However, the presence of lymphoid tissue can be misleading: adult patients with CVID or IgA deficiency may actually have enlarged lymphoid tissue and even hepatosplenomegaly. This occurs because the reticuloendothelial system undergoes hyperplasia in the absence of opsonic antibody.

Immunodeficiency and Autoimmunity

Deficiencies of the early complement components, such as C4 and C2, often present in adults as an associated autoimmune disease that manifests first with arthritis, frequently in conjunction with dermal vasculitis. A lupus-like rash with negative or low-titer antinuclear antibodies may occur in deficiencies of the early components of the classical complement pathway. Patients with some primary immunodeficiencies present with features of autoimmunity involving hematopoietic or other organ systems. For example, the diagnosis of CVID can be preceded by autoimmune hemolytic anemia (Chapter 163).

Immunodeficiency and Gastrointestinal Disease

Many patients with primary immunodeficiency disease have symptoms and clinical findings referable to the gastrointestinal tract. In a survey of 248 patients with CVID, 21% had significant gastrointestinal disease. Liver disease occurred in an additional 12%. Bacterial overgrowth of the small bowel, including infections with *Yersinia* and *Campylobacter,* parasitic infestations with such organisms as *G. lamblia,* and chronic viral enteritis caused by enteroviruses and cytomegalovirus are relatively common in patients with B- or T-cell immune defects. The incidence of lactose intolerance is high in patients with immunodeficiency. Similarly, patients with IgA deficiency often present with gastrointestinal manifestations.

Immunodeficiency and Family History

A detailed family history in patients with suspected immunodeficiency can add valuable information. Numerous immunodeficiencies are X-linked; therefore, a family history of maternal male relatives with unusually frequent infections or who died in early infancy should suggest the possibility of an X-linked form of immunodeficiency. The mother in these cases would be expected to be a carrier, although the rate of new mutations for X-linked disorders is significant; therefore, a negative family history may not exclude this inheritance pattern. CVID and IgA deficiency are familial disorders and often occur in a setting of other family members with autoimmune disorders.

DEFECTS IN THE INNATE IMMUNE SYSTEM: COMPLEMENT AND PHAGOCYTE DEFICIENCIES

Deficiencies of Complement Proteins

DEFINITION

The complement (C) system is important in host defense and is composed of a complex system of plasma proteins and cell surface receptors (Chapter 49). Important functions of the complement system include opsonization to enhance phagocytosis, clearance of immune complexes, induction of the humoral immune response, and clearance of apoptotic cells.

EPIDEMIOLOGY

Approximately 5% of patients with primary immunodeficiency diseases have complement deficiencies. Although rare, C2 deficiency is the most common of the early complement component diseases; it occurs in 1 in 10,000 whites. C6 deficiency is the most common of the late complement component disorders. The frequency of complement deficiency in sporadic cases of systemic meningococcal infection has been estimated at 15%. In patients with recurrent meningococcal disease, the prevalence is as high as 40%.

CLINICAL MANIFESTATIONS

These disorders are usually inherited as autosomal codominant traits: the parents of the patient have half-normal levels of the involved complement component, and the patient has a complete absence of the component in question. The complement deficiencies can be broadly divided into those of the early classical complement pathway (C1, C2, and C4), the components of the alternative complement pathway (factors B, D, and P), the mannose-binding proteins and their associated proteases (MASP-1 and MASP-2), and the late complement components (C5, C6, C7, C8, and C9). Persons deficient in C3 share characteristics of both early and late complement component deficiencies. Patients lacking one of the early complement components frequently present as adults with a rheumatologic disease. These patients may exhibit the typical features of systemic lupus erythematosus, except they often are seronegative; that is, anti-DNA antibodies are absent, and antinuclear antibodies are present in only low titers. Individuals with C2 deficiency may have either systemic lupus erythematosus or discoid lupus. Other rheumatologic disorders associated with early complement component deficiencies include dermatomyositis, scleroderma, vasculitis, and membranoproliferative glomerulonephritis. Homozygous deficiency of factor H, a complement regulatory protein, may manifest as hemolytic-uremic syndrome (Chapter 175). Likewise, deficiencies of the late complement components are occasionally associated with vasculitis or other lupus-like illnesses. Less frequently, patients with late component deficiencies develop Raynaud's syndrome, scleroderma, or dermatomyositis.

Patients with deficiencies in the late complement components usually present with recurrent, invasive meningococcal or gonococcal infections caused by *Neisseria* species, such as meningococcal meningitis, gonococcal arthritis, or gonococcal septicemia. However, patients with deficiencies of early or alternative pathway complement components, such as properdin deficiency, may also present with recurrent or invasive neisserial infections.

DIAGNOSIS

Individuals with recurrent blood-borne infection with encapsulated bacteria (e.g., *S. pneumoniae, H. influenzae,* invasive meningococcal or gonococcal disease) or immune complex disease should be screened for complement deficiency by determining the total hemolytic complement activity (CH_{50}) in the serum, a test of classical pathway activity. The CH_{50} should be undetectable. If the CH_{50} is normal, alternative pathway function should be tested with the AH_{50}. Hemolytic activity is very sensitive to heat degradation, so blood samples must be handled appropriately, and the serum should be separated and frozen at −70° C as soon as possible. Abnormalities in CH_{50} or AH_{50} may be followed by a determination of specific component concentrations in serum.

TREATMENT

Rx

Patients with late complement defects should be immunized with the conjugate meningococcal vaccine. There is controversy over the use of prophylactic antibiotics because this could lead to the emergence of resistant strains of *Neisseria.*

Phagocytic Cell and Other Innate Immune Defects

Patients with defects in phagocyte function (Chapter 172) experience repeated infections where the body surface interfaces with the environment. Because of defective phagocyte function, the manifestations of infection may be blunted; erythema, swelling, and pus formation may be limited or absent. Phagocyte defects frequently manifest as infections caused by bacteria of relatively low virulence, such as *S. aureus;* fungi; and gram-negative enteric bacteria, including *Klebsiella, E. coli, B. cepacia,* and *Serratia* species. These infections often fail to respond optimally to the usual courses of antimicrobial agents. Many patients also have a history of poor wound healing, reflecting the critical role of phagocytes in tissue repair. The clinical features of phagocytic cell defects are shown in Table 258-1.

Normal function of the phagocyte compartment requires adequate numbers of neutrophils and monocytes, as well as the full performance of a number of closely integrated functions that result in the effective killing of a pathogen by the leukocyte. Defects in neutrophil number (severe congenital neutropenia, cyclic neutropenia, Kostmann's syndrome, Shwachman-Diamond syndrome; Chapter 170), adherence, deformability, locomotion, chemotaxis, recognition of foreign particles, phagocytosis, oxidative respiratory metabolism, and intracellular microbial killing (Chapter 172) have all been reported. Data from the history and physical examination can help the clinician focus on which phagocyte function is most likely defective.

A critical aspect of host defense is the accumulation of neutrophils at the site of infection. Absence of pus at the site of infection, for example, suggests that the patient has a decreased number of granulocytes or that these cells have an impaired ability to concentrate at the site of bacterial invasion, that is, defective chemotaxis or adhesion. Conversely, a history of persistent abscesses with exudates suggests that the phagocytes can migrate to the appropriate site but are defective in intracellular bacterial killing. A history of recurrent gingivitis, skin infections with furunculosis, abscesses of the viscera or perirectal tissues, and lymphadenitis should prompt an evaluation of the phagocyte host immune defenses.

INTERFERON-γ/INTERLEUKIN-12 PATHWAY DEFICIENCIES

These patients have increased susceptibility to infections with nontuberculous mycobacteria, *Salmonella,* and certain viruses, as well as disseminated infection following bacille Calmette-Guérin vaccination. Several genetic defects of the monocyte-macrophage-T_H1 T-cell pathway have been identified. Patients with complete interferon-γ receptor defects have severe impairment in interferon-γ signaling and fail to form tuberculoid granulomas. Patients with a partial defect have a better prognosis. Other patients with a similar clinical phenotype have an interleukin (IL)-12p40 deficiency or a mutation in the IL-12 receptor.

There is significant redundancy in the innate immune system, such that mutations in genes that are important in host defense, such as the defects in the interferon/IL-12 pathway, lead to an increased susceptibility to a variety of pathogens. In contrast, mutations in UNC-93B and TLR3 lead to a pathogen-specific predisposition to herpes simplex viral encephalitis. Undoubtedly there will be more discoveries of primary immune deficiencies associated with gene mutations that lead to specific single-pathogen–associated diseases.

DEFICIENCIES OF T-CELL IMMUNITY

DEFINITION

Profound defects in T-lymphocyte function, or defects arresting the development of T cells early in ontogeny, not only affect cell-mediated immunity but also impair the development of B-lymphocyte function (humoral immunity) owing to the absence of T-cell help and T-cell–derived cytokines. The clinical syndromes resulting from these more profound immune defects are referred to as SCID. Recurrent infections with organisms of relatively low virulence in an immunologically normal host (i.e., opportunistic infections) occur. Patients with T-cell immunodeficiency may develop infection with *Candida albicans* involving the mucous membranes and skin, but this infection is not invasive. Other fungal infections, severe viral diseases, and infection with opportunistic pathogens such as *P. jirovecii* or *M. avium-intracellulare* should prompt an evaluation for disorders in T-cell function. Graft-versus-host disease can be a significant problem in patients with severe T-cell immunodeficiency, either after the transfusion of lymphocyte-containing blood products or as a result of intrapartum or prenatal maternal-fetal transfusion. The clinical characteristics of patients with T-cell deficiency are shown in Table 258-2.

DIAGNOSIS

Patients are evaluated for T-cell deficiency by enumerating peripheral blood T-cell subsets and natural killer (NK) cells by flow cytometry; in addition, lymphocyte proliferative responses to mitogens and specific antigens can be assessed in vitro. Delayed hypersensitivity skin testing can be an initial screening test for T-cell immunity, using the intracutaneous injection of 0.1 mL of recall antigens (i.e., *Candida*) at 1:100 dilution weight/volume, tetanus toxoid at 1:100 dilution weight/volume, or *Trichophyton* at 1:30 dilution. Negative results are seen in patients with impaired T-cell responses, but they can also occur because of the lack of prior antigen exposure. Severe illness or the use of immunosuppressive drugs or systemic corticosteroids can also diminish delayed hypersensitivity responses (anergy).

TABLE 258-1 CLINICAL CHARACTERISTICS OF DISEASES OF PHAGOCYTIC CELL DYSFUNCTION

Can range from mild skin infections to severe systemic infections
Skin infections, furunculosis, visceral or perirectal abscess with granuloma formation, lymphadenitis, gingivitis
Poor wound healing, lack of pus
Mainly susceptible to low-grade virulent bacterial infections
Staphylococcus species
Gram-negative organisms

TABLE 258-2

Onset of symptoms often in early infancy (4-5 mo)
Recurrent infections with fungi (*Candida*), viruses, and mycobacterial pathogens
Infections with opportunistic organisms: *Pneumocystis jirovecii*
Failure to thrive, often fatal in childhood
Fatal infections from live virus vaccines or bacille Calmette-Guérin vaccination
Graft-versus-host disease from transfusion of blood products containing viable T lymphocytes

TREATMENT Rx

The diagnosis of T-cell immunodeficiency needs to be established quickly, before severe infections and life-threatening complications occur; patients are best referred to established centers for bone marrow transplantation. Prophylaxis against *P. jirovecii* is recommended for patients with significant T-cell immunodeficiency. Live vaccines such as oral polio, measles-mumps-rubella, varicella, and bacille Calmette-Guérin should not be given to patients with suspected or diagnosed T-cell immunodeficiency owing to the risk of vaccine-induced infection. Inactivated polio vaccine (rather than oral polio vaccine) should be given to household members to prevent transmission of the virus, which can occur via shedding of the attenuated virus in the stool. If patients with T-cell defects need blood transfusions, only irradiated, leukocyte-poor, cytomegalovirus-free products should be used to avoid graft-versus-host disease and cytomegalovirus infection.

B-CELL IMMUNODEFICIENCIES

Unlike patients with SCID, who first manifest symptoms at 4 to 5 months of age, patients with severe B-cell deficiencies usually do not have problems with infections until 7 to 9 months of age. The onset of infection is later in this group of patients because they are protected initially by maternal antibodies that pass through the placenta during the third trimester of pregnancy. Patients with B-cell immunodeficiencies usually develop infections with encapsulated bacterial organisms such as pneumococci and *H. influenzae*. The types of infection, as discussed previously, include otitis media, meningitis, septicemia, sinusitis, pneumonia, abscess, and osteomyelitis. Occasionally, these patients have problems with fungal or viral pathogens. Male patients with infantile XLA are unusually susceptible to enteroviruses and may develop chronic enteroviral encephalomyelitis. Generally, one does not see severe growth failure in patients with B-cell deficiency, as occurs in T-cell–deficient patients. Patients with antibody deficiency can survive into adulthood and can lead normal lives with the use of replacement intravenous immunoglobulin (IVIG) therapy.

Patients with severe B-cell deficiency, such as infantile XLA, typically have a paucity of lymphoid tissue (tonsils, adenoids, and peripheral lymph nodes). In contrast, patients with CVID often have lymphoid hypertrophy or hepatosplenomegaly. The incidence of allergy and autoimmune disease is increased, particularly in patients with IgA deficiency and CVID. The clinical characteristics of patients with B-cell deficiency are shown in Table 258-3.

X-Linked Agammaglobulinemia

DEFINITION

XLA is an X-linked recessive B-cell immunodeficiency with agammaglobulinemia and absent circulating B cells.

EPIDEMIOLOGY

Worldwide, the incidence appears to be approximately 1 in 100,000 to 200,000, or 5 to 10 cases per 1 million population.

PATHOBIOLOGY

The gene responsible for XLA is located on the X chromosome, and it encodes for a cytoplasmic tyrosine kinase (i.e., Bruton's tyrosine kinase [Btk]), which is expressed mainly in lymphocytes of the B-cell lineage. Btk is critical in B-lymphocyte signal transduction pathways and B-cell differentiation. Numerous mutations of the *BTK* gene have been described in patients with XLA, most involving the kinase domain. Mutations in the *BTK* gene lead to a block in B-cell maturation from pro-B cells to pre-B cells.

Some patients with *BTK* mutations do not present until later in life. This variation may reflect different types of *BTK* mutations. In fact, the block in B-cell differentiation may be "leaky," leading to a low level of immunoglobulin synthesis. A study of one family with XLA showed marked phenotypic variation among the male members who had the same gene mutation; serum immunoglobulin levels were also variable. Investigators have estimated that approximately 10% of adult patients with a diagnosis of CVID may be misdiagnosed and may actually have XLA with deficient Btk.

TABLE 258-3 CLINICAL CHARACTERISTICS OF B-CELL DEFICIENCIES

Recurrent infections with encapsulated organisms
Sinopulmonary infections, otitis media, meningitis, sepsis, abscess, osteomyelitis, cellulitis
No problems with fungal or viral infections (except enteroviral infection in XLA)
Lymphoid tissues: absent in patients with XLA, hypertrophied in those with CVID
Increased incidence of atopy and autoimmune disease
Granulomatous lung disease in CVID
Gastrointestinal disease
Celiac disease
Lactose intolerance
Bacterial overgrowth of small bowel
Nodular lymphoid hyperplasia in CVID
Higher incidence of malignancy in CVID

CVID = common variable immunodeficiency; XLA = X-linked agammaglobulinemia.

CLINICAL MANIFESTATIONS

Infections in patients with XLA occur predominantly in the sinopulmonary tract (60% of patients) and include otitis media, chronic sinusitis, and pneumonia. Other types of infections include pyoderma (25%), chronic conjunctivitis (8%), gastroenteritis (35%), arthritis (20%), meningitis or encephalitis (16%), and, less commonly, osteomyelitis (3%) and septicemia (10%). The most common pathogens are *H. influenzae* and *S. pneumoniae.* Patients who are untreated experience repeated pulmonary tract infections, leading eventually to bronchiectasis (Chapter 90). Infections may also occur with *G. lamblia.* Because cellular immunity is intact, most viral infections, fungal infections, and tuberculosis do not present a problem in patients with XLA. Exceptions to this include viral hepatitis, disseminated polio, and chronic enteroviral encephalitis.

Physical findings are related to repeated bacterial infections of susceptible target organs, such as the middle ear, sinuses, and lungs. Patients have a paucity of lymphoid tissues (e.g., adenoids, lymph nodes, spleen), unlike patients with CVID, who often have lymphoid hyperplasia. Unusual complications of XLA include a dermatomyositis-like syndrome and enteroviral meningoencephalitis.

Arthritis occurs in less than half the patients with XLA. In some patients, joint inflammation results from infection with enteroviruses or *Ureaplasma urealyticum.* Joint symptoms usually improve or resolve with IVIG therapy. Patients with XLA are highly susceptible to poliovirus infection; vaccine-associated poliomyelitis has been reported in XLA.

Unlike patients with CVID, autoimmune disorders are not a frequent problem in patients with XLA. Although a predisposition to various cancers is common with many types of immunodeficiencies, it is unclear whether patients with XLA have the same predisposition. The primary immunodeficiency registry reported that only 4.2% of registry patients with malignancies had XLA; lymphoreticular and gastrointestinal malignant diseases were more common.

Patients with XLA have a total absence or marked deficiency of serum immunoglobulins, and they fail to make antibodies to even potent protein antigens. Circulating B cells or surface membrane immunoglobulin-positive lymphocytes are extremely low (≤2%) or absent. T lymphocytes and other lymphoid subpopulations and delayed skin reactivity to recall antigens are normal. The response of peripheral blood lymphocytes to mitogens and allogeneic cells is normal. Lymphoid tissues show an absence of plasma cells, lymphoid follicles, and germinal centers.

DIAGNOSIS

Serum immunoglobulin levels should be quantified; as noted, patients with XLA usually have a profound hypogammaglobulinemia or agammaglobulinemia and fail to make antibodies even to potent protein antigens. Flow cytometry for B-cell numbers shows absent or very low numbers of $CD19^+$ B cells (e.g., <2%). Molecular analysis for *BTK* gene mutations can be very helpful in diagnostic evaluations. T-cell number and function are normal.

TREATMENT Rx

Early diagnosis, broad-spectrum antibiotics, and replacement therapy with IVIG have changed the outcome of this disease. Infections, especially chronic enteroviral infections and chronic pulmonary disease, are still the two major complications of XLA. Early initiation of IVIG replacement therapy, with nadir serum IgG levels higher than 500 mg/dL, is important to prevent severe acute bacterial infections. Trough serum IgG levels higher than 800 mg/dL may be necessary to prevent chronic sinusitis, bronchiectasis, and enteroviral infections.

Immunodeficiency with Hyper–Immunoglobulin M (Immunoglobulin Class Switch Defects)

DEFINITION

Immunodeficiency with hyper-IgM is characterized by severe recurrent bacterial infections and decreased serum levels of IgG, IgA, and IgE but normal or elevated levels of IgM. The X-linked form of this syndrome (type 1) is most common, but a similar phenotype with an autosomal recessive inheritance occurs in female patients (type 3).

PATHOBIOLOGY

Immunodeficiency with hyper-IgM is primarily a disorder of B-cell isotype switching. Mutations in the CD40 ligand (CD40L or CD154) on T cells are responsible for the X-linked form of hyper-IgM (type 1), whereas mutations in the CD40 ligand receptor (e.g., CD40) on B cells are responsible for hyper-IgM type 3.

CLINICAL MANIFESTATIONS

Recurrent bacterial infections of the sinopulmonary tract usually begin in the first or second year of life. Stomatitis and mouth ulcers may occur in association with the neutropenia. *P. jirovecii* has been reported in patients with X-linked hyper-IgM. Other opportunistic pathogens include cytomegalovirus, *Cryptococcus,* and mycobacteria. Patients are susceptible to opportunistic organisms and have a high incidence of autoimmune diseases such as thrombocytopenia, hemolytic anemia, neutropenia, nephritis, and arthritis. Diarrhea is a frequent finding, occurring in more than 50% of patients, often as a result of cryptosporidiosis. Hepatitis B and hepatitis C viral infections produce chronic hepatitis in these patients. Unlike patients with XLA, these patients have marked hypertrophy of the lymphoid tissues, including the tonsils, lymph nodes, and spleen. However, the lymph nodes are poorly organized, with an absence of germinal centers. Proliferation of IgM-producing plasma cells, with extensive invasion of the gastrointestinal tract and liver, may occur by the second decade of life. Patients also have an increased risk of malignant diseases, especially lymphomas. An increased incidence of liver and biliary tumors is a unique feature of X-linked hyper-IgM.

DIAGNOSIS

Serum levels of IgM are often markedly increased and may exceed 1000 mg/dL; however, early in life the serum level of IgM may be normal. Patients can produce IgM antibody, but the secondary IgG response is usually markedly diminished or absent. Surface immunoglobulin–positive lymphocytes in the peripheral blood are primarily positive for IgM; IgA- and IgG-bearing lymphocytes are decreased or absent. T-lymphocyte numbers and mitogen responses are normal. Patients with X-linked hyper-IgM type 1 lack CD40L on activated T cells as a result of mutations in the gene for CD40L. Patients with hyper-IgM type 3 lack the receptor for CD40 ligand (CD40) on B cells and antigen-presenting cells.

TREATMENT

Rx

Supportive care, prophylactic antibiotics for *P. jirovecii,* and recognition and treatment of other opportunistic infections are important. Parenteral nutrition may be necessary for patients with severe gastrointestinal disturbances. Treatment consists of IVIG replacement therapy. The commonly associated autoimmune neutropenia responds well to treatment with IVIG and granulocyte colony-stimulating factor. Bone marrow transplantation has been used to treat patients with this disease.

OTHER FORMS OF HYPER–IMMUNOGLOBULIN M PHENOTYPES

Other patients with a hyper-IgM phenotype have been described with normal CD40L and CD40 expression; these patients may possess mutations in the activation-induced cytidine deaminase (type 2) gene *(AICDA)* or the uracil DNA glycosylase (type 5) gene *(UNG)*. These patients differ from those with the X-linked form by exhibiting marked lymph node hyperplasia, enlarged germinal centers with highly proliferating B cells, and the absence of T-cell defects or opportunistic infections.

Another rare form of X-linked hyper-IgM syndrome (sometimes called NEMO syndrome) is associated with ectodermal dysplasia characterized by the absence or hypoplasia of hair, teeth, and sweat glands and by the presence of immunodeficiency. These patients exhibit increased susceptibility to bacterial infections, including atypical mycobacteria, encapsulated bacteria, and herpes viral infections. Most patients have low serum levels of IgG, variable levels of IgM and IgA, and poor antibody production; NK cell function is also defective. This disorder is related to mutations in the gene that encodes the nuclear factor-κB (NF-κB) essential modulator (NEMO or IKKγ), which is required for activation of the transcription factor NF-κB. Treatment consists of IVIG and mycobacterial prophylaxis.

DISEASES OF IMMUNE DYSREGULATION AND IMMUNODEFICIENCY

DEFINITION

The majority of autoimmune diseases have a complex, multifactorial, polygenic cause in which environmental triggers play an important role in their pathogenesis. A separate group of immune disorders affects patients with monogenic defects that impact processes of immune tolerance. These immune deficiencies include autoimmune polyendocrinopathy with candidiasis and ectodermal dystrophy (APECED); immunodysregulation with polyendocrinopathy, enteropathy, and X-linked inheritance syndrome (IPEX); and autoimmune lymphoproliferative syndrome (ALPS).

PATHOBIOLOGY

APECED is an autosomal recessive disorder with a higher frequency in individuals of Finnish, Sardinian, and Iranian Jewish origin. This disorder is caused by mutations in the gene encoding the autoimmune regulator protein (AIRE), a transcription factor that is important in controlling the ectopic expression of self-antigens in the thymus. Mutations in the *AIRE* gene lead to a breakdown in central tolerance and the development of multiorgan autoimmune diseases. IPEX is an X-linked disorder that involves mutations in the *FOXP3* gene, which is important in peripheral tolerance and the function of T-regulatory cells. ALPS is a disorder of programmed cell death, with several different gene mutations leading to defective Fas-mediated lymphocyte apoptosis (Table 258-4).

CLINICAL MANIFESTATIONS

Chronic mucocutaneous candidiasis, hypoparathyroidism, and adrenocortical failure are the classic triad of findings in APECED, with only two of the three required to make the diagnosis. Associated autoimmune disorders include insulin-dependent diabetes mellitus, thyroiditis, premature ovarian failure, hepatitis, and hypergonadotropic hypogonadism. IPEX patients typically present during the first few months of life, most commonly with diabetes mellitus, intractable diarrhea, and failure to thrive. Eczema, hemolytic anemia, thyroiditis, and serious infections are also classic features of the syndrome. Patients with ALPS may present with splenomegaly and lymphadenopathy (Chapter 171), as well as with various autoimmune manifestations, including hemolytic anemia, thrombocytopenia, and neutropenia.

DIAGNOSIS

There are no specific diagnostic tests for APECED; if the disease is suspected based on the clinical presentation, establishing the diagnosis depends on sequencing the *AIRE* gene. For IPEX, evaluating T cells for *FOXP3* expression is helpful. In ALPS, flow cytometry for the presence of double-negative T cells (CD4 and CD8 negative), along with the clinical presentation, is useful to screen for the disorder.

TABLE 258-4 IMMUNE DISORDERS WITH ABNORMALITIES IN IMMUNE REGULATION

- Autoimmune polyendocrinopathy, candidiasis, ectodermal dystrophy (APECED): mutations in autoimmune regulator gene (*AIRE*)
- Immune dysregulation, polyendocrinopathy, enteropathy, X-linked disorder (IPEX): mutations in *FOXP3* gene
- Autoimmune lymphoproliferative syndrome (ALPS)
  - ALPS type Ia: mutations in Fas (*TNFRSF6*)
  - ALPS type Im: somatic mutation in the gene encoding Fas
  - ALPS type Ib: mutations in Fas ligand (*TNGSF6*)
  - ALPS type II: mutation in caspase 10 (*CASP10*)
  - ALPS type III: unknown mutation
  - ALPS type IV: mutation in *NRAS*

TREATMENT Rx

Therapy for APECED is directed at the autoimmune processes and the candidiasis. In IPEX, immunosuppression with calcineurin inhibitors is the most frequent approach. Bone marrow transplantation early in the disease can arrest the progression of diabetes. In ALPS, thrombocytopenia secondary to hypersplenism may respond to splenectomy, although the autoimmune cytopenias may require immunosuppressive therapy. Pneumococcal infections are frequent, and prophylactic antibiotics may be helpful. The increased risk of lymphoma in ALPS patients and family members requires careful vigilance.

COMMON VARIABLE IMMUNODEFICIENCY

DEFINITION

CVID comprises a heterogeneous group of disorders involving both B-cell and T-cell immune dysfunction in which the predominant manifestation is hypogammaglobulinemia. CVID is characterized by recurrent bacterial infections, decreased serum immunoglobulin levels (at least two immunoglobulin isotypes more than 2 standard deviations lower than normal for age), and abnormal specific antibody responses. These patients may present in early childhood, during adolescence, or as young adults. In most patients, the onset of symptoms occurs in the second or third decade of life. In a large study, the average age at onset of symptoms was 25 years, and the average age at diagnosis was 28 years.

EPIDEMIOLOGY

The estimated incidence of CVID ranges from 1 in 10,000 to 1 in 50,000. These figures may underestimate the true numbers of CVID patients because of the late onset of symptoms and underdiagnosis of this immunodeficiency disorder.

PATHOBIOLOGY

The number of immune deviations described in patients with CVID underscores the heterogeneous nature of the immune defects in this syndrome. A homozygous deletion in the gene encoding ICOS, a T-cell costimulatory molecule of the CD28 family that enhances the activation of T cells and is important in T-cell–B-cell interactions, was found in two German families of CVID patients. The clinical phenotype of ICOS deficiency is similar to that of other patients with CVID. Other genetic mutations associated with CVID include the CD19 receptor TACI (*TNFRSF13B*, a receptor for the B-cell growth factor cytokines BAFF and APRIL), the BAFF receptor (*TNFRSF13C*), and *MSH5*.

Family members of patients with CVID exhibit an unusually high incidence of IgA deficiency, autoimmune diseases, autoantibodies, and malignant disease. An inheritance pattern of autosomal dominance with variable penetrance has been suggested.

CLINICAL MANIFESTATIONS

The most frequent presenting infections in adults with CVID involve the respiratory tract, including recurrent otitis media, chronic sinusitis, and recurrent pneumonia, often resulting in bronchiectasis. The bacterial pathogens are similar to those described in XLA. The gastrointestinal tract is affected in approximately half the patients with CVID; patients often present with malabsorption or chronic diarrhea. These symptoms can be related to numerous underlying abnormalities, including lactose intolerance, protein-losing enteropathy, superimposed infection of the small bowel with bacteria such as *Campylobacter* or *Yersinia* or the parasite *G. lamblia,* or infection of the large bowel with normal flora (small bowel bacterial overgrowth syndrome). Atrophic gastritis with achlorhydria may lead to pernicious anemia.

Approximately 5 to 10% of patients with CVID present with noncaseating granulomatous lesions that infiltrate the liver, lymph nodes, skin, and, more commonly, lung. These lesions are often confused with sarcoidosis (Chapter 95). Chronic gastrointestinal disease is often associated with nodular lymphoid hyperplasia, characterized by hypertrophy of the Peyer's patches in the small bowel and diffuse lymphoid infiltration. Hypertrophy of other lymphoid tissues, including the peripheral lymph nodes, the spleen, and occasionally the liver, is also seen. Rarely, hepatosplenomegaly may be severe enough to result in secondary neutropenia or thrombocytopenia. The pathogenesis of this process is not known but may be related to increased production of tumor necrosis factor-α. Patients with granulomatous-lymphocytic interstitial lung disease have a worse prognosis, often developing a restrictive pulmonary pattern with a low-normal diffusing lung capacity for carbon monoxide and diminished T-cell function. High-resolution computed tomography of the chest is helpful in identifying these patients, who require higher replacement doses of IVIG and sometimes treatment with corticosteroids.

Autoimmune disorders occur frequently in CVID (20 to 25% of patients), including rheumatic diseases, hematologic disorders, neurologic diseases, chronic active hepatitis, and endocrinopathies. The incidence of malignant disease is increased (11 to 13%) in patients with CVID during the fifth and sixth decades of life. Most of these malignant diseases involve the gastrointestinal tract and the lymphoid tissues (e.g., non-Hodgkin's lymphoma).

DIAGNOSIS

The serum immunoglobulin levels are markedly diminished in patients with CVID; however, a large variability is seen in the degree of hypogammaglobulinemia. Specific antibodies are usually lacking, and isohemagglutinin titers are generally diminished. The proportions of circulating B cells in the peripheral blood are usually normal, but a subset of patients may lack circulating B lymphocytes. T-cell function can be quite variable, being normal in half of patients. The other half of patients with CVID may exhibit depressed T-cell function, with absent delayed hypersensitivity skin reactivity to recall antigens, low numbers of circulating peripheral blood $CD4^+$ T cells, often a decrease in the CD4/CD8 ratio, and depressed in vitro responses to mitogens and specific antigens. Other recent laboratory findings associated with CVID include the lack of isotype-switched memory B cells (e.g., $CD27^+$, IgM^-, IgD^- B cells).

TREATMENT Rx

Patients with CVID are treated with doses of IVIG ranging from 400 to 600 mg/kg every 4 weeks. Generally, this regimen should achieve a trough serum IgG level higher than 500 mg/dL. Patients who continue to experience recurrent infections or who develop bronchiectasis should be treated with higher doses of IVIG to achieve higher trough levels (e.g., >750 mg/dL).

PROGNOSIS

The prognosis is generally good for patients with CVID whose illness is diagnosed early and who undergo replacement IVIG therapy. The reported mortality rate over a 25-year period was 24%, mostly because of lymphoma (18%) and chronic pulmonary disease (11%). The mean age at the time of death was 45.5 years in women and 40 years in men. The patients who died were more likely to have lower levels of IgG at the time of diagnosis and poorer T-cell proliferative responses to phytohemagglutinin. Twenty-year survival after the diagnosis of CVID was 64% for men and 67% for women, compared with 92 to 94% for the general population. With early diagnosis and replacement IVIG therapy, survival is much improved.

Immunodeficiency with Thymoma

Immunodeficiency with thymoma (Good's syndrome) is a disorder of adults. It typically presents between the ages of 40 and 70 years with recurrent sinopulmonary infections. Affected individuals have adult-onset hypogammaglobulinemia, which may affect all major immunoglobulin isotypes. During the initial investigation of hypogammaglobulinemia, a thymoma (Chapter 99) may be detected as a mediastinal mass on the chest radiograph. Occasionally, the thymoma predates the hypogammaglobulinemia. Thymic tumors are predominantly of the spindle cell type and are usually benign. The clinical symptoms are similar to those found in patients with CVID. In contrast to CVID, however, frequently associated disorders include aregenerative (pure red cell) anemia, agranulocytosis, and myasthenia gravis. These conditions may improve after thymectomy, but the immunodeficiency may persist; $CD4^+$ T-cell lymphopenia and a decreased $CD4^+/CD8^+$ ratio are commonly seen. Infections associated with T-cell abnormalities can be seen in these patients, including mucocutaneous candidiasis, cytomegalovirus infection, herpes zoster, and *P. jirovecii* pneumonia.

IMMUNOGLOBULIN A DEFICIENCY

DEFINITION

IgA deficiency is defined as a serum IgA concentration lower than 7 mg/dL, with normal serum levels of IgM and IgG. It is one of the most common

B-cell immunodeficiencies, with an approximate incidence of 1 in 400 to 2000 individuals in the general population.

PATHOBIOLOGY

The genetic defect responsible for IgA deficiency is not known. IgA deficiency shares with CVID the inheritance of a restricted major histocompatibility complex extended haplotype. Although the pathogenesis of IgA deficiency is still unknown, it may share a common origin with CVID because these two disorders have many immune aspects in common. In fact, some patients with IgA deficiency have mutations in *TACI,* similar to the defects described in patients with CVID. IgA deficiency may occur in association with the administration of drugs such as phenytoin, sulfasalazine, hydroxychloroquine, and D-penicillamine. IgA deficiency has also been described in association with partial deletion of the long arm of chromosome 18 (18q syndrome) or with a ring chromosome 18.

CLINICAL MANIFESTATIONS

Many individuals with selective IgA deficiency do not have symptoms. The variability in clinical expression may be related to two factors. First, the IgA-deficient patients who are relatively asymptomatic appear to have a compensatory increase in secretory monomeric IgM in their saliva, upper respiratory tract secretions, and gastrointestinal fluids. Second, the association of IgG2/IgG4 or IgG4 subclass deficiencies with IgA deficiency may predispose IgA-deficient patients to more severe and recurrent sinopulmonary infections.

Symptoms of IgA deficiency include sinopulmonary infections and involvement of the gastrointestinal tract with giardiasis, nodular lymphoid hyperplasia, ulcerative colitis, Crohn's disease, or a sprue-like disease. An increased frequency of autoimmune disorders has also been associated with IgA deficiency, including arthritis, a lupus-like illness, endocrinopathies, chronic active hepatitis, and hematologic disorders. IgA-deficient patients are at risk for the development of anti-IgA antibodies on receipt of blood products. Caution must be exercised in the administration of IVIG for the treatment of IgG subclass deficiency in IgA-deficient patients because most of these preparations contain small amounts of IgA. However, this risk does not appear to be significant in patients with partial IgA deficiency.

DIAGNOSIS

Despite very low serum levels of IgA, the peripheral blood B cells of IgA-deficient patients coexpress IgA, IgM, and IgD, an immature phenotype. However, the lymphoid tissues are deficient in IgA-producing plasma cells. Studies of T-cell function have been normal in most patients with selective IgA deficiency.

TREATMENT

Rx

No specific treatment for IgA deficiency exists. Prophylactic antibiotics may be helpful in patients with recurrent sinopulmonary tract infections. Patients with chronic lung disease should receive conventional therapy to prevent the development of bronchiectasis (Chapter 90). IVIG is not indicated in patients with isolated IgA deficiency. Other supportive treatments are aimed at associated diseases. Patients should be transfused only with washed red cells to avoid sensitization to the IgA in blood products.

PROGNOSIS

The prognosis is good in most cases. Respiratory infections and autoimmune disease are more common in IgA-deficient patients. A few patients with IgA deficiency presenting in childhood may recover spontaneously; other patients may develop CVID.

IMMUNOGLOBULIN G SUBCLASS DEFICIENCIES AND SELECTIVE ANTIBODY DEFICIENCY

DEFINITION

Considerable controversy exists over the biologic significance of IgG subclasses and the clinical significance of an isolated IgG subclass level outside of the normal range. Because healthy individuals without recurrent infections may have abnormally low serum IgG subclass concentrations, immunologists have questioned whether IgG subclass deficiency represents a true immunodeficiency disease. Deficiency in an IgG subclass is defined as a serum IgG subclass concentration more than 2 standard deviations lower than the normal mean for age. The age at which each of the IgG subclasses reaches adult levels varies. In adults, IgG3 deficiencies are most common, whereas in children, IgG2 deficiencies are most prevalent. IgG subclass deficiency may be seen in conjunction with other primary immunodeficiency disorders such as ataxia-telangiectasia and IgA deficiency. IgG subclass deficiency occurs in approximately 18% of IgA-deficient patients. An IgG subclass deficiency may occur as an isolated immune defect, or two or more IgG subclass deficiencies may coexist (e.g., IgG2 and IgG4 deficiency).

Patients with *selective antibody deficiency* exhibit low responses to immunization with polysaccharides such as *H. influenzae* type b (Hib) capsular antigen or to the pneumococcal polysaccharide antigens, but they have normal serum immunoglobulin isotypes and IgG subclass concentrations. However, these patients respond normally to immunization with Hib-conjugate vaccine, in that the antibody response to the vaccine falls principally within the IgG1 subclass instead of the IgG2 subclass.

CLINICAL MANIFESTATIONS

The most frequent clinical problems associated with IgG subclass deficiency and selective antibody deficiency are recurrent infections of the upper and lower respiratory tracts. Pathogens are generally limited to encapsulated bacteria and respiratory viruses. Because IgG2 is important in the response to polysaccharide antigens, patients with IgG2 deficiency may have increased infections with *H. influenzae* or *S. pneumoniae.* Patients may be unable to produce specific antibodies after immunization with purified polysaccharide antigens (e.g., Pneumovax). Some patients with IgG2 subclass deficiency may be asymptomatic. In part, this may result from a shifting of the antibody response to another IgG subclass or immunoglobulin isotype to compensate for the IgG2 deficiency. IgG3 deficiency, more common in adults, has been associated with recurrent upper and lower respiratory tract infections and may occur in combination with IgG1 deficiency. Several studies have suggested that IgG3 is especially important in the primary response to viral respiratory agents. IgG3 is also the predominant antibody response in *Moraxella catarrhalis,* an organism frequently isolated from patients with chronic sinusitis. IgG4 deficiency occurs in the general population at a rate of approximately 10 to 15%. The clinical significance of IgG4 deficiency is not known.

DIAGNOSIS

Serum immunoglobulin concentrations should be measured by quantitative techniques (nephelometry). Levels in children must be compared with laboratory normals for age. Immunoelectrophoresis is semiquantitative and should not be used to evaluate patients with suspected antibody deficiency. Immunoelectrophoresis should be used only to examine serum for paraproteins such as those found in Waldenström's macroglobulinemia or multiple myeloma. IgG subclass quantification may be helpful, although controversy exists over the utility of these measurements. A careful history and physical examination, and the measurement of functional or specific antibodies, are important in determining the clinical relevance of an IgG subclass deficiency.

Patients may have normal levels of total serum immunoglobulins and normal IgG subclasses yet may fail to make specific antibodies to bacterial or common viral pathogens. Therefore, the assessment of specific antibody formation following vaccine administration is an important part of the laboratory evaluation in patients with suspected B-cell deficiency. Usually, specific antibody titers are obtained at baseline and at 4 weeks after immunization to assess the specific antibody response. Isohemagglutinins are naturally occurring IgM antibodies to the ABO blood group substances. Responses to protein antigens generally fall in the IgG1 subclass, whereas the immune response to the polysaccharide antigens resides in the IgG2 subclass. The antibody responses to conjugate vaccines for Hib and pneumococcal polysaccharides occur primarily in the IgG1 rather than IgG2 subclass. Therefore, these conjugate vaccines may not be helpful in the functional evaluation of an IgG2 subclass deficiency or a selective polysaccharide antibody deficiency. Because recurrent upper respiratory tract infections are common in these patients, one can test the serum for the presence of antibodies to common respiratory agents such as influenza A and B, mycoplasma, respiratory syncytial virus, adenovirus, and the parainfluenza viruses.