Immunology

PART XIV

Section 1

Evaluation of the Immune System

Chapter 122

Evaluation of Suspected Immunodeficiency

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Recurrent infections or fevers in children are among the most frequent clinical dilemmas for primary care physicians. A major reason for the apparent high rate of recurrent infections in children is repeated exposure to common and usually benign infectious agents in childcare and other group settings.

Primary care physicians must have a high index of suspicion if defects of the immune system are to be diagnosed early enough that appropriate treatment can be instituted before irreversible damage develops. Diagnosis is difficult because, until recently, primary immunodeficiency diseases have not been screened for at any time during life anywhere in the world, and most affected do not have abnormal physical features. Screening for severe combined immunodeficiency (SCID; T-cell lymphopenia) is part of the newborn screening programs in 21 states of the United States now; the hope is that it will eventually be performed nationwide. There is also a beginning effort to do this in Europe. Extensive use of antibiotics may mask the classic presentation of many primary immunodeficiency diseases. Evaluation of immune function should be initiated in those rare infants or children who do have clinical manifestations of a specific immune disorder and in all who have a positive family history of early infant death or a known immunodeficiency disorder, unusual, chronic, or recurrent infections such as (1) 1 or more systemic bacterial infections (sepsis, meningitis); (2) 2 or more serious respiratory or documented bacterial infections (cellulitis, abscesses, draining otitis media, pneumonia, lymphadenitis) within 1 yr; (3) serious infections occurring at unusual sites (liver, brain abscess); (4) infections with unusual pathogens *(Pneumocystis jiroveci, Aspergillus, Serratia marcescens, Nocardia, Burkholderia cepacia);* and (5) infections with common childhood pathogens but of unusual severity (Table 122-1). Additional clues to immunodeficiency include failure to thrive with or without chronic diarrhea, persistent infections after receiving live vaccines, and chronic oral or cutaneous moniliasis. Tables 122-2 and 122-3 note certain clinical features that are suggestive of immunodeficiency syndromes.

Children with defects in antibody production, phagocytic cells, or complement proteins have recurrent infections with encapsulated bacteria and may grow and develop normally despite their recurring infections, unless they develop bronchiectasis from repeated lower respiratory tract bacterial infections or persistent enteroviral infections of the central nervous system. Patients with only repeated benign viral infections (with the exception of persistent enterovirus infections) are not as likely to have an immunodeficiency. By contrast, patients with deficiencies in T-cell function usually develop opportunistic infections or serious illnesses from common viral agents early in life, and they fail to thrive (Table 122-4).

The initial evaluation of immunocompetence includes a thorough history, physical examination, and family history (Table 122-5). Most immunologic defects can be excluded at minimal cost with the proper choice of screening tests, which should be broadly informative, reliable, and cost-effective (Table 122-6 and Fig. 122-1). A complete blood count (CBC), manual differential count, and erythrocyte sedimentation rate are among the most cost-effective screening tests. If the erythrocyte sedimentation rate is normal, chronic bacterial or fungal infection is unlikely. If an infant's neutrophil count is persistently elevated in the absence of any signs of infection, a leukocyte adhesion deficiency should be suspected. If the absolute neutrophil count is normal, congenital and acquired neutropenias and leukocyte adhesion defects are excluded. If the absolute lymphocyte count is normal, the patient is not likely to have a severe T-cell defect, because T cells normally constitute 70% of circulating lymphocytes and their absence results in striking lymphopenia. Normal lymphocyte counts are higher in infancy and early childhood than later in life (Fig. 122-2). Knowledge of normal values for absolute lymphocyte counts at various ages in infancy and childhood is crucial in the detection of T-cell defects. At 9 mo of age, an age when infants affected with severe T-cell immunodeficiency are likely to present, the lower limit of normal is 4,500 lymphocytes/mm^3. Absence of Howell-Jolly bodies or pitted erythrocytes by microscopic examination of erythrocytes rules against congenital asplenia. Normal platelet size or count excludes Wiskott-Aldrich syndrome. If newborn screening for T-cell lymphopenia were to be performed on all infants, SCID could be detected at birth, and lifesaving immunologic reconstitution could then be provided to all affected infants shortly after birth and before they become infected.

Patients found to have abnormalities on any screening tests should be characterized as fully as possible before any type of immunologic treatment is begun, unless there is a life-threatening illness (Table 122-7). Some "abnormalities" may prove to be laboratory artifacts and, conversely, an apparently straightforward diagnosis may prove to be a much more complex disorder. For patients with recurrent or unusual bacterial infections, evaluation of T-cell and phagocytic cell functions is indicated even if results of initial screening tests including the CBC and manual differential, immunoglobulin levels, and CH_{50} are normal.

Because of the lack of screening, the true incidence and prevalence of primary immunodeficiency diseases are unknown, although the incidence has been estimated to be 1:10,000 births (Table 122-8). If true, this is higher than some disorders that are part of the newborn metabolic screening program (phenylketonuria is 1:16,000) (see Chapter 85.1). Approximately 80% of the mutated genes causing the more than 220 known primary immunodeficiency diseases have been identified. This is information crucial for genetic counseling and that could eventually be used in neonatal screening. Newborn or early childhood screening would be extremely valuable so that timely initiation of appropriate therapy can be initiated before infections develop; it is likely that many affected patients die before a diagnosis is determined.

B CELLS

Antibody production by B cells is easily evaluated by measuring serum immunoglobulin levels and determining antibody titers to protein and polysaccharide antigens.

A simple screening test for B-cell defects is the measurement of serum immunoglobulin (Ig) A. If the IgA level is normal, selective IgA

Table 122-1 Predisposition to Specific Infections in Humans

PATHOGEN	PRESENTATION	AFFECTED GENE/ CHROMOSOMAL REGION	FUNCTIONAL DEFECT	NOTES
BACTERIA				
Streptococcus pneumoniae	Invasive disease	*IRAK-4, MyD88*	Impaired production of inflammatory cytokines following TLR stimulation	Also susceptible to other pyogenic bacteria such as *Staphylococcus aureus*
Neisseria	Invasive disease	MAC components (C5, C6, C7, C8A, C8B, C8G, C9)	MAC deficiency	
	Invasive disease, poor prognosis	*PFC*	Properdin deficiency	
Mycobacteria	MSMD	*IL12B, IL12RB1, IKBKG*	Impaired IFN-γ response to IL-12, IL-23	Also susceptible to *Salmonella typhi* infections
		IFNGR1, IFNGR2, STAT1	Impaired cellular response to IFN-γ	
Mycobacterium leprae	Leprosy	*PARK2*	Unknown	Possible E3-ubiquitin ligase dysfunction
		LTA	Unknown	
VIRUSES				
Herpes simplex (type 1)	Herpes simplex encephalitis	*UNC93B1, TLR3, STAT1*	Impaired production of type 1 IFNs	STAT1 and NEMO deficiency also predispose to HSV infections, amongst other infections
Epstein-Barr virus	XLP	*SH2DIA*	SAP deficiency	Fulminant infectious mononucleosis, malignant and nonmalignant lymphoproliferative disorders, dysgammaglobulinemia, autoimmunity
		XIAP/BIRC4	XIAP deficiency	
Human papillomaviruses	Epidermodysplasia verruciformis	*EVER1/TMC6*	EVER1 deficiency	Altered neutrophil mobilization, T-cell lymphopenia, recurrent bacterial respiratory infections chronic cutaneous/genital papillomavirus disease
		EVER2/TMC8	EVER2 deficiency	
	WHIM	*CXCR4*	Truncated CXCR4	
PARASITES				
Plasmodium falciparum	Malaria fever episodes	10p15	Unknown	Linkage studies
	Severe malaria	*GNAS*	Unknown	SNP association studies
	Severe malaria	*IFNR1*	Unknown	SNP association studies
Schistosoma mansoni	Intensity of infection	5q311-q33	Unknown	
	Hepatic fibrosis	6q22-q23, *IFNR1*	Unknown	
Leishmania donovani	Visceral leishmaniasis (kala-azar)	22q12, 2q35 *(NRAMP1)*	Unknown	
YEAST				
Candida	APECED, chronic candidiasis	*Aire, STAT1, CARD9*	Unknown	APS-1 chronic candidiasis, chronic hyperthyroidism, Addison disease
Deep dermatophytosis	Tissue invasion	*CARD9*	Unknown	Autosomal recessive

APECED, autoimmune, polyendocrinopathy, candidiasis, ectodermal dystrophy; HSV, herpes simplex virus; IFN, interferon; IL, interleukin; MAC, membrane attack complex; MSMD, mendelian susceptibility to mycobacterial disease; NEMO, nuclear factor kappa B essential modulator; SAP, SLAM-associated protein; SNP, single-nucleotide polymorphism; TLR, Toll-like receptor; WHIM, warts, hypogammaglobulinemia, infections, and myelokathexis syndrome; XIAP, X-linked inhibitor of apoptosis; XLP, X-linked lymphoproliferative disease.

Modified from Pessach I, Walter J, Notarangelo LD: Recent advances in primary immunodeficiencies: identification of novel genetic defects and unanticipated phenotypes, Pediatr Res *65:3R–12R, 2009.*

deficiency, which is the most common B-cell defect, is excluded, as are most of the permanent types of hypogammaglobulinemia, as IgA is usually very low or absent in those conditions. If IgA is low, IgG and IgM should also be measured. Patients who are receiving corticosteroids or who have protein-losing states (nephrosis, protein-losing enteropathy) often have low serum IgG concentrations but produce antibodies normally. Thus, if immunoglobulins are low, it is crucial before starting intravenous immunoglobulin therapy that antibody titers to specific antigens are measured to determine whether the immunoglobulin levels are low because of inadequate antibody synthesis or due to protein loss. Antibody titers are not interpretable after the patient has received a blood transfusion, fresh-frozen plasma or intravenous immunoglobulin, which contains antibodies from a minimum of 10,000 normal donors.

One useful test for B-cell function is to determine the presence and titer of **isohemagglutinins,** or natural antibodies to type A and B red blood cell polysaccharide antigens. This test measures predominantly IgM antibodies. Isohemagglutinins may be absent normally in the 1st 2 yr of life and are always absent if the patient is blood type AB.

Because most infants and children are immunized with diphtheria-tetanus-pertussis, conjugated *Haemophilus influenzae* type b, and pneumococcal conjugate vaccine, it is often informative to test for specific antibodies to diphtheria, tetanus, *H. influenzae* polyribose phosphate, and pneumococcal antigens. If the titers are low, measurement of antibodies to diphtheria or tetanus toxoids before and 2 wk after a pediatric diphtheria-tetanus-pertussis or diphtheria-tetanus booster is helpful in assessing the capacity to form IgG antibodies to protein antigens. To evaluate a patient's ability to respond to

Table 122-2 Characteristic Clinical Patterns in Some Primary Immunodeficiencies

FEATURES	DIAGNOSIS
IN NEWBORNS AND YOUNG INFANTS (0-6 MO)	
Hypocalcemia, unusual facies and ears, heart disease	DiGeorge anomaly
Delayed umbilical cord detachment, leukocytosis, recurrent infections	Leukocyte adhesion defect
Persistent thrush, failure to thrive, pneumonia, diarrhea	Severe combined immunodeficiency
Bloody stools, draining ears, atopic eczema	Wiskott-Aldrich syndrome
Pneumocystis jiroveci pneumonia, neutropenia, recurrent infections	X-linked hyper-IgM syndrome
IN INFANTS AND YOUNG CHILDREN (6 MO-5 YR)	
Severe progressive infectious mononucleosis	X-linked lymphoproliferative syndrome
Recurrent staphylococcal abscesses, staphylococcal pneumonia with pneumatocele formation, coarse facial features, pruritic dermatitis	Hyper-IgE syndrome
Persistent thrush, nail dystrophy, endocrinopathies	Chronic mucocutaneous candidiasis
Short stature, fine hair, severe varicella	Cartilage hair hypoplasia with short-limbed dwarfism
Oculocutaneous albinism, recurrent infection	Chédiak-Higashi syndrome
Abscesses, suppurative lymphadenopathy, antral outlet obstruction, pneumonia, osteomyelitis	Chronic granulomatous disease
IN OLDER CHILDREN (OLDER THAN 5 YR) AND ADULTS	
Progressive dermatomyositis with chronic enterovirus encephalitis	X-linked agammaglobulinemia
Sinopulmonary infections, neurologic deterioration, telangiectasia	Ataxia-telangiectasia
Recurrent neisserial meningitis	C6, C7, or C8 deficiency
Sinopulmonary infections, splenomegaly, autoimmunity, malabsorption	Common variable immunodeficiency

Ig, immunoglobulin.
Modified from Stiehm ER, Ochs HD, Winkelstein JA: Immunologic disorders in infants and children, *ed 5, Philadelphia, 2004, WB Saunders.*

Table 122-3 Common Clinical Features of Immunodeficiency

Usually present	Recurrent upper respiratory infections Severe bacterial infections Persistent infections with incomplete or no response to therapy Paucity of lymph nodes and tonsils
Often present	Persistent sinusitis or mastoiditis (*Streptococcus pneumoniae, Haemophilus, Pneumocystis jiroveci, Staphylococcus aureus, Pseudomonas* spp.) Recurrent bronchitis or pneumonia Failure to thrive or growth retardation for infants or children; weight loss for adults Intermittent fever Infection with unusual organisms Skin lesions: rash, seborrhea, pyoderma, necrotic abscesses, alopecia, eczema, telangiectasia Recalcitrant thrush Diarrhea and malabsorption Hearing loss caused by chronic otitis Chronic conjunctivitis Arthralgia or arthritis Bronchiectasis Evidence of autoimmunity, especially autoimmune thrombocytopenia or hemolytic anemia Hematologic abnormalities: aplastic anemia, hemolytic anemia, neutropenia, thrombocytopenia History of prior surgery, biopsy
Occasionally present	Lymphadenopathy Hepatosplenomegaly Severe viral disease (e.g., EBV, CMV, adenovirus, varicella, herpes simplex) Chronic encephalitis Recurrent meningitis Deep infections: cellulitis, osteomyelitis, organ abscesses Chronic gastrointestinal disease, infections, lymphoid hyperplasia, sprue-like syndrome, atypical inflammatory bowel disease Autoimmune disease such as autoimmune thrombocytopenia, hemolytic anemia, rheumatologic disease, alopecia, thyroiditis, pernicious anemia Pyoderma gangrenosum Adverse reaction to vaccines Delayed umbilical cord detachment Chronic stomatitis or peritonitis

EBV, Epstein-Barr virus; CMV, cytomegalovirus.
Modified from Goldman L, Ausiello D: Cecil textbook of medicine, *ed 22, Philadelphia, 2004, WB Saunders, p 1598.*

polysaccharide antigens, anti-pneumococcal antibodies can be measured before and 3 wk after immunization with 23 valent unconjugated pneumococcal polysaccharide vaccine in patients 2-3 yr old or older. Antibodies detected in these tests are of the IgG isotype. These antibody studies can be performed in several different laboratories, but it is important to choose a reliable laboratory and to use the same laboratory for preimmunization and postimmunization titers. In children older than 2 yr of age with low anti-pneumococcal antibody titers after a pneumococcal polysaccharide vaccine immunization, it is useful to boost with conjugate pneumococcal vaccine twice, 1 mo apart, before giving a polysaccharide pneumococcal vaccine 1 mo later and then measuring antibody titers 3 wk later. Patients with significant or permanent B-cell defects do not produce either IgM or IgG antibodies normally. If results of these tests prove to be normal and the immunoglobulins remain low, studies should be performed to evaluate the possible loss of immunoglobulins through the urinary or gastrointestinal tracts (nephrotic syndrome, protein-losing enteropathies, intestinal lymphangiectasia). Very high serum concentrations of 1 or more immunoglobulin classes suggest HIV infection, chronic granulomatous disease, chronic inflammation, or autoimmune lymphoproliferative syndrome.

IgG subclass measurements are seldom helpful in assessing immune function in children with recurrent infections. It is difficult to know the biologic significance of the various mild to moderate deficiencies of IgG subclasses, particularly when completely asymptomatic individuals have been described as totally lacking IgG_1, IgG_2, IgG_4, and/or IgA_1 owing to immunoglobulin heavy-chain gene deletions. Many healthy children have been described as having low levels of IgG_2 but normal responses to polysaccharide antigens when immunized. When children with low IgG_2 subclass levels and histories of

Table 122-4 Characteristic Features of Primary Immunodeficiency

CHARACTERISTIC	PREDOMINANT T-CELL DEFECT	PREDOMINANT B-CELL DEFECT	GRANULOCYTE DEFECT	COMPLEMENT DEFECT
Age at the onset of infection	Early onset, usually 2-6 mo of age	Onset after maternal antibodies diminish, usually after 5-7 mo of age, later childhood to adulthood	Early onset	Onset at any age
Specific pathogens involved	Bacteria: common Gram-positive and Gram-negative bacteria and mycobacteria Viruses: CMV, EBV, adenovirus, parainfluenza 3, varicella, enterovirus Fungi: *Candida* and *Pneumocystis jiroveci*	Bacteria: pneumococci, streptococci, staphylococci, *Haemophilus, Campylobacter, Mycoplasma* Viruses: enterovirus* Fungi and parasites: giardia, cryptosporidia	Bacteria: staphylococci, *Pseudomonas, Serratia, Klebsiella, Salmonella* Fungi and parasites: *Candida, Nocardia, Aspergillus*	Bacteria: pneumococci, *Neisseria*
Affected organs	Extensive mucocutaneous candidiasis, lungs, failure to thrive, protracted diarrhea	Recurrent sinopulmonary infections, chronic gastrointestinal symptoms, malabsorption, arthritis, enteroviral meningoencephalitis*	Skin: abscesses, impetigo, cellulitis Lymph nodes: suppurative adenitis Oral cavity: gingivitis, mouth ulcers Internal organs: abscesses, osteomyelitis	Infections: meningitis, arthritis, septicemia, recurrent sinopulmonary infections
Special features	Graft-vs-host disease caused by maternal engraftment or nonirradiated blood transfusion Postvaccination disseminated BCG or varicella Hypocalcemic tetany in infancy†	Autoimmunity Lymphoreticular malignancy: lymphoma, thymoma Postvaccination paralytic polio	Prolonged attachment of umbilical cord, poor wound healing	Autoimmune disorders: SLE, vasculitis, dermatomyositis, scleroderma, glomerulonephritis, angioedema

*X-linked (Bruton) agammaglobulinemia.
†DiGeorge anomaly.
BCG, Bacille Calmette-Guérin; CMV, cytomegalovirus; EBV, Epstein-Barr virus; SLE, systemic lupus erythematosus.
Modified from Woroniecka M, Ballow M: Office evaluation of children with recurrent infection, Pediatr Clin North Am *47:1211–1224, 2000.*

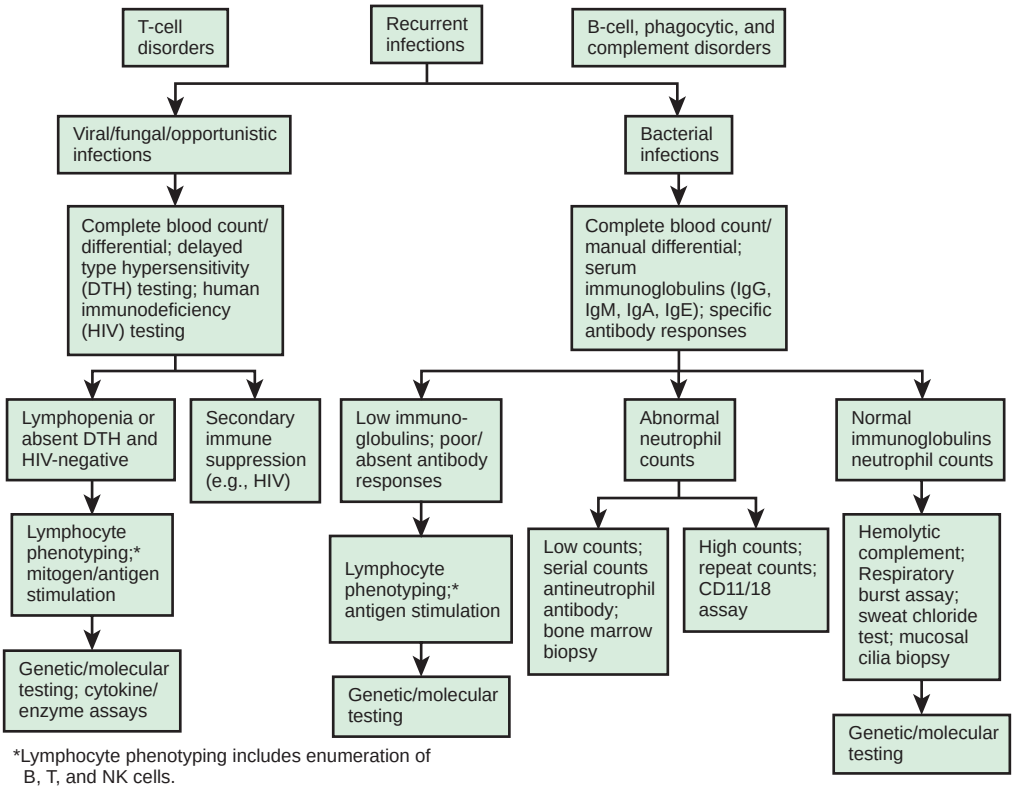


Figure 122-1 A diagnostic testing algorithm for primary immunodeficiency diseases. DTH, delayed-type hypersensitivity. *(From Lindegren ML, Kobrynski L, Rasmussen SA: Applying public health strategies to primary immunodeficiency diseases: a potential approach to genetic disorders,* MMWR Recomm Rep *53[RR-1]:1–29, 2004.)*

Table 122-5 Special Physical Features Associated with Immunodeficiency Disorders

CLINICAL FEATURES	DISORDERS
DERMATOLOGIC	
Eczema	Wiskott-Aldrich syndrome, IPEX, hyper-IgE syndromes, hypereosinophilia syndromes, IgA deficiency
Sparse and/or hypopigmented hair	Cartilage hair hypoplasia, Chédiak-Higashi syndrome, Griscelli syndrome
Ocular telangiectasia	Ataxia-telangiectasia
Oculocutaneous albinism	Chédiak-Higashi syndrome
Severe dermatitis	Omenn syndrome
Erythroderma	Omenn syndrome, SCID, graft-vs-host disease, Comel-Netherton syndrome
Recurrent abscesses with pulmonary pneumatoceles	Hyper-IgE syndromes
Recurrent organ granulomas or abscesses, lung, liver and rectum especially	Chronic granulomatous disease
Recurrent abscesses or cellulitis	Chronic granulomatous disease, hyper-IgE syndrome, leukocyte adhesion defect
Cutaneous granulomas	Ataxia telangiectasia, SCID, CVID, RAG deficiency
Oral ulcers	Chronic granulomatous disease, severe combined immunodeficiency, congenital neutropenia
Periodontitis, gingivitis, stomatitis	Neutrophil defects
Oral or nail candidiasis	T-cell immune defects, combined defects (SCIDs); mucocutaneous candidiasis; hyper-IgE syndromes; IL-12, -17, -23 deficiencies; *CARD9* deficiency; *STAT1* deficiency
Vitiligo	B-cell defects, mucocutaneous candidiasis
Alopecia	B-cell defects, mucocutaneous candidiasis
Chronic conjunctivitis	B-cell defects
EXTREMITIES	
Clubbing of the nails	Chronic lung disease due to antibody defects
Arthritis	Antibody defects, Wiskott-Aldrich syndrome, hyper-IgM syndrome
ENDOCRINOLOGIC	
Hypoparathyroidism	DiGeorge syndrome, mucocutaneous candidiasis
Endocrinopathies (autoimmune)	Mucocutaneous candidiasis
Diabetes, hypothyroid	IPEX and IPEX-like syndromes
Growth hormone deficiency	X-linked agammaglobulinemia
Gonadal dysgenesis	Mucocutaneous candidiasis
HEMATOLOGIC	
Hemolytic anemia	B- and T-cell immune defects, ALPS
Thrombocytopenia, small platelets	Wiskott-Aldrich syndrome
Neutropenia	Hyper-IgM syndrome, Wiskott-Aldrich variant, chronic granulomatous disease
Immune thrombocytopenia	B-cell immune defects, ALPS
SKELETAL	
Short-limb dwarfism	Short-limb dwarfism with T- and/or B-cell immune defects
Bony dysplasia	ADA deficiency, cartilage hair hypoplasia

ADA, Adenosine deaminase deficiency; AID, activation-induced cytidine deaminase; ALPS, autoimmune lymphoproliferative syndrome; CVID, common variable immunodeficiency; GVHD, graft-vs-host disease; Ig, immunoglobulin; IPEX, X-linked immune dysfunction enteropathy polyendocrinopathy; SCID, severe combined immunodeficiency.

From Goldman L, Ausiello D: Cecil textbook of medicine, *ed 22, Philadelphia, 2004, Saunders, p 1599.*

Table 122-6 Initial Screening Immunologic Testing of the Child with Recurrent Infections

COMPLETE BLOOD COUNT, MANUAL DIFFERENTIAL, AND ERYTHROCYTE SEDIMENTATION RATE
Absolute lymphocyte count (normal result [Chapter 727] rules against T-cell defect)
Absolute neutrophil count (normal result [Chapter 727] rules against congenital or acquired neutropenia and [usually] both forms of leukocyte adhesion deficiency, in which elevated counts are present even between infections)
Platelet count (normal result excludes Wiskott-Aldrich syndrome)
Howell-Jolly bodies (absence rules against asplenia)
Erythrocyte sedimentation rate (normal result indicates chronic bacterial or fungal infection unlikely)
SCREENING TESTS FOR B-CELL DEFECTS
Immunoglobulin (Ig) A measurement; if abnormal, IgG and IgM measurement
Isohemagglutinins
Antibody titers to blood group substances, tetanus, diphtheria, *Haemophilus influenzae*, and pneumococcus
SCREENING TESTS FOR T-CELL DEFECTS
Absolute lymphocyte count (normal result indicates T-cell defect unlikely)
Flow cytometry to examine for the presence of naïve T cells (CD3+CD45RA+ cells)
SCREENING TESTS FOR PHAGOCYTIC CELL DEFECTS
Absolute neutrophil count
Respiratory burst assay
SCREENING TEST FOR COMPLEMENT DEFICIENCY
CH_{50}

frequent infections were studied in depth, they were found to have broader immunologic dysfunction, including poor responses to protein antigens, suggesting that they may have been in the process of developing into **common variable immunodeficiency (CVID).** Only when profound antibody deficiencies are detected despite normal levels of immunoglobulins are IgG subclass measurements occasionally helpful. Children who completely lack IgG_2 are usually unable to make antibodies to polysaccharide antigens, although this may also be found among individuals with normal IgG_2. Thus, specific antibody measurements are far more cost-effective than IgG subclass determinations.

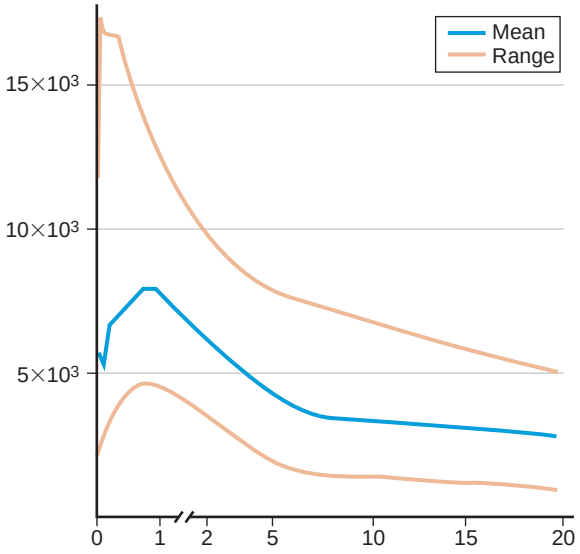


Figure 122-2 Absolute lymphocyte counts in normal individual during maturation. *(Data graphed from Altman PL:* Blood and other body fluids. *Prepared under the auspices of the Committee on Biological Handbooks. Washington, DC, 1961, Federation of American Societies for Experimental Biology.)*

Patients found to be **agammaglobulinemic** should have their blood B cells enumerated by **flow cytometry** using dye-conjugated monoclonal antibodies to B-cell–specific CD antigens (usually CD19 or CD20). Normally, approximately 8-10% of circulating lymphocytes are B cells. B cells are absent in X-linked agammaglobulinemia (XLA) and in several very rare autosomal recessive conditions, but they are present in CVID, IgA deficiency, and hyper-IgM syndromes. This distinction is important, because children with hypogammaglobulinemia from XLA and CVID can have different clinical problems, and the 2 conditions clearly have different inheritance patterns. Patients with XLA have a heightened susceptibility to persistent enteroviral infections, whereas those with CVID have more problems with autoimmune diseases and lymphoid hyperplasia. Molecular testing for XLA and other B-cell defects (see Chapter 124.1) is indicated in cases without a family history to aid genetic counseling.

T CELLS

T cells and T-cell subpopulations can be enumerated by **flow cytometry** using dye-conjugated monoclonal antibodies recognizing CD antigens present on T cells (i.e., CD2, CD3, CD4, and CD8). This is a particularly important test to perform on any infant who is lymphopenic, because $CD3^+$ T cells usually constitute 70% of peripheral lymphocytes. Regardless of molecular type, infants with SCID are unable to produce T cells so are lymphopenic at birth. The flow cytometry for infants suspected of having SCID should also include monoclonal antibodies to naïve (CD45RA) and memory (CD45RO) T cells. In normal infants, more than 95% of the T cells are CD45RA+ (naïve) T cells. If the infant is a SCID, there could be transplacentally transferred maternal T cells detected by flow cytometry, but they would be dominantly CD45RO+ T cells. SCID is a pediatric emergency that can be

Table 122-7 Laboratory Tests in Immunodeficiency

SCREENING TESTS	ADVANCED TESTS	RESEARCH/SPECIAL TESTS
B-CELL DEFICIENCY		
IgG, IgM, IgA, and IgE levels	B-cell enumeration (CD19 or CD20)	Advanced B-cell phenotyping
Isohemagglutinin titers		Biopsies (e.g., lymph nodes)
Ab response to vaccine antigens (e.g., tetanus, diphtheria, pneumococci, *Haemophilus influenzae*)	Ab responses to boosters or to new vaccines	Ab responses to special antigens (e.g., bacteriophage φX174), mutation analysis
T-CELL DEFICIENCY		
Lymphocyte count	T-cell subset enumeration (CD3, CD4, CD8)	Advanced flow cytometry
Chest x-ray examination for thymic size*	Proliferative responses to mitogens, antigens, allogeneic cells	Enzyme assays (e.g., ADA, PNP)
		Thymic imaging
Delayed skin tests (e.g., *Candida*, tetanus toxoid)	HLA typing	Mutation analysis
	Chromosome analysis	T-cell activation studies
		Apoptosis studies
		Biopsies
PHAGOCYTIC DEFICIENCY		
WBC count, morphology	Adhesion molecule assays (e.g., CD11b/CD18, selectin ligand)	Mutation analysis
Respiratory burst assay	Mutation analysis	Enzyme assays (e.g., MPO, G6PD, NADPH oxidase)
COMPLEMENT DEFICIENCY		
CH_{50} activity	AH50, activity	
C3 level	Component assays	
C4 level	Activation assays (e.g., C3a, C4a, C4d, C5a)	

*In infants only.

Ab, antibody; ADA, adenosine deaminase; C, complement; CH, hemolytic complement; G6PD, glucose-6-phosphate dehydrogenase; HLA, human leukocyte antigen; Ig, immunoglobulin; MPO, myeloperoxidase; NADPH, nicotinamide adenine dinucleotide phosphate; PNP, purine nucleoside phosphorylase; WBC, white blood cell; φX, phage antigen.

Modified from Stiehm ER, Ochs HD, Winkelstein JA: Immunologic disorders in infants and children, *ed 5, Philadelphia, 2004, Saunders.*

Table 122-8 2003 Modified IUIS Classification of Primary and Secondary Immunodeficiencies

GROUPS AND DISEASES	INHERITANCE
A. PREDOMINANTLY ANTIBODY DEFICIENCIES	
XL agammaglobulinemia	XL
AR agammaglobulinemia	AR
Hyper-IgM syndromes	XL and AR
a. CD40L defect	XL
b. AID defect	AR
c. CD40 defect	AR
d. UNG defect	AR
e. Other hyper-IgM defects	AR
Ig heavy-chain gene deletions	AR
κ Chain deficiency mutations	AR
Selective IgA deficiency	AD
Common variable immunodeficiency	AD
B. SEVERE COMBINED IMMUNODEFICIENCIES	
$T^-B^+NK^-$ SCID	
a. X-linked (γc deficiency)	XL
b. Autosomal recessive (Jak3 deficiency)	AR
$T^-B^+NK^+$ SCID	
a. IL-7 Rα deficiency	AR
b. CD3δ, CD3ε, or CD3ζ deficiencies	AR
c. CD45 deficiency	AR
$T^-B^-NK^+$ SCID	
a. RAG-1/2 deficiency	AR
b. Artemis defect	AR
Omenn Syndrome	
a. RAG-1/2 deficiency	AR
b. IL-7Rα deficiency	AR
c. γc deficiency	XL
Combined Immunodeficiencies	
a. Purine nucleoside phosphorylase deficiency	AR
b CD8 deficiency (ZAP-70 defect)	AR
c. MHC class II deficiency	AR
d. MHC class I deficiency caused by TAP-1/2 mutations	AR
Reticular dysgenesis	AR
C. OTHER CELLULAR IMMUNODEFICIENCIES	
Wiskott-Aldrich syndrome	XL
Ataxia-telangiectasia	AR
DiGeorge anomaly	?
D. DEFECTS OF PHAGOCYTIC FUNCTION	
Chronic Granulomatous Disease	
a. XL	XL
b. AR	AR
1. p22 phox deficiency	
2. p47 phox deficiency	
3. p67 phox deficiency	
Leukocyte adhesion defect 1	AR
Leukocyte adhesion defect 2	AR
Neutrophil G6PD deficiency	XL
Myeloperoxidase deficiency	AR
Secondary granule deficiency	AR
Shwachman syndrome	AR
Severe congenital neutropenia (Kostmann)	AR
Cyclic neutropenia (elastase defect)	AR
Leukocyte mycobacterial defects	AR
IFN-γR1 or R2 deficiency	AR
IFN-γR1 deficiency	AD
IL-12Rβ1 deficiency	AR
IL-12p40 deficiency	AR
STAT1 deficiency	AD
E. IMMUNODEFICIENCIES ASSOCIATED WITH LYMPHOPROLIFERATIVE DISORDERS	
Fas deficiency	AD
Fas ligand deficiency	
FLICE or caspase 8 deficiency	
Unknown (caspase 3 deficiency)	
F. COMPLEMENT DEFICIENCIES	
C1q deficiency	AR
C1r deficiency	AR
C4 deficiency	AR
C2 deficiency	AR
C3 deficiency	AR
C5 deficiency	AR
C6 deficiency	AR
C7 deficiency	AR
C8α deficiency	AR
C8β deficiency	AR
C9 deficiency	AR
C1 inhibitor	AD
Factor I deficiency	AR
Factor H deficiency	AR
Factor D deficiency	AR
Properdin deficiency	XL
G. IMMUNODEFICIENCY ASSOCIATED WITH OR SECONDARY TO OTHER DISEASES	
Chromosomal Instability or Defective Repair	
Bloom syndrome	
Fanconi anemia	
ICF syndrome	
Nijmegen breakage syndrome	
Seckel syndrome	
Xeroderma pigmentosum	
Chromosomal Defects	
Down syndrome	
Turner syndrome	
Chromosome 18 rings and deletions	
Skeletal Abnormalities	
Short-limbed skeletal dysplasia	
Cartilage-hair hypoplasia	
Immunodeficiency with Generalized Growth Retardation	
Schimke immuno-osseous dysplasia	
Immunodeficiency with absent thumbs	
Dubowitz syndrome	
Growth retardation, facial anomalies, and immunodeficiency	
Progeria (Hutchinson-Gilford syndrome)	
Immunodeficiency with Dermatologic Defects	
Partial albinism	
Dyskeratosis congenita	
Netherton syndrome	
Acrodermatitis enteropathica	
Anhidrotic ectodermal dysplasia	
Papillon-Lefèvre syndrome	
Hereditary Metabolic Defects	
Transcobalamin 2 deficiency	
Methylmalonic acidemia	
Type 1 hereditary orotic aciduria	
Biotin-dependent carboxylase deficiency	
Mannosidosis	
Glycogen storage disease, type 1b	
Chédiak-Higashi syndrome	
Hypercatabolism of Immunoglobulin	
Familial hypercatabolism	
Intestinal lymphangiectasia	
H. OTHER IMMUNODEFICIENCIES	
Hyper-IgE syndromes	AD and AR
Chronic mucocutaneous candidiasis	
Chronic mucocutaneous candidiasis with polyendocrinopathy (APECED)	AR
Hereditary or congenital hyposplenia or asplenia	
Ivemark syndrome	
IPEX syndromes	XL
Ectodermal dysplasia (NEMO defect)	XL

AD, autosomal dominant; ADA, adenosine deaminase; AID, activation-induced cytidine deaminase; APECED, autoimmune, polyendocrinopathy, candidiasis, ectodermal dystrophy; AR, autosomal recessive; caspase, cysteinyl aspartate specific proteinase; FLICE, Fas-associating protein with death domain–like IL-1–converting enzyme; G6PD, glucose 6-phosphate dehydrogenase; ICF, immunodeficiency, centromeric instability, facial anomalies; IFN, interferon; Ig, immunoglobulin; IL, interleukin; IPEX, immune dysregulation, polyendocrinopathy, enteropathy; IUIS, International Union of Immunological Societies; MHC, major histocompatibility complex; NEMO, nuclear factor B essential modulator; SCID, severe combined immunodeficiency; TAP-2, transporter associated with antigen presentation; UNG, uracil-N-glycosylase; XL, X-linked.

Modified from (no authors listed) Primary immunodeficiency diseases. Report of an International Union of Immunological Studies Scientific Committee, Clin Exp Immunol *118:1–28, 1999; Chapel H, Geha R, Rosen F: IUIS PID (Primary Immunodeficiencies) Classification committee: Primary immunodeficiency diseases: an update,* Clin Exp Immunol *132:9–15, 2003; Stiehm ER, Ochs HD, Winkelstein JA:* Immunologic disorders in infants and children, *ed 5, Philadelphia, 2004, WB Saunders.*

successfully treated by nonablative stem cell transplantation in more than 92% of cases if diagnosed before serious, untreatable infections develop. Normally, there are roughly twice as many $CD4^+$ (helper) T cells as there are $CD8^+$ (cytotoxic) T cells. Because there are examples of severe immunodeficiency in which phenotypically normal T cells are present, tests of T-cell function are far more informative and cost-effective than enumeration of T-cell subpopulations by flow cytometry. T cells are normally stimulated through their T-cell receptors by antigen present in the groove of major histocompatibility complex molecules. The T-cell receptor can also be stimulated directly with **mitogens** such as phytohemagglutinin, concanavalin A, or pokeweed mitogen. After 3-5 days of incubation with the mitogen, the proliferation of T cells is measured by the incorporation of radiolabeled thymidine into DNA. Other stimulants that can be used to assess T-cell function in the same type of assay include antigens (*Candida,* tetanus toxoid) and allogeneic cells (see Table 122-6).

NATURAL KILLER CELLS

Natural killer (NK) cells can be enumerated by flow cytometry using monoclonal antibodies to NK-specific CD antigens, CD16 and CD56. NK function is assessed by a radiolabeled chromium-release assay, using the cell line K562, which is readily killed by NK cells.

PHAGOCYTIC CELLS

Killing defects of phagocytic cells, which should be suspected if a patient has recurrent staphylococcal abscesses or gram-negative infections, can be evaluated by screening tests measuring the neutrophil respiratory burst after phorbol ester stimulation. The most reliable and useful test of this type is a flow cytometric assessment of the respiratory burst using rhodamine dye. Leukocyte adhesion deficiencies can be easily diagnosed by flow cytometric assays of blood lymphocytes or neutrophils, using monoclonal antibodies to CD18 or CD11 (LAD1) or to CD15 (LAD2).

Phagocytic cell defects can be further defined according to their molecular cause. Mutations in the genes encoding 5 different components of the NADPH pathway have been discovered in various patients with chronic granulomatous disease. It is important to identify the specific molecular type of chronic granulomatous disease to provide appropriate genetic counseling, as 1 type is X linked and the other 4 types are autosomal recessive. Early diagnosis of leukocyte adhesion deficiency is of crucial importance because stem cell transplantation can be lifesaving.

COMPLEMENT

The most effective screening test for complement defects is a CH_{50} assay, which is a bioassay that measures the intactness of the entire complement pathway and yields abnormal results if complement has been consumed from the specimen for any reason. Genetic deficiencies in the complement system are usually characterized by extremely low CH_{50} values. The most common cause of an abnormal CH_{50} result, however, is a delay in or improper transport of the specimen to the laboratory. Specific immunoassays for C3 and C4 are commercially available, but further identification of other complement component deficiencies is usually possible only in research laboratories. Nevertheless, it is extremely important to identify which component is missing, because there are different disease susceptibilities depending on whether there are deficiencies of early or late components (see Chapter 134). Identifying the mode of inheritance is also important for genetic counseling. Properdin deficiency is X linked, but all of the other complement deficiencies are autosomal. Measurement of C4 can be helpful in assessing suspected hereditary angioedema.

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Section 2

The T-, B-, and NK-Cell Systems

Chapter 123

T Lymphocytes, B Lymphocytes, and Natural Killer Cells

Rebecca H. Buckley

Defense against infectious agents is secured through a combination of anatomic physical barriers including the skin, mucous membranes, mucous blanket, and ciliated epithelial cells, as well as the various components of the immune system. The **immune system** of vertebrates integrates 2 fundamental response mechanisms. **Innate (natural) immunity** responds to infection regardless of previous exposure to the agent and includes polymorphonuclear leukocytes, dendritic and mononuclear phagocytic cells, natural killer (NK) cells, various receptors that recognize common pathogen antigens (Toll-like receptors) and the complement system. **Acquired (adaptive) immunity** is a highly specific response that includes T and B lymphocytes. The immune system also helps protect against malignancy and autoimmunity.

LYMPHOPOIESIS IN THE FETUS

Origin of the Lymphoid System

The human immune system arises in the embryo from gut-associated tissue. Pluripotential hematopoietic stem cells first appear in the yolk sac at 2.5-3 wk of gestational age, migrate to the fetal liver at 5 wk of gestation, and later reside in the bone marrow, where they remain throughout life (Fig. 123-1). Lymphoid stem cells develop from such precursor cells and differentiate into T, B, or NK cells, depending on the organs or tissues to which the stem cells traffic. Development of the **primary lymphoid organs**—thymus and bone marrow—begins during the middle of the 1st trimester of gestation and proceeds rapidly. Development of the **secondary lymphoid organs**—spleen, lymph nodes, tonsils, Peyer patches, and lamina propria—soon follows. These organs serve as sites of differentiation of T, B, and NK lymphocytes from stem cells throughout life. Both the initial organogenesis and the continued cell differentiation occur as a consequence of the interaction of a vast array of lymphocytic and microenvironmental cell surface molecules and proteins secreted by the involved cells. The complexity and number of lymphoid cell surface molecules led to the development of an international nomenclature for **clusters of differentiation (CD)** (Table 123-1).

T and B lymphocytes are the only components of the immune system that have antigen-specific recognition capabilities and are responsible for adaptive immunity. NK cells are lymphocytes that are also derived from hematopoietic stem cells and are thought to have a role in host defense against viral infections, tumor surveillance, and immune regulation, but they do not have antigen receptors. Nonantibody proteins synthesized and secreted by T, B, and NK cells, and by the cells with which they interact, act as intercellular mediators and are referred to as **cytokines** or **interleukins (ILs)** (Table 123-2). Cytokines have the ability to act in an autocrine, paracrine, or endocrine manner

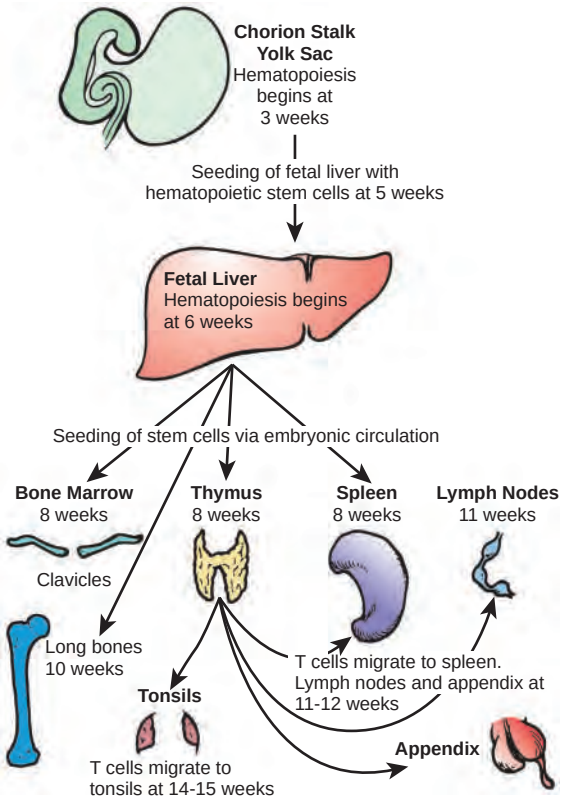


Figure 123-1 Migration patterns of hematopoietic stem cells and mature lymphocytes during human fetal development. *(From Haynes BF, Denning SM: Lymphopoiesis. In Stamatoyannopoulis G, Nienhuis A, Majerus P, editors:* Molecular basis of blood diseases, *ed 2, Philadelphia, 1994, WB Saunders.)*

to promote and facilitate differentiation and proliferation of the cells of the immune system.

T-Cell Development and Differentiation

The primitive thymic rudiment is formed from the ectoderm of the 3rd branchial cleft and endoderm of the 3rd branchial pouch at 4 wk gestation. Beginning at 7-8 wk, the right and left rudiments move caudally and fuse in the midline. Bloodborne T-cell precursors from the fetal liver then begin to colonize the perithymic mesenchyme at 8 wk gestation, and at 8-8.5 wk gestation are found intrathymically. The earliest cells to enter the thymus are found in the subcapsular region and do not express CD3, CD4, CD8, or either type of T-cell receptor. These lymphoid cell precursors are triggered to proliferate and become thymocytes through interactions with the thymic stroma. These cells express CD44 and c-kit (CD117) and slightly later the α chain of the IL-2 receptor. The cells are arrested at this stage until they productively rearrange the β chain locus of the T-cell receptor. The inframe β chain then pairs with the surrogate pre-T α chain and is expressed on the cell surface, which triggers entry into the cell cycle. The presence of small amounts of pre-T α:β on the cell surface in association with CD3 triggers rapid proliferation of these cells, the loss of CD25 and the termination of β-chain gene rearrangement. After cell proliferation ceases, CD4 and CD8 are expressed simultaneously (i.e., they are double-positive thymocytes). Fetal cortical thymocytes are among the most rapidly dividing cells in the body and increase in number by 100,000-fold within 2 wk after stem cells enter the thymus. As these cells proliferate and mature, they migrate deeper into the thymic cortex. The double-positive thymocytes begin efficient rearrangement of the α-chain locus, express low levels of an α:β **T-cell receptor (TCR)** and the associated CD3 complex and are then ready for thymic selection. TCR gene rearrangement begins shortly after colonization of the thymus with stem cells, and the establishment of the T-cell repertoire begins at 8-10 wk of gestation. The mature TCR is a heterodimer of 2 chains, either α and β or γ and δ, that is coexpressed on the cell surface with **CD3,** a complex of 5 polypeptide chains (γ, δ, ε, ζ, η). TCR gene rearrangement occurs by a process in which large, noncontiguous blocks of DNA are spliced together. These segments, known as **V (variable), D (diversity),** and **J (joining),** each have a number of variants. VDJ segments are joined to a constant region of the α gene, and VDJ segments are joined to the β gene to complete the receptor polypeptide genes. Random combinations of the segments account for much of the enormous diversity of TCRs that enables humans to recognize millions of different antigens. TCR gene rearrangement requires the presence of **recombinase activating genes,** *RAG-1* and *RAG-2,* as well as other recombinase components. This process is flawed in both mice and humans with severe combined immunodeficiency (SCID) because of mutations in genes that encode components of the VDJ recombination process. By 9.5-10 wk, more than 95% of thymocytes express CD2, CD4, CD7, CD8, and c (cytoplasmic) CD3, and ≈30% bear the CD1 inner cortical thymocyte antigen. By 10 wk, 25% of thymocytes bear αβ TCRs. Ti αβ T cells gradually increase in number during embryonic life and represent more than 95% of thymocytes postnatally.

As immature cortical thymocytes begin to express TCRs, the processes of positive and negative selection take place. **Positive selection** occurs through the interaction of immature thymocytes, which express low levels of TCR, with major histocompatibility complex (MHC) antigens present on cortical thymic epithelial cells. As a result, thymocytes with TCR capable of interacting with foreign antigens presented on self human leukocyte antigen (HLA) molecules are activated and develop to maturity. Most (>98%) of the cells die by failing to be positively selected or as a consequence of negative selection, but some are selected to mature into CD4 or CD8 single positive cells. Mature thymocytes that survive the selection process either express CD4 and are restricted to interacting with self class II HLA antigens, or express CD8 and are restricted to interacting with self class I HLA antigens when foreign antigens are presented by these MHC molecules. **Negative selection** occurs next in the medulla and is mediated by interaction of the surviving thymocytes, which have much higher levels of TCR expression, with host peptides presented by HLA class I or II antigens present on bone marrow-derived thymic macrophages, dendritic cells, and possibly B cells. This interaction mediates **apoptosis** (programmed cell death) of such autoreactive thymocytes. The thymic medulla contains only mature single-positive T cells that eventually leave the thymus and enter the bloodstream. T-cell functions are acquired concomitantly with the development of single-positive thymocytes, but they are not fully developed until the cells emigrate from the thymus. T cells begin to emigrate from the thymus to the spleen, lymph nodes, and appendix at 11-12 wk of embryonic life, and to the tonsils by 14-15 wk. They leave the thymus via the bloodstream and are distributed throughout the body, with the heaviest concentrations in the paracortical areas of lymph nodes, the periarteriolar areas of the spleen, and the thoracic duct lymph. Recent thymic emigrants coexpress the CD45RA isoforms and CD62L (L-selectin). Rearrangement of the TCR locus during intrathymic T-cell development results in the excision of DNA and the excised elements form circular episomes as a by-product. These **TCR recombination excision circles** can be detected in T cells that are recent thymic emigrants, whereas T cells that develop extrathymically do not contain these episomes. Inability to detect TCR recombination excision circles by real-time polymerase chain reaction of DNA from the dried blood spots collected from infants shortly after birth is the test used for newborn screening for SCID. The homing of lymphocytes to peripheral lymphoid organs is directed by the interaction of a lymphocyte surface adhesion molecule, L-selectin, with carbohydrate moieties on specialized regions of lymphoid organ blood vessels called **high endothelial venules.** By 12 wk gestation, T cells can proliferate in response to plant lectins, such as phytohemagglutinin and concanavalin A, and to allogeneic cells; antigen-binding T cells have been found by 20 wk gestation. **Hassall's corpuscles (bodies),** which are swirls of terminally differentiated medullary epithelial cells, are first seen in the thymic medulla at 16-18 wk of embryonic life.

Table 123-1 CD Classification of Some Lymphocyte Surface Molecules

CD NUMBER	OTHER NAMES	TISSUE/LINEAGE	FUNCTION
CD1	T6	Cortical thymocytes; Langerhans cells	Lipid antigen presentation to TCRγδ cells
CD2	SRBC receptor	T and NK cells	Binds LFA-3 (CD58); alternative pathway of T-cell activation
CD3	T3, Leu 4	T cells	TCR-associated; transduces signals from TCR
CD4	T4, Leu3a	Helper T-cell subset	Receptor for HLA class II antigens; associated with p56 *lck* tyrosine kinase
CD7	3A1, Leu 9	T and NK cells and their precursors	Comitogenic for T lymphocytes
CD8	T8, Leu2a	Cytotoxic T-cell subset; also on 30% of NK cells	Receptor for HLA class I antigens; associated with p56 *lck* tyrosine kinase
CD10	cALLA	B-cell progenitors	Peptide cleavage
CD11a	LFA-1a ∀ chain	T, B, and NK cells	With CD18, ligand for ICAMs 1, 2, and 3
CD11b, c	MAC-1, CR3; CR4	NK cells	With CD18, receptors for C3bi
CD16	FcRIII	NK cells	FcR for IgG
CD19	B4	B cells	Regulates B-cell activation
CD20	B1	B cells	Mediates B-cell activation
CD21	B2	B cells	C3d, also the receptor for EBV; CR2
CD25	IL-2Rα	T, B, and NK cells	Mediates signaling by IL-2
CD34	My10	Stem cells	Binds to L-selectin
CD38	T10	T, B, and NK cells and monocytes	Associates with hyaluronic acid
CD40	CD40	B cells and monocytes	Initiates isotype switching in B cells when ligated
CD44	CD44	Bone marrow stromal and many other cells.	Matrix adhesion molecule
CD45	Leukocyte common antigen, T200	All leukocytes	Tyrosine phosphatase that regulates lymphocyte activation; CD45R0 isoform on memory T cells, CD45RA isoform on naïve T cells
CD56	NCAM; NKH-1	NK cells	Mediates NK homotypic adhesion
CD62L	L-selectin	Marker for recent thymic emigrants. Also found on other leukocytes.	Cell adhesion molecule
CD69	CD69	T cells and NK cells	Early activation marker
CD73	Ecto-5′-nucleotidase	T and B cells	Associates with AMP
CD80	B7.1	B cells	Costimulatory with CD28 on T cells to upregulate high affinity IL-2 receptor
CD86	B7.2	B cells	Costimulatory with CD28 on T cells to upregulate high affinity IL-2 receptor
CD117	c-kit	Pro-B cells, double-negative thymocytes	Receptor for stem cell factor
CD127	IL-7Rα	T cells	Mediates IL-7 signaling
CD132	Common γ chain (γc)	T, B, and NK cells	Mediates signaling by IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21
CD154	CD40 ligand, gp39	Activated $CD4^+$ T cells	Ligates CD40 on B cells and initiates isotype switching
CD278	ICOS	T cells	Interacts with B7-H2

AMP, Adenosine monophosphate; CD, cluster of differentiation; EBV, Epstein-Barr virus; HLA, human leukocyte antigen; ICAM, intracellular adhesion molecule; ICOS, inducible costimulator; Ig, immunoglobulin; IL, interleukin; LFA, lymphocyte function-associated antigen; MAC, membrane attack complex; NCAM, neural cell adhesion molecule; NK, natural killer; SRBC, sheep red blood cell; TCR, T-cell receptor.

B-Cell Development and Differentiation

In parallel with T-cell differentiation, B-cell development begins in the fetal liver before 7 wk of gestation. Fetal liver CD34 stem cells are seeded to the bone marrow of the clavicles by 8 wk of embryonic life and to that of the long bones by 10 wk (see Fig. 123-1). **As B cells differentiate from primitive stem cells, they proceed through stages that are marked by the sequential rearrangement of immunoglobulin gene segments to generate a diverse repertoire of antigen receptors.** The early **pro-B cell** is the first descendent of the pluripotential stem cell committed to B-lineage development and in this stage, the heavy chain locus rearranges first. In the early pro-B cell, D-J rearrangements are made on both chromosomes. In the late pro-B cell, the V segment rearranges to a D-J gene segment, but it is a matter of chance whether the juxtaposed J sequence and the μ constant region sequence downstream can be read in the correct reading frame. There is a roughly 2 in 3 chance that an out-of-frame sequence will occur,

Table 123-2 Functional Classification of Cytokines*

1. Cytokines involved in natural immune responses
   - Type I interferons (IFN-α and IFN-β): inhibit viral replication, inhibit cell proliferation, activate NK cells, and upregulate class I MHC molecule expression
   - TNF-α: mediates host response to Gram-negative bacteria and other infectious agents
   - IL-1α and -1β: mediate host inflammatory response to infectious agents
   - IL-1Ra: a natural antagonist of IL-1, blocks signals delivered by IL-1
   - IL-6: mediates and regulates inflammatory responses
   - Chemokines (IL-8, monocyte chemotactic protein-1 or MCP-1, RANTES, and others): mediate leukocyte chemotaxis and activation
2. Lymphocyte regulatory cytokines
   a. Immunostimulatory or growth-promoting
      - IL-1: costimulates activation of T cells
      - IL-2: growth factor for T, B, NK cells; activates NK and T effector cells
      - IL-4: T- and B-cell growth factor; stimulates IgE production; upregulates classes I and II MHC molecules and FcRεII expression on macrophages; expansion of Th2 subset
      - IL-5: B-cell growth and activation
      - IL-6: growth factor for B cells
      - IL-7: stromal cell factor; growth factor for precursor B and T cells, T-cell homeostatic factor
      - IL-10: growth and differentiation factor for B cells
      - IL-9: growth factor for T cells, B cells, mast cells, eosinophils, neutrophils, endothelial cells
      - IL-12: expansion of Th1 subset; activates effector cells
      - IL-13: growth and differentiating factor for B cells; stimulates IgE production; upregulates Classes I and II MHC molecules and FcRεII expression on macrophages
      - TNF-β: stimulates effector cell function
      - IL-15: regulates NK-cell development and memory cell homeostasis
      - IL-17: promotes inflammation by acting on local tissue cells to cause them to produce chemokines, such as IL-8, that recruit neutrophils and other innate effector cells.
      - IL-18: induces IFN-γ, GM-CSF, TNF-α in immunocompetent cells
      - IL-21: together with IL-4 regulates IgG and IgE class-switching and Ig synthesis
      - IL-23: autocrine growth factor for Th17 cells
      - IL-27: produced by antigen presenting cells and regulates both T and B cell activity
      - IFN-γ: activates macrophages, NK cells; upregulates classes I and II MHC molecules expression; inhibits IL-4– or IL-13–induced IgE production
   b. Immunosuppressive
      - IL-1Rα: regulates IL-1 activities
      - TGF-β: antagonizes lymphocyte responses
      - IL-10: inhibits activities of Th1 cells
      - IFN-α/β: inhibits production of IFN-γ
3. Hematopoiesis regulating cytokines
   - GM-CSF, G-CSF, M-CSF: colony-stimulating factors
   - Erythropoietin (EPO): differentiation of erythroid precursors
   - IL-3, SCF, c-kit receptor: regulate stem cell development
   - IL-4: mast cell development
   - IL-5: eosinophil differentiation and proliferation
   - IL-6: differentiation of B cells
   - IL-7: differentiation of B and T cells
   - IL-8: promotes cell survival in response to hematopoietic cytokines
   - IL-9: mast-cell growth factor
   - IL-11: elevates platelet count in patients given chemotherapy
   - IL-12: expands and activates resting NK cells
   - IL-15: expands and activates resting NK cells
   - IL-21: limits viability of NK cells
4. Proinflammatory cytokines
   - IL-1, TNF-α, IL-6: participate in the acute-phase response and synergize to mediate inflammation, shock, and death
   - IL-12: stimulates IFN (production by T and NK cells)
   - IL-17: acts on monocytes to induce secretion of proinflammatory mediators such as IL-8, TNF, and GM-CSF
   - IL-18: induces IFN-γ, GM-CSF, TNF-α; upregulates chemokine receptors
   - IL-23: drives the development of autoreactive IL-17–producing T cells and promotes chronic inflammation
5. Antiinflammatory cytokines
   - IL-4: reduces endotoxin-induced TNF and IL-1 production
   - IL-6: inhibits TNF production
   - IL-10: suppresses lymphocyte functions and downregulates production of proinflammatory cytokines; antiatherogenic
   - IL-11: cytoprotective effect on bowel mucosa, skin and joint inflammation
   - IL-13: downregulates functions of macrophages, suppresses production of proinflammatory cytokines
   - TGF-β: has immunosuppressive effects, inhibits IL-1 and TNF gene expression
   - IL-1Rα: competes with the binding of IL-1 to its cell surface receptors and blocks IL-1R
   - TNFsR: soluble TNF receptor; by binding TNF, blocks interaction of TNF with the target cell

*This is not an exhaustive list.

G-CSF, Granulocyte colony-stimulating factor; GM-CSF, granulocyte macrophage colony-stimulating factor; IFN, interferon; Ig, immunoglobulin; IL, interleukin; IL-1R, interleukin-1 receptor; M-CSF, macrophage colony-stimulating factor; MHC, major histocompatibility complex; MCP-1, monocyte chemotactic protein; NK, natural killer; RANTES, regulated on activation normal t cell expressed and secreted; SCF, stem cell factor; TGF, transforming growth factor; Th1, Th2, Th17, T-helper types 1, 2, and 17; TNF, tumor necrosis factor.

Modified from Whiteside TL: Cytokine measurements and interpretation of cytokine assays in human disease, J Clin Immunol *14:327–339, 1994.*

and only those cells that have productive rearrangements will survive, so a majority of cells are lost. The next stage is the **pre-B cell,** during which immunoglobulin (Ig) light chain genes are rearranged. The **pre-B cell** is distinguished by the expression of cytoplasmic μ heavy chains but no sIgM, because immunoglobulin light chains are not yet produced. The pre-B cells must rearrange the same light chain gene on both chromosomes for a productive rearrangement, so when this does not happen the cells are lost. Fewer cells are lost between the pre-B and immature B cell stages than in the pro-B to pre-B transition. Next is the **immature B-cell** stage, during which the light-chain genes have already been rearranged and sIgM but not sIgD is expressed. The last stage of antigen-independent B-cell development is the **mature or virgin B cell,** which co-expresses both sIgM and sIgD. Pre-B cells can be found in fetal liver at 7 wk gestation, sIgM+ and sIgG+ B cells at between 7 and 11 wk, and sIgD+ and sIgA+ B cells by 12-13 wk. By 14 wk of embryonic life, the percentage of circulating lymphocytes bearing sIgM and sIgD is the same as in cord blood and slightly higher than in the blood of adults.

Antigen-dependent stages of B-cell development are those that develop after the mature or virgin B cell is stimulated by antigen through its antigen receptor (sIg); the outcome is the differentiation of the cell and its progeny into sIg+ memory (CD27) B cells (for that particular antigen) and plasma cells, which synthesize and secrete antibody, which is **antigen-specific immunoglobulin.** Deficiency of activation-induced cytidine deaminase (AICDA) or of uracil DNA glycosylase (UNG), as seen in 2 forms of autosomal recessive hyper IgM, can result in a failure of isotype switching so that only IgM antibodies are formed.

There are 5 **immunoglobulin isotypes**, which are defined by unique heavy-chains: IgM, IgG, IgA, IgD, and IgE. IgG and IgM, the only complement-fixing isotypes, are the most important immunoglobulins in the blood and other internal body fluids for protection against infectious agents. IgM is confined primarily to the intravascular compartment because of its large size, whereas IgG is present in all internal body fluids. IgA is the major protective immunoglobulin of external secretions—in the gastrointestinal, respiratory, and urogenital tracts—but it is also present in the circulation. IgE, present in both internal and external body fluids, has a major role in host defense against parasites. Because of high-affinity IgE receptors on basophils and mast cells, however, IgE is the principal mediator of allergic reactions of the immediate type. The significance of IgD is still not clear. There are also **immunoglobulin subclasses** including 4 subclasses of IgG (IgG_3, IgG_2, IgG_3, and IgG_4) and 2 subclasses of IgA (IgA_1 and IgA_2). These subclasses each have different biologic roles. For example, antipolysaccharide antibody activity is found predominantly in the IgG_2 subclass. Secreted IgM and IgE have been found in abortuses as young as 10 wk, and IgG as early as 11-12 wk. Even though these B-cell developmental stages have been described in the context of B-cell ontogeny in utero, it is important to recognize that the process of B-cell development from pluripotential stem cells goes on throughout postnatal life. Despite the capacity of fetal B lymphocytes to differentiate into immunoglobulin-synthesizing and -secreting cells, plasma cells are not usually found in lymphoid tissues of a fetus until about 20 wk gestation, and then only rarely, because of the sterile environment of the uterus. Peyer patches have been found in significant numbers by the 5th intrauterine mo, and plasma cells have been seen in the lamina propria by 25 wk gestation. Before birth there may be primary follicles in lymph nodes, but secondary follicles are usually not present.

A human fetus begins to receive significant quantities of maternal IgG transplacentally at around 12 wk gestation, and the quantity steadily increases until, at birth, cord serum contains a concentration of IgG comparable to or greater than that of maternal serum. IgG is the only class to cross the placenta to any significant degree. All 4 IgG subclasses cross the placenta, but IgG_2 does so least well. A small amount of IgM (10% of adult levels) and a few nanograms of IgA, IgD, and IgE are normally found in cord serum. Because none of these proteins crosses the placenta, they are presumed to be of fetal origin. These observations raise the possibility that certain antigenic stimuli normally cross the placenta to provoke responses, even in uninfected fetuses. Some atopic infants occasionally have IgE antibodies to antigens, such as egg white, to which they have had no known exposure during postnatal life, suggesting that synthesis of these antibodies could have been induced in the fetus by antigens ingested by the mother.

Natural Killer–Cell Development

NK cell activity is found in human fetal liver cells at 8-11 wk of gestation. NK lymphocytes are also derived from bone marrow precursors. Thymic processing is not necessary for NK-cell development, although NK cells have been found in the thymus. After release from bone marrow, NK cells enter the circulation or migrate to the spleen, with very few NK cells in lymph nodes. In normal individuals, NK cells represent 8-10% of lymphocytes, but the percentages are sometimes slightly lower in cord blood.

Unlike T and B cells, NK cells do not rearrange antigen receptor genes during their development but are defined by their functional capacity to mediate non–antigen-specific cytotoxicity. NK cells have killer inhibitory receptors that recognize certain MHC antigens and inhibit the killing of normal allogeneic cells in 4 specific patterns of reactivity. The genetic loci controlling these receptors are different from MHC alloantigenic loci, and have been mapped to chromosome 19. Virtually all NK cells express CD56, and more than 90% bear CD16 (FcγRIII) on the cell surface. Other CD antigens found on NK cells include CD57 (50-60%), CD7 and CD2 (70-90%), and CD8 (30-40%) (see Table 123-1). Although NK cells share surface antigens with T and myeloid cells, the lineage relationship of NK cells to the latter is still unclear. Some humans with autosomal recessive SCID who have profound deficiencies in T and B cells, have abundant NK cells, whereas those with X-linked and Jak3-deficient SCID have no T or NK cells.

Immune Cell Interactions

Immune cell interaction is of crucial importance to all phases of the adaptive immune response. Unlike the B-cell antigen receptor (Ig), which can recognize native antigen, the TCR can recognize only processed antigenic peptides presented to it by MHC molecules such as **HLA-A, -B, and -C antigens (class I)** and **HLA-DR, -DP, and -DQ antigens (class II)**. The MHC molecules have a groove in their protein structure where peptides fit. Class I MHC molecules are found on most nucleated cells in the body. Class II MHC molecules are found on **antigen-presenting cells (APCs),** which include macrophages, dendritic cells, and B cells. The peptides found in the groove of class I HLA molecules come from proteins normally made in the cell that are degraded and inserted into the groove. The peptides include viral peptides if the cell is infected with a virus. The peptides present in the groove of class II molecules come from exogenous native antigens such as vaccine and bacterial proteins. These proteins are taken up by APCs, degraded, and expressed on the cell surface in the groove of class II HLA molecules. The TCR then interacts with the peptide-bearing HLA molecule and, through its functional and physical link to the CD3 complex of signal-transducing molecules, sends a signal to the T cell to produce cytokines that ultimately result in T-cell activation and proliferation.

Two of the main functions of T cells are to signal B cells to make antibody by producing cytokines and membrane molecules that can serve as ligands for non–antigen-receptor B-cell surface molecules and to kill virally infected cells or tumor cells. For a T cell to perform either of these functions, it first must bind to an APC or to a target cell (the immunologic synapse). For high-affinity binding of T cells to APCs or target cells, several molecules on T cells, in addition to TCRs, bind to molecules on APCs or target cells. The CD4 molecule binds directly to MHC class II molecules on APCs. CD8 on cytotoxic T cells binds the MHC class I molecule on the target cell. Both CD4 and CD8 molecules are directly involved in the regulation of T-cell activation and are physically linked intracellularly to the p56-lck protein tyrosine kinase. The cytoplasmic tail of CD45, the common leukocyte antigen, is a tyrosine phosphatase capable of regulating T-cell signal-transduction events by virtue of the fact that p56-lck is a substrate for CD45 phosphatase activity. Depending on which isoform of CD45 is present on

the T cell (CD45RO on memory T cells, CD45RA on naïve T cells), mechanisms by which CD45 could upregulate or downregulate T-cell triggering have been proposed. Indeed, one form of human SCID is caused by a deficiency of CD45. Lymphocyte function-associated antigen 1 (LFA-1) on the T cell binds a protein called ICAM-1 (intracellular adhesion molecule 1), designated CD54, on APCs. CD2 on T cells binds LFA-3 (CD58) on the APCs. With the adhesion of T cells to APCs (the immunologic synapse), T-helper (Th) cells are stimulated to make interleukins and upregulate cell surface molecules, such as the CD40 ligand (CD154), that provide help for B cells, and cytotoxic T cells are stimulated to kill their targets.

In the **primary antibody response,** native antigen is carried to a lymph node draining the site, taken up by specialized cells called **follicular dendritic cells (FDCs),** and expressed on their surfaces. Virgin B cells bearing sIg specific for that antigen then bind to the antigen on the surfaces of the FDCs. If the affinity of the B-cell sIg antibody for the antigen present on the FDCs is sufficient, and if other signals are provided by activated Th cells, the B cell develops into an antibody-producing plasma cell. If the affinity is not high enough or if T-cell signals are not received, the B cell dies through apoptosis. The signals from activated Th cells include several cytokines (IL-4, IL-5, IL-6, IL-10, IL-13, and IL-21) that they secrete (see Table 123-2) and a surface T-cell molecule, the CD40 ligand or CD154, which, on contact of the activated CD4 positive T cell with the B cell, binds to CD40 on the B-cell surface. CD40 is a type I integral membrane glycoprotein expressed on B cells, monocytes, some carcinomas, and a few other types of cells. It belongs to the tumor necrosis factor/nerve growth factor receptor family. Crosslinking of CD40 on B cells by CD154 on T cells in the presence of certain cytokines causes the B cells to undergo proliferation and to initiate immunoglobulin synthesis. In the primary immune response, only IgM antibody is usually made, and most of it is of relatively low affinity. Some B cells become memory B cells during the primary immune response. These cells switch their immunoglobulin genes so that IgG, IgA, and/or IgE antibodies of higher affinity are formed on a secondary exposure to the same antigen. The **secondary antibody response** occurs when these memory B cells again encounter that antigen. Plasma cells form, just as in the primary response; however, many more cells are rapidly generated, and IgG, IgA, and IgE antibodies are made. In addition, genetic changes in immunoglobulin genes (somatic hypermutation) lead to increased affinity of those antibodies. A lack of somatic hypermutation is seen in deficiency of activation-induced cytidine deaminase (AID) or uracil-N-glycosylase (UNG). The exact pattern of isotype response to antigen in normal individuals varies, depending on the type of antigen and the cytokines present in the microenvironment.

For NK-mediated lysis, binding to the target is of crucial importance. This is best exemplified by persons with leukocyte adhesion deficiency type I (LAD-1) who have mutations in the gene encoding CD18, or the β chain of 3 different adhesion molecules (LFA-1, CR3, and p150,95), and who lack NK function. Thus, binding of NK cells to their targets is facilitated by LFA-1-ICAM interactions. CD56 or NCAM (neural cell adhesion molecule) also mediates homotypic adhesion of NK cells. FcγRIII, or the low-affinity IgG receptor, has a higher affinity for IgG when it is present on NK cells than when it is on neutrophils. FcγRIII also permits NK cells to mediate **antibody-dependent cellular cytotoxicity,** where antibody is bound through its Fc region to the FcγRIII. The antibody-combining portion of the IgG attaches to the target cell, and the NK cell, attached to the target by the Fc portion of the antibody, kills the target cell.

POSTNATAL LYMPHOPOIESIS

T Cells and T-Cell Subsets

Although the percentage of CD3 T cells in cord blood is somewhat less than in the peripheral blood of children and adults, T cells are actually present in higher number because of a higher absolute lymphocyte count in normal infants. An additional distinction is that the ratio of CD4 to CD8 T cells is usually higher (3.5-4:1) in cord blood than in blood of children and adults (1.5-2:1). Virtually all T cells in cord blood bear the CD45RA (naïve) isoform, and a dominance of CD45RA over CD45RO T cells persists during the 1st 2-3 yr of life, after which time the numbers of cells bearing these 2 isoforms gradually equalize. Th cells can be further subdivided according to the cytokines they produce when activated. **Th1 cells** produce IL-2 and IFN-γ, which promote cytotoxic T-cell or delayed hypersensitivity types of responses, whereas **Th2 cells** produce IL-4, IL-5, IL-6, IL-13, and IL-21 (see Table 123-2), which promote B-cell responses and allergic sensitization, and **Th17** cells produce IL-17. Development of Th cells into Th17 cells occurs when IL-6 and transforming growth factor β are present but IL-4 and IL-12 are absent. Th17 cells produce IL-21, which acts in an autocrine manner to activate STAT3, a transcription factor required for their further development as Th17 cells. Th17 cells express the receptor for the cytokine IL-23, stimulation that is required for development of Th17 effector activity. Th17 promotes inflammation by acting on local tissue cells to cause them to produce chemokines, such as IL-8, that recruit neutrophils and other innate effector cells. It is thought that the absence of these cells in the autosomal dominant form of the hyper-IgE syndrome (see Chapter 126) accounts for those patients' infection susceptibility to *Candida*. There are important additional subsets of T cells that have regulatory functions. These include CD25 high + T cells (**Treg cells**), also characterized by the presence of FOXp3 (absent in IPEX syndrome [see Chapter 126]) and considered to be important in the prevention of autoimmune diseases, and T cells that have phenotypic characteristics of NK cells (NKT cells). Cord blood T cells have the capacity to respond normally to **T-cell mitogens** (phytohemagglutinin, concanavalin A, and pokeweed mitogen) and are capable of mounting a normal mixed leukocyte response. Normal newborn infants also have the capacity to develop antigen-specific T-cell responses at birth, as evidenced by vigorous tuberculin reactivity a few wk after bacillus Calmette-Guérin vaccination on day 1 of life. Because patients in the 1st few mo of life may have unrecognized severe T-cell defects, most hospitals now routinely irradiate all blood products given young infants. T-cell defects can readily be detected even at birth by calculating the absolute lymphocyte count because T cells normally constitute 70% of circulating lymphocytes and their absence results in striking lymphopenia (see Fig. 122-2). T-cell lymphopenia also serves as the basis for the currently used newborn screening test for SCID.

B Cells and Immunoglobulins

Newborn infants have increased susceptibility to infections with Gram-negative organisms because IgM antibodies, which are heat-stable opsonins, do not cross the placenta. The level of the heat-labile opsonin, C3b, is also lower in newborn serum than in adults. These factors probably account for impaired phagocytosis of some organisms by newborn polymorphonuclear cells. Maternally transmitted IgG antibodies serve quite adequately as heat-stable opsonins for most Gram-positive bacteria, and IgG antibodies to viruses afford adequate protection against those agents. Because there is a relative deficiency of the IgG_2 subclass, antibodies to capsular polysaccharide antigens may be deficient. Because premature infants have received less maternal IgG by the time of birth than full-term infants, their serum opsonic activity is low for all types of organisms.

B lymphocytes are present in cord blood in slightly higher percentages but considerably higher numbers than in the blood of children and adults, reflecting the higher absolute lymphocyte counts in all normal infants. Cord blood B cells do not synthesize the range of immunoglobulin isotypes made by B cells from children and adults when stimulated with anti-CD40 plus IL-4 or IL-10, producing primarily IgM and at a much reduced quantity.

Neonates begin to synthesize antibodies of the IgM class at an increased rate very soon after birth in response to the immense antigenic stimulation of their new environment. Premature infants appear to be as capable of doing this as do full-term infants. At about 6 days after birth, the serum concentration of IgM rises sharply. This rise continues until adult levels are achieved by ≈1 yr of age. Cord serum from noninfected normal newborns does not contain detectable IgA. Serum IgA is normally first detected at around the 13th day of postnatal life; the level gradually increases during early childhood until adult levels are achieved by 6-7 yr of age. Cord serum contains an IgG

concentration comparable to or greater than that of maternal serum. Maternal IgG gradually disappears during the 1st 6-8 mo of life, while the rate of infant IgG synthesis increases (IgG_1 and IgG_3 faster than IgG_2 and IgG_4 during the 1st yr) until adult concentrations of total IgG are reached and maintained by 7-8 yr of age. IgG_1 and IgG_4 reach adult levels first, followed by IgG_3 at 10 yr and IgG_2 at 12 yr of age. The serum IgG level in infants usually reaches a low point at ≈3-4 mo of postnatal life. The rate of development of IgE generally follows that of IgA. After adult concentrations of each of the 3 major immunoglobulins are reached, these levels remain remarkably constant for a normal individual. The capacity to produce specific antibodies to protein antigens is intact at the time of birth. Normal infants cannot usually produce antibodies to polysaccharide antigens until after 2 yr of age unless the polysaccharide is conjugated to a protein carrier, as is the case for the conjugate *Haemophilus influenzae* type b and *Streptococcus pneumoniae* vaccines.

Natural Killer Cells

The percentage of NK cells in cord blood is usually lower than in the blood of children and adults, but the absolute number of NK cells is approximately the same, owing to the higher lymphocyte count. The capacity of cord blood NK cells to mediate target lysis in either NK-cell assays or antibody-dependent cellular cytotoxicity assays is roughly two-thirds that of adults.

Lymphoid Organ Development

Lymphoid tissue is proportionally small but rather well developed at birth and matures rapidly in the postnatal period. The thymus is largest relative to body size during fetal life and at birth is ordinarily two-thirds of its mature weight, which it attains during the 1st yr of life. It reaches its peak mass, however, just before puberty, and then gradually involutes thereafter. By 1 yr of age, all lymphoid structures are mature histologically. Absolute lymphocyte counts in the peripheral blood also reach a peak during the 1st yr of life (see Fig. 122-2). Peripheral lymphoid tissue increases rapidly in mass during infancy and early childhood. It reaches adult size by approximately 6 yr of age, exceeds those dimensions during the prepubertal years, and then undergoes involution coincident with puberty. The spleen, however, gradually accrues its mass during maturation and does not reach full weight until adulthood. The mean number of Peyer patches at birth is one-half the adult number, and gradually increases until the adult mean number is exceeded during adolescent years.

INHERITANCE OF ABNORMALITIES IN T-, B-, AND NATURAL KILLER–CELL DEVELOPMENT

More than 220 immunodeficiency syndromes have been described (see Table 122-8). Specific molecular defects have been identified in approximately 80% of these diseases. Most are recessive traits, several of which are caused by mutations in genes on the X chromosome and others by mutations on autosomal chromosomes. The molecular bases of 7 X-linked immunodeficiency disorders affecting T, B, and/or NK cells are known (see Chapters 124-126): X-linked immunodeficiency with hyper-IgM, X-linked lymphoproliferative syndrome, XIAD, X-linked agammaglobulinemia, X-linked SCID, the Wiskott-Aldrich syndrome, and nuclear factor kappa B essential modulator (NEMO). A few of the autosomal defects for which the molecular basis is known include (1) combined immunodeficiencies caused by abnormalities of purine salvage pathway enzymes, either adenosine deaminase (encoded by a gene on chromosome 20q13-ter) or purine nucleoside phosphorylase (encoded by a gene on chromosome 14q13.1); (2) combined immunodeficiencies caused by mutations in the gene encoding ZAP-70 (localized to chromosome 2q12), a non-src family protein tyrosine kinase important in T-cell signaling; (3) SCID caused by mutations in the gene on chromosome 19p13.1 encoding Janus kinase 3 (Jak3), the primary signal transducer from the common cytokine receptor γ chain (γc); (4) mutations in genes on chromosome 11 that encode components of the TCR, that is, CD3 γ, δ, and ε; (5) SCID caused by mutations in recombinase activating genes (*RAG1* and *RAG2*); and (6) SCID caused by mutations in the gene on chromosome 5p13 that encodes the α chain of the IL-7 receptor. These are only a few of the conditions for which the mutated genes have been discovered and the number is steadily growing.

PRENATAL DIAGNOSIS AND CARRIER DETECTION

Intrauterine diagnosis of adenosine deaminase and purine nucleoside phosphorylase deficiencies can be established by enzyme analyses on amnion cells (fresh or cultured) obtained before 20 wk gestation. Diagnosis of X-linked or autosomal defects causing SCID, other severe T-cell deficiencies, MHC class I and/or II antigen deficiencies, chronic granulomatous disease, or Wiskott-Aldrich syndrome can be established by direct mutation analysis of cells obtained by chorionic villus sampling or by amniocentesis if the mutation is known in the family or, if not known, by appropriate tests of phenotype or function on small samples of blood obtained by fetoscopy at 18-22 wk of gestation. The same diagnostic procedures can be performed on cord blood, but the only immunodeficiency disorder being routinely screened for is SCID and only 21 states are currently doing this (see Chapter 122). Carriers of any of these conditions can be identified by direct mutation analysis if the family's mutation is known.

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Chapter 124

Primary Defects of Antibody Production

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Of all of the primary immunodeficiency diseases, those affecting antibody production are most frequent. Selective absence of serum and secretory immunoglobulin (Ig)A is the most common defect, with rates ranging from 1 in 333 to 1 in 18,000 persons among different races and ethnicities. By contrast, agammaglobulinemia is estimated to occur with a frequency of only 1 in 10,000 to 1 in 50,000 persons. Patients with antibody deficiency are usually recognized because they have recurrent infections with encapsulated bacteria, predominantly in the upper and lower respiratory tracts; some individuals with selective IgA deficiency or infants with transient hypogammaglobulinemia may have few or no infections. The defective gene products for many primary antibody deficiency disorders have been identified (Table 124-1) and localized (Fig. 124-1). Sometimes the defect is not in the B cell itself but in T cells, which are required for complete B-cell function; some disorders are caused by unknown factors or are secondary to an underlying disease or its treatment (Table 124-2).

X-LINKED AGAMMAGLOBULINEMIA

Patients with X-linked agammaglobulinemia (XLA), or **Bruton agammaglobulinemia,** have a profound defect in B-lymphocyte development resulting in severe hypogammaglobulinemia, an absence of circulating B cells, small to absent tonsils, and no palpable lymph nodes.

Genetics and Pathogenesis

The abnormal gene in XLA maps to q22 on the long arm of the X chromosome and encodes the B-cell protein tyrosine kinase **Btk (Bruton tyrosine kinase).** Btk is a member of the Tec family of cytoplasmic protein tyrosine kinases and is expressed at high levels in all B-lineage cells, including pre-B cells. It appears to be necessary for

Table 124-1 Genetic Basis of Primary Antibody Deficiency Disorders

CHROMOSOME AND REGION	GENE PRODUCT	DISORDER	FUNCTIONAL DEFICIENCIES
1q32	CD21	CVID	Low IgG, low binding of EBV-gp350
2p11	κ Chain	κ Chain deficiency	Absence of immunoglobulins bearing κ chains
2q33	ICOS	ICOS-deficient CVID	Low or absent concentrations of all immunoglobulins
5q13.1	PI3K	B-cell–negative agammaglobulinemia	Low or absent concentrations of all immunoglobulins
6p21.3	Unknown	Selective IgA deficiency; CVID	Low or absent IgA; low concentrations of all immunoglobulins and of switched memory B cells in CVID
11p15.5	CD81	CVID caused by a lack of CD19	Low IgG concentration and poor response to antigens
11q12	CD20	CVID	Low IgG concentration and poor response to polysaccharide antigens
12p13	AID*	Autosomal recessive HIGM type 2	Failure to produce IgG, IgA, and IgE antibodies
12p13	CD27	EBV Lymphoproliferation	Memory B-cell deficiency Hypogammaglobulinemia
12q23-q24.1	UNG	Autosomal recessive HIGM type 5	Failure to produce IgG, IgA, and IgE antibodies
14q32.3	Immunoglobulin heavy chains*	B-cell–negative agammaglobulinemia; in others, selective isotype deficiencies	Absence of antibody production, lack of B cells, in μ heavy-chain mutations; in others, subclasses missing but B cells present
16p11.2	CD19	CD19 deficient CVID	Low or absent concentrations of all immunoglobulins
17p11.2	TACI*	TACI-deficient CVID	Low or absent concentrations of all immunoglobulins
20	CD40*	Autosomal recessive HIGM type 3	Failure to produce IgG, IgA, and IgE antibodies
22q13.1-q13.31	BAFF-R	BAFF-R–deficient CVID	Low or absent concentrations of all immunoglobulins
Xq22	Btk*	XLA or Bruton agammaglobulinemia	Absence of antibody production, lack of B cells
Xq25	SLAM-associated protein (SH2D1A)*	XLP	Lack of anti-EBNA and long-lived T-cell immunity; low immunoglobulins
Xq26	CD154 (CD40 ligand)*	X-linked HIGM type 1	Failure to produce IgG, IgA, and IgE antibodies
Xq28	NEMO	Anhidrotic ectodermal dysplasia with immunodeficiency	Hyper-IgM or -IgG subclass and antipolysaccharide antibody deficiencies

*The gene has been cloned and sequenced.
AID, Activation-induced cytidine deaminase; BAFF-R, B-cell–activating factor of the tumor necrosis factor family receptor; Btk, Bruton tyrosine kinase; CVID, common variable immunodeficiency; EBNA, Epstein-Barr virus nuclear antigen; EBV, Epstein-Barr virus; HIGM, hyper-IgM syndrome; ICOS, inducible costimulatory; NEMO, nuclear factor κB essential modulator; PI3K, phosphatidylinositol 3 kinase; TACI, transmembrane activator, calcium modulator, and cyclophilin ligand interactor; UNG, uracil DNA glycosylase; XLA, X-linked agammaglobulinemia; XLP, X-linked lymphoproliferative disease.

pre–B-cell expansion and maturation into surface Ig-expressing B cells, but probably has a role at all stages of B-cell development; it has also been found in cells of the myeloid series. More than 500 different mutations in the human *Btk* gene are recognized; they encompass most parts of the coding portions of the gene. There is not a clear correlation between the location of the mutation and the clinical phenotype. Carriers are detected by mutation analysis, and prenatal diagnosis of affected male fetuses is possible if the mutation is known in the family.

The expression of Btk in cells of myeloid lineage is of interest because boys with XLA often have neutropenia at the height of an acute infection. It is conceivable that Btk is only one of the signaling molecules participating in myeloid maturation and that neutropenia is observed in XLA only when rapid production of such cells is needed. Some pre-B cells are found in the bone marrow; the percentage of peripheral blood B lymphocytes is <1%. The percentage of T cells is increased, ratios of T-cell subsets are normal, and T-cell function is intact. The thymus is normal.

Seven autosomal recessive defects have also been shown to result in **agammaglobulinemia with an absence of circulating B cells** (Table 124-3), including mutations in the genes encoding: (1) the μ heavy chain gene; (2) the Igα and (3) Igβ signaling molecules; (4) B-cell linker adaptor protein (BLNK); (5) the surrogate light chain, λ5/14.1; (6) leucine-rich repeat-containing 8 (LRRC8); and (7) the p85α subunit of phosphatidylinositol-3 kinase.

Clinical Manifestations

Most boys afflicted with XLA remain well during the 1st 6-9 mo of life by virtue of maternally transmitted IgG antibodies. Thereafter, they acquire infections with extracellular pyogenic organisms, such as *Streptococcus pneumoniae* and *Haemophilus influenzae*, unless they are given prophylactic antibiotics or immunoglobulin therapy. Infections include sinusitis, otitis media, pneumonia, or, less often, sepsis or meningitis. Infections with *Mycoplasma* are also particularly problematic. Chronic fungal infections are seen; *Pneumocystis jiroveci* pneumonia rarely occurs. Viral infections are usually handled normally with the exceptions of hepatitis viruses and enteroviruses. There were several examples of **paralysis** when live polio vaccine was administered to these patients, and chronic, eventually fatal, central nervous system infections with various echoviruses and coxsackieviruses have occurred in a significant number of them. Echovirus-associated **myositis** resembling dermatomyositis has also been observed. These observations suggest a primary role for antibody, particularly secretory IgA, in host defense against enteroviruses. Growth hormone deficiency has also been reported in association with XLA. Neutropenia, responsive to G-CSF, may be present in patients with XLA.

Diagnosis

The diagnosis of XLA should be suspected if **lymphoid hypoplasia** is found on physical examination (minimal or no tonsillar tissue and no

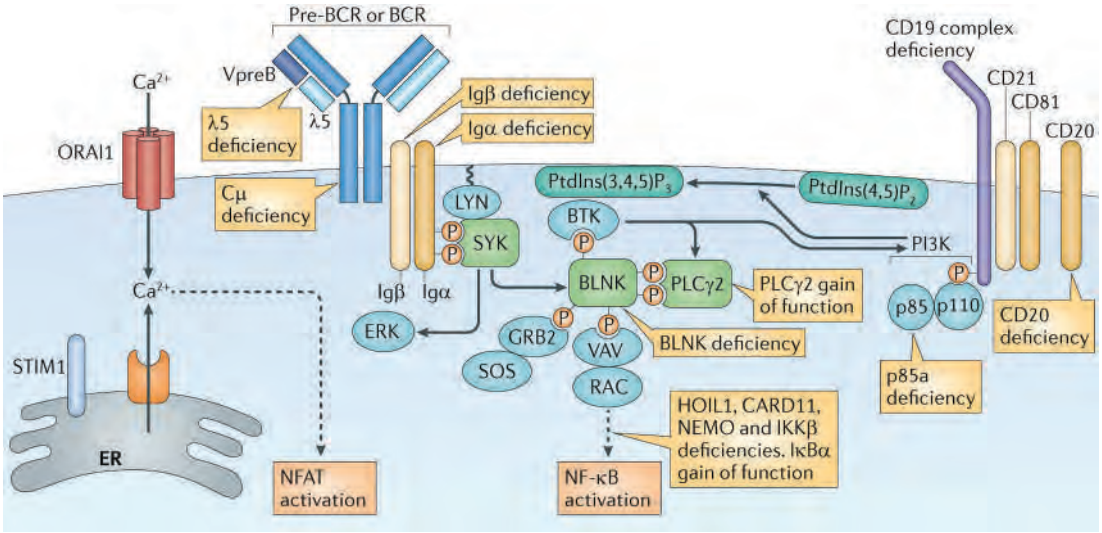


Figure 124-1 The pre-B cell receives proliferation and differentiation signals through the pre–B-cell receptor (BCR) and the coreceptors Igα and Igβ. Signaling from the pre-BCR involves the immunoreceptor tyrosine-based activation motifs (ITAMs) of the coreceptors Igα and Igβ, which scaffold and activate the tyrosine kinase SYK. SYK either activates the extracellular signal-regulated kinase (ERK) pathway or phosphorylates (P) (together with LYN) the adaptor protein B-cell linker (BLNK) and Bruton's tyrosine kinase (BTK), leading to the activation of phospholipase Cγ2 (PLCγ2) and the phosphoinositide-3 kinase (PI3K) pathway. Defects in this pathway affect the pre-BCR (in Cμ or pseudo light-chain λ5), the pre-BCR signal transduction molecules Igα and Igβ, the downstream molecules BTK, BLNK, and PI3K, components of the costimulatory CD19 complex (CD19, CD21, and CD81) and the B-cell marker CD20. The BCR triggers the canonical nuclear factor-κB (NF-κB) pathway through the scaffolding protein CARD11 and activation of the IκB kinase (IKK) complex (comprising IKKα, IKKβ, and NEMO [NF-κB essential modulator]). IKK activation leads to the phosphorylation and degradation of NF-κB inhibitor-α (IκBα) and the subsequent release of the p50-p65 NF-κB heterodimer, which then translocates to the nucleus to regulate gene transcription (not shown). Following antigen binding to antigen receptors (such as the BCR), endoplasmic reticulum Ca^{2+} stores are depleted, STIM1 is activated and ORAI1 Ca^{2+} release-activated Ca^{2+} channels open, resulting in store-operated Ca^{2+} entry. This influx results in activation of the transcription factor NFAT (nuclear factor of activated T cell). The *dashed arrows* indicate downstream signaling events. ER, endoplasmic reticulum; PAD, primary antibody deficiency; PtdIns(4,5)P_2, phosphatidylinositol-4,5-bisphosphate; PtdIns(3,4,5)P_3, phosphatidylinositol-3,4,5-trisphosphate. *(From Durandy A, Kracker S, Fischer A. Primary antibody deficiencies.* Nat Rev Immunol *13:519–533, 2013, Fig. 1, p. 521).*

palpable lymph nodes), and serum concentrations of IgG, IgA, IgM, and IgE are far below the 95% confidence limits for appropriate age- and race-matched controls usually with total immunoglobulins <100 mg/dL. Levels of natural antibodies to type A and B red blood cell polysaccharide antigens (isohemagglutinins) and antibodies to antigens given during routine immunizations are abnormally low in this disorder, whereas they are normal in transient hypogammaglobulinemia of infancy. **Flow cytometry** is an important test to demonstrate the **absence of circulating B cells**, which will distinguish this disorder from common variable immunodeficiency, the hyper-IgM syndrome and transient hypogammaglobulinemia of infancy.

COMMON VARIABLE IMMUNODEFICIENCY

Common variable immunodeficiency (CVID) is a syndrome characterized by hypogammaglobulinemia with phenotypically normal B cells. It has also been called **acquired hypogammaglobulinemia** because of a generally later age of onset of infections. CVID patients may appear similar clinically to those with XLA in the types of infections experienced and bacterial etiologic agents involved, except that echovirus meningoencephalitis is rare in patients with CVID (see Table 124-3). In contrast to XLA, the sex distribution in CVID is almost equal, the age at onset is later (although it may be present in infancy), and infections may be less severe.

Genetics and Pathogenesis

Most patients have no identified molecular diagnosis. CVID is a category of primary immunodeficiency disorders that likely consists of several different genetic defects with autosomal recessive or dominant inheritance. Genes known to produce the CVID phenotype when mutated include *ICOS* (inducible costimulator) deficiency, *SH2DIA* (responsible for X-linked lymphoproliferative disease [XLP]), *CD19, CD20, CD21, CD81, BAFF-R* (B-cell–activating factor of the tumor necrosis factor family receptors), *TACI* (transmembrane activator, calcium modulator, and cyclophilin ligand interactor), and 2 genes that encode DNA methyl transferase (DNMT3B and ZBTB24). These mutations in aggregate account for less than 10% of all cases of CVID.

Because CVID occurs in 1st-degree relatives of patients with selective IgA deficiency, and some patients with IgA deficiency later become panhypogammaglobulinemic, a large subtype of CVID may have a common genetic basis with IgA deficiency. The high incidence of abnormal immunoglobulin concentrations, autoantibodies, autoimmune disease, and malignancy in both CVID and IgA deficiency and in other members of those patients' families also suggests a shared hereditary influence. This concept is supported by the discovery of a high incidence of C4-A gene deletions and C2 rare gene alleles in the class III major histocompatibility complex (MHC) region in individuals with either IgA deficiency or CVID, suggesting that a common susceptibility gene is on chromosome 6. Only a few human leukocyte antigen (HLA) haplotypes are shared by individuals affected with IgA deficiency and CVID, with at least 1 of 2 particular haplotypes being present in 77% of those affected. In 1 large family with 13 members, 2 had IgA deficiency and 3 had CVID. All of the immunodeficient patients in the family had at least 1 copy of an MHC haplotype that is abnormally frequent in IgA deficiency and CVID: HLA-DQB1 *0201, HLA-DR3, C4B-Sf, C4A-deleted, G11-15, Bf-0.4, C2a, HSP70-7.5, TNFa-5, HLA-B8, and HLA-A1. In a study of 83 multiply affected families with IgA deficiency and CVID, increased allele sharing at chromosome 6p21 in the proximal part of the MHC was observed in a susceptibility locus now designated as *IGAD1*. More sensitive genetic analysis in 101 multiple-case and 110 single-case families further localized the defect to the *HLADQ/DR* locus. Environmental factors, particularly drugs such as phenytoin, D-penicillamine, gold, and sulfasalazine are suspected to be triggers for disease expression in individuals with the permissive genetic background.

Most cases of CVID are sporadic or follow an autosomal dominant pattern of inheritance. Patients who lack ICOS, a surface protein on

Table 124-2 Other Conditions Associated with Humoral Immunodeficiency

GENETIC DISORDERS	
Monogenic diseases	Ataxia-telangiectasia
	Autosomal forms of severe combined immunodeficiency (SCID)
	Transcobalamin II deficiency and hypogammaglobulinemia
	Wiskott-Aldrich syndrome
	X-linked lymphoproliferative disorder (Epstein-Barr virus [EBV] associated)
	X-linked SCID
Chromosomal anomalies	Chromosome 18q– syndrome
	Monosomy 22
	Trisomy 8
	Trisomy 21
SYSTEMIC DISORDERS	
Malignancy	Chronic lymphocytic leukemia
	Immunodeficiency with thymoma
	T-cell lymphoma
Metabolic or physical loss	Immunodeficiency caused by hypercatabolism of immunoglobulin
	Immunodeficiency caused by excessive loss of immunoglobulins and lymphocytes
ENVIRONMENTAL EXPOSURES	
Drug induced	Antimalarial agents
	Captopril
	Carbamazepine
	Glucocorticoids
	Fenclofenac
	Gold salts
	Imatinib
	Penicillamine
	Phenytoin
	Sulfasalazine
Infectious diseases	Congenital rubella
	Congenital infection with cytomegalovirus
	Congenital infection with *Toxoplasma gondii*
	EBV
	Human immunodeficiency virus

From Schroeder HW, Szymanska-Mroczek E. Primary antibody deficiencies. In Rich RR, Fleisher TA, Shearer, WT, et al, editors: Clinical immunology: principles and practice, *ed 4, St Louis, 2013, WB Saunders.*

activated T cells, have an autosomal recessive pattern of inheritance. Nine such patients from 6 families in the Black Forest of Germany have been found to have identical homozygous large genomic deletions of the *ICOS* gene, suggesting a founder effect. Those who have XLP have an X-linked pattern of inheritance and those with autosomally inherited *TACI* defects may have heterozygous or homozygous mutations.

Despite normal numbers of circulating immunoglobulin-bearing B lymphocytes and the presence of lymphoid cortical follicles, blood B lymphocytes from CVID patients do not differentiate normally into immunoglobulin-producing cells when stimulated with pokeweed mitogen in vitro, even when cocultured with normal T cells. They also have a deficiency of switched memory B cells. B cells from some CVID and some IgA-deficient patients can be stimulated both to switch isotype and to synthesize and secrete some immunoglobulin when stimulated with anti-CD40 and interleukin (IL)-4 or IL-10. T cells and T-cell subsets are usually present in normal percentages, although T-cell function is depressed in some patients.

Clinical Manifestations

The serum immunoglobulin and antibody deficiencies in CVID may be as profound as in XLA. Patients with CVID often have autoantibody formation and normal-sized or enlarged tonsils and lymph nodes; ≈25% of patients have splenomegaly. CVID has also been associated with a sprue-like enteropathy with or without nodular follicular lymphoid hyperplasia of the intestine, thymoma, alopecia areata, hemolytic anemia, gastric atrophy, achlorhydria, thrombocytopenia, and pernicious anemia. Lymphoid interstitial pneumonia, intestinal lung disease, pseudolymphoma, B-cell lymphomas, amyloidosis, and noncaseating sarcoid-like granulomas of the lungs, spleen, skin, and liver also occur. There is a 438-fold increase in lymphomas among affected women in the 5th and 6th decades of life. CVID has been reported to resolve transiently or permanently in patients who acquire HIV infection.

Recurrent or chronic infections include pneumonia, sinusitis, otitis media, and diarrhea (bacterial, giardiasis). Repeated pulmonary infections may produce bronchiectasis. Sepsis and meningitis with encapsulated bacteria occur more frequently than in the general population. There is often a delay in the diagnosis of more than 5 yr between the first infections and a definitive diagnosis.

SELECTIVE IgA DEFICIENCY

An isolated absence or near absence (<10 mg/dL) of serum and secretory IgA is the most common well-defined immunodeficiency disorder, with a disease frequency as high as 0.33% in some populations. This condition can also be and often is associated with ill health.

The basic defect resulting in IgA deficiency is unknown. Phenotypically normal blood B cells are present. IgA deficiency occasionally remits spontaneously or after discontinuation of phenytoin therapy. The occurrence of IgA deficiency in both males and females and in members of successive generations within families suggests autosomal dominant inheritance with variable expressivity. This defect also occurs commonly in pedigrees containing individuals with CVID. Indeed, IgA deficiency may evolve into CVID, and the finding of rare alleles and deletions of MHC class III genes in both conditions suggests that the susceptibility gene common to these 2 conditions may reside in the MHC region on chromosome 6. IgA deficiency is noted in patients treated with the same drugs associated with producing CVID (phenytoin, D-penicillamine, gold, and sulfasalazine), suggesting that environmental factors may trigger this disease in a genetically susceptible person.

Clinical Manifestations

Infections occur predominantly in the respiratory, gastrointestinal, and urogenital tracts. Bacterial agents responsible are the same as in other antibody deficiency syndromes. Intestinal giardiasis is common. Children with IgA deficiency vaccinated intranasally with killed poliovirus produced local IgM and IgG antibodies. Serum concentrations of other immunoglobulins are usually normal in patients with selective IgA deficiency, although IgG_2 (and other) subclass deficiency has been reported, and IgM (usually elevated) may be monomeric.

Patients with IgA deficiency often have IgG antibodies against cow's milk and ruminant serum proteins. These antiruminant antibodies may cause false-positive results in immunoassays for IgA that use goat (but not rabbit) antisera. IgA deficiency is associated with a celiac-like syndrome, which may or may not respond to a gluten-free diet. The incidence of autoantibodies, autoimmune diseases, and malignancy is increased. Serum antibodies to IgA are reported in as many as 44% of patients with selective IgA deficiency. If these antibodies are of the IgE isotype, they can cause severe or fatal anaphylactic reactions after intravenous administration of blood products containing IgA. Only 5-times washed (in 200-mL volumes) normal donor erythrocytes (frozen blood would have this done routinely), or blood products from other IgA-deficient individuals, should be administered to patients with IgA deficiency. Many intravenous immunoglobulin (IVIG) preparations contain sufficient IgA to cause anaphylactic reactions. Administration of IVIG, which is >99% IgG, is not indicated because most IgA-deficient patients make IgG antibodies normally.

IgG SUBCLASS DEFICIENCIES

Some patients have deficiencies of 1 or more of the 4 subclasses of IgG despite normal or elevated total IgG serum concentration. Some

Table 124-3 The Main Phenotypes of Primary Antibody Deficiencies

PHENOTYPE	MAIN CLINICAL FEATURES	MAIN B-CELL BIOLOGIC FEATURES	KNOWN AFFECTED PROTEINS
Pan-agammaglobulinemia (absence of IgM, IgG, and IgA)	Bacterial infections (in the respiratory tract) and enterovirus infections	Absence of CD19*B cells	λ5, BLNK, Btk, Cμ, Igα, Igβ, and PI3K
Variable pan-hypogammaglobulinemia (CVID)	Bacterial infections (in the respiratory tract and gut), autoimmunity, cancer and increased risk of granuloma	Decreased frequency of CD27* memory B cells: defective plasma cells in tissues	CD19, CD20, CD21, CD27, CD81, DNMT3B, ZBTB24, ICOS, SAP, TACI, and BAFF-R
CSR deficiencies (absence or decrease in levels of IgG and IgA)	Bacterial and opportunistic infections Bacterial infections, autoimmunity and lymphadenopathies	Decreased frequency of CD27* memory B cells Normal frequency of CD27* memory B cells.	CD40 and CD40L AID and UNG
Selective IgA deficiency	Most often asymptomatic	ND	ND
Selective IgM deficiency	Frequent infections with encapsulated bacteria	No IgM antibody production (absence of allohemagglutinins and polysaccharide-specific antibodies)	
Selective IgG_2 and/or IgG_4 deficiency	Frequent bacterial infections, diagnosis after 2 yr of age; sometimes transient in childhood	Defective polysaccharide-specific antibody production	
Selective polysaccharide antibody deficiency	Bacterial infections (after 2 yr of age)	Normal IgG (including IgG_2 and IgG_4) levels	NF-κB pathway proteins (CARD11, HIOL1 and NEMO), Btk, and CD20

AID, Activation-induced cytidine deaminase; BAFF-R, B-cell–activating factor of the tumor necrosis factor family receptor; BLNK, B-cell linker; Btk, Bruton tyrosine kinase; Cμ, constant region-μ; CD40L, CD40 ligand; CSR, class-switch recombination; CVID, common variable immunodeficiency; ICOS, inducible costimulatory; ND, not determined; NEMO, nuclear factor kappa B essential modulator; NF-κB, nuclear factor kappa B; PI3K, phosphatidylinositol 3 kinase; SAP, signaling lymphocyte activation molecule (SLAM)-associated protein; TACI, transmembrane activator, calcium modulator, and cyclophilin ligand interactor; UNG, uracil DNA glycosylase.

Modified from Durandy A, Kracker S, Fischer A. Primary antibody deficiencies. Nat Rev Immunol *13:519–533, 2013, Table, p. 524.*

patients with absent or very low concentrations of IgG_2 also have IgA deficiency. Other patients with IgG subclass deficiency have gone on to develop CVID, suggesting that the presence of IgG subclass deficiency may be a marker for more generalized immune dysfunction. The biologic significance of the numerous moderate deficiencies of IgG subclasses that have been reported is difficult to assess, particularly because commercial laboratory measurement of IgG subclasses is problematic. IgG subclass measurement is not cost-effective in evaluating immune function in the child with recurrent infection. The more relevant issue is a patient's capacity to make specific antibodies to protein and polysaccharide antigens, because profound deficiencies of antipolysaccharide antibodies have been noted even in the presence of normal concentrations of IgG_2. IVIG should not be administered to patients with IgG subclass deficiency unless they are shown to have a deficiency of antibodies to a broad array of antigens.

IMMUNOGLOBULIN HEAVY- AND LIGHT-CHAIN DELETIONS

Some completely asymptomatic individuals have been documented to have a total absence of IgG_1, IgG_2, IgG_4, and/or IgA_1 as a result of gene deletions. These abnormalities were discovered fortuitously in 16 individuals, 15 of whom had no history of undue susceptibility to infection, and all of whom produced antibodies of all other isotypes in normal quantities. These patients illustrate the importance of assessing specific antibody formation before deciding to initiate IVIG therapy in IgG subclass-deficient patients.

HYPER-IgM SYNDROME

The hyper-IgM syndrome is genetically heterogeneous and characterized by normal or elevated serum IgM levels associated with low or absent IgG, IgA, and IgE serum levels, indicating a defect in the class-switch recombination (CSR) process. Causative mutations have been identified in 2 genes on the X chromosome, the CD40 ligand (hyper-IgM syndrome type 1 [HIGM1]) and NEMO (nuclear factor κB essential modulator, XHM-ED) genes; and 3 genes on autosomal chromosomes, the activation-induced cytidine deaminase (AID) gene (hyper-IgM type 2 [HIGM2]) on chromosome 12, the uracil DNA glycosylase gene (UNG, hyper-IgM type 5 [HIGM5]), on chromosome 12, and the CD40 gene (hyper-IgM type 3 [HIGM3]) on chromosome 20. Distinctive clinical features permit presumptive recognition of the type of mutation in these patients, thereby aiding proper choice of therapy. All such patients should undergo molecular analysis to ascertain the affected gene for purposes of genetic counseling, carrier detection, and decisions regarding definitive therapy.

X-Linked Hyper-IgM Caused By Mutations in the CD40 Ligand: Hyper-IgM Type 1

HIGM1 is caused by mutations in the gene that encodes the CD40 ligand (CD154, CD40L), which is expressed on activated T-helper cells. Boys with this syndrome have very low serum concentrations of IgG and IgA, with a usually normal or sometimes elevated concentration of polyclonal IgM, may or may not have small tonsils, usually have no palpable lymph nodes, and often have profound **neutropenia.**

Genetics and Pathogenesis

B cells from boys with the CD40 ligand defect are capable of synthesizing not only IgM but also IgA and IgG when cocultured with normal activated T-helper cells, indicating that the B cells are actually normal in this condition and that the defect is in the T cells. The abnormal gene is localized to Xq26, and the gene product, CD154 (CD40L), is the ligand for CD40, which is present on B cells and monocytes. CD154 is upregulated on activated T cells. Mutations in CD154 result in an inability to signal B cells to undergo isotype switching, and thus the B cells produce only IgM. The failure of T cells to interact with B cells through this receptor–ligand pair also causes a failure of upregulation of the B cell and monocyte surface molecules CD80 and CD86 that interact with CD28/CTLA4 on T cells, resulting in failure of "crosstalk" between immune system cells. The failure of interaction of the molecules of those pathways results in a propensity for tolerogenic T-cell signaling and defective recognition of tumor cells. More than 73

distinct point mutations or deletions in the gene encoding CD154 have been identified in 87 unrelated families, giving rise to frame shifts, premature stop codons, and single amino acid substitutions, most of which are clustered in the domain with homology to tumor necrosis factor (TNF), located in the carboxyterminal region.

Clinical Manifestations

Similar to patients with XLA, boys with the CD40 ligand defect become symptomatic during the 1st or 2nd yr of life with recurrent pyogenic infections, including otitis media, sinusitis, pneumonia, and tonsillitis. They have marked susceptibility to *P. jiroveci* pneumonia, and are frequently profoundly neutropenic. Lymph node histology shows only abortive germinal center formation with severe depletion and phenotypic abnormalities of follicular dendritic cells. These patients have normal numbers of circulating B lymphocytes, but a decreased frequency of CD27+ memory B cells. Circulating T cells are also present in normal number and in vitro responses to mitogens are normal, but there is decreased antigen-specific T-cell function. In a study of patients with the CD40 ligand defect, 23.3% had died at a mean age at death of 11.7 yr. In addition to opportunistic infections such as *P. jiroveci* pneumonia, there is an increased incidence of extensive verruca vulgaris lesions, *Cryptosporidium* enteritis, subsequent liver disease, and an increased risk of malignancy. Because of the poor prognosis, the treatment of choice is an HLA-identical hematopoietic stem cell transplant at an early age. Alternative treatment for this condition is monthly infusion of IVIG. In patients with severe neutropenia, the use of granulocyte colony-stimulating factor has been beneficial.

X-Linked Hyper-IgM Caused By Mutations in the Gene Encoding Nuclear Factor κB Essential Modulator; XHM-ED

This syndrome in males is characterized most often clinically as **anhydrotic ectodermal dysplasia with associated immunodeficiency (EDA-ID).** The condition results from missense mutations in the IKBKG gene at position 28q on the X chromosome that encodes **NEMO,** a regulatory protein required for the activation of the transcription factor NF-κB. Germ line loss-of-function mutations cause the X-linked dominant condition incontinentia pigmenti in females and are lethal in male fetuses. Mutations in the coding region of IKBKG are associated with EDA-ID. The immunodeficiency is variable, with most patients showing impaired antibody responses to polysaccharide antigens. Some patients with EDA-ID have hyper-IgM. Pharmacologic inhibitors of NF-κB activation have been shown to downregulate CD154 messenger RNA and protein levels, suggesting the mechanism of hyper-IgM in this condition. The hyper-IgM patients with this defect should be easily recognizable because of the presence of ectodermal dysplasia, although there are some patients with this condition who do not have ectodermal dysplasia.

Autosomal Recessive Hyper-IgM Caused By Mutations in the Gene for Activation-Induced Cytidine Deaminase: Hyper-IgM Type 2

An autosomal recessive form of hyper-IgM syndrome is caused by mutations in the gene for AID.

Genetics and Pathogenesis

Patients with autosomal recessive hyper-IgM usually have normal numbers of circulating B lymphocytes, but, in contrast to patients with the CD40 ligand defect, B cells from these patients are not able to switch from IgM-secreting to IgG-, IgA-, or IgE-secreting cells, even when cocultured with normal T cells or with monoclonal antibodies to CD40 and a variety of cytokines. When their B cells are cultured in vitro, they spontaneously secrete large amounts of IgM, but this is not further augmented by the addition of cytokines. Thus, in these patients, there is truly an intrinsic B-cell abnormality. The defect in many such patients has been identified as due to mutations in a gene on chromosome 12p13 that encodes AID. AID is a single-stranded DNA deaminase required for somatic hypermutation (SHM) and class-switch recombination (CSR) of immunoglobulin genes. Histologic examination of the enlarged lymph nodes reveals the presence of giant germinal centers (5-10 times larger than normal) filled with highly proliferating B cells. Proliferating B cells coexpress IgM, IgD, and CD38, a phenotype previously described for a small B-cell subset corresponding to germinal center founder cells. These cells are thought to correspond to a transitional stage between follicular mantle and germinal center B cells, at the onset of somatic mutation of the Ig variable region gene and antigen-driven selection. Deficiency of AID results in impaired terminal differentiation of B cells, a failure of CSR, and lack of immunoglobulin gene SHM. They have a normal frequency of CD27+ memory B cells.

Clinical Manifestations

Concentrations of serum IgG, IgA, and IgE are very low in AID deficiency. In contrast to the CD40 ligand defect, however, the serum IgM concentration in patients with AID deficiency is usually markedly elevated and polyclonal. Patients with this form of hyper-IgM have lymphoid hyperplasia, are generally older at age at onset, do not have susceptibility to *P. jiroveci* pneumonia, often do have isohemagglutinins, and are much less likely to have neutropenia unless it occurs on an autoimmune basis. They have a tendency, however, to develop autoimmune and inflammatory disorders including diabetes mellitus, polyarthritis, autoimmune hepatitis, hemolytic anemia, immune thrombocytopenia, Crohn disease, and chronic uveitis. With early diagnosis and monthly infusions of IVIG, as well as good management of infections with antibiotics, patients with AID mutations generally have a more benign course than do boys with the CD40 ligand defect.

Autosomal Recessive Hyper-IgM Caused By Mutations in the Gene for Uracil DNA Glycosylase; Hyper-IgM Type 5

Genetics and Pathogenesis

AID deaminates cytosine into uracil in targeted DNA, which is followed by uracil removal by UNG. Severely impaired CSR was found in 3 hyper-IgM patients reported to have UNG deficiency. Their clinical characteristics were similar to those with AID deficiency, with increased susceptibility to bacterial infections and lymphoid hyperplasia. The patients had a markedly elevated serum IgM and profoundly decreased serum IgG and IgA concentrations. Their B cells had an intrinsic defect in CSR when stimulated with anti-CD40 and IL-4 and constitutively produced high quantities of IgM. They had only a partial defect in SHM, however, and they have a normal frequency of CD27+ memory B cells.

Autosomal Recessive Hyper-IgM Caused By Mutations in CD40: Hyper-IgM Type 3

Five patients with autosomal recessive hyper-IgM from 4 unrelated families failed to express CD40 on their B-cell surfaces and were found to have mutations in the CD40 gene. Clinical manifestations included recurrent sinopulmonary infections, *P. jiroveci* pneumonia and *Cryptosporidium parvum* infections. The patients had very low levels of IgG and IgA and normal or high levels of IgM. More recently, 2 patients were identified with such mutations who did express the CD40 protein on their B cells and monocytes, so mutation analysis was required to make the diagnosis.

Genetics and Pathogenesis

CD40 is a type I integral membrane glycoprotein encoded by a gene on chromosome 20 and belonging to the TNF and nerve growth factor receptor superfamily. It is expressed on B cells, macrophages, dendritic cells, and a few other types of cells. Mutations in the CD40 gene cause an autosomal recessive form of hyper-IgM syndrome that is clinically indistinguishable from HIGM1, resulting from the X-linked CD40 ligand (CD154) defect. In contrast to the CD40 ligand defect, however, the B cells in the autosomal recessive condition are intrinsically abnormal and cannot isotype switch. The T cells are normal except to the extent that they cannot cause upregulation of CD80 and CD86 on B cells and macrophages to interact with CD28/CTLA4 on T cells.

Hyper-IgM Type 4

The defective gene in a 4th autosomal recessive form of hyper-IgM syndrome has not yet been identified, but appears to be in a gene downstream of AID. These patients all have defective CSR with preserved SHM.

X-LINKED LYMPHOPROLIFERATIVE DISEASE

XLP disease, also referred to as **Duncan disease** after the original kindred in which it was described, is an X-linked recessive trait characterized by an inadequate immune response to infection with Epstein-Barr virus (EBV).

Genetics and Pathogenesis

The defective gene in XLP was localized to Xq25, cloned, and the gene product was initially named SAP (for SLAM-associated protein), but is now known officially as SH2D1A. SLAM (signaling lymphocyte activation molecule) is an adhesion molecule that is upregulated on both T and B cells with infection and other stimulation. SH2D1A is highly expressed in thymocytes and peripheral blood T and NK cells, with a prevalent expression on T-helper type 1 cells. Its presence on B lymphocytes is unclear. Thus, although antibody deficiency is frequently present, this is really a T- and natural killer (NK)-cell defect. SH2D1A competes with SHP-2 for binding to SLAM and, as such, is a regulatory molecule. In XLP patients, the absence of SH2D1A can lead to an uncontrolled cytotoxic T-cell immune response to EBV. The SH2D1A protein associates permissively with 2B4 on NK cells; thus, selective impairment of 2B4-mediated NK-cell activation also contributes to the immunopathology of XLP.

XLP type 2 is less common and is caused by a mutation in *XIAP* (X-linked inhibitor of apoptosis protein); disease manifestations are similar to XLP. X-linked immunodeficiency with magnesium defect (XMEN syndrome) is due to a loss of function mutation of the magnesium transporter protein and manifests with chronic EBV infection, EBV lymphoproliferative disorders, and CD4 lymphopenia.

Clinical Manifestations

Affected males are usually healthy until they acquire EBV infection. The mean age of presentation is <5 yr. There are 3 major clinical phenotypes: (1) fulminant, often fatal, infectious mononucleosis (50% of cases); (2) lymphomas, predominantly involving B-lineage cells (25%); and (3) acquired hypogammaglobulinemia (25%). There is a marked impairment in production of antibodies to the EBV nuclear antigen, whereas titers of antibodies to the viral capsid antigen have ranged from absent to markedly elevated. XLP has an unfavorable prognosis; 70% of affected boys die by age 10 yr. Only 2 XLP patients are known to have survived beyond 40 yr of age. Unless there is a family history of XLP, diagnosis prior to the onset of complications is difficult because affected individuals are asymptomatic initially. Using mutation analysis, it is possible to identify affected males within identified kindreds before they develop primary EBV infection. Approximately half of the few patients with XLP given HLA-identical related or unrelated stem cell transplants are surviving without signs of the disease.

Two pedigrees have been reported in which boys in one arm of each pedigree were diagnosed with CVID, whereas those in the other arms had fulminant infectious mononucleosis. The family members with CVID never gave a history of infectious mononucleosis. All affected members of each pedigree had the same distinct SH2D1A mutation, however, despite the different clinical phenotypes. Because the SH2D1A mutation was the same but the phenotype varied in these families, XLP should be considered in all males with a diagnosis of CVID, particularly if there is more than one male family member with this phenotype.

CD27 Deficiency

CD27 deficiency, an autosomal recessive condition, was found to be associated with EBV lymphoproliferation, EBV lymphoma and hypogammaglobulinemia. CD27 is commonly used as marker of memory B cells for the classification of B-cell deficiencies including common variable immune deficiency. It is a member of the TNF receptor family and interacts with CD70 to influence T-, B-, and NK-cell functions. Disturbance of this axis impairs immunity and memory generation against viruses including EBV, influenza, and others.

Bibliography is available at Expert Consult.

124.1 Treatment of B-Cell Defects

Rebecca H. Buckley

Except for the CD40 ligand defect and XLP, for which stem cell transplantation is recommended, judicious use of antibiotics to treat documented infections and regular administration of IVIG are the only effective treatments for primary B-cell disorders. The most common forms of replacement therapy are either intravenous or subcutaneous immunoglobulin (IVIG or SCIG). Broad antibody deficiency should be carefully documented before such therapy is initiated. The rationale for the use of IVIG or SCIG is to provide missing antibodies, not to raise the serum IgG or IgG subclass level. The development of safe and effective immunoglobulin preparations is a major advance in the treatment of patients with severe antibody deficiencies, although it is expensive and there have been national shortages. Almost all commercial preparations are isolated from normal plasma by the Cohn alcohol fractionation method or a modification of it. Cohn fraction II is then further treated to remove aggregated IgG. Additional stabilizing agents such as sugars, glycine, and albumin are added to prevent reaggregation and protect the IgG molecule during lyophilization. The ethanol used in preparation of immunoglobulin inactivates HIV; and an organic solvent/detergent step inactivates hepatitis B and C viruses. Some preparations are also nanofiltered to remove infectious agents. Most commercial lots are produced from plasma pooled from 10,000 to 60,000 donors and therefore contain a broad spectrum of antibodies. Each pool must contain adequate levels of antibody to antigens in various vaccines, such as tetanus and measles. However, there is no standardization based on titers of antibodies to more clinically relevant organisms, such as *S. pneumoniae* and *H. influenzae* type b.

The IVIG and SCIG preparations available in the United States have similar efficacy and safety. Rare transmission of hepatitis C virus has occurred in the past, but the potential transmission of hepatitis C virus has been resolved by additional treatment with an organic solvent/detergent mixture. There has been no documented transmission of HIV by any of these preparations. **IVIG or SCIG at a dose of 400 mg/kg per month** achieves trough IgG levels close to the normal range. Higher doses are indicated in patients with chronic or severe respiratory infections. Systemic reactions may occur, but rarely are these true anaphylactic reactions. Anaphylactic reactions caused by a patient's IgE antibodies to IgA in the IVIG or SCIG preparation may occur in patients with CVID or IgA deficiency. Newly diagnosed patients with CVID should be screened through the American Red Cross for anti-IgA antibodies. If anti-IgA antibodies are detected, IVIG therapy should consist of the one available immunoglobulin preparation containing almost no IgA (Gammagard S/D, Baxter).

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Chapter 125

Primary Defects of Cellular Immunity

Rebecca H. Buckley

In general, patients with defects in T-cell function have infections or other clinical problems that are more severe than in patients with antibody deficiency disorders (see Table 122-4). The defective gene products for some primary T-cell diseases are identified (Table 125-1). These individuals rarely survive beyond infancy or childhood. Transplantation of thymic tissue, or of major histocompatibility complex–compatible sibling or haploidentical (half-matched) parental hematopoietic stem cells, is the treatment of choice for patients with primary T-cell defects (see Chapter 135).

THYMIC HYPOPLASIA (DIGEORGE SYNDROME)

Thymic hypoplasia results from dysmorphogenesis of the 3rd and 4th pharyngeal pouches during early embryogenesis, leading to hypoplasia or aplasia of the thymus and parathyroid glands. Other structures forming at the same age are also frequently affected, resulting in anomalies of the great vessels (right-sided aortic arch), esophageal atresia, bifid uvula, congenital heart disease (conotruncal, atrial, and ventricular septal defects), a short philtrum of the upper lip, hypertelorism, an antimongoloid slant to the eyes, mandibular hypoplasia, and low-set, often notched ears (see Chapters 81 and 108). The diagnosis is often first suggested by hypocalcemic seizures during the neonatal period.

Genetics and Pathogenesis

DiGeorge syndrome occurs in both males and females. Microdeletions of specific DNA sequences from chromosome 22q11.2, the **DiGeorge chromosomal region,** are found in a majority of cases. Several candidate genes have been identified in this region. A T-box transcription family member, *TBX1,* is implicated as an etiology for most of the major signs of DiGeorge syndrome. There appears to be an excess of 22q11.2 deletions of maternal origin. Polymerase chain reaction–based genotyping using microsatellite DNA markers located within the commonly deleted region permits rapid detection of such microdeletions. Conotruncal heart defects and 22q deletions are observed in DiGeorge syndrome, velocardiofacial syndrome, and conotruncal anomaly face syndrome. The **CATCH 22 syndrome** (*c*ardiac, *a*bnormal facies, *t*hymic hypoplasia, *c*left palate, *h*ypocalcemia) includes the broad clinical spectrum of conditions with 22q11.2 deletions. Other deletions associated with DiGeorge and velocardiofacial syndromes have been identified on chromosome 10p13 (see Chapter 81).

Variable hypoplasia of the thymus and parathyroid glands defines **partial DiGeorge syndrome,** which is more frequent than total aplasia; aplasia is present in <1% of patients with DiGeorge syndrome and defines **complete DiGeorge syndrome.** Slightly less than half of patients with complete DiGeorge syndrome are hemizygous at chromosome 22q11. Approximately 15% are born to diabetic mothers. Another 15% of infants have no identified risk factors. Approximately one-third of infants with complete DiGeorge syndrome have **CHARGE association** (*c*oloboma, *h*eart defect, choanal *a*tresia, growth or developmental *r*etardation, *g*enital hypoplasia, and *e*ar anomalies including deafness). Mutations in the chromodomain helicase DNA binding protein 7 (CHD7) gene on chromosome 8q12.2 are found in approximately 60-65% of individuals with CHARGE syndrome. Concentrations of serum immunoglobulins in DiGeorge syndrome are usually normal, but immunoglobulin (Ig) A may be diminished and IgE elevated. Other laboratory findings vary depending on the degree of thymic dysfunction.

Table 125-1 Genetic Basis of Primary Cellular Immunodeficiency Diseases

CHROMOSOME AND REGION	GENE PRODUCT	DISORDER	FUNCTIONAL DEFICIENCIES
1p35-p34.3	Lck	↓↓ CD4 CD8	Lack of T-cell responses to mitogens or to anti-CD3
2p12	CD8α	↓↓ CD8 deficiency	Lack of cytotoxic T cells
2q12	ZAP-70	CD8 deficiency	Failure of CD4 T cells to respond to usual signals
4p13	RhoH	↓ Naïve CD4+ cells	Low number of recent thymic emigrants, restricted T-cell repertoire
5q31-34	ITK	↓ Naïve CD4+ cells Absence of NKT cells	Poor T-cell responses to mitogens, antigens, and anti-CD3
10p13	Unknown	Thymic hypoplasia (DiGeorge syndrome, velocardiofacial syndrome)	Low number of T cells and impaired T-cell function
11q23	CD3γ and ε	CD3 deficiency	Poor T-cell responses to mitogens; lack of cytotoxic T cells; IgG subclass deficiency
14q11.2	TRAC	TCR αβ T-cell deficiency	Poor T-cell responses to mitogens
16p11.2	Coronin-1A	↓↓ CD4 ↓↓ CD8	Poor T-cell response to phytohemagglutinin; impaired antibody responses
20q13.12	MST1/STK4	↓ Naïve T cells Low number of recent thymic emigrants, restricted T-cell repertoire	Poor T-cell responses to mitogens, antigens, and anti-CD3 Decreased switched memory B cells
21q22.3	AIRE	APECED, chronic mucocutaneous candidiasis, parathyroid and adrenal autoimmunity	Poor response to *Candida* antigen; autoimmune responses
22q11.22	?TBX1	Thymic hypoplasia (DiGeorge syndrome, velocardiofacial syndrome)	Low number of T cells and impaired T-cell function

AIRE, Autoimmune regulator; APECED, autoimmune polyendocrinopathy-candidiasis ectodermal dysplasia; Ig, immunoglobulin; ITK, IL-2–inducible tyrosine kinase deficiency; MST1, macrophage-stimulating factor 1; NKT, natural killer T; RhoH, Ras homology family member H; STK4, serine threonine kinase 4; TCR, T-cell receptor; TRAC, T-cell receptor α chain constant region; ZAP-70, zeta-associated protein 70.

Absolute lymphocyte counts are usually only moderately low for age. The CD3 T-cell counts are variably decreased in number, corresponding to the degree of thymic hypoplasia, resulting in an increased percentage of B cells. Lymphocyte responses to mitogen stimulation are absent, reduced, or normal, depending on the degree of thymic deficiency. Thymic tissue, when found, contains Hassall corpuscles, a normal density of thymocytes, and corticomedullary distinction. Lymphoid follicles are usually present, but lymph node paracortical areas and thymus-dependent regions of the spleen show variable degrees of depletion.

Clinical Manifestations

Children with partial thymic hypoplasia may have little trouble with infections and grow normally. Patients with complete DiGeorge syndrome resemble patients with severe combined immunodeficiency in their susceptibility to infections with low-grade or opportunistic pathogens, including fungi, viruses, and *Pneumocystis jiroveci*, and to graft-versus-host disease from nonirradiated blood transfusions. Patients with complete DiGeorge syndrome can develop an atypical phenotype in which oligoclonal T-cell populations appear in the blood associated with rash and lymphadenopathy. These atypical patients appear phenotypically to be similar to patients with **Omenn syndrome** or maternal T lymphocyte engraftment.

It is critical to confirm the diagnosis of complete DiGeorge syndrome in a timely manner because this disease is fatal without treatment. A T-cell count should be obtained on all infants born with primary hypoparathyroidism, CHARGE syndrome, truncus arteriosus, and interrupted aortic arch type B. If a patient has findings consistent with DiGeorge syndrome with or without a rash and lymphadenopathy, the patient should be referred to an immunologist for evaluation.

Treatment

The immune deficiency in the complete DiGeorge syndrome is correctable by cultured unrelated thymic tissue transplants. Some have been given nonirradiated unfractionated bone marrow or peripheral blood transplants from an human leukocyte antigen–identical sibling with subsequent improved immune function because of adoptively transferred donor immunity; however, they have no way of renewing T-cell production because they have no thymus.

DEFECTIVE EXPRESSION OF THE T-CELL RECEPTOR–CD3 COMPLEX

The first type of this disorder was found in 2 brothers in a Spanish family. The proband presented with severe infections and died at 31 mo of age with autoimmune hemolytic anemia and viral pneumonia. His lymphocytes had responded poorly to mitogens and to anti-CD3 in vitro, and could not be stimulated to develop cytotoxic T cells. His antibody responses to protein antigens had been normal, indicating normal T-helper cell function. His 12 yr old brother was healthy but had almost no CD3-bearing T cells and had IgG_2 deficiency similar to his sibling. The defect in this family was caused by mutations in the gene encoding the CD3γ chain (Fig. 125-1).

The second type of this disorder was diagnosed in a 4 yr old French boy who had recurrent *Haemophilus influenzae* pneumonia and otitis media in early life but was later healthy. He had a partial defect in expression of T-cell receptor–CD3 complex, and thus the percentage of CD3 cells was about half-normal, but the level of expression was markedly decreased. The defect was caused by 2 independent CD3ε gene mutations, leading to defective CD3ε chain synthesis. There was a splice site mutation on one allele that did not totally abrogate the normal intron 7 splicing, resulting in partial expression of CD3 on the T cells. Thus, this mutation did not result in failure of T-cell development, whereas mutations in the portions of the gene that encode the extracellular component of CD3ε result in a profound deficiency of circulating mature CD3 T cells.

Two additional unrelated patients from Pakistan were discovered to lack T-cell receptor (TCR)-αβ–positive T cells and were found to have mutations in the TCR α-chain constant (*TRAC*) gene. Clinically they

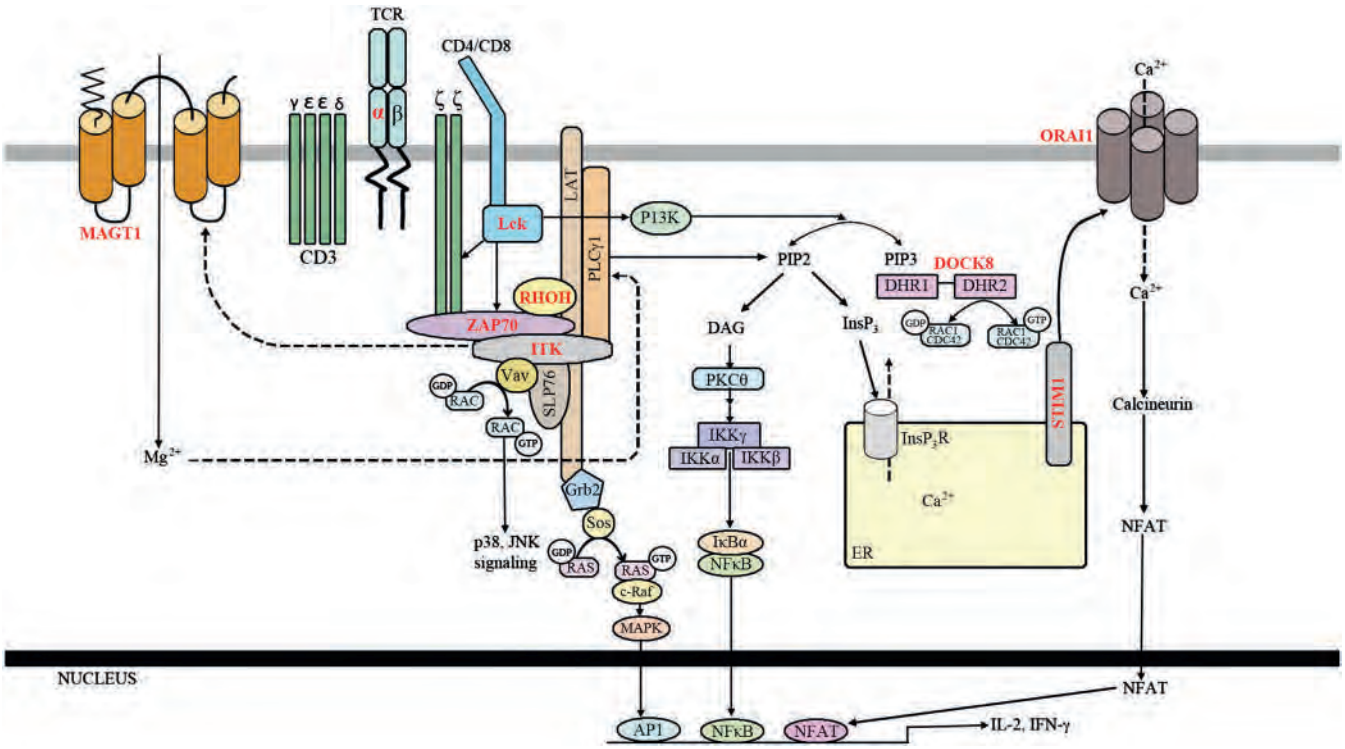


Figure 125-1 Schematic representation of signaling through the T-cell receptor–CD3 complex. Molecules the mutations of which have been associated with partial defect of T-cell development and impaired T-cell function are indicated in *red* and highlighted in *boldface*. *AP1*, Activator protein 1; *DHR*, DOCK-homology region; *Grb2*, growth factor receptor-bound protein 2; *IKK*, IκB kinase; *JNK*, c-Jun N-terminal kinase; *MAPK*, mitogen-activated protein kinase; *NFAT*, nuclear factor of activated T cells; *NFκB*, nuclear factor κB; *PI3K*, phosphoinositide-3 kinase; *PIP3*, phosphatidylinositol (3,4,5)-triphosphate. *(From Notarangelo L: Partial defects of T-cell development associated with poor T-cell function.* J Allergy Clin Immunol *131:1297–1305, 2013, Fig. 1, p. 1299.)*

had increased susceptibility to infections, autoimmunity and profound T cell dysfunction but normal antibody responses. All of their T cells contained TCR gamma delta receptors.

T-CELL ACTIVATION DEFECTS

T-cell activation defects are characterized by the presence of normal or elevated numbers of blood T cells that appear phenotypically normal but fail to proliferate or produce cytokines normally in response to stimulation with mitogens, antigens, or other signals delivered to the TCR, owing to defective signal transduction from the TCR to intracellular metabolic pathways (see Fig. 125-1). These patients have problems similar to those of other T-cell–deficient individuals, and some with severe T-cell activation defects may clinically resemble severe combined immunodeficiency patients. At least 8 new forms of T-cell activation defects have been discovered. The description of only a few of these conditions is included here (see Table 125-1) and DOCK8 deficiency is discussed in Chapter 126.

CD8 LYMPHOCYTOPENIA CAUSED BY MUTATIONS IN THE GENE ENCODING ZETA-ASSOCIATED PROTEIN 70

Patients with this T-cell activation defect present during infancy with severe, recurrent, and often fatal infections. The majority of cases are reported among Mennonites. These patients have normal or elevated numbers of blood B cells and low to elevated serum immunoglobulin concentrations. Their blood lymphocytes exhibit normal expression of the T-cell surface antigens CD3 and CD4, but CD8 cells are almost totally absent. These cells fail to respond normally to mitogens or to allogeneic cells in vitro or to generate cytotoxic T lymphocytes. Natural killer (NK) cell activity is normal. The thymus of 1 patient exhibited normal architecture with normal numbers of CD4:CD8 double-positive thymocytes, but an absence of CD8 single-positive thymocytes. This condition is caused by mutations in the gene encoding **zeta-associated protein 70 (ZAP-70),** a non-src family protein tyrosine kinase important in T-cell signaling that is localized to chromosome 2q12 (see Fig. 125-1). The normal number of CD4:CD8 double-positive T cells results because the thymocytes can use the other member of the same tyrosine kinase family, Syk, to facilitate positive selection. Syk is present at 4-fold higher levels in thymocytes than in peripheral T cells, possibly accounting for the lack of normal responses by the CD4 blood T cells.

Another condition that can result in CD8 deficiency is a mutation in the gene that encodes CD8α. There is a deficiency of cytotoxic T cells in that condition, but the functional immune defect is mild compared to that of ZAP-70 deficiency.

T-Cell Defects Characterized By Epstein-Barr Virus Lymphoproliferation/Lymphoma

In addition to the X-linked lymphoproliferative and X-linked inhibitor of apoptosis protein syndromes and CD27 deficiency characterized primarily as antibody deficiencies (see Chapter 124), there are at least 4 additional primarily T-cell defects that predispose to Epstein-Barr virus (EBV) infections or lymphomas. These include Ras homology family member H (RhoH) deficiency, macrophage-stimulating 1 (MST1)/serine threonine kinase 4 (STK4) deficiency, interleukin (IL)-2–inducible tyrosine kinase (ITK) deficiency and Coronin-1A deficiency (see Table 125-1).

RhoH Deficiency

Two siblings who had a homozygous nonsense mutation in the *RhoH* gene had persistent cutaneous human papillomavirus infections and the older sibling had Burkitt lymphoma. RhoH plays an important role in T-cell activation. Following stimulation of the TCR, RhoH becomes tyrosine phosphorylated and mediates recruitment of ZAP-70 and LCK to the TCR/linker of activation in T cells (LAT) signalosome (see Fig. 125-1). Immunologic findings in the 2 patients included a reduced number of naïve CD4+ T cells and recent thymic emigrants, restricted T-cell diversity and impaired responsiveness of the cells to anti-CD3.

MST1/STK4 Deficiency

Autosomal recessive MST1/STK4 deficiency is associated with recurrent bacterial and viral infections, candidiasis and autoimmunity. The viral infections include warts, molluscum contagiosum, and EBV lymphoproliferative disease. Congenital heart disease and moderate neutropenia have also been reported. Immunologically, there is a severe reduction in naïve T cells, a near absence of recent thymic emigrants, oligoclonal T cells and increased apoptosis of T cells. Thus, MST1/STK4 plays a major role in T-cell development, survival, and migration.

ITK Deficiency

Several patients with EBV lymphoproliferative disease have been described who had mutations in the *ITK* gene. In addition, some also had *P. jiroveci* pneumonia, candidiasis, and BK polyoma infection. The immunologic abnormalities described included marked lymphopenia, a predominance of activated T cells, an absence of NK T cells, and poor T-cell responses to mitogens, antigens and anti-CD3. ITK is a Tec nonreceptor tyrosine kinase expressed in T lymphocytes. The ITK pleckstrin homology domain binds to phosphatidylinositol monophosphates and this binding permits ITK recruitment to the T cell membrane where, upon TCR crosslinking, ITK increases phospholipase Cγ (PLCγ) 1 activation and calcium influx.

Coronin-1a Deficiency

Three siblings from a consanguineous family presented with EBV-associated B-cell lymphoproliferation at an early age (12, 7, and 14 mo) and profound naïve T-cell lymphopenia. In addition, there was impaired development of a diverse T-cell repertoire and near absent invariant NK T cells. They were discovered to have a missense mutation in the gene encoding Coronin-1A that abrogated protein expression. Coronin-1A is a member of a family of proteins that bind F-actin and the Arp2,3 complex; it has an important role in cytoskeletal organization.

LCK DEFICIENCY

A female infant presented at age 15 mo with protracted diarrhea, failure to thrive and recurrent respiratory tract infections. She developed recurring fevers, multiple nodular skin lesions and inflammation of the interphalangeal joints as well as retinal vasculitis and polyserositis. At age 29 mo, she developed a normocytic aregenerative anemia and peripheral thrombocytopenia with antiplatelet autoantibodies. She died from venoocclusive disease shortly after a chemoablated bone marrow transplant. Immunologic investigation revealed CD4 T-cell lymphopenia and low levels of CD4 and CD8 expression on the T-cell surfaces. The T cells present had an oligoclonal T-cell repertoire and exhibited a profound TCR signaling defect. She was found to have a homozygous missense mutation of the *LCK* gene.

Very closely related to this defect is a deficiency of uncoordinated 119 (UNC119), which is a chaperone involved in LCK-mediated signaling. Through LCK, UNC119 regulates T-cell proliferation, differentiation into T effector cells and immunologic synapse formation. A heterozygous dominant-negative missense mutation of the *UNC119* gene was reported in a 32 yr old female with idiopathic CD4 T lymphopenia who had a history of recurrent respiratory infections, shingles, oral herpes infections and persistent fungal infections of the skin and nails. Both LCK deficiency and UNC119 deficiency should be considered when there is idiopathic CD4 T lymphopenia.

CHRONIC MUCOCUTANEOUS CANDIDIASIS

Chronic mucocutaneous candidiasis is a syndrome characterized by impaired immune responsiveness to *Candida.* Some of the known immunodeficiencies that have this complication as a prominent feature include autoimmune polyendocrinopathy syndrome type I (APS1, or autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy [APECED], described below), homozygous caspase recruitment domain-containing protein 9 *(CARD9)* mutations, both types of hyperimmunoglobulin E syndromes (see Chapter 126), an autosomal recessive deficiency in the IL-17 receptor A (IL-17RA) chain, and an

autosomal dominant deficiency of *STAT1* and of the cytokine IL-17F. IL-17RA deficiency is complete, abolishing cellular responses to IL-17A and IL-17F homo- and heterodimers. By contrast, IL-17F deficiency is partial, with mutant IL-17F–containing homo- and heterodimers displaying impaired, but not abolished, activity.

Although the underlying immune disorders are varied, the clinical presentation of chronic mucocutaneous candidiasis is usually similar. Symptoms can begin in the 1st mo of life or as late as the 2nd decade of life. The disorder is characterized by chronic and severe *Candida* skin and mucous membrane infections. Patients rarely develop systemic *Candida* disease except as noted below. Topical antifungal therapy can provide limited improvement early in the course of the disease, but systemic courses of azoles are usually necessary. The infection usually responds temporarily to treatment but is not eradicated and recurs. Patients with *CARD9* gene mutations have a more severe fungal susceptibility than typical chronic mucocutaneous candidiasis patients. Two described patients with *CARD9* gene mutations had fungal sepsis in addition to chronic mucocutaneous candidiasis; deep tissue dermatophyte infections were also present.

AUTOIMMUNE POLYENDOCRINOPATHY-CANDIDIASIS ECTODERMAL DYSPLASIA

Patients with this syndrome present with chronic mucocutaneous candidiasis and autoimmune polyendocrinopathy, usually producing hypoparathyroidism and Addison disease. Additional features include hypogonadism, chronic active hepatitis, alopecia, vitiligo, pernicious anemia, enamel hypoplasia, type 1diabetes, and Sjögren syndrome. APECED, or APS1, is caused by a mutation in the autoimmune regulator *(AIRE)* gene (see Table 125-1). The gene product, AIRE, is expressed at high levels in purified human thymic medullary stromal cells and is thought to regulate the cell surface expression of tissue-specific proteins such as insulin and thyroglobulin. Expression of these self-proteins allows for the negative selection of autoreactive T cells during their development. Failure of negative selection results in organ-specific autoimmune destruction. The overall significance of AIRE in the establishment and maintenance of T-cell self-tolerance is not well understood.

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Chapter 126

Primary Combined Antibody and Cellular Immunodeficiencies

Rebecca H. Buckley

Patients with combined antibody and cellular defects have severe, frequently opportunistic infections that lead to death in infancy or childhood unless they are provided hematopoietic stem cell transplantation early in life. These are thought to be rare defects, although the true incidences are unknown because until recently there had been no newborn screening for any of these defects. It is possible that many affected children died of infection during infancy without being diagnosed. The causative mutated genes for many combined immunodeficiencies have been identified (Table 126-1). Because life-threatening infections may occur early in infancy, the U.S. Secretary of Health and Human Services recommends that routine screening for severe combined immunodeficiency (SCID) be included in state newborn screening testing. Live, vaccine-derived rotaviral infections have already occurred during the 1st few mo of life in SCID infants, so very early knowledge of this diagnosis could prevent such vaccine-acquired infections. In addition, early identification and subsequent bone marrow transplantation before infections develop result in a very high (92%) survival rate.

126.1 Severe Combined Immunodeficiency

Rebecca H. Buckley

The syndromes of SCID are caused by diverse genetic mutations that lead to absence of all adaptive immune function and, in some, a lack of B cells and natural killer (NK) cells. Patients with this group of disorders have the most severe immunodeficiency.

PATHOGENESIS

SCID results from mutations in any 1 of at least 13 known genes that encode components of the immune system crucial for lymphoid cell development (Table 126-2). All patients with SCID have very small thymuses (<1 g) that usually fail to descend from the neck, contain no thymocytes, and lack corticomedullary distinction or Hassall corpuscles. The thymic epithelium appears histologically normal. Both the follicular and paracortical areas of the spleen are depleted of lymphocytes. Lymph nodes, tonsils, adenoids, and Peyer patches are absent or extremely underdeveloped.

CLINICAL MANIFESTATIONS

Affected infants present within the 1st few mo of life with recurrent or persistent diarrhea, pneumonia, otitis media, sepsis, and cutaneous infections. Growth may appear normal initially, but extreme wasting usually ensues after diarrhea and infections begin. Persistent infections with opportunistic organisms including *Candida albicans, Pneumocystis jiroveci*, parainfluenza 3 virus, adenovirus, respiratory syncytial virus, rotavirus vaccine virus, cytomegalovirus, Epstein-Barr virus (EBV), varicella- zoster virus, measles virus, MMR-V (measles, mumps, rubella, varicella) vaccine virus, or bacillus Calmette-Guérin (BCG) lead to death. Affected infants also lack the ability to reject foreign tissue and are therefore at risk for severe or fatal graft-versus-host disease (GVHD) from T lymphocytes in nonirradiated blood products or in allogeneic stem cell transplants or less severe GVHD from maternal immunocompetent T cells that crossed the placenta while the infant was in utero.

Because all molecular types of SCID lack T cells, the profound T-cell **lymphopenia can be detected on dried blood spots routinely collected from heel sticks shortly after** birth for the purpose of newborn screening by assaying for the presence of T-cell receptor recombination excision circles by real time polymerase chain reaction. T-cell receptor recombination excision circles are absent or extremely low in SCID infants. These infants also have an absence of lymphocyte proliferative responses to mitogens, antigens, and allogeneic cells in vitro. Patients with adenosine deaminase (ADA) deficiency have the lowest absolute lymphocyte counts, usually <500/mm^3, but infants with all molecular types of SCID are lymphopenic because they lack T cells (normally accounting for 70% of circulating lymphocytes). Serum immunoglobulin concentrations are low or absent, and no antibodies are formed after immunizations. Analyses of lymphocyte populations and subpopulations demonstrate distinctive phenotypes for the various genetic forms of SCID (see Table 126-2). T cells are extremely low or absent in all types; when detected, in most cases they are transplacentally derived maternal T cells.

TREATMENT

SCID is a true pediatric emergency. Unless immunologic reconstitution is achieved through stem cell transplantation or gene therapy, death usually occurs during the 1st yr of life and almost invariably before 2 yr of age. If diagnosed at birth or within the 1st 3.5 mo of life, >92% of cases can be treated successfully with human leukocyte antigen (HLA)-identical or T-cell–depleted haploidentical (half-matched) parental hematopoietic stem cell transplantation without the need for pretransplant chemoablation or posttransplant GVHD prophylaxis. ADA-deficient SCID and X-linked SCID have been treated

Table 126-1 Genetic Basis of Combined Immunodeficiency Disorders

CHROMOSOME AND REGION	GENE PRODUCT	DISORDER	FUNCTIONAL DEFICIENCIES
1q	RFX5	MHC class II antigen deficiency	Low immunoglobulins, lack of T-cell responses to antigens, CD4 deficiency
1q31-q32	CD45	T–B+NK+ SCID	Absence of T- and B-cell functions
3p22.2	Myd88	Toll-receptor innate immune defect	T and B cell functions normal; Failure of activation of nuclear factor κB (NF-κB) and mitogen-activated protein kinase (MAPK) by Toll receptor stimuli
5p13	IL-7Rα	T–B+NK+ SCID	Absence of T- and B-cell functions
6p21.3	TAP1, TAP2	MHC class I antigen deficiency	Marked deficiency of CD8 T cells; combined B- and T-cell defects
6q22-q23	IFN-γR1 IFN-γR2 IL-12Rβ$_1$	Disseminated mycobacterial infections	Failure of macrophages and other cells to produce TNF-α in response to IFN-γ
9p21-p13	Endoribonuclease RNase MRP*	Cartilage-hair hypoplasia	Combined B- and T-cell defects of varying severity
9p24	DOCK8	Autosomal recessive Hyper-IgE syndrome	↓↓ CD4, CD8 and Th17 T cells ↓ Naïve T cells; poor T-cell responses to mitogens; elevated serum IgE levels Decreased switched memory B cells Decreased antibody responses
10p13	Artemis	T–B–NK+ SCID	Absence of T- and B-cell functions
11p13	RAG1 or RAG2	T–B–NK+ SCID	Absence of T- and B-cell functions
11q22.3	ATM, a DNA-dependent kinase	Ataxia-telangiectasia	Selective IgA deficiency; T-cell deficiency
11q23	CD3δ or CD3ζ	T–B+NK+ SCID	Absence of T- and B-cell functions
12q12	IRAK4	Toll-receptor innate immune defect	T- and B-cell functions normal; failure of activation of NF-κB and MAPK by Toll receptor stimuli
13q	RFXAP	MHC class II antigen deficiency	Low immunoglobulins, lack of T-cell responses to antigens, CD4 deficiency
14q13.1	Purine nucleosidase	PNP deficiency	Severe T-cell deficiency; may have normal immunoglobulins
16p13	CIITA	MHC class II antigen deficiency	Low immunoglobulins, lack of T-cell responses to antigens, CD4 deficiency
17q21.3	STAT3	Autosomal dominant hyper-IgE syndrome	Elevated IgE and IgD, low CD45RO (memory) T cells, no Th17 T cells
19p13.1	Jak3	T–B+NK– SCID	Absence of T-, B-, and NK-cell functions
20q13.11	ADA	T–B–NK– SCID	Absence of T- and B-cell functions
Xp11.4-11.21	WASP	Wiskott-Aldrich syndrome	Thrombocytopenia; poor antibody production to polysaccharides; T-cell deficiency
Xp11.23	FOXP3	Immune-dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome	Early onset of diarrhea and autoimmune diseases Elevated IgE
Xq13.1	Common γ chain (γc) for several cytokine receptors (including IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21)	T–B+NK– SCID	Absence of T-, B-, and NK-cell functions

ADA, Adenosine deaminase; CIITA, class II transactivator; DOCK8, dedicator of cytokinesis 8; FOXP3, forkhead-winged helix transcription factor; IFN-γR1, interferon receptor chain 1; Ig, immunoglobulin; IL, interleukin; IL-7Rα, interleukin 7 receptor α chain; IL-12Rβ$_1$, interleukin 12 receptor β$_1$ chain; IFN, interferon; IRAK4, interleukin-1 receptor-associated kinase 4; Jak3, Janus kinase 3; MHC, major histocompatibility complex; Myd88, myeloid differentiation factor 88; NK, natural killer; PNP, purine nucleoside phosphorylase; RAG1 and RAG2, recombinase activating genes 1 and 2; SCID, severe combined immunodeficiency; STAT3, signal transducer and activator of transcription 3; TAP, transporter of antigenic peptide; Th17, T-helper cell type 17; TNF, tumor necrosis factor; WASP, Wiskott-Aldrich syndrome protein.

successfully with somatic gene therapy; although serious adverse events occurred in the case of X-linked SCID. ADA-deficient SCID can also be treated with repeated injections of polyethylene glycol modified bovine ADA (PEG-ADA), although the immune reconstitution achieved is not nearly as good as with stem cell or gene therapy. PEG-ADA should not be started if nonablative stem cell transplantation is contemplated because it will enable the infant to reject the graft.

X-LINKED SEVERE COMBINED IMMUNODEFICIENCY CAUSED BY MUTATIONS IN THE GENE ENCODING THE COMMON CYTOKINE RECEPTOR γ CHAIN

X-linked SCID (X-SCID) is the most common form of SCID in the United States, accounting for 47% of cases (Fig. 126-1). Clinically, immunologically, and histopathologically, affected individuals appear

Table 126-2 Genetic Basis of SCID and SCID Variants

DISEASE	INHERITANCE	PRESUMED PATHOGENESIS	ADDITIONAL FEATURES	TREATMENT
Reticular dysgenesis	AR	Impaired mitochondrial energy metabolism and leukocyte differentiation	Severe neutropenia, deafness. Mutations in adenylate kinase 2	GCSF HSCT
Adenosine deaminase deficiency	AR	Accumulation of toxic purine nucleosides	Neurologic, hepatic, renal, lung, and skeletal and bone marrow abnormalities	HSCT, PEG-ADA, gene therapy
IL-2Rγ deficiency	X-linked	Abnormal signaling through by IL-2 receptor and other receptors containing γc (IL-4, -7, -9, -15, -21)	None	HSCT
Jak3 deficiency	AR	Abnormal signaling downstream of γc	None	HSCT
RAG1 and 2 deficiency	AR	Defective V(D)J recombination	None	HSCT
Artemis deficiency	AR	Defective V(D)J recombination, radiation sensitivity	DCLERE1C gene defects	HSCT
DNA-PK deficiency	AR	Defective V(D)J recombination	None	HSCT
DNA ligase IV deficiency	AR	Defective V(D)J recombination, radiation sensitivity	Growth delay, microcephaly, bone marrow abnormalities, lymphoid malignancies	HSCT
Cernunnos-XLF	AR	Defective V(D)J recombination, radiation sensitivity	Growth delay, microcephaly, bird-like facies, bone defects	HSCT
CD3δ deficiency	AR	Arrest of thymocytes differentiation at the CD4–CD8– stage	Thymus size may be normal	HSCT
CD3ε deficiency	AR	Arrest of thymocytes differentiation at the CD4–CD8– stage	γ/δ T cells absent	HSCT
CD3ζ deficiency	AR	Abnormal signaling	None	HSCT
IL-7Rα deficiency	AR	Abnormal IL-7R signaling	Thymus absent	HSCT
CD45 deficiency	AR		None	HSCT
Coronin-1A deficiency	AR	Abnormal T-cell egress from thymus and lymph nodes	Normal thymus size. Attention deficit disorder.	HSCT

AR, autosomal recessive; GCSF, granulocyte colony stimulating factor; HSCT, hematopoietic stem cell transplantation; IL, interleukin; Jak3, Janus kinase 3; PEG-ADA, polyethylene glycol-modified adenosine deaminase; RAG1 and RAG2, recombinase activating genes 1 and 2; V(D)J, variable, diversity, joining.

(Modified from Roifman, CM. Grunebaum E. Primary T-cell immunodeficiencies. In Rich RR, Fleisher TA, Shearer WT, et al, editors: Clinical Immunology, *ed 4. Philadelphia, 2013, WB Saunders, Tables 35-1, 35-2, 35-3, 35-4, pp. 440–441).*

similar to those with other forms of SCID except for having uniformly **low percentages of T and NK cells** and an **elevated percentage of B cells** (T–, B+, NK–), a characteristic feature shared only with Janus kinase 3 (Jak3)–deficient SCID. The abnormal gene in X-SCID was mapped to Xq13, cloned, and found to encode the common γ chain (γc) for several cytokine receptors, including interleukin (IL)-2, IL-4, IL-7, IL-9, IL-15, and IL-21. The shared γc functions both to increase the affinity of the receptor for the respective cytokine and to enable the receptors to mediate intracellular signaling. Incapacitation of the receptors for all of these developmentally crucial cytokines by genetic mutations in γc provides an explanation for the severity of the immunodeficiency in X-SCID. In the 1st 136 patients studied, 95 distinct mutations spanning all 8 IL-2RG exons were identified, most of them consisting of small changes at the level of 1 to a few nucleotides. These mutations resulted in abnormal γc chains in two-thirds of the cases and absent γc protein in the remainder. Carriers can be detected by demonstrating the deleterious mutation in their lymphocytes. Unless donor B or NK cells develop, patients with X-SCID lack B- and NK-cell function after bone marrow transplantation because the abnormal γc persists in those host cells, despite excellent reconstitution of T-cell function by donor-derived T cells.

AUTOSOMAL RECESSIVE SEVERE COMBINED IMMUNODEFICIENCY

This pattern of inheritance of SCID is less common in the United States than in other countries. Mutated genes on autosomal chromosomes have been identified in 12 forms of SCID: ADA deficiency; Jak3 deficiency; IL-7 receptor α chain (IL-7Rα) deficiency; recombinase-activating gene 1 or 2 (RAG1 or RAG2) deficiency; Artemis deficiency; ligase 4 deficiency; DNA–protein kinase catalytic subunit (DNA-PKcs) deficiency; CD3δ, CD3ε, CD3ζ deficiency; and CD45 deficiency (see Fig. 126-1).

Adenosine Deaminase Deficiency

An absence of the enzyme ADA is observed in approximately 15% of patients, the second most common form of SCID, resulting from various point and deletional mutations in the ADA gene on chromosome 20q13-ter. Marked accumulations of adenosine, 2′-deoxyadenosine, and 2′-*O*-methyladenosine lead directly or indirectly to T-cell apoptosis, which causes the immunodeficiency. ADA-deficient patients usually have a much more profound **lymphopenia** than do infants with other types of SCID, with mean absolute lymphocyte counts of <500/mm^3; the absolute numbers of T, B, and NK cells are very low. NK function is normal. After T-cell function is conferred by hematopoietic stem cell transplantation without pretransplant chemotherapy, there is generally excellent B-cell function despite the fact that the B cells are of host origin. This is because ADA deficiency affects primarily T-cell function. Milder forms of ADA deficiency have led to delayed diagnosis of immunodeficiency, even to adulthood. Other **distinguishing features** of ADA-deficient SCID include the presence of rib cage abnormalities similar to a rachitic rosary and numerous skeletal abnormalities of chondroosseous dysplasia, which occur predominantly at the costochondral junctions, at the apophyses of the iliac bones, and in the vertebral bodies where a "bone-in-bone" effect is observed.

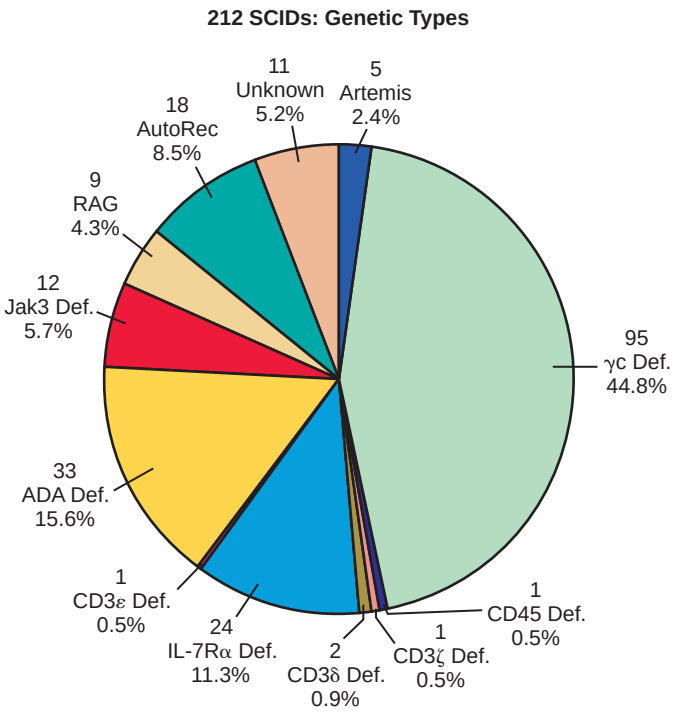


Figure 126-1 Relative frequencies of the different genetic types among 212 patients with severe combined immunodeficiency seen consecutively over 4 decades. *ADA,* adenosine deaminase; *IL-7Rα,* interleukin 7 receptor α chain; *Jak3,* Janus kinase 3; *RAG,* recombinase activating gene.

As with other types of SCID, ADA deficiency can be cured by HLA-identical or haploidentical T-cell–depleted stem cell transplantation without the need for pre- or posttransplant chemotherapy; this remains the treatment of choice. Enzyme replacement therapy should not be initiated if stem cell transplantation is possible because it confers graft-rejection capability. Enzyme replacement provides protective immunity but over time there is a decline of lymphocyte counts and proliferative responses. A number of infants with ADA deficiency have become successfully immune reconstituted by gene therapy in Italy, Great Britain and the United States; in all cases, PEG-ADA was withheld. Spontaneous reversion to normal of a mutation in the ADA gene has also been reported.

Jak3 Deficiency

Patients with this autosomal recessive defect resemble all other types of SCID patients clinically. They have a lymphocyte phenotype similar only to that of patients with X-SCID, with an elevated percentage of B cells and very low or no T and NK cells. Because Jak3 is the only signaling molecule known to be associated with γc, it was a candidate gene for mutations leading to autosomal recessive SCID. Jak3 deficiency accounts for 6% of SCID cases. Even after successful T-cell reconstitution by transplantation of haploidentical stem cells, patients with Jak3-deficient SCID fail to develop NK cells or normal B-cell function owing to the defective function of those host cells that bear abnormal cytokine receptors that share γc.

IL-7Rα Deficiency

Patients with IL-7Rα–deficient SCID have a distinctive lymphocyte phenotype in that, although lacking T cells, they have normal or elevated numbers of both B and NK cells (T–, B+, NK+). This is the **third most common** form of SCID, accounting for 12% of cases in the United States (see Fig. 126-1). In contrast to patients with γc- and Jak3-deficient SCID, the immunologic defect in these patients is completely correctable by T-cell reconstitution alone, because the host B and NK cells appear to be normal.

RAG1 or RAG2 Deficiencies

Infants with these causes of SCID have a different lymphocyte phenotype from those of patients with SCID caused by γc, Jak3, IL-7Rα, or ADA deficiencies in that they lack both B and T lymphocytes and have primarily NK cells in their circulation (T–, B–, NK+). This suggested a problem with their antigen receptor genes, which led to the discovery of mutations in *RAG1* or *RAG2*. Such mutations result in a functional inability to form antigen receptors through genetic recombination. **Omenn syndrome** is an autosomal recessive condition characterized by profound susceptibility to infection and by clonal T-cell infiltration of skin, intestines, liver, and spleen leading to an exfoliative erythroderma, lymphadenopathy, hepatosplenomegaly, and intractable diarrhea. Mutations in the *RAG1* and *RAG2*, as well as rarely in other SCID-causing mutated genes, have been found in patients with this condition. These infants have persistent leukocytosis with marked eosinophilia and lymphocytosis; elevated serum immunoglobulin (Ig) E; low IgG, IgA, and IgM; and low or absent B cells. There is dominance of clonal T-helper (Th)2-like cells, with severely impaired T-cell function as the result of the restricted heterogeneity of the host T-cell repertoire.

Artemis Deficiency

Another cause of SCID is a deficiency of a novel V(D)J (variable, diversity, joining) recombination/DNA repair factor, named Artemis, that belongs to the metallo-β-lactamase superfamily, which is encoded on chromosome 10p by a gene named *DCLRE1C*. Deficiency of Artemis results in an inability to repair DNA after double-stranded cuts by the *RAG1* or *RAG2* gene products in rearranging antigen receptor genes from their germline configuration. Similar to RAG1- and RAG2-deficient SCID, this defect results in failure to develop T and B cells and is, therefore, another form of T–, B–, NK+ SCID, which is called **Athabascan SCID**. There is increased radiation sensitivity of both skin fibroblasts and bone marrow cells of those affected with this type of SCID as well as with DNA-PKcs and ligase 4 deficiencies.

CD45 Deficiency

Another molecular defect causing SCID is a mutation in the gene encoding the common leukocyte surface protein CD45. This hematopoietic cell–specific transmembrane protein tyrosine phosphatase functions to regulate src kinases required for T- and B-cell antigen receptor signal transduction. Three examples of this have been reported. One was found to have a large deletion on 1 CD45 allele and a point mutation causing an alteration of the intervening sequence 13 donor splice site on the other allele. The author has evaluated and treated a third case that was caused by uniparental disomy of chromosome 1 with an inactivating mutation in the gene encoding CD45.

CD3δ, CD3ε, and CD3ζ Deficiencies

Other causes of autosomal recessive SCID are deficiencies of components of the T-cell receptor (CD3δ, CD3ε, and CD3ζ chains). Mutations in the portions of these genes that encode the extracellular components of the proteins result in a profound deficiency of circulating mature CD3 T cells. Thus, CD3δ, CD3ε, and CD3ζ appear to be essential for intrathymic development of T cells. Because only T-cell development is affected in these defects, both B and NK cells are normal. Thus, the lymphocyte phenotype resembles that of SCID infants with IL-7Rα chain deficiency (T–B+NK+).

RETICULAR DYSGENESIS

Reticular dysgenesis was first described in identical twin boys who exhibited a total lack of both lymphocytes and granulocytes in their peripheral blood and bone marrow. The thymus glands weigh <1 g, have no Hassall corpuscles, and have few or no thymocytes. Reticular dysgenesis is considered a variant of SCID. The molecular basis of this autosomal recessive disorder is caused by mutations in the gene encoding adenylate kinase 2. The condition is fatal without definitive therapy and the treatment of choice is a fully myeloablative matched sibling bone marrow transplant. However, such transplants have been successful in only 7 of 17 evaluable patients so transplanted.

126.2 Combined Immunodeficiency

Rebecca H. Buckley

Combined immunodeficiency (CID) is distinguished from SCID by the presence of low but not absent T-cell function. Similar to SCID, CID is a syndrome of diverse genetic causes (see Table 126-1). Patients with CID have recurrent or chronic pulmonary infections, failure to thrive, oral or cutaneous candidiasis, chronic diarrhea, recurrent skin infections, Gram-negative bacterial sepsis, urinary tract infections, and severe varicella in infancy. Although they usually survive longer than infants with SCID, they fail to thrive and die early in life. Neutropenia and eosinophilia are common. Serum immunoglobulins may be normal or elevated for all classes, but selective IgA deficiency, marked elevation of IgE, and elevated IgD levels occur in some cases. Although antibody-forming capacity is impaired in most patients, it is not absent.

Studies of cellular immune function show lymphopenia, profound deficiencies of T cells, and extremely low but not absent lymphocyte proliferative responses to mitogens, antigens, and allogeneic cells in vitro. Peripheral lymphoid tissues demonstrate paracortical lymphocyte depletion. The thymus is very small, with a paucity of thymocytes and usually no Hassall corpuscles. An autosomal recessive pattern of inheritance is common.

PURINE NUCLEOSIDE PHOSPHORYLASE DEFICIENCY

More than 40 patients with CID have been found to have purine nucleoside phosphorylase deficiency. Point mutations identified in the purine nucleoside phosphorylase gene on chromosome 14q13.1 account for these deficiencies. In contrast to ADA deficiency, no characteristic physical or skeletal abnormalities have been noted, but serum and urinary uric acid are usually markedly deficient. Deaths result from generalized vaccinia, varicella, lymphosarcoma, or GVHD mediated by allogeneic T cells in nonirradiated blood or bone marrow. Two-thirds of patients have neurologic abnormalities, one-third of patients have autoimmune diseases, and some have had allergic diseases. Lymphopenia is striking, primarily because of a marked deficiency of T cells; T-cell function is decreased to various degrees. B cell function may be near normal. The proportion of circulating NK cells is increased. Prenatal diagnosis or diagnosis at birth is possible. Bone marrow transplantation is the only successful form of therapy.

CARTILAGE HAIR HYPOPLASIA

Cartilage hair hypoplasia (CHH) is an unusual form of **short-limbed dwarfism** with frequent and severe infections. It occurs predominantly among the Amish, but non-Amish patients have been described.

Genetics and Pathogenesis

CHH is an autosomal recessive condition. Numerous mutations that cosegregate with the CHH phenotype have been identified in the untranslated *RNase MRP* (*RMRP*) gene, which has been mapped to chromosome 9p21-p13 in Amish and Finnish families (see Table 126-1). The RMRP endoribonuclease consists of an RNA molecule bound to several proteins and has at least 2 functions: cleavage of RNA in mitochondrial DNA synthesis and nucleolar cleaving of pre-RNA. Mutations in RMRP cause CHH by disrupting a function of RMRP RNA that affects multiple organ systems. In vitro studies show decreased numbers of T cells and defective T-cell proliferation because of an intrinsic defect related to the G1 phase, resulting in a longer cell cycle for individual cells. NK cells are increased in number and function.

Clinical Manifestations

Clinical features include short, pudgy hands; redundant skin; hyperextensible joints of hands and feet but an inability to extend the elbows completely; and fine, sparse, light hair and eyebrows. Severe and often fatal varicella infections, progressive vaccinia, and vaccine-associated poliomyelitis have been observed. Associated conditions include deficient erythrogenesis, Hirschsprung disease, and an increased risk of malignancies. The bones radiographically show scalloping and sclerotic or cystic changes in the metaphyses and flaring of the costochondral junctions of the ribs. Three patterns of immune dysfunction have emerged: defective antibody-mediated immunity, CID (most common), and SCID. The severity of the immunodeficiency varies; in 1 series, 11 of 77 patients died before age 20 yr, but 2 were still alive at age 76 yr. Stem cell transplantation has resulted in immunologic reconstitution in some CHH patients who had the SCID phenotype.

DEFECTIVE EXPRESSION OF MAJOR HISTOCOMPATIBILITY COMPLEX ANTIGENS

The 2 main forms of immunodeficiency and abnormalities of expression of the major histocompatibility complex (MHC) are MHC class I (HLA-A, -B, and -C) antigen deficiency and MHC class II (HLA-DR, -DQ, and -DP) antigen deficiency. The associated defects of both B- and T-cell immunity and of HLA expression emphasize the important biologic role for HLA determinants in effective immune cell cooperation.

Major Histocompatibility Complex Class I Antigen Deficiency

Isolated deficiency of MHC class I (HLA-A, -B, and -C) antigens, the **bare lymphocyte syndrome**, is rare. The resulting immunodeficiency is much milder than in SCID, contributing to a later age of presentation. Sera from affected children contain normal quantities of MHC class I antigens and β_2-microglobulin, but MHC class I antigens are not detected on any cells in the body. There is a deficiency of CD8 but not CD4 T cells. Mutations have been found in 2 genes within the MHC locus on chromosome 6 that encode the peptide transporter proteins TAP1 and TAP2. TAP functions to transport antigenic peptides from the cytoplasm across the Golgi apparatus membrane to join the α chain of MHC class I antigens and β_2-microglobulin. All these are then assembled into a MHC class I complex that can then move to the cell surface. If the assembly of the complex cannot be completed because there is no antigenic peptide, the MHC class I complex is destroyed in the cytoplasm.

Major Histocompatibility Complex Class II Antigen Deficiency

Many affected with MHC class II (HLA-DR, -DQ, and -DP) deficiency are of North African descent. Patients present in early infancy with persistent diarrhea that is often associated with cryptosporidiosis and enteroviral infections (e.g., poliovirus, coxsackievirus). They also have an increased frequency of infections with herpesviruses and other viruses, oral candidiasis, bacterial pneumonia, *P. jiroveci* pneumonia, and septicemia. The immunodeficiency is not as severe as in SCID, as evidenced by their failure to develop disseminated infection after BCG vaccination or GVHD from nonirradiated blood transfusions.

Four different molecular defects resulting in impaired expression of MHC class II antigens have been identified (see Table 126-1 and Fig. 124-1). One form is a mutation in the gene on chromosome 1q that encodes a protein called RFX5, a subunit of RFX, which is a multiprotein complex that binds the X box motif of MHC-II promoters. A second form is caused by mutations in a gene on chromosome 13q that encodes a second 36-kD subunit of the RFX complex, called RFX-associated protein (RFXAP). The most common cause of MHC class II defects is a mutation in RFXANK, the gene encoding a 3rd subunit of RFX. In a 4th type, there is a mutation in the gene on chromosome 16p13 that encodes a novel MHC class II transactivator, a non–DNA-binding coactivator that controls the cell-type specificity and inducibility of MHC-II expression. All 4 of these defects cause impairment in the coordinate expression of MHC class II molecules on the surface of B cells and macrophages.

MHC class II–deficient patients have a very low number of CD4 T cells but normal or elevated numbers of CD8 T cells. Lymphopenia is only moderate. The MHC class II antigens HLA-DP, -DQ, and -DR are undetectable on blood B cells and monocytes, even though B cells are present in normal number. Patients are hypogammaglobulinemic owing to impaired antigen-specific responses caused by the absence of these antigen- presenting molecules. In addition, MHC antigen-deficient B cells fail to stimulate allogeneic cells in mixed leukocyte culture. Lymphocyte proliferation studies show normal responses to

mitogens but no response to antigens. The thymus and other lymphoid organs are severely hypoplastic, and the lack of class II molecules results in abnormal thymic selection with circulating CD4 T cells that have altered CDR3 profiles.

IMMUNODEFICIENCY WITH THROMBOCYTOPENIA AND ECZEMA (WISKOTT-ALDRICH SYNDROME)

Wiskott-Aldrich syndrome, an X-linked recessive syndrome, is characterized by atopic dermatitis, thrombocytopenic purpura with normal-appearing megakaryocytes but small defective platelets, and undue susceptibility to infection.

Genetics and Pathogenesis

The abnormal gene, on the proximal arm of the X chromosome at Xp11.22-11.23 near the centromere, encodes a 501 amino acid proline-rich cytoplasmic protein restricted in its expression to hematopoietic cell lineages. The Wiskott-Aldrich syndrome protein (WASP) binds CDC42H2 and rac, members of the Rho family of guanosine triphosphatases. Wiskott-Aldrich syndrome protein appears to control the assembly of actin filaments required for microvesicle formation downstream of protein kinase C and tyrosine kinase signaling. Carriers can be detected by demonstration of the deleterious mutation.

Clinical Manifestations

Patients often have prolonged bleeding from the circumcision site or bloody diarrhea during infancy. The thrombocytopenia is not initially due to antiplatelet antibodies. Atopic dermatitis and recurrent infections usually develop during the 1st yr of life. *Streptococcus pneumoniae* and other bacteria having polysaccharide capsules cause otitis media, pneumonia, meningitis, and sepsis. Later, infections with agents such as *P. jiroveci* and the herpesviruses become more frequent. Survival beyond the teens is rare; infections, bleeding, and EBV-associated malignancies are major causes of death.

Patients with this defect uniformly have an impaired humoral immune response to polysaccharide antigens, as evidenced by absent or markedly diminished isohemagglutinins, and poor or absent antibody responses after immunization with polysaccharide vaccines. IgG_2 subclass concentrations, surprisingly, are normal. Anamnestic responses to protein antigens are poor or absent. There is an accelerated rate of synthesis as well as hypercatabolism of albumin, IgG, IgA, and IgM, resulting in highly variable concentrations of different immunoglobulins, even within the same patient. The predominant immunoglobulin pattern is a low serum level of IgM, elevated IgA and IgE, and a normal or slightly low IgG concentration. Because of their profound antibody deficiencies, these patients should be given monthly infusions of intravenous immunoglobulin (IVIG) regardless of their serum levels of the different immunoglobulin isotypes. Percentages of T cells are moderately reduced, and lymphocyte responses to mitogens are variably depressed.

Treatment

Good supportive care includes appropriate nutrition, routine IVIG, use of killed vaccines, aggressive management of eczema and associated cutaneous infections, platelet transfusion for serious bleeding episodes, splenectomy if a transplant is not going to be done, and high-dose IVIG with systemic steroids for autoimmune complications. Bone marrow or cord blood transplantation is the treatment of choice and is usually curative.

ATAXIA-TELANGIECTASIA

Ataxia-telangiectasia is a complex syndrome with immunologic, neurologic, endocrinologic, hepatic, and cutaneous abnormalities.

Genetics and Pathogenesis

The mutated gene responsible for this defect, ataxia-telangiectasia mutation *(ATM)*, was mapped to the long arm of chromosome 11 (11q22-23) and has been cloned. The gene product is a DNA-dependent protein kinase localized predominantly to the nucleus and involved in mitogenic signal transduction, meiotic recombination, and cell-cycle control. Cells from patients, as well as from heterozygous carriers, have increased sensitivity to ionizing radiation, defective DNA repair, and frequent chromosomal abnormalities.

In vitro tests of lymphocyte function have generally shown moderately depressed proliferative responses to T- and B-cell mitogens. Percentages of CD3 and CD4 T cells are moderately reduced, with normal or increased percentages of CD8 and elevated numbers of Tiγ/δ T cells. The thymus is very hypoplastic, exhibits poor organization, and lacks Hassall corpuscles.

Clinical Manifestations

The most prominent clinical features are progressive cerebellar ataxia, oculocutaneous telangiectasias, chronic sinopulmonary disease, a high incidence of malignancy, and variable humoral and cellular immunodeficiency. Ataxia typically becomes evident soon after these children begin to walk and progresses until they are confined to a wheelchair, usually by the age of 10-12 yr. The telangiectasias begin to develop at 3-6 yr of age. The most frequent humoral immunologic abnormality is the selective absence of IgA, which occurs in 50-80% of these patients. Hypercatabolism of IgA also occurs. IgE concentrations are usually low, and the IgM may be of the low-molecular-weight variety. IgG_2 or total IgG levels may be decreased, and specific antibody titers may be decreased or normal. Recurrent sinopulmonary infections occur in approximately 80% of these patients. Although common viral infections have not usually resulted in untoward sequelae, fatal varicella has occurred. The malignancies associated with ataxia-telangiectasia are usually of the lymphoreticular type, but adenocarcinomas also occur. Unaffected relatives have an increased incidence of malignancy.

126.3 Defects of Innate Immunity

Rebecca H. Buckley

A number of defects in non–antigen-specific immunity (innate immunity) affect antigen-specific immune responses, as there is interaction between the adaptive and innate immune systems.

INTERFERON-γ RECEPTORS 1 AND 2, IL-12 RECEPTOR β_1, AND IL-12P40 MUTATIONS

Disseminated BCG and other severe nontuberculosis mycobacterial infections (sepsis, osteomyelitis) occur in patients with severe T-cell defects; however, no specific host defect is identified in approximately half of such cases. The first report was a 2.5 mo old Tunisian girl with fatal idiopathic disseminated BCG infection; 4 children from Malta had disseminated atypical mycobacterial infections in the absence of a recognized immunodeficiency. There was consanguinity in all, and all had a functional defect in the upregulation of tumor necrosis factor (TNF) α production by their blood macrophages in response to stimulation with interferon-γ (IFN-γ). All also had a mutation in the gene on chromosome 6q22-q23 that encodes the IFN-γ receptor 1 (IFN-γR1). IFN-γR1 deficiency may be inherited as a complete autosomal recessive (early onset ≈3 yr of age, more episodes, more severe disease, and higher mortality) or partial dominant (onset ≈10 yr of age) disease. Patients with mutations in the IFN-γR2 have also been identified. Related defects were found in other patients who had disseminated mycobacterial infections, who have mutations in either the gene encoding the β_1 chain of the IL-12 receptor (IL-12Rβ_1) or in the gene encoding IL-12p40. IL-12 is a powerful inducer of IFN-γ production by T and NK cells, and the mutated receptor chain gene resulted in unresponsiveness of the cells of these patients to IL-12 and inadequate IFN-γ production. The children deficient in IFN-γR1, IFN-γR2, IL-12Rβ_1, or IL-12p40 appeared not to be susceptible to infection with many agents other than mycobacteria (occasionally *Salmonella*, *Listeria, Histoplasma*). Th1 responses appeared to be normal in these patients, and the susceptibility to mycobacterial infections thus apparently results from an intrinsic impairment of the IFN-γ pathway response to these particular intracellular pathogens, showing that IFN-γ is obligatory for efficient macrophage antimycobacterial activity.

GERMLINE STAT-1 MUTATION

Interferons induce the formation of 2 transcriptional activators: gamma-activating factor (GAF) and interferon-stimulated gamma factor 3 (ISGF3). A natural heterozygous dominant germline *STAT-1* mutation associated with susceptibility to mycobacterial but not viral disease was found in 2 unrelated patients with unexplained mycobacterial disease. This mutation caused a loss of GAF and ISGF3 activation but was dominant for 1 cellular phenotype and recessive for the other. The mutation impaired the nuclear accumulation of GAF, but not of ISGF3, in cells stimulated by interferons, implying that the antimycobacterial but not the antiviral effects of human interferons are mediated by GAF. Two patients were identified with homozygous *STAT-1* mutations; they developed both post–BCG vaccination disseminated disease and lethal viral infections. The mutations in these patients caused a complete lack of STAT-1 and resulted in a lack of formation of both GAF and ISGF3.

IL-1R–ASSOCIATED KINASE 4 DEFICIENCY AND MYELOID DIFFERENTIATION FACTOR 88

Members of IL-1R and the Toll-like receptor superfamily share an intracytoplasmic Toll–IL-1 receptor (TIR) domain, which mediates recruitment of the IL-1R–associated kinase (IRAK) complex via TIR-containing adapter molecules. Three unrelated, otherwise healthy children with recurrent pyogenic infections caused by pneumococci and staphylococci had normal immunocompetence by standard immune studies. They had normal titers of antipneumococcal antibodies. Their blood and fibroblast cells did not activate nuclear factor κB, and mitogen-activated protein kinase and failed to induce downstream cytokines in response to any of the known ligands of TIR-bearing receptors. All were found to have an inherited deficiency of IRAK-4. The TIR-IRAK signaling pathway appears to be crucial for protective immunity against specific bacteria but is redundant against most other microorganisms. There are now more than 50 documented cases of IRAK4 deficiency, and a commonality among cases is susceptibility to pyogenic bacterial infection with pneumococcus and *Pseudomonas*. The pneumococcal infections have the potential to be invasive (even as a presenting feature) and lead to poor clinical outcomes. Severe viral and fungal infections are atypical. The myeloid differentiation factor 88 (MYD88) is an effective phenocopy of IRAK4 deficiency. While discovered later than IRAK4 deficiency, myeloid differentiation factor 88 is an upstream adaptor for IRAK4 and links it to Toll-like receptors, which results in a very similar immunologic defect and clinical syndrome.

NATURAL KILLER CELL DEFICIENCY

NK cells are the major lymphocytes of the innate immune system. NK cells recognize virally infected and malignant cells and mediate their elimination. Individuals with absence or functional deficiencies of NK cells are rare, and they typically have susceptibility to the herpesviruses (including varicella-zoster virus, herpes simplex virus, cytomegalovirus, and EBV) as well as papillomaviruses. A number of gene defects are associated with these isolated abnormalities in NK cells. Autosomal recessive CD16 gene mutations were described in 3 separate families and they altered the first immunoglobulin-like domain of this important NK cell activation receptor. Patients with these mutations have NK cells that are functionally impaired and have clinical susceptibility to herpesviruses. **Autosomal dominant** deficiency of NK cells occurs in individuals with mutations in the GATA2 transcription factor. These patients also have low numbers of monocytes. They have extreme susceptibility to human papilloma virus as well as mycobacteria—the latter presumably from the monocytic defect. **Autosomal recessive** mutations in the MCM4 gene have been identified in a cohort of consanguineous Irish who had growth failure and susceptibility to herpesviruses. These individuals possessed the immature $CD56^{bright}$ minor subset, but lacked the major mature $CD56^{dim}$ subset of NK cells. The reason why MCM4, which encodes a DNA helicase, would interfere with NK cell development remains unclear. Therapeutically, patients should be maintained on antiviral prophylaxis, and allogeneic stem cell transplantation has been successful in certain cases.

HYPER-IGE SYNDROMES

The hyper-IgE syndromes are relatively rare primary immunodeficiency syndromes characterized by recurrent severe staphylococcal abscesses of the skin, lungs, and other sites and markedly elevated levels of serum IgE (Table 126-3). They occur in 2 forms: autosomal dominant and autosomal recessive.

Autosomal Dominant Hyper-IgE Syndrome

This is the most common form in the United States. More than 200 patients with autosomal dominant hyper-IgE syndrome, also known as the Buckley syndrome, have been reported.

Genetics and Pathogenesis

The autosomal dominant hyper-IgE syndrome is caused by heterozygous mutations in the gene encoding STAT-3. These mutations result in a dominant negative effect on the expression of STAT-3 by the other nonmutated gene. It is not clear exactly how the STAT-3 mutation causes all parts of the syndrome, but it is thought that IL-17 deficiency may account in part for the susceptibility to *Candida* infection. IL-17 is a cytokine that acts on monocytes to induce secretion of proinflammatory mediators such as IL-8, TNF, and granulocyte-macrophage colony-stimulating factor.

Clinical Manifestations

The characteristic clinical features of the autosomal dominant form of the hyper-IgE syndrome are staphylococcal abscesses, pneumatoceles, osteopenia, and unusual facial features. There is a history from infancy of recurrent staphylococcal abscesses involving the skin, lungs, joints, viscera and other sites. Persistent pneumatoceles develop as a result of recurrent pneumonia. They often have histories of sinusitis and mastoiditis. *C. albicans* is the second most common pathogen. Allergic respiratory symptoms are usually absent. The pruritic dermatitis that occurs is not typical atopic eczema and does not always persist. The first 2 reported patients were described as having **coarse facial features**, including a prominent forehead, deep-set wide-spaced eyes, a broad nasal bridge, a wide fleshy nasal tip, mild prognathism, facial asymmetry, and hemihypertrophy. In older children, delay in shedding primary teeth, recurrent fractures, and scoliosis occur.

These patients demonstrate an exceptionally high serum IgE concentration; an elevated serum IgD concentration; usually normal concentrations of IgG, IgA, and IgM; pronounced blood and sputum eosinophilia; abnormally low anamnestic antibody responses; and poor antibody and cell-mediated responses to neoantigens. Traditionally, IgE levels >2000 IU/mL confirm the diagnosis. However, IgE levels may fluctuate and even decrease in adults. In neonates and infants with the pruritic pustular dermatosis, IgE levels will be elevated for age and are usually in the 100s. In vitro studies show normal percentages of blood T, B, and NK lymphocytes, except for a decreased percentage of T cells with the memory (CD45RO) phenotype and an absence or deficiency of Th17 T cells. Most patients have normal T-lymphocyte proliferative responses to mitogens but very low or absent responses to antigens or allogeneic cells from family members. Blood, sputum, and histologic sections of lymph nodes, spleen, and lung cysts show striking eosinophilia. Hassall corpuscles and thymic architecture are normal. Phagocytic cell ingestion, metabolism, killing, and total hemolytic complement activity are normal in all patients, and results of chemotaxis studies have been mostly normal.

Autosomal Recessive Hyper-IgE Syndrome

Genetics and Pathogenesis

With the exception of 1 patient who had a mutation in the gene encoding Tyk2, most reported patients with autosomal recessive hyper-IgE syndrome have had mutations in the gene encoding DOCK8, which is on chromosome 9. DOCK8 is a member of the 11-member DOCK protein family. DOCK8 is likely to function as a guanine exchange factor for the Rho-guanosine triphosphatases Cdc42 and Rac1. Guanosine triphosphatase activation induces dynamic filamentous actin rearrangements and lamellipodia formation, leading to cell growth, migration, and adhesion. DOCK8 may be important for the formation

Table 126-3 Hyperimmunoglobulin E Syndromes

	AUTOSOMAL DOMINANT OR SPORADIC (JOB SYNDROME)	AUTOSOMAL RECESSIVE
Gene	*STAT3*	*DOCK8:* less often *TYK2*
INFECTIONS		
Sinopulmonary		
Recurrent bacterial	*S. aureus*, pneumococcus, *H. influenzae*	*S. aureus*, pneumococcus, *H. influenzae*
Pneumatoceles/bronchiectasis	Common	No
Fungal	Aspergillus species	No
Cutaneous		
Abscesses	*S. aureus*	*S. aureus*
Viral	No	HPV, HSV, VZV, MCV
Mucocutaneous candidiasis	Common	Common
ATOPIC DISORDERS		
Newborn eosinophilic pustules	Common	No
Eczema	Common	Common
Asthma	No	Common
Allergies/Anaphylaxis	No	Common
MUSCULOSKELETAL		
Osteopenia, pathologic fractures	Common	No
Scoliosis	Common	No
Retained primary teeth	Common	No
Hyperextensible	Common	No
OTHER FEATURES		
Coarse facies*	Common in adolescent	No
Coronary artery tortuosity/aneurysm	Common	No
UBO on brain MRI	Common	No
Lymphomas	Yes	Higher incidence
Cutaneous malignancy	No	Yes
Mortality	Adulthood	Childhood

*Coarse facies includes broad nose, prominent forehead and chin, deep set eyes
HPV, human papillomavirus; HSV, herpes simplex virus; MCV, molluscum virus; UBO, unidentified bright objects of cerebral cortex on T_2 MRI; VZV, varicella-zoster virus.

of the immunologic synapse that leads to T-cell activation, proliferation, and differentiation. Of the 33 patients reported, 25 were from Turkey, 2 each were from Mexico and Iran, and 1 each was from Lebanon, Oman, Italy, and Ireland. Autosomal recessive hyper-IgE syndrome may rarely be due to mutations in phosphoglucomutase 3 (PGM3 deficiency).

Clinical Manifestations

Unlike those with the autosomal dominant form of this syndrome, a large majority of patients with autosomal recessive hyper-IgE have severe atopic dermatitis, asthma, food allergies, and anaphylaxis. They also have recurrent skin viral infections, including severe herpes simplex, herpes zoster, molluscum contagiosum, and papillomavirus skin infections (see Table 126-3). In addition, patients can have abscesses, mucocutaneous candidiasis, upper respiratory infections, and pneumonia. Neurologic problems, including strokes, meningitis, and aneurysms, are prominent. Malignancies are also more common than in the autosomal dominant form. Patients with the autosomal recessive hyper-IgE syndrome do not have pneumatoceles, a history of fractures, unusual facial features, or delayed shedding of the baby teeth, as seen with the autosomal dominant form of the hyper-IgE syndrome (see Table 126-3).

Most patients with autosomal recessive hyper-IgE have elevated serum IgE levels, low serum IgM levels, and variable IgG antibody responses. They also have eosinophilia and lymphopenia, low T-cell numbers and impaired T-cell function. Their immunologic phenotype is that of a CID.

Treatment

The most effective **therapy** for the autosomal dominant hyper-IgE syndrome is long-term administration of therapeutic doses of a penicillinase-resistant antistaphylococcal antibiotic, adding other agents as required for specific infections. IVIG should be administered to antibody-deficient patients, and appropriate thoracic surgery should be provided for superinfected pneumatoceles or those persisting beyond 6 mo. Bone marrow transplantation has been variably successful in this condition. The prognosis in the autosomal recessive form of the hyper-IgE syndrome is much poorer than in the autosomal dominant form, and most patients die early (see Table 126-3). The treatment of choice for the autosomal recessive form is allogeneic bone marrow transplantation.

126.4 Treatment of Cellular or Combined Immunodeficiency

Rebecca H. Buckley

Good supportive care, including prevention and treatment of infections, is critical while patients await more definitive therapy (Table 126-4). Having knowledge of the pathogens causing disease with specific immune defects is also useful (see Table 126-4).

Transplantation of MHC-compatible sibling or rigorously T-cell–depleted haploidentical (half-matched) parental hematopoietic stem cells is the treatment of choice for patients with fatal T-cell or combined T- and B-cell defects. The major risk to the recipient from transplants of bone marrow or peripheral blood stem cells is GVHD from donor T cells. Patients with less severe forms of cellular immunodeficiency, including some forms of CID, Wiskott-Aldrich syndrome, cytokine deficiency, and MHC antigen deficiency, reject even HLA-identical marrow grafts unless chemoablative treatment is given before transplantation. Several patients with these conditions have been treated successfully with hematopoietic stem cell transplantation after conditioning.

More than 90% of patients with primary immunodeficiency transplanted with HLA-identical related marrow will survive with immune reconstitution. T-cell–depleted haploidentical-related marrow transplants in patients with primary immunodeficiency have had their greatest success in patients with SCID, who do not require

Table 126-4 Infection in the Host Compromised by B- and T-Cell Immunodeficiency Syndromes

IMMUNODEFICIENCY SYNDROME	OPPORTUNISTIC ORGANISMS ISOLATED MOST FREQUENTLY	APPROACH TO TREATMENT OF INFECTIONS	PREVENTION OF INFECTIONS
B-cell immunodeficiencies	Encapsulated bacteria (*Streptococcus pneumoniae, Staphylococcus aureus, Haemophilus influenzae,* and *Neisseria meningitidis*), *Pseudomonas aeruginosa, Campylobacter* sp., enteroviruses, rotaviruses, *Giardia lamblia, Cryptosporidium* sp., *Pneumocystis jiroveci, Ureaplasma urealyticum,* and *Mycoplasma pneumoniae*	1. IVIG 200-800 mg/kg 2. Vigorous attempt to obtain specimens for culture before antimicrobial therapy 3. Incision and drainage if abscess present 4. Antibiotic selection on the basis of sensitivity data	1. Maintenance IVIG for patients with quantitative and qualitative defects in IgG metabolism (400-800 mg/kg q 3-5 wk) 2. In chronic recurrent respiratory disease, vigorous attention to postural drainage 3. In selected cases (recurrent or chronic pulmonary or middle ear), prophylactic administration of ampicillin, penicillin, or trimethoprim-sulfamethoxazole
T-cell immunodeficiencies	Encapsulated bacteria (*S. pneumoniae, H. influenzae, S. aureus*), facultative intracellular bacteria (*Mycobacterium tuberculosis*, other *Mycobacterium* sp., and *Listeria monocytogenes*); *Escherichia coli; P. aeruginosa; Enterobacter* sp.; *Klebsiella* sp.; *Serratia marcescens; Salmonella* sp.; *Nocardia* sp.; viruses (cytomegalovirus, herpes simplex virus, varicella-zoster virus, Epstein-Barr virus, rotaviruses, adenoviruses, enteroviruses, respiratory syncytial virus, measles virus, vaccinia virus, and parainfluenza viruses); protozoa (*Toxoplasma gondii* and *Cryptosporidium* sp.); and fungi (*Candida* sp., *Cryptococcus neoformans, Histoplasma capsulatum,* and *P. jiroveci*)	1. Vigorous attempt to obtain specimens for culture before antimicrobial therapy 2. Incision and drainage if abscess present 3. Antibiotic selection on the basis of sensitivity data 4. Early antiviral treatment for herpes simplex, cytomegalovirus, and varicella-zoster viral infections 5. Topical and nonadsorbable antimicrobial agents frequently are useful	1. Prophylactic administration of trimethoprim-sulfamethoxazole for prevention of *P. jiroveci* pneumonia 2. Oral nonadsorbable antimicrobial agents to lower concentration of gut flora 3. No live virus vaccines or bacillus Calmette-Guérin vaccine 4. Careful tuberculosis screening

IVIG, intravenous immunoglobulin.
From Stiehm ER, Ochs HD, Winkelstein JA: Immunologic disorders in infants and children, *ed 5, Philadelphia, 2004, WB Saunders.*

pretransplant conditioning or GVHD prophylaxis. Of patients with SCID, 92% have survived after T-cell–depleted parental marrow is given soon after birth when the infant is healthy without pretransplant chemotherapy or posttransplant GVHD prophylaxis. Currently, bone marrow transplantation remains the most important and effective therapy for SCID. Early in 2000, there was remarkable success with gene therapy in X-SCID. Unfortunately, leukemic-like clonal T cells or lymphomas developed in 5 of 20 children so treated as a result of insertional mutagenesis, which led to a cessation of those trials. By contrast, in ADA-deficient SCID, there has been outstanding success without insertional oncogenesis. More recently, gene therapy has been successful in the Wiskott-Aldrich syndrome but unfortunately with the problem of insertional mutagenesis.

126.5 Immune Dysregulation with Autoimmunity or Lymphoproliferation

Rebecca H. Buckley

AUTOIMMUNE LYMPHOPROLIFERATIVE SYNDROME

Autoimmune lymphoproliferative syndrome (ALPS), also known as Canale-Smith syndrome, is a disorder of abnormal lymphocyte apoptosis leading to polyclonal populations of T cells (double-negative T cells), which express CD3 and α/β antigen receptors but do not have CD4 or CD8 coreceptors (CD3 + T cell receptor α/β^+ $CD4^-$ $CD8^-$). These T cells respond poorly to antigens or mitogens and do not produce growth or survival factors (IL-2). The genetic deficit in most patients is a germline or somatic mutation in the Fas gene, which produces a cell-surface receptor of the TNF receptor superfamily (TNFRSF6), which, when stimulated by its ligand, will produce programmed cell death (Table 126-5). Persistent survival of these lymphocytes leads to immune dysregulation and autoimmunity. ALPS is also caused by other genes in the Fas pathway (*FASLG* and *CASP10*). In addition, ALPS-like disorders are associated with other mutations; RAS-associated autoimmune lymphoproliferative disorder (RALD), CASPASE-8 deficiency syndrome (CEDS), Fas-associated protein with death domain deficiency (FADD), and protein kinase C delta deficiency (PRKCD). These disorders have varying degrees of immune deficiency, autoimmunity and lymphoproliferation.

Clinical Manifestations

ALPS is characterized by autoimmunity, chronic persistent or recurrent lymphadenopathy, splenomegaly, hepatomegaly (in 50%), and hypergammaglobulinemia (IgG, IgA). Many patients present in the 1st yr of life, and most are symptomatic by yr 5. Lymphadenopathy can be striking (Fig. 126-2). Splenomegaly may produce hypersplenism with cytopenias. Autoimmunity also produces anemia (Coombs-positive hemolytic anemia) or thrombocytopenia or a mild neutropenia. The lymphoproliferative process (lymphadenopathy, splenomegaly) may regress over time, but autoimmunity does not and is characterized by frequent exacerbations and recurrences. Other autoimmune features include urticaria, uveitis, glomerulonephritis, hepatitis, vasculitis, glomerulonephritis, vasculitis, panniculitis, arthritis, and central nervous system involvement (seizures, headaches, encephalopathy).

Malignancies are also more common in patients with ALPS and include Hodgkin and non-Hodgkin lymphomas and solid-tissue tumors of thyroid, skin, heart, or lung. ALPS is one cause of Evan syndrome (immune thrombocytopenia and immune hemolytic anemia).

Diagnosis

Laboratory abnormalities depend on the lymphoproliferative organ response (hypersplenism) or the degree of autoimmunity (anemia, thrombocytopenia). There may be lymphocytosis or lymphopenia. Table 126-5 lists the criteria for the diagnosis. Flow cytometry helps identify the lymphocyte type (see Fig. 126-2). Functional genetic analysis for the *TNFRSF6* gene often reveals a heterozygous mutation.

Table 126-5 Diagnostic Criteria for Autoimmune Lymphoproliferative Syndrome

REQUIRED
1. Chronic nonmalignant lymphoproliferation (>6 mo lymphadenopathy and/or splenomegaly)
2. Elevated peripheral blood double-negative T cells

ACCESSORY
Primary
Defective in vitro Fas-mediated apoptosis (in 2 separate assays)
Somatic or germline mutation in ALPS causative gene (FAS, FASL, CASP10)
Secondary
1. Elevated biomarkers (Any of following)
   a. Plasma soluble FASL >200 pg/mL
   b. Plasma IL-10 >20 pg/mL
   c. Plasma or serum vitamin B_{12} >1500 ng/L
   d. Plasma IL-18 >500 pg/mL
2. Immunohistochemical findings consistent with ALPS as determined by experienced histopathologist
3. Autoimmune cytopenias and polyclonal hypergammaglobulinemia
4. Family history of ALPS or nonmalignant lymphoproliferation

DIAGNOSIS
Definitive: Required plus 1 primary accessory criterion
Probable: Required plus 1 secondary accessory criterion
Of note, probable and definitive ALPS should be treated the same in the clinic

Modified from Teachey DT: New advances in the diagnosis and treatment of autoimmune lymphoproliferative syndrome. Curr Opin Pediatr *24:1–8, 2013, Table 2, p. 4.*

Treatment

Lymphoproliferative manifestations have been managed with corticosteroids and immunosuppressive agents (Cytoxan [cyclophosphamide], methotrexate, azathioprine); once weaned, the manifestation recurs. Hypersplenism may require splenectomy. Malignancies can be treated with the usual protocols used in patients unaffected by ALPS. Stem cell transplantation is another possible option in treating the autoimmune manifestations of ALPS.

IMMUNE-DYSREGULATION, POLYENDOCRINOPATHY, ENTEROPATHY, X-LINKED SYNDROME

This immune dysregulation syndrome is characterized by onset within the 1st few wk or mo of life with watery diarrhea (autoimmune enteropathy), an eczematous rash (erythroderma in neonates), insulin-dependent diabetes mellitus, hyperthyroidism or more often hypothyroidism, severe allergies, and other autoimmune disorders (Coombs-positive hemolytic anemia, thrombocytopenia, neutropenia). Psoriasiform or ichthyosiform rashes and alopecia have also been reported,

Immune-dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome is caused by a mutation in the *FOXP3* gene, which encodes a forkhead-winged helix transcription factor *(scurfin)* involved in the function and development of CD4+CD25+ regulatory T cells. The absence of regulatory cells may predispose to abnormal activation of effector T cells. Dominant gain of function mutations in *STAT1* and other gene mutations (Table 126-6) produces an IPEX-like syndrome.

Clinical Manifestations

Watery diarrhea with intestinal villous atrophy leads to failure to thrive in most patients. Cutaneous lesions (usually eczema) and

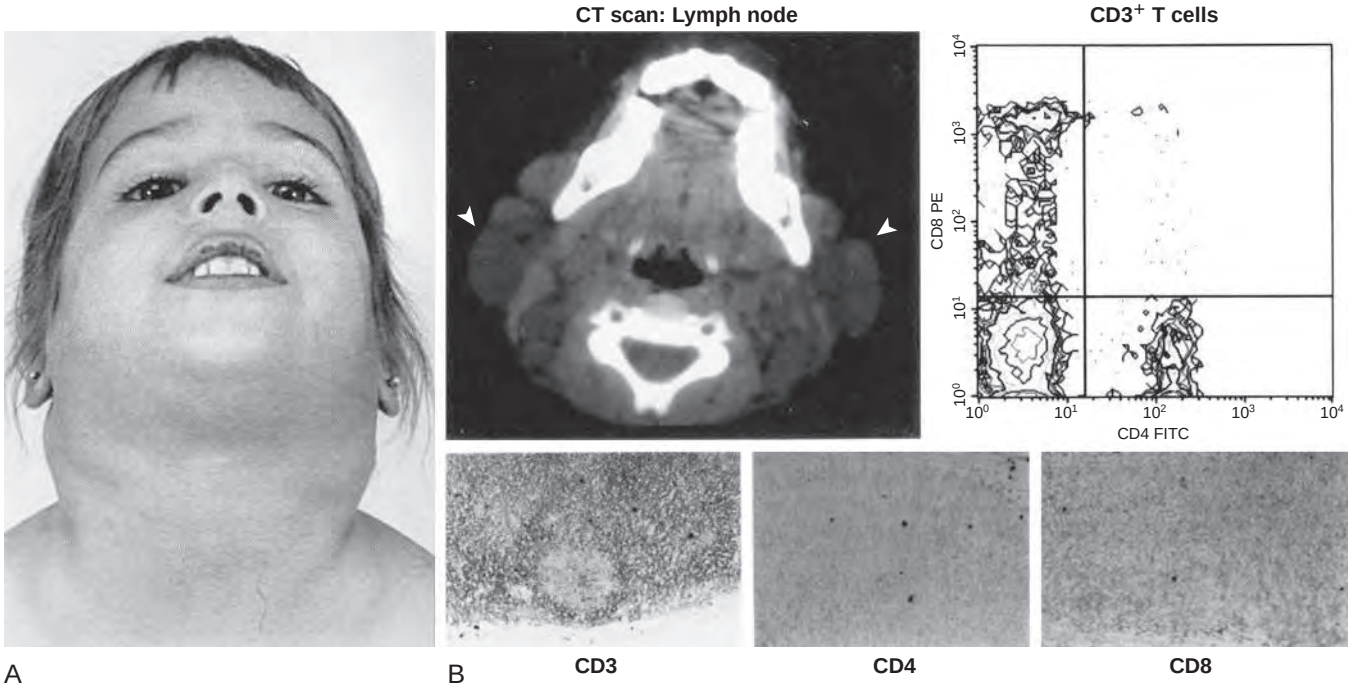


Figure 126-2 Clinical, radiographic, immunologic, and histologic characteristics of the autoimmune lymphoproliferative syndrome. **A,** Front view of the National Institutes of Health patient. **B,** *Top middle,* a CT scan of the neck is shown demonstrating enlarged preauricular, cervical, and occipital lymph nodes. *Arrowheads* denote the most prominent lymph nodes. The *top right* panels show the flow-cytometric analysis of peripheral blood T cells from a patient with autoimmune lymphoproliferative syndrome (ALPS), with CD8 expression on the vertical axis and CD4 on the horizontal axis. The *lower left quadrant* contains CD4-CD8 (double-negative) T cells, which are usually present at <1% of T cells expressing the αβ T-cell receptor. The *bottom panels* show CD3, CD4, and CD8 staining on serial sections of a lymph node biopsy specimen from a patient with ALPS and also shows that large numbers of DNCD3+ CD4-CD8 (double-negative) T cells are present in the interfollicular areas of the lymph node. *(Adapted from Siegel RM, Fleisher TA: The role of Fas and related death receptors in autoimmune and other disease states,* J Allergy Clin Immunol *103:729–738, 1999.)*

Table 126-6 Clinical and Laboratory Features of IPEX and IPEX-Like Disorders

	IPEX	CD25	STAT5B	STAT1	ITCH
AUTOIMMUNITY					
Eczema	+++	+++	++	++	++
Enteropathy	+++	+++	++	++	++
Endocrinopathy	+++	++	+	++	++
Allergic disease	+++	+	+	++	++
Cytopenias	++	++	++	–	
Lung disease	+	++	+++	+	+++
INFECTIONS					
Yeast	–	++	–	+++	–
Herpes virus	–	+++ (EBV/CMV)	++ (VZV)	++	–
Bacterial	+/–	++	++	++	+
Associated features	None	None	Growth failure	Vascular anomalies	Dysmorphic growth failure
Serum immunoglobulins	Elevated	Elevated or normal	Elevated or normal	Low, normal, or high	Elevated
Serum IgE	Elevated	Normal or elevated	Normal or elevated	Normal or mildly elevated	Elevated
CD25 expression	Normal	Absent	Normal or low	Normal	Not tested
CD4+CD45RO	Elevated	Elevated	Elevated	Normal or high	Not tested
FOXP3 expression	Absent or normal	Normal or low	Normal or low	Normal	Not tested
IGF-1, IGFBP-3	Normal	Normal	Low	Normal	Not tested
Prolactin	Normal	Normal	Elevated	Normal	Not tested

CMV, cytomegalovirus; EBV, Epstein Barr Virus; IGF-1, insulin-like growth factor 1; IGFBP-3, insulin-like growth factor–binding protein 3; IPEX, immune dysregulation, polyendocrinopathy, enteropathy, X-linked; VZV, varicella zoster virus; ITCH, ubiquitin ligase deficiency.

From: Verbsky JW, Chatila TA: Immune dysregulation, polyendocrinopathy, enteropathy, X–linked (IPEX) and IPEX–related disorders: an evolving web of heritable autoimmune diseases. Curr Opin Pediatr *25:708–715, 2013, Table 1, p. 709.*

insulin-dependent diabetes begin in infancy. Lymphadenopathy and splenomegaly are also present. Serious bacterial infections (meningitis, sepsis, pneumonia, osteomyelitis) may be related to neutropenia, malnutrition, or immune dysregulation. Laboratory features reflect the associated autoimmune diseases, dehydration, and malnutrition. In addition, serum IgE levels are elevated with normal levels of IgM, IgG, and IgA. The diagnosis is made clinically and by mutational analysis of the *FOXP3* gene.

Treatment

Inhibition of T-cell activation by cyclosporine, tacrolimus, or sirolimus with steroids is the treatment of choice, along with the specific care of the endocrinopathy and other manifestations of autoimmunity. Stem cell transplantation is the only possibility for curing IPEX. Overall, the combination of the risks for serious bacterial infection in the untreated condition and the risks of immunosuppression and bone marrow transplantation gives IPEX a poor prognosis. Untreated, most die by 2 yr of age.

Bibliography is available at Expert Consult.

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Section 3

The Phagocytic System

Chapter 127

Neutrophils

Thomas D. Coates

THE PHAGOCYTIC INFLAMMATORY RESPONSE

The phagocyte system includes both granulocytes (neutrophils, eosinophils, and basophils) and mononuclear phagocytes (monocytes and tissue macrophages). Neutrophils and mononuclear phagocytes share primary functions, including the defining properties of large particle ingestion and microbial killing. Phagocytes participate primarily in the innate immune response but also help initiate acquired immunity. Mononuclear phagocytes, including tissue macrophages and circulating monocytes, are discussed in Chapter 128.

Neutrophils provide the rapid effector arm of the innate immune system. They circulate in the bloodstream for only about 6 hr (Table 127-1), but upon encountering specific chemotactic signals, they adhere to the vascular endothelium and transmigrate into tissues, where they ingest and kill microbes and release chemotactic signals to recruit more neutrophils and to attract dendritic cells and other initiators of the acquired immune response.

HEMATOPOIESIS

The hematopoietic progenitor system can be envisioned as a continuum of functional compartments with the most primitive compartment composed of very rare **pluripotential stem cells**, which have high self-renewal capacity and give rise to more mature stem cells, including cells that are committed to either lymphoid or myeloid development (Fig. 127-1). Common lymphoid progenitor cells give rise to

Table 127-1 Neutrophil and Monocyte Kinetics

NEUTROPHILS	
Average time in mitosis (myeloblast to myelocyte)	7-9 days
Average time in postmitosis and storage (metamyelocyte to neutrophil)	3-7 days
Average half-life in the circulation	6 hr
Average total body pool	6.5×10^8 cells/kg
Average circulating pool	3.2×10^8 cells/kg
Average marginating pool	3.3×10^8 cells/kg
Average daily turnover rate	1.8×10^8 cells/kg
MONONUCLEAR PHAGOCYTES	
Average time in mitosis	30-48 hr
Average half-life in the circulation	36-104 hr
Average circulating pool (monocytes)	1.8×10^7 cells/kg
Average daily turnover rate	1.8×10^9 cells/kg
Average survival in tissues (macrophages)	Months

From Boxer LA: Function of neutrophils and mononuclear phagocytes. In Bennett JC, Plum F, editors: Cecil textbook of internal medicine, *ed 20, Philadelphia, 1996, WB Saunders.*

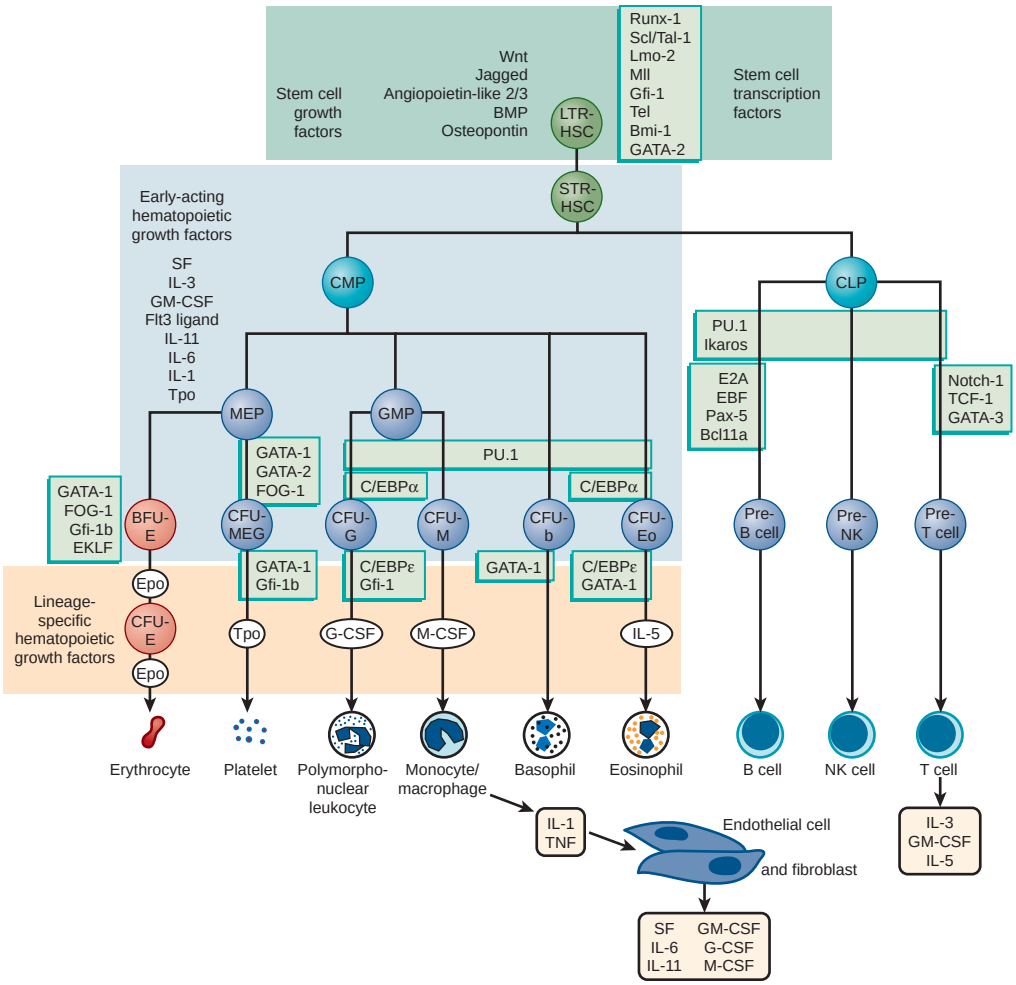


Figure 127-1 Major cytokine sources and actions and transcription factor requirements. Cells of the bone marrow microenvironment such as macrophages, endothelial cells, and reticular fibroblastoid cells, produce macrophage colony-stimulating factor (M-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), granulocyte colony-stimulating factor (G-CSF), interleukin (IL)-6, and probably stem cell factor (SCF) after induction with endotoxin (macrophage) or IL-1/tumor necrosis factor (TNF) (endothelial cells and fibroblasts). T-cells produce IL-3, GM-CSF, and IL-5 in response to antigenic and IL-1 stimulation. These cytokines have overlapping actions during hematopoietic differentiation, as indicated, and for all lineages optimal development requires a combination of early- and late-acting factors. Transcription factors important for survival or self-renewal of stem cells are shown at the top *(light green panel)* and stages of hematopoiesis blocked after the depletion of indicated transcription factors for multipotent and committed progenitors are shown in light green boxes throughout. *CFU-E*, erythroid colony-forming unit; *CFU-E/b/M*, erythrocyte, basophil, and megakaryocyte colony-forming unit; *CFU-Eo*, eosinophil colony-forming unit; *CFU-G*, granulocyte colony-forming unit; *CFU-M*, macrophage colony-forming unit; *MSC*, myeloid stem cells; *NK*, natural killer; *PSC*, pluripotent stem cells. *(From Nathan DG, Orkin SH, Ginsburg D, et al, editors:* Nathan and Oski's hematology of infancy and childhood, *ed 7, Philadelphia, 2009, WB Saunders.)*

T- and B-cell precursors and their mature progeny (see Chapter 123). Common myeloid progenitor cells eventually give rise to committed single-lineage progenitors of the recognizable precursors through a random process of lineage restriction in a stepwise process (see Chapter 446). The capacity of lineage-specific committed progenitors to proliferate and differentiate in response to demand provides the hematopoietic system with a remarkable range of response to changing requirements for mature blood cell production.

The proliferation, differentiation, and survival of immature hematopoietic progenitor cells are governed by hematopoietic growth factors, a family of glycoproteins (see Chapter 446). Besides regulating proliferation and differentiation of progenitors, these factors influence the survival and function of mature blood cells. During granulopoiesis and monopoiesis, multiple cytokines regulate the cells at each stage of differentiation from pluripotent stem cells to non-dividing terminally differentiated cells (monocytes, neutrophils, eosinophils, and basophils). As cells mature, they lose receptors for most cytokines, especially those that influence early cell development; however, they retain receptors for cytokines that affect their mobilization and function, such as granulocyte colony-stimulating factor and macrophage colony–stimulating factor. Mature phagocytes also express receptors for chemokines, which help direct the cells to sites of inflammation. Chemokine receptors such as CXCR4 and its ligand SDF-1 play a key role in retention of developing myeloid cells within bone marrow.

NEUTROPHIL MATURATION AND KINETICS

The process of intramedullary granulocyte maturation involves changes in nuclear configuration and accumulation of specific intracytoplasmic granules. The bone marrow microenvironment supports the normal steady-state renewal of peripheral blood neutrophils through the generation of growth and differentiation factors by stromal cells. Growth factors such as granulocyte colony-stimulating factor and granulocyte-macrophage colony-stimulating factor not only stimulate cell division, but also induce the expression of transcription factors that regulate the biosynthesis of functional components of the neutrophil, such as granule proteins. The transcription factor PU.1 is essential for myelopoiesis, both as a positive regulatory element and as a suppressor of GATA-1, a transcription factor that directs nonmyeloid differentiation. Other transcription factors, such as Runx1 (AML1), c-myb, CDP, C/EBPα, C/EBPγ, and MEF, are expressed in the myeloblast and promyelocyte, and some of these are required for azurophil granule protein expression. As cells enter the myelocyte stage, RUNX1 and

myb are downregulated, whereas PU.1 and C/EBPε expression rises to initiate terminal differentiation.

Granulocytes survive for only 6-12 hr in the circulation, and therefore daily production of 2×10^4 granulocytes/μL of blood is required to maintain a level of circulating granulocytes of 5×10^3/μL (see Table 127-1). The relatively small peripheral blood pool includes the rapidly interchanging circulating and marginating pools; the latter provides entrance into the tissue phase, where neutrophils may survive for hours or days. The circulating pool is fed and buffered by a much larger marrow population of mature neutrophils and myeloid precursors, representing the marrow reserve and proliferating pools, respectively. Proliferation of myeloid cells, encompassing approximately 5 mitotic divisions, takes place only during the 1st 3 stages of neutrophil development, in myeloblasts, promyelocytes, and myelocytes. After the myelocyte stage, the cells terminally differentiate into nondividing, maturing metamyelocytes, bands, and neutrophils.

Neutrophil maturation is associated with nuclear condensation and lobulation and with the sequential production of characteristic granule populations. A myeloblast is a relatively undifferentiated cell with a large oval nucleus, a sizeable nucleolus, and a deficiency of granules. Promyelocytes acquire peroxidase-positive azurophilic (primary) granules, and then myelocytes and metamyelocytes acquire specific (secondary) granules; tertiary granules and secretory vesicles develop in the final stage of neutrophil maturation.

NEUTROPHIL FUNCTION

Neutrophil responses are initiated as circulating neutrophils flowing through the postcapillary venules detect low levels of chemokines and other chemotactic substances released from a site of infection. The sequence of events as the neutrophil moves from circulating in the blood to the encounter and destruction of bacteria is carefully orchestrated by a series of biochemical events, defects of which are associated with genetic disorders of neutrophil function (Fig. 127-2). In fact, these disorders of neutrophil function lead to our understanding of the cell biology of phagocyte function. A subset of circulating neutrophils loosely adheres to the endothelium through low-affinity receptors called selectins and rolls along the endothelium forming the marginated pool. Soluble effectors of inflammation trigger subtle changes in surface adhesion molecules on endothelial cells at the site of infection. The rolling of neutrophils allows more intense exposure of neutrophils to activating factors such as tumor necrosis factor or interleukin-1 (Fig. 127-2). Exposure of neutrophils ti these same activating factors induces

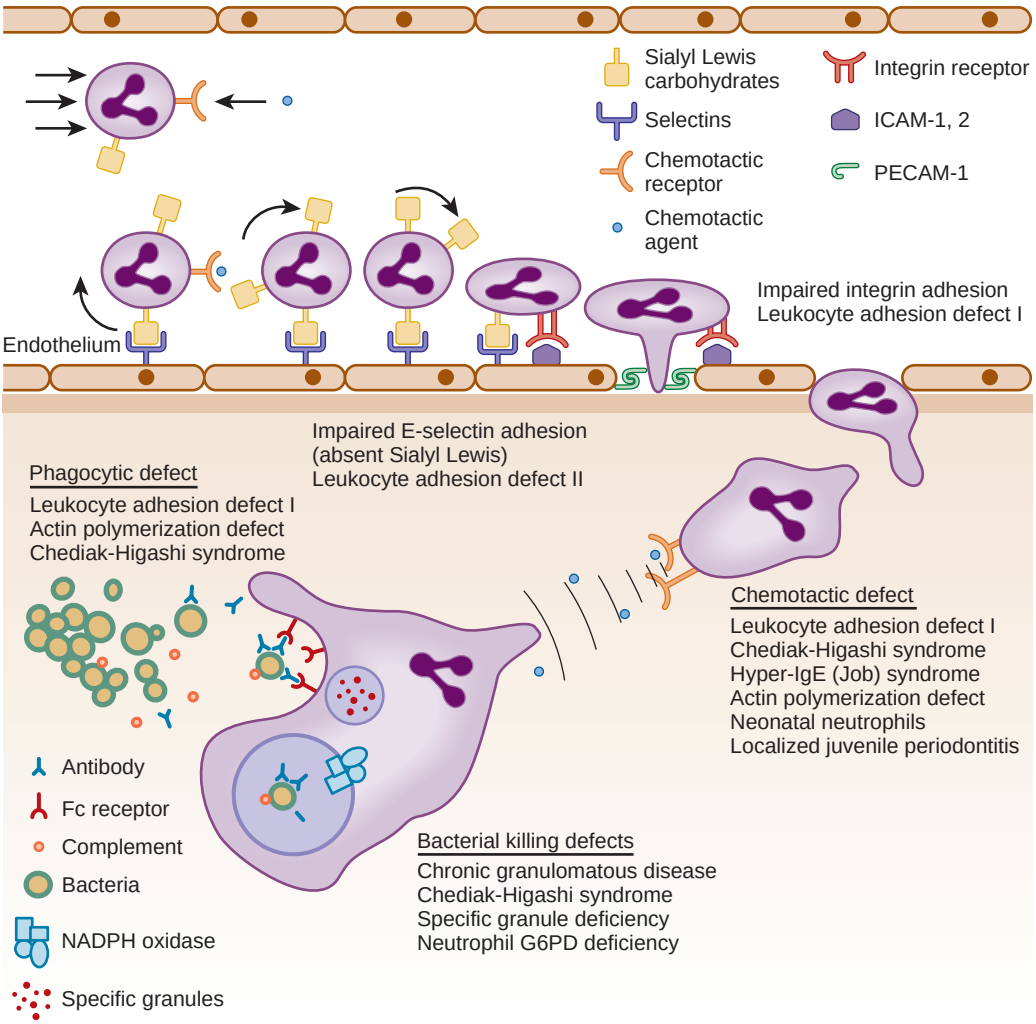


Figure 127-2 The neutrophil-mediated inflammatory response and associated neutrophil dysfunction syndromes. Circulating neutrophils loosely attach to endothelium via selectins and roll along the vessel wall until they arrive at the site of infection. Inflammatory monokines, interleukin 1 (IL-1), and tumor necrosis factor (TNF), activate endothelial cells to express E- and P-selectins. E- and P-selectins serve as counter receptors for neutrophils sialyl Lewis X and Lewis X to cause low-avidity neutrophil rolling. Activated endothelial cells express ICAM-1, which serves as a counter-receptor for neutrophil β_2 integrin molecules, leading to high-avidity leukocyte spreading and the start of transendothelial migration at the infection site. Neutrophils invade through the vascular basement membrane with the release of proteases and reactive oxidative intermediates, causing local destruction of surrounding tissue at sites of high concentrations of chemotactic factors and migrate to the site of infection where they ingest and kill the bacteria. *(Modified from Kyono W, Coates TD: A practical approach to neutrophil disorders.* Pediatr Clin North Am *49:929, 2002.)*

qualitative and quantitative changes in the family of β_2-integrin adhesion receptors (the CD11/CD18 group of surface molecules), leading to tight adhesion between neutrophils and endothelial cells at the site of inflammation and ultimately to transmigration of the neutrophil into the tissue.

Once through the endothelium, the neutrophil senses the gradient of chemokines or other chemoattractants and migrates to sites of infection. Neutrophil migration is a complex process involving rounds of receptor engagement, signal transduction, and remodeling of the actin-microfilaments composing in part the cytoskeleton. Actin polymerization–depolymerization occurs in approximately 8 sec cycles and drives cyclic extension and retraction of the actin-rich lamella at the front of the neutrophil. Receptors at the leading edge of the lamella detect the gradient of attractant and follow microorganisms, ingest and destroy them. When the neutrophil reaches the site of infection, it recognizes pathogens by means of Fc immunoglobulin and complement receptors, Toll-like receptors, fibronectin receptors, and other adhesion molecules.

The neutrophil ingests microbes that are coated by **opsonins**, serum proteins such as immunoglobulin and complement component C3. The pathogens are engulfed into a closed vacuole, the **phagosome** (Fig. 127-3) where 2 cellular responses essential for optimal microbicidal activity occur concomitantly: degranulation and activation of nicotinamide-adenine dinucleotide phosphate (NADPH)–dependent oxidase. Fusion of neutrophil granule membranes with the phagosome membrane delivers potent antimicrobial proteins and small peptides into the phagosome.

Assembly and activation of NADPH oxidase at the phagosome membrane as well (see Fig. 127-3) generating large amounts of superoxide (O_2^-) from molecular oxygen that, in turn, decomposes to produce hydrogen peroxide (H_2O_2) and singlet oxygen. **Myeloperoxidase,** a major azurophil granule component, catalyzes the reaction of H_2O_2 with ubiquitously present chloride ions to create hypochlorous acid (HOCl) in the phagosome. Hypochlorous acid is essentially Clorox bleach. H_2O_2 and HOCl are potent microbicidal agents that break down and clear pathogens from sites of infection.

In addition, neutrophils secrete a wide variety of cytokines and chemokines that recruit more neutrophils to fight the infection, attract monocytes and macrophages that possess both microbicidal and scavenger functions, and promote antigen presentation to help initiate the adaptive immune response. Also, the reactive oxidants can inactivate chemotactic factors and may serve to terminate the process of neutrophil influx, thereby attenuating the inflammatory process. Finally, the release of reactive oxygen species, granule proteins, and cytokines can also damage local tissues, leading to the classic signs of inflammation or to more permanent impairment of tissue integrity and function.

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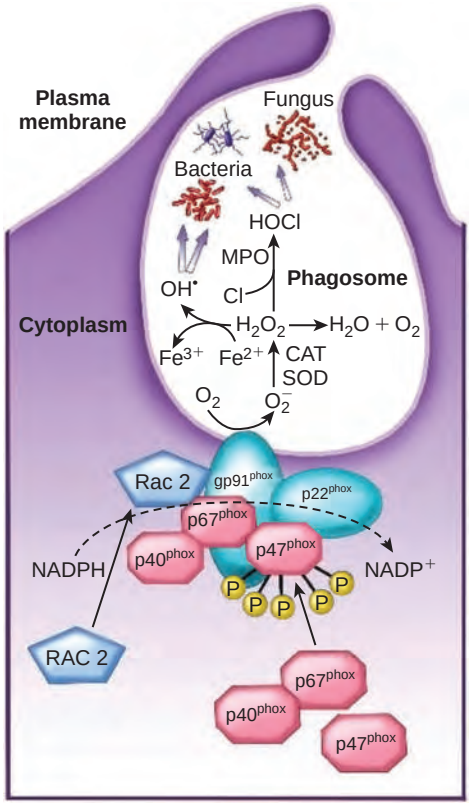


Figure 127-3 Nicotinamide-adenine dinucleotide phosphate (NADPH) oxidase components and activation. On activation of phagocytic cells, the 3 cytosolic components *(red)* of the NADPH oxidase ($p67^{phox}$, $p47^{phox}$, and $p40^{phox}$), plus the small guanosine triphosphatase (GTPase) protein Rac2, are translocated to the membrane of the phagocytic vacuole. The $p47^{phox}$ subunit binds to the flavocytochrome$_{b558}$ membrane component *(blue-green)* of the NADPH oxidase ($gp91^{phox}$ plus $p22^{phox}$). The NADPH oxidase catalyses the formation of superoxide by transferring an electron from NADPH to molecular oxygen (O_2), thereby forming the superoxide free radical. The unstable superoxide anion is converted to hydrogen peroxide, either spontaneously or by superoxide dismutase (SOD). Hydrogen peroxide can follow different metabolic pathways into more potent reactive oxidants (such as $OH^•$ or HOCl) or degradation to $H_2O + O_2$. *(Modified from Stiehm ER, Ochs HD, Winkelstein JA:* Immunologic disorders in infants and children, *ed 5, Philadelphia, 2004, WB Saunders, p 622.)*

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Chapter 128

Monocytes, Macrophages, and Dendritic Cells

Richard B. Johnston Jr.

Mononuclear phagocytes (monocytes, macrophages) are distributed across all body tissues and play a central role in maintaining homeostasis. They are essential for innate host defense against infection, tissue repair and remodeling, and the antigen-specific adaptive immune response. No human has been identified as having congenital absence of this cell line, probably because macrophages are required to remove primitive tissues during fetal development as new tissues develop to replace them. Monocytes and tissue macrophages in their several forms (Table 128-1) have variable morphology and surface markers and different transcriptional profiles but common functions, particularly phagocytosis. **Dendritic cells** (DCs) are specialized derivatives of this system that develop from myeloid–lymphoid cell precursors.

DEVELOPMENT

Monocytes develop more rapidly during bone marrow hematopoiesis and remain longer in the circulation than do neutrophils (see Table 127-1). The first recognizable monocyte precursor is the monoblast, followed by the promonocyte with cytoplasmic granules and an indented nucleus, and, finally, the fully developed monocyte with cytoplasm filled with granules containing hydrolytic enzymes. The transition from monoblast to mature circulating monocyte requires about 6 days.

Two major subsets of human blood monocytes can be identified on the basis of surface antigens: CD14++ CD16–, originally termed

Table 128-1 Principal Sites of Macrophages in Tissues

Liver (Kupffer cells)
Lung (interstitial and alveolar macrophages)
Connective tissue, adipose tissue, and interstitium of major organs and skin
Serosal cavities (pleural and peritoneal macrophages)
Synovial membrane (type A synoviocytes)
Bone (osteoclasts)
Brain and retina (microglial cells)
Spleen, lymph nodes, bone marrow
Intestinal wall
Breast milk
Placenta
Granulomas (multinucleated giant cells)

Table 128-2 Upregulated Functions in Macrophages Activated in Response to Infection

Microbicidal and tumoricidal activity
Phagocytosis (of most particles) and pinocytosis
Phagocytosis-associated respiratory burst (O_2^-, H_2O_2)
Generation of nitric oxide
Chemotaxis
Glucose transport and metabolism
Membrane expression of MHC, CD40, TNF receptor
Antigen presentation
Secretion
Complement components
Lysozyme, acid hydrolases, and cytolytic proteinases
Collagenase
Plasminogen activator
Interleukins, including IL-1, IL-12, and IL-15
TNF-α
Interferons, including IFN-α and IFN-β
Antimicrobial peptides (cathelicidin, defensins)
Angiogenic factors

H_2O_2, hydrogen peroxide; IFN, interferon; IL, interleukin; MHC, major histocompatibility complex; O_2^-, superoxide anion; TNF, tumor necrosis factor.

"classical monocytes" because they constitute 90-95% of total monocytes, and the more mature CD14+ CD16+ "proinflammatory" monocytes, which produce more proinflammatory tumor necrosis factor-α (TNF-α) and less immunosuppressive interleukin (IL)-10 in response to microbial stimuli. Monocytes of either subset migrate into tissues in response to localized inflammation or, apparently, randomly in the absence of inflammation.

Most organ macrophages probably arise from macrophage progenitors that develop in the embryo before hematopoiesis occurs. Exceptions are macrophage populations in the skin and intestines and at sites of active inflammation, which appear to derive commonly from blood monocytes.

Whether tissue macrophages originate from blood monocytes or in the embryo, organ-specific factors must influence differentiation of the precursor cells and endow each tissue macrophage type with its characteristic features. Monocytes or embryonic progenitors in the liver become **Kupffer cells** that bridge the sinusoids separating adjacent plates of hepatocytes. Those at the lung airway surface become large ellipsoid **alveolar macrophages,** and those in the bone become **osteoclasts.** All macrophages have at least 3 major functions in common: phagocytosis, presentation of antigens to lymphocytes, and enhancement or suppression of the immune response through release of a variety of potent hormone-like factors termed cytokines. At sites of inflammation, monocytes and macrophages can fuse to form multinucleated giant cells; these cells maintain the antimicrobial functions of macrophages.

ACTIVATION

The most important step in the maturation of tissue macrophages is the conversion from a resting to a more functionally active cell, a process driven primarily by certain cytokines and microbial products. **Macrophage activation** is a generic term, with the functional characteristics of an activated macrophage population varying with the cytokine or other stimulus (microbial, chemical) to which the population has been exposed.

Classical activation refers to a response to infection that is driven by specifically activated T-helper (Th) type 1 (Th1)–type lymphocytes and natural killer cells through their release of interferon-γ (IFN-γ). TNF-α secreted by activated macrophages amplifies their activation, as does bacterial cell wall protein or endotoxin through Toll-like receptors. **Alternative activation** is driven by Th2–type lymphocytes through release of IL-4 and IL-13, cytokines that regulate antibody responses, allergy, and resistance to parasites. Alternatively activated macrophages may have particular functional advantages, such as in wound healing and immunoregulation. In the traditional context of host defense, the term *activated macrophage* indicates that the "classically activated" cell has an enhanced capacity to kill microorganisms or tumor cells. These macrophages are larger, with more pseudopods and pronounced ruffling of the plasma membrane, and they exhibit accelerated activity of many functions (Table 128-2). Considering the variety of macrophage activities essential to the maintenance of homeostasis, it seems likely that so-called classically and alternatively activated macrophages are examples of a continuum of physiologic functions expressed by these long-lived cells in response to the specific task at hand.

Classical macrophage activation is accomplished during infection with intracellular pathogens (e.g., mycobacteria, *Listeria*) through crosstalk between Th1 lymphocytes and antigen-presenting macrophages mediated by the engagement of a series of ligands and receptors on the 2 cell types, including CD40 on macrophages and CD40 ligand on Th cells, and through secretion of cytokines. Macrophages encountering microorganisms release IL-12, which stimulates T cells to release IFN-γ. These interactions constitute the basis of cell-mediated immunity. IFN-γ is an especially important macrophage-activating cytokine; it is currently used as a therapeutic agent.

FUNCTIONAL ACTIVITIES

Numerous functions are upregulated when the macrophage is activated in response to infection (see Table 128-2). Obviously important are the ingestion and killing of intracellular pathogens such as mycobacteria, *Listeria, Leishmania, Toxoplasma,* and some fungi; however, splenic and hepatic macrophages also clear extracellular pathogens such as pneumococci from the bloodstream. Killing of the ingested organisms depends heavily on products of the respiratory burst (e.g., hydrogen peroxide) and on nitric oxide, and release of these metabolites is enhanced in activated macrophages.

The activity of mononuclear phagocytes against cancers in humans is less-well understood. This activity may involve more than the phagocytic process. Macrophages may kill tumor cells by means of secreted products, including lysosomal enzymes, nitric oxide, oxygen metabolites, cytolytic proteinases, and TNF-α. Proteolytic enzymes and cytocidal factors present on the surface membrane of monocytes may have a role in tumor rejection. In contrast, tumor-associated macrophages also appear to stimulate growth of certain tumors through secretion of growth and angiogenic factors.

The capacity to undergo diapedesis across the endothelial wall of blood vessels and to migrate to sites of microbial invasion is essential to monocyte function. Chemotactic factors for monocytes include complement products and chemokines derived from neutrophils, lymphocytes, and other cell types. Phagocytosis of the invading organisms can then occur, influenced by the presence of opsonins for the invader (antibody, complement, mannose-binding and surfactant proteins), the inherent surface properties of the microorganism, and the state of activation of the macrophage.

Monocytes migrating to intestinal mucosa are modified by stromal factors so that they lose innate receptors for microbial products such

as endotoxin, and they do not effectively produce proinflammatory cytokines. They retain, however, the capacity to ingest and kill microbes. They have been modified during evolution to allow the absence of inflammation typical of normal intestinal mucosa in spite of its constant exposure to huge numbers of microbes and their inflammatory by-products.

Macrophages play an essential role in the disposal of damaged and dying cells, helping resolve the inflammatory response and heal wounds. Brain microglia demonstrate these functions particularly well. In conditions such as stroke, neurodegenerative disease, and tumor invasion, these cells can become activated, surround damaged and dead cells, and clear cellular debris. Macrophages lining the sinusoids of the spleen are especially important in ingesting aged or autoantibody-coated erythrocytes or platelets; splenectomy is used to manage autoimmune cytopenias. Macrophages in inflammatory sites can recognize changes in phosphatidylserine on the membrane of neutrophils undergoing apoptosis, and these can be removed before they become necrotic and spill their toxic contents into the tissue. Macrophages also remove the extracellular traps exuded by inflammatory neutrophils, thus reducing the risk of autoimmunity. Macrophages can be identified early in fetal development, where they function to remove debris as one maturing embryonic tissue replaces another. They are also important in removing immune complexes, protein fragments, and inorganic particles such as elements of cigarette smoke that enter the alveoli.

Macrophages are integrally involved in the induction and expression of adaptive immune responses, including antibody formation and cell-mediated immunity. This involvement depends on their capacity to break down foreign material in phagocytic and pinocytic vesicles and then present individual antigens on their surface as peptides or polysaccharides bound to class II major histocompatibility complex (MHC) molecules. B lymphocytes and, most effectively, DCs can also present antigens to T cells for the specific immune response. Expression of MHC class II molecules is increased in activated macrophages, and antigen presentation is more effective.

The heightened capacity of activated macrophages to synthesize and release various hydrolytic enzymes and microbicidal materials (see Table 128-2) probably plays a part in their increased killing capacity, although not every macrophage product is secreted in increased amounts when the cell is activated. The macrophage is an extraordinarily active secretory cell. It has been shown to secrete more than 100 distinct substances, including cytokines, growth factors, and sterol hormones, placing it in a class with the hepatocyte. Because of the profound effect of some of these secretory products on other cells and the large number and widespread distribution of macrophages, this network of cells can be viewed as an important endocrine organ. IL-1 illustrates this point well. Microbes and microbial products, burns, ischemia–reperfusion, and other causes of inflammation or tissue damage stimulate the release of IL-1, mainly by monocytes, macrophages, and epithelial cells. In turn, IL-1 elicits fever, sleep, and release of IL-6, which induces production of acute-phase proteins.

As traumatic damage and infection subside, the macrophage population shifts toward playing an essential role in tissue repair and healing through removal of apoptotic cells and secretion of IL-10, transforming growth factor-β, lipoxins, and omega-3 fatty acid–derived resolvins, protectins, and maresins (macrophage mediators in resolving inflammation).

DENDRITIC CELLS

DCs are derived from both myeloid and lymphoid bone marrow progenitors. They are specialized to capture, process, and present antigens to T cells to generate adaptive immunity or tolerance to self-antigens. Human monocytes can be induced to differentiate into DCs in some circumstances, particularly inflammation. DCs express retractable dendritic (branched) extensions and potent endocytic capacity but are a heterogeneous population from the standpoint of location, surface markers, level of antigen-presenting activity, and function. There are 2 major functional types of DCs, *conventional DCs,* which include Langerhans cells in the epithelial surfaces of skin and mucosa, and dermal or interstitial DCs in subepithelial skin and interstitia of solid organs; and *plasmacytoid DCs*, sentinels for viral infection and principal source of antiviral IFN-α and IFN-β.

DCs migrating from the bloodstream enter skin, epithelial surfaces, and lymphoid organs where, as immature cells, they internalize self- and foreign-antigens. Microbial products, cytokines, or molecules exposed in damaged tissue ("danger signals" or "alarmins") induce DC maturation, with upregulation of cytokine receptors and MHC class II and costimulatory molecules. Stimulated DCs in the periphery migrate to lymphoid organs where they continue to mature. They function there as the most potent cells that present antigens to T lymphocytes and induce their proliferation, activities that are central to the antigen-specific adaptive immune response. Macrophage IL-10 acts to suppress DC maturation during resolution of inflammation.

DCs from cancer patients have been used in an attempt to control their cancer. The patient's DCs are amplified and matured from blood monocytes or marrow progenitor cells by cytokines, exposed to antigens from the patient's tumor, then injected into the patient as a "vaccine" against the cancer.

ABNORMALITIES OF MONOCYTE-MACROPHAGE OR DENDRITIC CELL FUNCTION

Mononuclear phagocytes, as well as neutrophils, from patients with **chronic granulomatous disease** exhibit a profound defect of phagocytic killing (see Chapter 130). The inability of affected macrophages to kill ingested organisms leads to abscess formation and characteristic granulomas at sites of macrophage accumulation beneath the skin and in the liver, lungs, spleen, and lymph nodes. IFN-γ is currently used for preventing infection in patients with chronic granulomatous disease and for treating the decreased bone resorption of **congenital osteopetrosis**, which is caused by decreased function of osteoclasts. Genetic deficiency of the CD11/CD18 complex of membrane adherence glycoproteins **(leukocyte adhesion defect-1),** which includes a receptor for opsonic complement component 3, results in impaired phagocytosis by monocytes (see Chapter 130).

The monocyte–macrophage system is prominently involved in **lipid storage diseases** called sphingolipidoses (see Chapter 86.3). In these conditions, the expression in macrophages of a systemic enzymatic defect permits the accumulation of cell debris that is normally cleared. Resistance to infection can be impaired, at least partly because of impairment in macrophage function. **Gaucher disease** is the prototype for these disorders. In this condition, the enzyme glucocerebrosidase functions abnormally, thus allowing accumulation of glucocerebroside from cell membranes in Gaucher cells throughout the body. In all locations, the Gaucher cell is an altered macrophage. These patients can be treated with infusions of the normal enzyme modified to expose mannose residues, which bind to mannose receptors on macrophages.

The cytokine IL-12 is a powerful inducer of IFN-γ production by T cells and natural killer cells. Individuals with inherited deficiency in macrophage receptors for IFN-γ or lymphocyte receptors for IL-12, or in IL-12 itself, suffer a severe, profound, and selective susceptibility to infection by nontuberculous mycobacteria such as *Mycobacterium avium* complex or bacillus Calmette-Guérin (see Chapter 126). About half of these patients have had disseminated *Salmonella* infection. These abnormalities are now grouped as **defects in the IFN-γ–IL-12 axis**.

Monocyte–macrophage function has been shown to be partially abnormal in various clinical conditions. Cultured mononuclear phagocytes of newborns are more readily infected than adult cells by HIV-1 and measles virus. Macrophages from newborns release less granulocyte colony-stimulating factor and IL-6 in culture, and this deficiency is accentuated in cells from preterm infants. This finding supports the observations that levels of granulocyte colony-stimulating factor are significantly decreased in blood from newborns, and that the marrow granulocyte storage pool is diminished in infants, particularly preterm infants. Mononuclear cells from newborns produce less IFN-γ and IL-12 than do adult cells, and macrophages cultured from cord blood are not activated normally by IFN-γ. This combination of deficiencies

would be expected to blunt the newborn's response to infection by viruses, fungi, and certain bacteria such as *Listeria*.

There are 2 disorders in which macrophage activation is pathologically excessive. **Familial and acquired hemophagocytic lymphohistiocytosis** is characterized by uncontrolled activation of T cells and macrophages, with resultant fever, hepatosplenomegaly, lymphadenopathy, pancytopenia, marked elevation of serum proinflammatory cytokines, and macrophage hemophagocytosis (see Chapter 507). Up to 5% of children with systemic onset juvenile rheumatoid arthritis develop an acute severe complication termed **macrophage activation syndrome,** with persistent fever (rather than typical febrile spikes), hepatosplenomegaly, pancytopenia, macrophage hemophagocytosis, and coagulopathy, which can progress to disseminated intravascular coagulation and death if not recognized (see Chapter 155).

Two genetic autoinflammatory diseases result from dysregulation of the mononuclear phagocyte–produced proinflammatory cytokine IL-1. In **neonatal onset multisystem inflammatory disorder** monocytes overproduce IL-1**.** In **deficiency of the IL-1-receptor antagonist**, normal activity levels of IL-1 go unopposed. In both conditions patients present in the 1st few days or weeks of life with pustular or urticarial rash, bony overgrowth, sterile osteomyelitis, elevated sedimentation rate, and other evidence of systemic inflammation. The recombinant IL-1-receptor antagonist anakinra is effective treatment for both these disorders.

The term *histiocyte* was originally used to describe cells thought to be macrophages in fixed tissue preparations. Histiocytosis X represents a malignancy-like overgrowth of Langerhans-type DCs (see Chapter 507). Thus, the term **Langerhans cell histiocytosis** better describes this disorder, because histiocyte is a histologic term and not cell specific.

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Chapter 129

Eosinophils

Brian P. Vickery

Eosinophils are distinguished from other leukocytes by their morphology, constituent products, and association with specific diseases. Eosinophils are nondividing fully differentiated cells with a diameter of ≈8 μm and a bilobed nucleus. They differentiate from stem cell precursors in the bone marrow under the control of T-cell–derived interleukin (IL)-3, granulocyte-macrophage colony-stimulating factor, and, especially, IL-5. Their characteristic membrane-bound specific granules stain reddish brown with eosin and consist of a crystalline core made up of major basic protein (MBP) surrounded by a matrix containing the eosinophil cationic protein, eosinophil peroxidase, and eosinophil-derived neurotoxin. These basic proteins are cytotoxic for the larval stages of helminthic parasites and are also thought to contribute to much of the inflammation associated with chronic allergic diseases such as asthma (see Chapter 144).

Both eosinophil MBP and eosinophil cationic protein are also present in large quantities in the airways of patients who have died of asthma and are thought to inflict epithelial cell damage leading to airway hyperresponsiveness. Eosinophil granule contents also contribute to Loeffler endocarditis associated with hypereosinophilic syndrome. MBP has the potential to activate other proinflammatory cells, including mast cells, basophils, neutrophils, and platelets. Eosinophils have the capacity to generate large amounts of the lipid mediators platelet-activating factor and leukotriene C_4, both of which can cause vasoconstriction, smooth muscle contraction, and mucus hypersecretion. Eosinophils are a source of a number of proinflammatory cytokines, including IL-1, IL-3, IL-4, IL-5, IL-9, IL-13, and granulocyte-macrophage colony-stimulating factor; they can also function as antigen-presenting cells. Thus, eosinophils have considerable potential to initiate and sustain inflammatory response of the innate and acquired immune systems.

Eosinophil migration from the vasculature into the extracellular tissue is mediated by the binding of leukocyte adhesion receptors to their ligands or counterstructures on the postcapillary endothelium. Similar to neutrophils (see Fig. 127-2), transmigration begins as the eosinophil selectin receptor binds to the endothelial carbohydrate ligand in loose association, which promotes eosinophils rolling along the endothelial surface until they encounter a priming stimulus such as a chemotactic mediator. Eosinophils then establish a high-affinity bond between integrin receptors and their corresponding immunoglobulin-like ligand. Unlike neutrophils, which become flattened before transmigrating between the tight junctions of the endothelial cells, eosinophils can use unique integrins, known as VLA-4, to bind to vascular cell adhesion molecule-1, which enhances eosinophil adhesion and transmigration through endothelium. Eosinophils are recruited to tissues in inflammatory states by the chemokine **eotaxin.** These unique pathways account for selective accumulation of eosinophils in allergic and inflammatory disorders. Eosinophils normally dwell primarily in tissues, especially tissues with an epithelial interface with the environment, including the respiratory, gastrointestinal, and lower genitourinary tracts. The life span of eosinophils may extend for weeks within tissues.

IL-5 selectively enhances eosinophil production, adhesion to endothelial cells, and function. Considerable evidence shows that IL-5 has a pivotal role in promoting eosinophil accumulation. It is the predominant cytokine in allergen-induced pulmonary late-phase reaction, and antibodies against IL-5 block eosinophil infiltration into the lungs in animal models associated with airway hyperresponsiveness following allergen challenge. Eosinophils also bear unique receptors for several chemokines, including RANTES (regulated upon activation, normal T-cell expressed and secreted), eotaxin, and monocyte chemotactic proteins 3 and 4. These chemokines appear to be key mediators in the induction of tissue eosinophilia.

DISEASES ASSOCIATED WITH EOSINOPHILIA

The **absolute eosinophil count** (AEC) is used to quantify eosinophilia. Calculated as the white blood cell count/μL × percent of eosinophils, it is usually <450 cells/μL and varies diurnally, with eosinophil numbers higher in the early morning and diminishing as endogenous glucocorticoid levels rise.

Many diseases with allergic, infectious, hematologic, autoimmune, or idiopathic origins are associated with moderate (AEC 1,500-5,000 cells/μL) or severe (AEC >5,000 cells/μL) eosinophilia in peripheral blood (Table 129-1). These disorders may range from mild and transient to chronic and life-threatening, and, importantly, blood eosinophil numbers do not always reflect the extent of eosinophil involvement in disease-affected tissues. Because prolonged eosinophilia is associated with end-organ damage, especially involving the heart, patients with persistently elevated AECs should undergo a thorough evaluation to search for an underlying cause.

Allergic Diseases

Allergy is the most common cause of eosinophilia in children in the United States. Patients with allergic asthma commonly have eosinophils in the blood, sputum, and/or lung tissue. Hypersensitivity drug reactions can elicit eosinophilia, and when associated with organ dysfunction (e.g., DRESS [drug rash with eosinophilia and systemic symptoms]), these reactions can be serious (see Chapter 152). If a drug is suspected of triggering eosinophilia, biochemical evidence of organ dysfunction should be sought and if found, the drug should be discontinued. Various skin diseases have also been associated with eosinophilia, including atopic dermatitis/eczema, pemphigus, urticaria, and toxic epidermal necrolysis.

Table 129-1 Causes of Eosinophilia

ALLERGIC DISORDERS
Allergic rhinitis
Asthma
Acute and chronic urticaria
Pemphigoid
Hypersensitivity drug reactions (drug rash with eosinophilia and systemic symptoms [DRESS])
Eosinophilic gastrointestinal disorders
Interstitial nephritis
INFECTIOUS DISEASES
Tissue-Invasive Helminth Infections
Trichinosis
Toxocariasis
Strongyloidosis
Ascariasis
Filariasis
Schistosomiasis
Echinococcosis
Pneumocystis carinii
Toxoplasmosis
Scarlet fever
Amebiasis
Malaria
Bronchopulmonary aspergillosis
Coccidioidomycosis
Scabies
MALIGNANT DISORDERS
Brain tumors
Hodgkin disease and T-cell lymphoma
Acute myelogenous leukemia
Myeloproliferative disorders
Eosinophilic leukemia
GASTROINTESTINAL DISORDERS
Inflammatory bowel disease
Peritoneal dialysis
Chronic active hepatitis
Eosinophilic gastrointestinal disorders:
• Eosinophilic esophagitis
• Eosinophilic gastroenteritis
• Eosinophilic colitis
RHEUMATOLOGIC DISEASE
Rheumatoid arthritis
Eosinophilic fasciitis
Scleroderma
IMMUNODEFICIENCY DISEASE
Hyperimmunoglobulin E syndromes
Wiskott-Aldrich syndrome
Graft-versus-host disease
Omenn syndrome
Severe congenital neutropenia
Hypersensitivity pneumonia
MISCELLANEOUS
Thrombocytopenia with absent radii
Churg-Strauss syndrome (eosinophilic granulomatosis with vasculitis)
Vasculitis
Adrenal insufficiency
Postirradiation of abdomen
Histiocytosis with cutaneous involvement
Hypereosinophilic syndromes
Autoimmune lymphoproliferative syndromes (ALPS)
Immune dysregulation, polyendocrinopathy, X-linked (IPEX)

Eosinophilic gastrointestinal diseases are important emerging allergic causes of eosinophilia in tissue and, in some cases, peripheral blood (see Chapter 337). In these conditions, eosinophils are inappropriately recruited to esophagus, stomach, and/or intestine, where they induce tissue inflammation and clinical symptoms such as dysphagia, food aversion, abdominal pain, vomiting, and diarrhea. Treatment options include allergen elimination diets and swallowed topical corticosteroids.

Infectious Diseases

Eosinophilia is often associated with invasive infection with multicellular helminthic parasites, which are the most common cause in developing countries. Table 129-1 includes examples of specific organisms. The level of eosinophilia tends to parallel the magnitude and extent of tissue invasion, especially by larvae such as visceral larva migrans (see Chapter 298). Eosinophilia often *does not* occur in established parasitic infections that are well contained within tissues or are solely intraluminal in the gastrointestinal tract, such as *Giardia lamblia* and *Enterobius vermicularis* infection.

In evaluating patients with unexplained eosinophilia, the dietary history and geographic or travel history may indicate potential exposures to helminthic parasites. It is frequently necessary to examine the stool for ova and larvae at least 3 times. Additionally, the diagnostic parasite stages of many of the helminthic parasites that cause eosinophilia never appear in feces. Thus, normal results of stool examinations do not absolutely preclude a helminthic cause of eosinophilia; diagnostic blood tests or tissue biopsy may be needed. *Toxocara* causes **visceral larva migrans** usually in toddlers with pica (see Chapter 298). Most young children are asymptomatic, but some develop fever, pneumonitis, hepatomegaly, and hypergammaglobulinemia accompanied by severe eosinophilia. Isohemagglutinins are frequently elevated. Serology can establish the diagnosis.

Two fungal diseases may be associated with eosinophilia: aspergillosis in the form of **allergic bronchopulmonary aspergillosis** (see Chapter 237.1) and coccidioidomycosis (see Chapter 240) following primary infection, especially in conjunction with erythema nodosum. HIV can also be associated with peripheral eosinophilia.

Hypereosinophilic Syndrome

The idiopathic hypereosinophilic syndrome is a heterogeneous group of disorders characterized by sustained overproduction of eosinophils. The 3 diagnostic criteria for this disorder are (1) AEC >1,500 cells/μL persisting for 6 mo or longer or at least on 2 occasions or with evidence of tissue eosinophilia; (2) absence of another diagnosis to explain the eosinophilia; and (3) signs and symptoms of organ involvement. The clinical signs and symptoms of hypereosinophilic syndrome can be heterogeneous because of the diversity of potential organ (pulmonary, cutaneous, neurologic, serosal, gastrointestinal) involvement. Loeffler endocarditis, one of the most serious and life-threatening complications, can cause heart failure from endomyocardial thrombosis and fibrosis. Eosinophilic leukemia, a clonal myeloproliferative variant, may be distinguished from idiopathic hypereosinophilic syndrome by demonstrating a clonal interstitial deletion on chromosome 4q12 that fuses the platelet-derived growth factor receptor-α (PDGFRA) and FIP1-like-1 (FIP1L1) genes; this disorder is treated with imatinib mesylate, which helps target the fusion oncoprotein (Fig. 129-1).

Therapy is aimed at suppressing eosinophilia and is initiated with corticosteroids. Imatinib mesylate, a tyrosine kinase inhibitor, may be effective in FIP1L1-PDGFRA–negative patients. Hydroxyurea may be beneficial in patients unresponsive to corticosteroids. Specific anti–IL-5 monoclonal antibodies (mepolizumab) target this cytokine, which has a central role in eosinophil differentiation, mobilization and activity. With therapy, the eosinophil count declines and corticosteroid doses may be reduced. For patients with prominent organ involvement who fail to respond to therapy, the mortality is ≈75% after 3 yr.

Miscellaneous Diseases

Eosinophilia is observed in many patients with primary immunodeficiency syndromes, especially hyperimmunoglobulin E syndrome (see Chapters 122 and 126), Wiskott-Aldrich syndrome, and Omenn syndrome. Eosinophilia is also frequently present in the syndrome of thrombocytopenia with absent radii and in familial

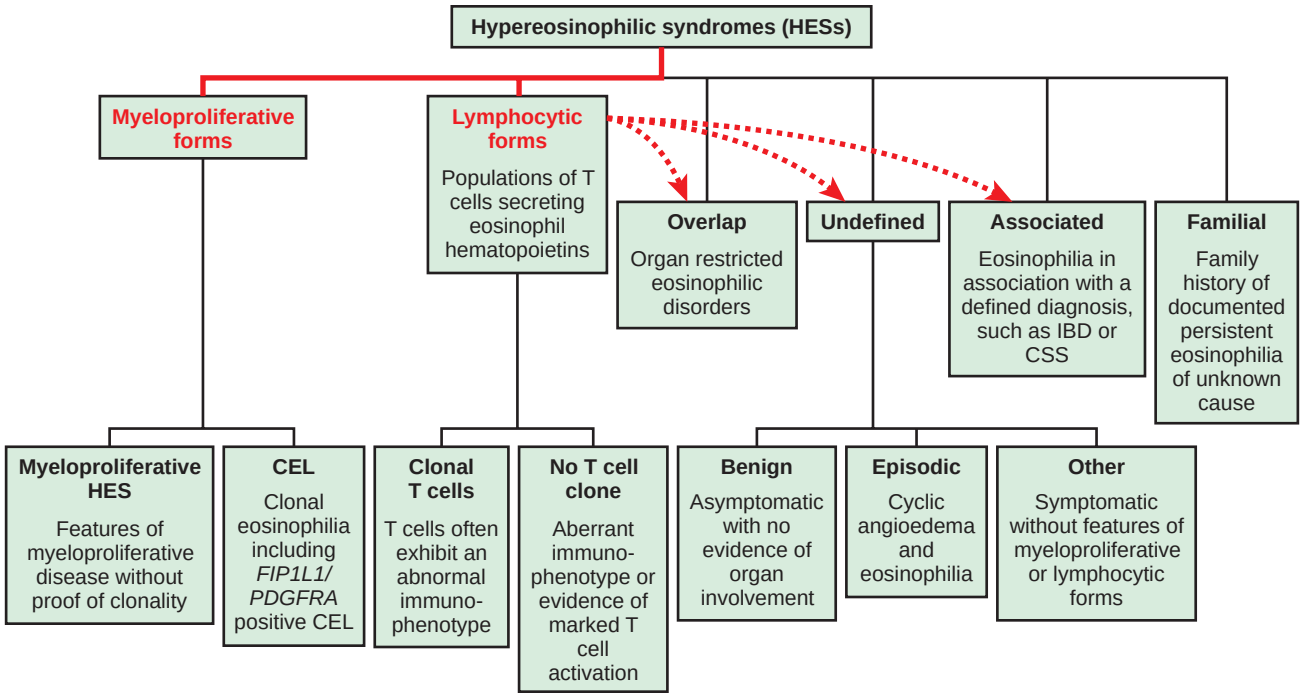


Figure 129-1 **Revised classification of hypereosinophilic syndromes.** Changes from the previous classification are indicated in *red*. *Dashed arrows* identify hypereosinophilic syndrome (HES) forms for which at least some patients have T-cell–driven disease. Classification of myeloproliferative forms has been simplified, and patients with HES and eosinophil hematopoietin–producing T cells in the absence of a T-cell clone are included in the lymphocytic forms of HES. *IBD,* Inflammatory bowel disease. *(From Simon HU, Rothenberg ME, Bocher BS, et al: Refining the definition of hypereosinophilic syndrome.* J Allergy Clin Immunol *126:45–49, 2010, Fig. 1, p. 47.)*

reticuloendotheliosis with eosinophilia. Eosinophilia can be found in patients with Hodgkin disease, as well as in acute lymphoid and myeloid leukemia. Other considerations include gastrointestinal disorders such as ulcerative colitis, Crohn disease during symptomatic phases, chronic hepatitis, Churg-Strauss vasculitis, and adrenal insufficiency.

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Chapter 130

Disorders of Phagocyte Function

Thomas D. Coates

Neutrophils are the first-line of defense against microbial invasion. They arrive at the site of inflammation during the critical 2-4 hr after microbial invasion to contain the infection and prevent hematogenous dissemination. This well-orchestrated process is one of the most interesting stories in modern cell biology. In fact, much of our knowledge about neutrophil function derives from studies done in patients with genetic errors in neutrophil function. These critical functions and their associated disorders are depicted in Figure 127-2. Children with phagocytic dysfunction present at a young age with recurrent infections that are often involve unusual organisms and are poorly responsive to treatment.

Primary defects of phagocytic function comprise fewer than 20% of immunodeficiencies and there is significant overlap in the presenting signs and symptoms between phagocytic disorders and lymphocyte and humeral disorders. Children with phagocytic defects present with deep tissue infection, pneumonia, adenitis, or osteomyelitis rather than blood stream infections (Tables 130-1 and 130-2, and Fig. 130-1). A few clinical features point to phagocyte defects rather than other immunodeficiencies, but correct diagnosis relies on highly specialized laboratory tests.

Chemotaxis, the direct migration of cells into sites of infection, involves a complex series of events (see Chapter 127). Disorders of adhesion or granule abnormalities can have intermediate or profound motility defects and the propensity to infections is related to a combination of these functional deficits. However, studies of a Tongan family with recessively inherited neutrophil actin dysfunction tell us that a pure severe chemotactic defect can result in fatal recurrent infection. Defective in vitro chemotaxis of neutrophils can be detected in children having various clinical conditions. However, unless chemotaxis is essentially absent, it is difficult to establish whether frequent infections arise from a primary chemotactic abnormality or occur as secondary medical complications of the underlying disorder. For example, dental infection with *Capnocytophaga* is associated with a clear neutrophil motility defect that resolves when the infection is eliminated.

Motility defects present with significant skin and mucosal infections. They can also have tender cutaneous nodular lesions that characteristically do not contain any neutrophils. In fact, presence of a true abscess makes the diagnosis of a significant chemotactic defect less likely.

Laboratory tests of chemotaxis are biologic assays and have high variability except in the most experienced of hands. The assays must be done on freshly obtained blood and are affected by many factors related to blood sampling itself. It is best to assay other features of the suspected disorder, such as surface marker expression, to establish a specific diagnosis.

LEUKOCYTE ADHESION DEFICIENCY

Leukocyte adhesion deficiency 1 (LAD-1), 2 (LAD-2), and 3 (LAD-3) are rare autosomal recessive disorders of leukocyte function. LAD-1 affects about 1 per 10 million individuals and is characterized by

Table 130-1 Infections and WBC Defects: Features That Can Be Seen in Phagocyte Disorders

SEVERE INFECTIONS		RECURRENT INFECTIONS		SPECIFIC INFECTIONS		UNUSUALLY LOCATED INFECTIONS	
TYPE OF INFECTION	**DIAGNOSIS TO CONSIDER**	**SITE OF INFECTION**	**DIAGNOSIS TO CONSIDER**	**MICROORGANISM**	**DIAGNOSIS TO CONSIDER**	**SITE OF INFECTION**	**DIAGNOSIS TO CONSIDER**
Cellulitis	Neutropenia, LAD CGD, HIES	Cutaneous	Neutropenia, CGD, LAD, HIES	*Staphylococcus epidermidis*	Neutropenia, LAD	Umbilical cord	LAD
Colitis	Neutropenia, CGD	Gums	LAD, neutrophil motility disorders	*Serratia marcescens, Nocardia, Burkholderia cepacia*	CGD	Liver abscess	CGD
Osteomyelitis	CGD, MSMD pathway defects	Upper and lower respiratory tract	Neutropenia, HIES, functional neutrophil disorders	*Aspergillus*	Neutropenia, CGD, HIES	Gums	LAD, neutrophil motility disorders
		Gastrointestinal tract	CGD, MSMD pathway defects (salmonella)	Nontuberculous mycobacteria, BCG	MSMD pathway defects, SCID, CGD		
		Lymph nodes	CGD, MSMD pathway defects (mycobacteria)	*Candida*	Neutropenia, CGD, MPO		
		Osteomyelitis	CGD, MSMD				

BCG, bacille Calmette-Guérin; CGD, chronic granulomatous disease; HIES, hyperimmunoglobulin E syndrome; LAD, leukocyte adhesion deficiency; MSMD, Mendelian susceptibility to mycobacterial disease; SCID, severe combined immunodeficiency.

From Leung DYM: Pediatric allergy principles and practice, *ed 2, Philadelphia, 2010, WB Saunders, Table 12-1, p. 134.*

Table 130-2 Clinical Disorders of Neutrophil Function

DISORDER	ETIOLOGY	IMPAIRED FUNCTION	CLINICAL CONSEQUENCE
DEGRANULATION ABNORMALITIES			
Chédiak-Higashi syndrome	Autosomal recessive; disordered coalescence of lysosomal granules; responsible gene is *CHSI/LYST*, which encodes a protein hypothesized to regulate granule fusion	Decreased neutrophil chemotaxis, degranulation, and bactericidal activity; platelet storage pool defect; impaired NK function, failure to disperse melanosomes	Neutropenia; recurrent pyogenic infections, propensity to develop marked hepatosplenomegaly as a manifestation of the hemophagocytic syndrome
Specific granule deficiency	Autosomal recessive; functional loss of myeloid transcription factor arising from a mutation or arising from reduced expression of *Gfi-1* or *C/EBP*ε, which regulates specific granule formation	Impaired chemotaxis and bactericidal activity; bilobed nuclei in neutrophils; defensins, gelatinase, collagenase, vitamin B_{12}–binding protein, and lactoferrin	Recurrent deep-seated abscesses
ADHESION ABNORMALITIES			
Leukocyte adhesion deficiency 1	Autosomal recessive; absence of CD11/CD18 surface adhesive glycoproteins (β_2 integrins) on leukocyte membranes most commonly arising from failure to express CD18 messenger RNA	Decreased binding of C3bi to neutrophils and impaired adhesion to ICAM1 and ICAM2	Neutrophilia; recurrent bacterial infection associated with a lack of pus formation
Leukocyte adhesion deficiency 2	Autosomal recessive; loss of fucosylation of ligands for selectins and other glycol-conjugates arising from mutations of the GDP-fucose transporter	Decreased adhesion to activated endothelium expressing ELAM	Neutrophilia; recurrent bacterial infection without pus
Leukocyte adhesion deficiency 3 (LAD-1 variant syndrome)	Autosomal recessive; impaired integrin function arising from mutations of *FERMT3* which encodes kindlin-3 in hematopoietic cells; kindlin-3 binds to β-integrin and thereby transmits integrin activation	Impaired neutrophil adhesion and platelet activation	Neutrophilia; recurrent infections, bleeding tendency

Continued

Table 130-2 Clinical Disorders of Neutrophil Function—cont'd

DISORDER	ETIOLOGY	IMPAIRED FUNCTION	CLINICAL CONSEQUENCE
DISORDERS OF CELL MOTILITY			
Enhanced motile responses; FMF	Autosomal recessive gene responsible for FMF on chromosome 16 which encodes for a protein called pyrin; pyrin regulates caspase-1 and thereby IL-1β secretion; mutated pyrin may lead to heightened sensitivity to endotoxin, excessive IL-1β production, and impaired monocyte apoptosis	Excessive accumulation of neutrophils at inflamed sites, which may be the result of excessive IL-1β production	Recurrent fever, peritonitis, pleuritis, arthritis, and amyloidosis
DEPRESSED MOTILE RESPONSES			
Defects in the generation of chemotactic signals	IgG deficiencies; C3 and properdin deficiency can arise from genetic or acquired abnormalities; mannose-binding protein deficiency predominantly in neonates	Deficiency of serum chemotaxis and opsonic activities	Recurrent pyogenic infections
Intrinsic defects of the neutrophil, e.g., LAD, Chédiak-Higashi syndrome, specific granule deficiency, neutrophil actin dysfunction, neonatal neutrophils	In the neonatal neutrophil there is diminished ability to express β_2 integrins, and there is a qualitative impairment in β_2-integrin function	Diminished chemotaxis	Propensity to develop pyogenic infections
Direct inhibition of neutrophil mobility, e.g., drugs	Ethanol, glucocorticoids, cyclic AMP	Impaired locomotion and ingestion; impaired adherence	Possible cause for frequent infections; neutrophilia seen with epinephrine arises from cyclic AMP release from endothelium
Immune complexes	Bind to Fc receptors on neutrophils in patients with rheumatoid arthritis, systemic lupus erythematosus, and other inflammatory states	Impaired chemotaxis	Recurrent pyogenic infections
Hyper-IgE syndrome	Autosomal dominant; responsible gene is *Stat3*	Impaired chemotaxis at times; impaired regulation of cytokine production	Recurrent skin and sinopulmonary infections, eczema, mucocutaneous candidiasis, eosinophilia, retained primary teeth, minimal trauma fractures, scoliosis, and characteristic facies
Hyper-IgE syndrome–AR	Autosomal recessive; more than 1 gene likely contributes to its etiology	High IgE levels, impaired lymphocyte activation to staphylococcal antigens	Recurrent pneumonia without pneumatoceles sepsis, enzyme, boils, mucocutaneous candidiasis, neurologic symptoms, eosinophilia
MICROBICIDAL ACTIVITY			
Chronic granulomatous disease	X-linked and autosomal recessive; failure to express functional $gp91^{phox}$ in the phagocyte membrane in $p22^{phox}$ (AR). Other AR forms of CGD arise from failure to express protein $p47^{phox}$ or $p67^{phox}$	Failure to activate neutrophil respiratory burst leading to failure to kill catalase-positive microbes	Recurrent pyogenic infections with catalase-positive microorganisms
G6PD deficiency	Less than 5% of normal activity of G6PD	Failure to activate NADPH-dependent oxidase, and hemolytic anemia	Infections with catalase-positive microorganisms
Myeloperoxidase deficiency	Autosomal recessive; failure to process modified precursor protein arising from missense mutation	H_2O_2-dependent antimicrobial activity not potentiated by myeloperoxidase	None
Rac2 deficiency	Autosomal dominant; dominant negative inhibition by mutant protein of Rac2-mediated functions	Failure of membrane receptor–mediated O_2^- generation and chemotaxis	Neutrophilia, recurrent bacterial infections
Deficiencies of glutathione reductase and glutathione synthetase	AR; failure to detoxify H_2O_2	Excessive formation of H_2O_2	Minimal problems with recurrent pyogenic infections

AMP, adenosine monophosphate; AR, autosomal recessive; C, complement; CD, cluster of differentiation; CGD, chronic granulomatous disease; ELAM, endothelial-leukocyte adhesion molecule; FMF, familial Mediterranean fever; G6PD, glucose-6-phosphate dehydrogenase; GDP, guanosine diphosphate; ICAM, intracellular adhesion molecule; Ig, immunoglobulin; IL-1, interleukin-1; LAD, leukocyte adhesion deficiency; NADPH, nicotinamide adenine dinucleotide phosphate; NK, natural killer.

Modified from Curnutte JT, Boxer LA: Clinically significant phagocytic cell defects. In Remington JS, Swartz MN, editors: Current clinical topics in infectious disease, *ed 6, New York, 1985, McGraw-Hill, p 144.*

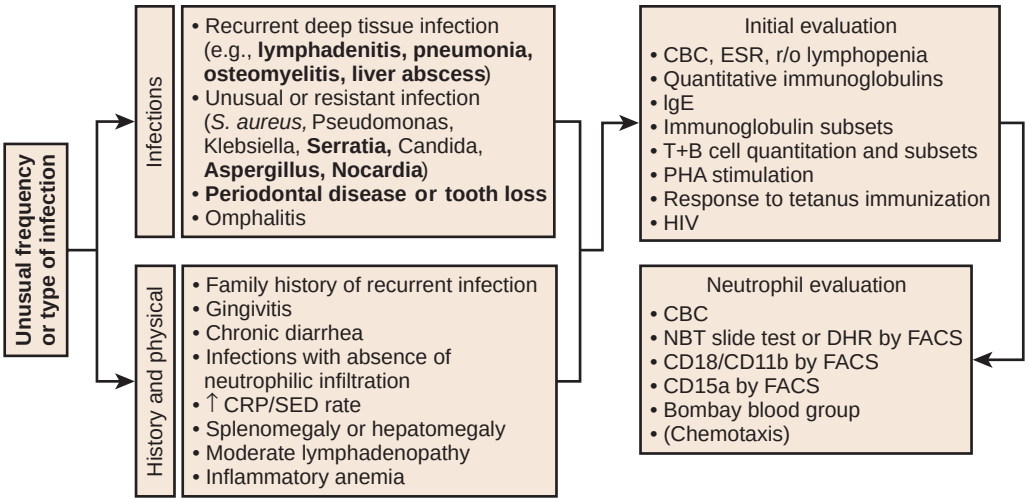


Figure 130-1 Algorithm for clinical evaluation of patients with recurrent infections. Shown are the evaluations that can be done in a routine clinical laboratory. The CBC can detect marked leukocytosis in LAD and giant granules of Chédiak-Higashi may be seen on the smear. Chemotaxis and all other neutrophil functions assays require highly specialized research laboratories. *CBC*, complete blood count; *CD*, cluster of differentiation; *CRP*, C-reactive protein; *DHR*, dihydrorhodamine; *ESR*, erythrocyte sedimentation rate; *HIV*, human immunodeficiency virus; *Ig*, immunoglobulin; *NBT*, nitro blue tetrazolium. *(Modified from Dinauer, MC, Coates TD, Disorders of neutrophil function. In Hoffman R, Benz EJ, Silberstein LE, Helsop H, Weitz J, Anastasi J, editors:* Hematology: basic principles and practice, *ed 6, Philadelphia, 2012, WB Saunders, pp. 655–674.)*

Table 130-3 Leukocyte Adhesion Deficiency Syndromes

LEUKOCYTE ADHESION DEFICIENCY (LAD)	TYPE 1 (LAD1)	TYPE 2 (LAD2 OR CDG-IIC)	TYPE 3 (LAD3)	E-SELECTIN DEFICIENCY	RAC2 DEFICIENCY
OMIM	116920	266265	612840	131210	602049
Inheritance pattern	Autosomal recessive	Autosomal recessive	Autosomal recessive	Unknown	Autosomal dominant
Affected protein(s)	Integrin β_2 common chain (CD18)	Fucosylated proteins (e.g., sialyl-Lewis^x, CD15s)	Kindlin 3	Endothelial E-selectin expression	Rac2
Neutrophil function affected	Chemotaxis, tight adherence	Rolling, tethering	Chemotaxis, adhesion, superoxide production	Rolling, tethering	Chemotaxis, superoxide production
Delayed umbilical cord separation	Yes (severe phenotype only)	Yes	Yes	Yes	Yes
Leukocytosis/ neutrophilia	Yes	Yes	Yes	No (mild neutropenia)	Yes

OMIM, Online Mendelian Inheritance in Man.
From Leung DYM: Pediatric allergy principles and practice, *ed 2, Philadelphia, 2010, WB Saunders, Table 12-4, p. 139.*

recurrent bacterial and fungal infections and depressed inflammatory responses despite striking blood neutrophilia (Table 130-3). The neutrophils have significant defects in adhesion, motility, and ability to phagocytose bacteria.

Genetics and Pathogenesis

LAD-1 results from mutations of the gene on chromosome 21q22.3 encoding CD18, the 95-kDa β_2-leukocyte transmembrane integrin subunit. Normal neutrophils express 4 heterodimeric adhesion molecules: LFA-1 (CD11a/CD18), Mac-1 (CD11b/CD18, also known as CR3 or iC3b receptor), p150,95 (CD11c/CD18), and α_1 β_2 (CD11d/CD18). These 4 transmembrane adhesion molecules are composed of unique extracellular α_1 encoded on chromosome 16, and share a common β_2 subunit (CD18) that links them to the membrane and connects them to intracellular signal transduction machinery. This group of leukocyte integrins is responsible for the tight adhesion of neutrophils to the endothelial cell surface, egress from the circulation, and adhesion to iC3b-coated microorganisms, which promotes phagocytosis and particulate activation of the phagocyte nicotinamide adenine dinucleotide phosphate (NADPH) oxidase. Some mutations of CD11/CD18 allow a low level of assembly and activity of integrin molecules, resulting in retention of some neutrophil integrin adhesion function and a moderate phenotype.

Because of their inability to adhere firmly to intercellular adhesion molecules 1 (ICAM-1) and 2 (ICAM-2) expressed on inflamed endothelial cells (see Chapter 127), neutrophils cannot transmigrate through the vessel wall and move to the site infection. Furthermore, neutrophils that do arrive at inflammatory sites fail to recognize microorganisms opsonized with complement fragment iC3b, an important stable opsonin formed by the cleavage of C3b. Hence, other neutrophil functions such as degranulation and oxidative metabolism normally triggered by iC3b binding are also markedly compromised in LAD-1 neutrophils, resulting in impaired phagocytic function and high risk for serious and recurrent bacterial infections.

Monocyte function is also impaired, with poor fibrinogen-binding function, an activity that is promoted by the CD11/CD18 complex. Consequently, such cells are unable to participate effectively in wound healing.

Children with **LAD-2** share the clinical features of LAD-1 but have normal CD11/CD18 integrins. Features unique to LAD-2 include neurologic defects, cranial facial dysmorphism, and absence of the erythrocyte ABO blood group antigen (Bombay phenotype). LAD-2 (also known as congenital disorder of glycosylation IIc) derives from mutations in the gene encoding a specific GDP-L-fucose transporter of the Golgi apparatus. This abnormality prevents the incorporation of fucose into various cell surface glycoproteins, including the carbohydrate structure sialyl Lewis X that is critical for low-affinity rolling adhesion of neutrophils to vascular endothelium. This is an important initial step necessary for subsequent integrin-mediated activation, spreading, and transendothelial migration. Infections in LAD-2 are milder than that in LAD-1.

LAD-3 is characterized by a Glanzmann thrombasthenia-like bleeding disorder, delayed separation of the umbilical cord, and serious skin and soft-tissue infections similar to that seen in LAD-1, and failure of leukocytes to undergo β_2- and β_1-integrin–mediated adhesion and migration. Mutations in *KINDLIN3* affect integrin activation.

Clinical Manifestations

Patients with the severe clinical form of LAD-1 express <0.3% of the normal amount of the β_2-integrin molecules, whereas patients with the moderate phenotype may express 2-7% of the normal amount. Children with severe forms of LAD present in infancy with recurrent, indolent bacterial infections of the skin, mouth, respiratory tract, lower intestinal tract, and genital mucosa. Significant neutrophilic leukocytosis, often >25,0000/mm^3, is a prominent feature. They may have a history of delayed separation of the umbilical cord, usually with associated infection of the cord stump. The presence of significant omphalitis is an important feature that distinguishes these rare patients from the 10% of healthy infants can have cord separation at age 3 wk or later. Skin infection may progress to large chronic ulcers with polymicrobial infection, including anaerobic organisms (Fig. 130-2). The ulcers heal slowly, need months of antibiotic treatment, and often require plastic surgery grafting. Severe gingivitis can lead to early loss of primary and secondary teeth (Fig. 130-3). Infected areas characteristically have very little neutrophilic infiltration.

The pathogens infecting patients with LAD-1 are similar to those affecting patients with severe neutropenia (see Chapter 131) and include *Staphylococcus aureus* and enteric Gram-negative organisms such as *Escherichia coli.* These patients are also susceptible to opportunistic infection by fungi such as *Candida* and *Aspergillus.* Typical signs of inflammation, such as swelling, erythema, and warmth, may be absent. Pus does not form, and few neutrophils are identified microscopically in biopsy specimens of infected tissues. Despite the paucity of neutrophils within the affected tissue, the circulating neutrophil count during infection typically exceeds 30,000/μL and can surpass 100,000/μL. During intervals between infections, the peripheral blood neutrophil count may chronically exceed 12,000/μL. LAD-1 genotypes with only moderate, rather than absent, amounts of functional integrins at the surface of the neutrophil, significantly have reduced severity and frequency of infections compared to children with the severe form, although gingival disease is still a prominent feature.

Laboratory Findings

The diagnosis of LAD-1 is established most readily by **flow cytometric** measurements of surface CD11b/CD18 in stimulated and unstimulated neutrophils. Neutrophil and monocyte adherence, aggregation, chemotaxis, and iC3b-mediated phagocytosis demonstrate striking abnormalities. However, these assays are not clinically available. Delayed-type hypersensitivity reactions are normal, and most individuals have normal specific antibody synthesis. However, some patients have impaired T-lymphocyte–dependent antibody responses. The diagnosis of LAD-2 is established by flow cytometric measurement of sialyl Lewis X (CD15) on neutrophils. It is important to note that the flow cytometric assays are not done the same as the more common lymphocyte subset analysis and require specialized approaches to detect levels of surface expression, especially to detect milder phenotypes.

Treatment

Treatment of LAD-1 depends on the phenotype as determined by the level of expression of functional CD11/CD18 integrins. Early **allogeneic hematopoietic stem cell transplantation (HSCT)** is the treatment of choice for severe LAD-1 (and LAD-3). Other treatment is largely supportive. Patients can be maintained on prophylactic trimethoprim-sulfamethoxazole and should have close surveillance for early identification of infections and initiation of empirical treatment with broad-spectrum antibiotics. Specific determination of the etiologic agent by culture or biopsy is important because of the prolonged antibiotic treatment required in the absence of neutrophil function.

Some LAD-2 patients have responded to fucose supplementation, which induced a rapid reduction in the circulating leukocyte count and appearance of the sialyl Lewis X molecules accompanied by marked improvement in leukocyte adhesion.

Prognosis

The severity of infectious complications correlates with the degree of β_2-integrin deficiency. Patients with severe deficiency may die in infancy, and those surviving infancy have a susceptibility to severe life-threatening systemic infections. Patients with moderate deficiency have infrequent life-threatening infections and relatively long survival.



Figure 130-2 Skin infection of a patient with leukocyte adhesion deficiency type 1. Failure to form pus, inability to demarcate the fibrotic skin debris, and limited inflammation. Enterococcus gallinarium was cultured from the wound. *(From Rich RR:* Clinical immunology principles and practices, *ed 4, Philadelphia, 2013, WB Saunders, Fig. 21-3, p. 273).*



Figure 130-3 Oral pathology in a patient with leukocyte adhesion deficiency type 1. Gingivitis and severe periodontitis are hallmarks of LAD 1. *(From Rich RR:* Clinical immunology principles and practices, *ed 4, Philadelphia, 2013, WB Saunders, Fig. 21-2, p. 273.)*

CHÉDIAK-HIGASHI SYNDROME

Chédiak-Higashi syndrome (CHS) is a rare autosomal recessive disorder characterized by increased susceptibility to infection caused by defective degranulation of neutrophils, a mild bleeding diathesis, partial oculocutaneous albinism, progressive peripheral neuropathy, and a tendency to develop a life-threatening form of hemophagocytic lymphohistiocytosis (see Chapter 507). CHS is caused by a fundamental defect in granule morphogenesis that results in abnormally large granules in multiple tissues. Pigmentary dilution involving the hair, skin, and ocular fundi results from pathologic aggregation of melanosomes. Neurologic deficits are associated with a failure of decussation of the optic and auditory nerves. Patients exhibit an increased susceptibility to infection that can be explained only in part by defects in neutrophil function. The patients have progressive neutropenia as well abnormalities in natural killer (NK) function, again related to granule dysfunction.

Genetics and Pathogenesis

LYST (for lysosomal traffic regulator), the gene mutated in CHS, is located at chromosome 1q2-q44. The LYST/CHS protein is thought to regulate vesicle transport by mediating protein–protein interaction and protein–membrane associations. Loss of function may lead to indiscriminate interactions with lysosomal surface proteins, yielding giant granules through uncontrolled fusion of lysosomes with each other.

Almost all cells of patients with CHS show some oversized and dysmorphic lysosomes, storage granules, or related vesicular structures. Melanosomes are oversized, and delivery to the keratinocytes and hair follicles is compromised, resulting in hair shafts devoid of pigment granules. This abnormality in melanosomes leads to the macroscopic impression of hair and skin that is lighter than expected from parental coloration. The same abnormality in melanocytes leads to the partial ocular albinism associated with light sensitivity.

Beginning early in neutrophil development, spontaneous fusion of giant primary granules with each other or with cytoplasmic membrane components results in huge secondary lysosomes with reduced contents of hydrolytic enzymes, including proteinases, elastase, and cathepsin G. This deficiency of proteolytic enzymes may be responsible for the impaired killing of microorganisms by CHS neutrophils.

Clinical Manifestations

Patients with CHS have light skin and silvery hair and frequently complain of solar sensitivity and photophobia that is associated with rotary nystagmus. Other signs and symptoms vary considerably, but frequent infections and neuropathy are common. The infections involve mucous membranes, skin, and respiratory tract. Affected children are susceptible to Gram-positive bacteria, Gram-negative bacteria, and fungi, with *S. aureus* being the most common offending organism. The **neuropathy** may be sensory or motor in type, and ataxia may be a prominent feature. Neuropathy often begins in the teenage years and becomes the most prominent problem.

Patients with CHS have prolonged bleeding times with normal platelet counts, resulting from impaired platelet aggregation associated with a deficiency of the dense granules containing adenosine diphosphate and serotonin.

The most life-threatening complication of CHS is the development of an accelerated phase characterized by pancytopenia, high fever, and lymphohistiocytic infiltration of liver, spleen, and lymph nodes. The onset of the accelerated phase, which can occur at any age, is now recognized to be a genetic form of **hemophagocytic lymphohistiocytosis.** This occurs in 85% of patients and usually results in death.

Laboratory Findings

The diagnosis of CHS is established by finding large inclusions in all nucleated blood cells. These can be seen on Wright-stained blood films and are accentuated by a peroxidase stain. Because of impaired egress from the bone marrow, cells containing the large inclusions may be missed on peripheral blood smear but readily identified on bone marrow examination. The patients have progressive neutropenia and abnormal platelet, neutrophil, and NK function.

Treatment

High-dose ascorbic acid (200 mg/day for infants, 2,000 mg/day for adults) may improve the clinical status of some children in the stable phase. Although controversy surrounds the efficacy of ascorbic acid, given the safety of the vitamin, it is reasonable to administer ascorbic acid to all patients.

The only curative therapy to prevent the accelerated phase is **HSCT.** Normal stem cells reconstitute hematopoietic and immunologic function, correct the NK cell deficiency, and prevent conversion to the accelerated phase, but cannot correct or prevent the neuropathy. If the patient is in the accelerated phase with active hemophagocytic lymphohistiocytosis, HSCT often fails to prevent death.

MYELOPEROXIDASE DEFICIENCY

Myeloperoxidase (MPO) deficiency is an autosomal recessive disorder of oxidative metabolism and is one of the most common inherited disorders of phagocytes, occurring at a frequency approaching 1 per 2,000 individuals. MPO is a green heme protein located in the azurophilic lysosomes of neutrophils and monocytes and is the basis for the greenish tinge to pus accumulated at a site of infection.

Clinical Manifestations

MPO deficiency is usually clinically silent. Rarely, patients may have disseminated candidiasis, usually in conjunction with diabetes mellitus. Acquired partial MPO deficiency can develop in acute myelogenous leukemia and in myelodysplastic syndromes.

Laboratory Findings

Deficiency of neutrophil and monocyte MPO can be identified by histochemical analysis. Severe MPO deficiency can cause the dihydrorhodamine (DHR) flow cytometric assay for chronic granulomatous disease to be falsely positive. Unlike chronic granulomatous disease (CGD), eosinophils in severe MPO deficiency will still reduce DHR and yield a normal reaction.

Treatment

There is no specific therapy. Aggressive treatment with antifungal agents should be provided for candidal infections. The prognosis is usually excellent.

CHRONIC GRANULOMATOUS DISEASE

CGD is characterized by neutrophils and monocytes capable of normal chemotaxis, ingestion, and degranulation, but unable to kill **catalase-positive microorganisms** because of a defect in the generation of microbicidal oxygen metabolites. CGD is a rare disease with an incidence of 4-5 per 1 million individuals; it is caused by 4 genes, 1 X-linked and 3 autosomal recessive in inheritance.

Genetics and Pathogenesis

Activation of the phagocyte NADPH oxidase requires stimulation of the neutrophils and involves assembly from cytoplasmic and integral membrane subunits (see Fig. 127-3). Oxidase activation initiates with phosphorylation of a cationic cytoplasmic protein, $p47^{phox}$ (47-kDa phagocyte oxidase protein). Phosphorylated $p47^{phox}$, together with 2 other cytoplasmic components of the oxidase, $p67^{phox}$ and the low-molecular-weight guanosine triphosphatase Rac2, translocates to the membrane where they combine with the cytoplasmic domains of the transmembrane flavocytochrome b_{558} to form the active oxidase complex (see Fig. 127-3). The flavocytochrome is a heterodimer composed of $p22^{phox}$ and highly glycosylated $gp91^{phox}$. The $gp91^{phox}$ glycoprotein catalyzes electron transport through its NADPH-binding, flavin-binding, and heme-binding domains.. Defects in any of these NADPH oxidase components can lead to CGD.

Approximately 65% of patients with CGD are males who inherit their disorder as a result of mutations in *CYBB*, an X-chromosome gene encoding $gp91^{phox}$. Approximately 35% of patients inherit CGD in an autosomal recessive fashion resulting from mutations in the *NCF1* gene on chromosome 7, encoding $p47^{phox}$. Defects in the genes

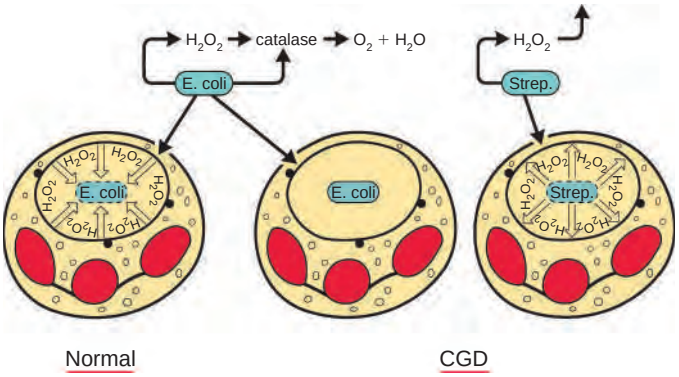


Figure 130-4 The pathogenesis of chronic granulomatous disease (CGD). The manner in which the metabolic deficiency of the CGD neutrophil predisposes the host to infection is shown schematically. Normal neutrophils stimulate hydrogen peroxide in the phagosome containing ingested *Escherichia coli*. Myeloperoxidase is delivered to the phagosome by degranulation, as indicated by the *closed circles*. In this setting, hydrogen peroxide acts as a substrate for myeloperoxidase to oxidize halide to hypochlorous acid and chloramines that kill the microbes. The quantity of hydrogen peroxide produced by the normal neutrophil is sufficient to exceed the capacity of catalase, a hydrogen peroxide-catabolizing enzyme of many aerobic microorganisms, including *Staphylococcus aureus,* most Gram-negative enteric bacteria, *Candida albicans,* and *Aspergillus*. When organisms such as *E. coli* gain entry into CGD neutrophils, they are not exposed to hydrogen peroxide because the neutrophils do not produce it, and the hydrogen peroxide generated by microorganisms themselves is destroyed by their own catalase. When CGD neutrophils ingest streptococci, which lack catalase, the organisms generate enough hydrogen peroxide to result in a microbicidal effect. As indicated *(middle),* catalase-positive microbes such as *E. coli* can survive within the phagosome of the CGD neutrophil. *(Modified from Boxer LA: Quantitative abnormalities of granulocytes. In Beutler E, Lichtman MA, Coller BS, et al, editors:* Williams hematology, *ed 6, New York, 2001, McGraw-Hill, p. 845.)*

encoding $p67^{phox}$ (*NCF2* on chromosome 1) and $p22^{phox}$ (*CYBA* on chromosome 16) are inherited in an autosomal recessive manner and account for approximately 5% of cases of CGD.

The CGD phagocytic vacuoles lack microbicidal reactive oxygen species and remain acidic, so bacteria are not killed or digested properly (Fig. 130-4). Hematoxylin-and-eosin–stained sections from patients' tissues show multiple granulomas that give CGD its descriptive name.

Clinical Manifestations

Although the clinical presentation is variable, several features suggest the diagnosis of CGD. Any patient with recurrent pneumonia, lymphadenitis, hepatic or subcutaneous or other abscesses, osteomyelitis at multiple sites, a family history of recurrent infections, or any infection with an unusual catalase-positive organism requires evaluation. Other clinical features include chronic colitis or enteritis, gastric outlet or ureteral obstruction from granulomas, or blood stream infection caused by *Salmonella*, *Burkholderia cepacia,* or *Candida*.

The onset of clinical signs and symptoms usually occurs in early infancy, though a few patients with very rare subtypes have presented later in life. The attack rate and severity of infections are exceedingly variable thought the infection incidence does decrease in the second decade coincident with maturation of the lymphocyte and humoral immunity. The most common pathogen is *S. aureus,* although any catalase-positive microorganism may be involved. Other organisms frequently causing infections include *Serratia marcescens, B. cepacia, Aspergillus, Candida albicans, Nocardia,* and *Salmonella.* There may also be increased susceptibility to mycobacterium, including the bacillus Calmette-Guérin vaccine. Pneumonia, lymphadenitis, osteomyelitis, and skin infections are the most common illnesses encountered. Bacteremia or fungemia occurs but is much less common than focal infections and usually only occurs when local infections have been inappropriately treated for long periods of time. Patients may suffer from the sequelae of chronic infection, including anemia of chronic disease, poor growth, lymphadenopathy, hepatosplenomegaly, chronic purulent dermatitis, restrictive lung disease, gingivitis, hydronephrosis, esophageal dysmotility, and pyloric outlet narrowing. Perirectal abscesses and recurrent skin infections, including folliculitis, cutaneous granulomas, and discoid lupus erythematosus also suggest the possibility of CGD. **Granuloma formation** and inflammatory processes are a hallmark of CGD and may be the presenting symptoms that prompt testing for CGD if they cause pyloric outlet obstruction, bladder outlet or ureter obstruction, or rectal fistulas and granulomatous colitis simulating Crohn disease. More than 80% of CGD patients have positive serology for Crohn disease. Persistent fever especially with splenomegaly and cytopenia warrants an evaluation for secondary macrophage activation syndrome. This has been seen in CGD and may require treatment with steroids and discontinuation of interferon-γ treatment.

Laboratory Findings

The diagnosis is most often made by performing **flow cytometry** using dihydrorhodamine 123 (DHR) to measure oxidant production through its increased fluorescence when oxidized by H_2O_2. The nitroblue tetrazolium dye test is frequently cited in the literature but is now only rarely used clinically. The X-linked carrier state is usually easily diagnosed in the mother by DHR fluorescence by presence of a bimodal response to stimulation. It is important to test the mother as some extremely Lyonized carriers with <5% positive cells may have chronic clinical problems as well. Ideally, at least the first patient in a kindred should have DNA analysis to facilitate prenatal diagnosis and for genetic counseling purposes.

A few individuals have been described with apparent CGD caused by severe glucose-6-phosphate dehydrogenase deficiency, leading to insufficient NADPH substrate for the phagocyte oxidase. The erythrocytes of these patients also lack the enzyme, leading to chronic hemolysis.

Treatment

HSCT is the only known **cure** for CGD, although gene therapy has been transiently successful in a few patients and is the topic of active research. We strongly recommend HSCT transplant for all patients with CGD if a suitable sibling or unrelated donor can be identified. The long-term outcome for survival late into adulthood is not good even in the hands of experienced CGD clinicians.

Patients with CGD should be given daily oral trimethoprim-sulfamethoxazole as it reduces the number of bacterial infection. A placebo-controlled study found that **interferon-γ** 50 μg/m^2 3 times/wk significantly reduces the number of hospitalizations and serious infections, although the mechanism of action is unclear. **Itraconazole** (200 mg/day for patients weighing >50 kg and 100 mg/day for patients weighing <50 kg and 5 yr of age or younger) administered prophylactically reduces the frequency of fungal infections.

Management of infection is dramatically different than in normal children. CGD patients are always at risk for deep-seated, indolent bacterial infections that can become widespread if not treated properly. They also develop the same kinds of infections that occur in normal children so determination of the appropriate treatment can be difficult. The erythrocyte sedimentation rate (ESR) can be quite helpful. If the child does not have a deep-seated infection, the ESR will be normal or will normalize within several days with standard management. However, if it does not, a search for deep tissues is warranted, as is consideration of empiric antibiotics. Cultures should be obtained, but are usually negative. Because all neutrophil functions in CGD except killing are normal, there is often an exuberant inflammatory reaction to a very small number of organisms. Thus, blood cultures and direct cultures of biopsy samples are usually negative unless there are a lot of organisms. Most abscesses require surgical drainage for therapeutic

and diagnostic purposes. Prolonged use of antibiotics is required even for common bacterial infections. A simple pneumonia may require 6-8 wk of parenteral antibiotics. Infections should be treated for at least 1 wk past normalization of the sedimentation rate to prevent recurrence. Severe pneumonias can be cleared completely but may require many months of parenteral antibiotics. Especially because cultures are often not helpful, we support an "antibiotic sensitivity by sedimentation rate response" approach to treatment. The ESR rates are often in the 40-80 mm/hr or more range with severe infection and will drop monotonically over a week or so after starting antibacterial drugs. It is important to check the ESR daily or every other day as there is moderate variability in this test and changes in treatment need to be based on trends rather than individual values. If there is a clear downward trend over 3-6 days, we continue with antibacterials alone. If this is not the case, parenteral voriconazole should be added to cover *Aspergillus*. Failure of the ESR to come down suggests another antimicrobial approach needs to be tried. Because of the rarity of this disorder, it is critical to seek counsel from someone with significant direct experience with management of several CGD patients. Granulocyte transfusions have been used but it is not clear that they are very helpful. The ESR should be regularly monitored in well patients and whenever they appear ill. A high ESR itself is usually not enough to trigger treatment. However, in the presence of symptoms, one should search for sources at least by contrast CT of the sinus, chest, and abdomen. If the patient is unstable or has very high fevers, *B. cepacia* should be considered and empirically covered. This organism can cause septic shock quickly, unlike the usual smoldering infections seen in CGD. We treat with antibiotics until the ESR is normal and radiographic evidence of infection has been cleared, if possible. The overall incidence of infection decreases in the second decade of life as nonneutrophil immunity matures, but increased risk of infection is lifelong.

Corticosteroids may be useful for the treatment of children with antral and urethral obstruction or severe granulomatous colitis. They can also be helpful in pneumonia to shrink granulomas in the lung and promote drainage. We favor short (4-6 days) pulses of 1-2 mg/kg prednisone with rapid taper to avoid long-term side effects and risk of fungus. Pulses can be repeated if clinical effect has not been achieved.

Genetic Counseling

Identifying a patient's specific genetic subgroup by DNA analysis is useful primarily for genetic counseling and prenatal diagnosis. In X-linked CGD, all possibly affected females should be tested by DHR to exclude carrier state. Counseling is best done by a physician who has direct knowledge of the clinical manifestations of CGD.

Prognosis

The overall mortality rate for CGD is about 2 patient deaths/yr per 100 cases, with the highest mortality among young children. The development of effective infection prophylactic regimens, close surveillance for signs of infections, and aggressive surgical and medical interventions has improved the prognosis.

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Chapter 131

Leukopenia

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Leukopenia refers to an abnormally low number of white blood cells (WBCs) in the circulating blood secondary to a paucity of lymphocytes, granulocytes or both. Because there are marked developmental changes in normal values for WBC counts during childhood (see Chapter 727), normal ranges must be considered in the context of age. For newborns, the mean WBC count at birth is high, followed by a rapid fall beginning at 12 hr through the 1st wk of life. Thereafter, values are stable until 1 yr of age, after which a slow steady decline in the WBC count continues throughout childhood until adult values are reached during adolescence. Evaluation of patients with leukopenia begins with a thorough history, physical examination, and at least 1 confirmatory complete blood count with differential. Further evaluation then depends upon whether the leukopenia represents a decreased number of neutrophils, lymphocytes, or both cell populations (Table 131-1). Treatment depends upon the etiology and clinical manifestations of the leukopenia.

NEUTROPENIA

Neutropenia is defined as a decrease in the absolute number of circulating segmented neutrophils and bands in the peripheral blood. The **absolute neutrophil count (ANC)** is determined by multiplying the total WBC count by the percentage of segmented neutrophils plus bands. Normal neutrophil counts must be stratified for age and race. Neutrophils predominate at birth but rapidly decrease in the 1st few days of life. During infancy, neutrophils constitute 20-30% of circulating leukocyte populations. Near equal numbers of neutrophils and lymphocytes are found in the peripheral circulation at 5 yr of age, and the characteristic 70% predominance of neutrophils that occurs in adulthood is usually attained during puberty. For white children older than 12 mo of age, the lower limit of normal for the ANC is 1,500/μL; for black children older than 12 mo of age the lower limit of normal is 1,200/μL. The relatively lower limit of normal in blacks likely reflects the prevalence of the Duffy negative (Fy–/–) blood group, which is selectively enriched in populations in the malarial belt of Africa and is associated with ANCs 200-600/μL less than those who are Duffy positive.

Neutropenia may be characterized as **mild neutropenia,** with an ANC of 1,000-1,500/μL; **moderate neutropenia,** with an ANC of 500-1,000/μL; or **severe neutropenia,** with an ANC <500/μL. ANC <200 is also termed *agranulocytosis*. This stratification aids in predicting the risk of pyogenic infection in patients who have neutropenia as a resulting from disorders of bone marrow production as only patients with severe neutropenia have a significantly increased susceptibility to life-threatening infections. Neutropenia associated with monocytopenia, lymphocytopenia, or hypogammaglobulinemia increases the risk for infection compared to isolated neutropenia. *Patients with neutropenia caused by increased destruction (e.g., autoimmune) may tolerate very low ANCs without increased frequency of infection.*

Acute neutropenia evolves over a few days and is often a result of rapid neutrophil use and/or compromised neutrophil production. **Chronic neutropenia** by definition lasts longer than 3 mo and arises from reduced production, increased destruction or excessive splenic sequestration of neutrophils. The etiology of neutropenia can be classified as either an acquired disorder or extrinsic insult (Table 131-2), or, more rarely, an inherited, intrinsic defect (Table 131-3).

Clinical Manifestations of Neutropenia

Individuals with neutrophil counts <500/μL are at substantial risk for developing infections, primarily from their endogenous flora as well as from nosocomial organisms. However, some patients with isolated chronic neutropenia may not experience many serious infections, probably because the remainder of the immune system remains intact or because neutrophil delivery to tissues is preserved, as in autoimmune neutropenias. In contrast, children whose neutropenia is secondary to acquired disorders of production such as with cytotoxic therapy, immunosuppressive drugs, or radiation therapy are likely to develop serious bacterial infections because many arms of the immune system are markedly compromised. Neutropenia associated with additional monocytopenia or lymphocytopenia, is more highly associated with serious infection than neutropenia alone. The integrity of skin and mucous membranes, the vascular supply to tissues, and nutritional status also influence the risk of infection.

The most common **clinical presentation of profound neutropenia** includes fever, aphthous stomatitis, and gingivitis. Infections

Table 131-1 Diagnostic Approach for Patients with Leukopenia

EVALUATION	ASSOCIATED CLINICAL DIAGNOSES
INITIAL EVALUATION	
• History of acute or chronic leukopenia	
• General medical history	Congenital syndromes (Shwachman-Diamond, Wiskott-Aldrich, Fanconi anemia, dyskeratosis congenita, glycogen storage disease type Ib, disorders of vesicular transport)
• Physical examination: stomatitis, gingivitis, dental defects, congenital anomalies	
• Spleen size	Hypersplenism
• History of drug exposure	Drug-associated neutropenia
• Complete blood count with differential and reticulocyte counts	Neutropenia, aplastic anemia, autoimmune cytopenias
IF ANC <1,000/μL	
Evaluation of Acute Onset Neutropenia	
• Repeat blood counts in 3-4 weeks	Transient myelosuppression (e.g., viral)
• Serology and cultures for infectious agents	Active or chronic infection with viruses (e.g., EBV, CMV), bacteria, mycobacteria, rickettsia
• Discontinue drug(s) associated with neutropenia	Drug-associated neutropenia
• Test for antineutrophil antibodies	Autoimmune neutropenia
• Measure quantitative immunoglobulins (G, A, and M), lymphocyte subsets	Neutropenia associated with disorders of immune function
IF ANC <500/μL ON 3 SEPARATE TESTS	
• Bone marrow aspiration and biopsy, with cytogenetics	Severe congenital neutropenia, Shwachman-Diamond syndrome, myelokathexis; chronic benign or idiopathic neutropenia
• Glucocorticoid stimulation test	Chronic benign or idiopathic neutropenia, some autoimmune neutropenias
• Serial CBCs (3/wk for 6 wk)	Cyclic neutropenia
• Exocrine pancreatic function	Shwachman-Diamond syndrome
• Skeletal radiographs	Shwachman-Diamond syndrome, cartilage-hair hypoplasia, Fanconi anemia
IF ALC <1000/μL	
• Repeat blood counts in 3-4 weeks	Transient leukopenia (e.g., viral)
IF ALC <1000/μL ON 3 SEPARATE TESTS	
• HIV-1 antibody or RNA test	HIV-1 infection, AIDS
• Quantitative immunoglobulins (G, A, and M), lymphocyte subsets	Congenital or acquired disorders of immune function
IF THERE IS PANCYTOPENIA	
• Bone marrow aspiration and biopsy	Bone marrow replacement by malignancy, fibrosis, granulomata, storage cells; aplastic anemia
• Bone marrow cytogenetics	Myelodysplasia, leukemia
• Vitamin B_{12} and folate levels	Vitamin deficiencies

ALC, absolute lymphocyte count; ANC, absolute neutrophil count; CBC, complete blood count; CMV, cytomegalovirus; EBV, Epstein-Barr virus.

commonly associated with neutropenia include cellulitis, furunculosis, perirectal inflammation, colitis, sinusitis, and otitis media, as well as more serious infections such as pneumonia, deep tissue abscess, and sepsis. The most common pathogens causing infections in neutropenic patients are *Staphylococcus aureus* and Gram-negative bacteria. Isolated neutropenia does not heighten a patient's susceptibility to parasitic or viral infections or to bacterial meningitis. The usual signs and symptoms of local infection and inflammation such as exudate, fluctuance, and regional lymphadenopathy may be diminished in the absence of neutrophils because of the inability to form pus, but patients with agranulocytosis still experience fever and feel pain at sites of inflammation.

Laboratory Findings

Isolated absolute neutropenia has a limited number of causes (Tables 131-2 through 131-5). The duration and severity of the neutropenia greatly influence the extent of laboratory evaluation. Patients with chronic neutropenia since infancy and a history of recurrent fevers and chronic gingivitis should have WBC counts and differential counts determined 3 times/wk for 6-8 wk to evaluate the periodicity suggestive of **cyclic neutropenia**. Bone marrow aspiration and biopsy should be performed on select patients to assess cellularity and myeloid maturation. Additional marrow studies such as cytogenetic analysis and special stains for detecting leukemia and other malignant disorders should be obtained for patients with suspected intrinsic defects in the myeloid progenitors and for patients with suspected malignancy. If malignancy is not a concern, assessing the ANC before and 4-6 hr after a single dose of glucocorticosteroid (usually prednisone 1-2 mg/kg) measures mobilization of the bone marrow reserve pool of mature neutrophils; an increase in the ANC to a normal or only moderately low level indicates "chronic benign" or idiopathic neutropenia, and may render bone marrow examination unnecessary. Selection of further laboratory tests is determined by the duration and severity of the neutropenia and the associated findings on physical examination (see Table 131-1).

Acquired Neutropenia

Infection-Related Neutropenia. Transient neutropenia often accompanies or follows viral infections (see Table 131-4) and is the most frequent cause of neutropenia in childhood. Viruses commonly causing acute neutropenia include influenzas A and B, adenovirus, respiratory syncytial virus, enteroviruses, human herpes virus 6, measles, rubella, and varicella. Parvovirus B19 and hepatitides A and B may also cause neutropenia, but are more commonly associated with pure red cell aplasia or multiple cytopenias, respectively. Viral-associated acute neutropenia often occurs during the 1st 24-48 hr of illness and usually persists for 3-8 days, which generally corresponds to the period of viremia. The neutropenia is related to virus-induced redistribution of neutrophils from the circulating to the marginating pool. In addition, neutrophil sequestration may occur after virus-induced tissue damage or splenomegaly. Significant neutropenia also may be associated with severe bacterial, protozoal, rickettsial, and fungal infections (see Table 131-4). Bacterial sepsis is a particularly serious cause of neutropenia, especially among younger infants and

Table 131-2 Causes of Neutropenia Extrinsic to Marrow Myeloid Cells

CAUSE	ETIOLOGIC FACTORS/AGENTS	ASSOCIATED FINDINGS
Infection	Viruses, bacteria, protozoa, rickettsia, fungi	Clinical features and laboratory findings of the infectious agent
Drug-induced	Phenothiazines, sulfonamides, anticonvulsants, penicillins, aminopyrine	Usually none; occasional hypersensitivity reaction (fever, lymphadenopathy, rash, hepatitis, nephritis, pneumonitis, aplastic anemia) or antineutrophil antibody
Immune neutropenia	Alloimmune, autoimmune	Myeloid hyperplasia with left shift in bone marrow (may appear to be "arrest" at metamyelocyte or band stage)
Reticuloendothelial sequestration	Hypersplenism	Anemia, thrombocytopenia
Bone marrow replacement	Malignancy (leukemia, lymphoma, metastatic solid tumor, etc.)	Anemia, thrombocytopenia, malignant cells in bone marrow
Cancer chemotherapy or radiation therapy	Suppression of myeloid cell production	Anemia, thrombocytopenia, bone marrow hypoplasia

Table 131-3 Acquired Disorders of Myeloid Cells

CAUSE	ETIOLOGIC FACTORS/AGENTS	ASSOCIATED FINDINGS
Aplastic anemia	Stem cell destruction and depletion	Pancytopenia
Vitamin B_{12} or folate deficiency	Malnutrition; congenital deficiency of B_{12} absorption, transport, and storage; vitamin avoidance	Megaloblastic anemia, hypersegmented neutrophils
Acute leukemia, chronic myelogenous leukemia	Bone marrow replacement with malignant cells	Pancytopenia, leukocytosis
Myelodysplasia	Dysplastic maturation of stem cells	Bone marrow hypoplasia with megaloblastoid red cell precursors, thrombocytopenia
Prematurity with birth weight <2 kg	Impaired regulation of myeloid proliferation and reduced size of postmitotic pool	Maternal preeclampsia
Chronic idiopathic neutropenia	Impaired myeloid proliferation and/or maturation	None
Paroxysmal nocturnal hemoglobinuria	Acquired stem cell defect secondary to mutation of *PIG-A* gene	Pancytopenia, thrombosis

Table 131-4 Infections Associated with Neutropenia

Viral	Cytomegalovirus, dengue, Epstein-Barr virus, hepatitis viruses, HIV, influenza, measles, parvovirus B19, rubella, varicella
Bacterial	*Anaplasma* (formerly *Ehrlichia*) *phagocytophilum*, brucella, paratyphoid, pertussis, tuberculosis (disseminated), tularemia, typhoid; any form of sepsis
Fungal	Histoplasmosis (disseminated)
Protozoan	Malaria, leishmaniasis (kala-azar)
Rickettsial	Psittacosis, Rocky Mountain spotted fever, typhus, rickettsialpox

Table 131-5 Forms of Drug-Induced Neutropenia

	IMMUNOLOGIC	TOXIC	HYPERSENSITIVITY
Paradigm drugs	Aminopyrine, propylthiouracil, penicillins	Phenothiazines, clozapine	Phenytoin, phenobarbital
Time to onset	Days to weeks	Weeks to months	Weeks to months
Clinical appearance	Acute, often explosive symptoms	Often asymptomatic or insidious onset	May be associated with fever, rash, nephritis, pneumonitis, or aplastic anemia
Rechallenge	Prompt recurrence with small test dose	Latent period; high doses required	Latent period; high doses required
Laboratory findings	Antineutrophil antibody may be positive; bone marrow myeloid hyperplasia	Bone marrow myeloid hypoplasia	Bone marrow myeloid hypoplasia

children. Premature neonates are especially prone to exhausting their marrow reserve and rapidly succumbing to bacterial sepsis.

Chronic neutropenia often accompanies infection with Epstein-Barr virus, cytomegalovirus, or HIV. The neutropenia associated with AIDS probably arises from a combination of viral bone marrow suppression, antibody-mediated destruction of neutrophils, and effects of antiretroviral or other drugs.

Drug-Induced Neutropenia. Drugs constitute a common cause of neutropenia (see Table 131-5). The incidence of drug-induced neutropenia increases dramatically with age; only 10% of cases occur among children and young adults. The majority of cases occur among adults older than age 65 yr, likely reflecting the more frequent use of multiple medications in that age group. Almost any drug can cause neutropenia. The most common offending drug classes are antimicrobial agents, antithyroid drugs, antipsychotics, antipyretics, and antirheumatics. Drug-induced neutropenia has several underlying mechanisms—immune-mediated, toxic, idiosyncratic, hypersensitivity, idiopathic—that are distinct from the severe neutropenia that predictably occurs after administration of antineoplastic drugs or radiotherapy.

Drug-induced neutropenia from immune mechanisms usually develops abruptly, is accompanied by fever, and lasts for about 1 wk after the discontinuation of the drug. The process likely arises from effects of drugs, such as propylthiouracil or penicillin, that act as haptens to stimulate antibody formation, or drugs, such as quinine, that induce immune complex formation. Other drugs, including the antipsychotic drugs such as the phenothiazines, can cause neutropenia when given in toxic amounts, but some individuals, such as those with preexisting neutropenia, may be susceptible to levels at the high end of the usual therapeutic range. Late-onset neutropenia can occur after rituximab therapy. Idiosyncratic reactions, for example to chloramphenicol, are unpredictable with regard to dose or duration of use. Hypersensitivity reactions are rare and may involve arene oxide metabolites of aromatic anticonvulsants. Fever, rash, lymphadenopathy, hepatitis, nephritis, pneumonitis, and aplastic anemia are often associated with hypersensitivity-induced neutropenia. Acute hypersensitivity reactions such as those caused by phenytoin or phenobarbital may last for only a few days if the offending drug is discontinued. Chronic hypersensitivity may last for months to years.

Once neutropenia occurs, the most effective therapeutic measure is withdrawal of nonessential drugs, particularly drugs most commonly associated with neutropenia. Usually the neutropenia will resolve soon after withdrawal of the offending drug. If the neutropenia fails to improve with drug withdrawal and the patient is symptomatic with infection or stomatitis, subcutaneous administration of recombinant human granulocyte colony-stimulating factor (filgrastim) 5 μg/kg/day should be considered. Drug-induced neutropenia may be asymptomatic and noted only as an incidental finding or because of regular monitoring of WBC counts during drug therapy. For patients who are asymptomatic, continuation of the suspected offending drug depends on the relative risks of neutropenia vs discontinuation of a possibly essential drug. If the drug is continued, blood counts should be monitored for possible progression to agranulocytosis.

Neutropenia commonly and predictably follows the use of anticancer drugs or radiation therapy, especially radiation therapy directed at the pelvis or vertebrae, secondary to cytotoxic effects on rapidly replicating myeloid precursors. A decline in the WBC count typically occurs 7-10 days after administration of the anticancer drug and may persist for 1-2 wk. The neutropenia accompanying malignancy or following cancer chemotherapy is frequently associated with compromised cellular immunity and barrier compromise secondary to central venous lines and mucositis, thereby predisposing patients to a much greater risk of infection (see Chapter 178) than found in disorders associated with isolated neutropenia. Patients with chemotherapy/radiation-related neutropenia and fever must be treated aggressively with broad-spectrum antibiotics.

Nutrition-Related Neutropenia. Poor nutrition can contribute to neutropenia. Ineffective myelopoiesis may result in neutropenia caused by acquired dietary vitamin B_{12} or folic acid deficiency. In addition, megaloblastic pancytopenia also can result from extended use of antibiotics such as trimethoprim-sulfamethoxazole, which inhibit folic acid metabolism, and from the use of phenytoin, which may impair folate absorption in the small intestine, or from surgical resection of the small intestine. Neutropenia also occurs with starvation and marasmus in infants, with anorexia nervosa, and occasionally among patients receiving prolonged parenteral nutrition without vitamin supplementation.

Immune-Mediated Neutropenia. Immune-mediated neutropenia is usually associated with the presence of circulating antineutrophil antibodies, which may mediate neutrophil destruction by complement-mediated lysis or splenic phagocytosis of opsonized neutrophils, or by accelerated apoptosis of mature neutrophils or myeloid precursors.

Alloimmune neonatal neutropenia occurs after transplacental transfer of maternal alloantibodies directed against antigens on the infant's neutrophils, analogous to Rh hemolytic disease. Prenatal sensitization induces maternal IgG antibodies to neutrophil antigens on fetal cells. The neutropenia is often severe and infants may present within the 1st 2 wk of life with skin or umbilical infections, fever, and pneumonia caused by the usual microbes that cause neonatal disease. By 7 wk of age, the neutrophil count usually returns to normal, reflecting the decay of maternal antibodies in the infant's circulation. **Treatment** consists of supportive care and appropriate antibiotics for clinical infections, plus filgrastim for severe infections without neutrophil recovery.

Mothers with autoimmune disease may give birth to infants who develop transient neutropenia, known as **neonatal passive autoimmune neutropenia**. The duration of the neutropenia depends on the time required for the infant to clear the maternally transferred circulating immunoglobulin G antibody. It persists in most cases for a few weeks to a few months. Neonates almost always remain asymptomatic.

Autoimmune neutropenia (AIN) of infancy is a benign condition with an annual incidence of approximately 1 per 100,000 among children between infancy and 10 yr of age. Patients usually have severe neutropenia on presentation, with ANC <500/μL, but the total WBC count is generally within normal limits. Monocytosis or eosinophilia may occur but does not impact the low rate of infection. The median age of presentation is 8-11 mo with a range of 2-54 mo. There is a slight female predominance. The diagnosis is often evident when a blood count incidentally reveals neutropenia in a child with a minor infection. Occasionally, children may present with more severe infections, including abscesses, pneumonia, or sepsis. The diagnosis may be established by the presence of antineutrophil antibodies in serum; however, the test has frequent false-negative and false-positive results, so the absence of detectable antibody does not exclude the diagnosis and a positive result does not exclude other conditions. The diagnosis may also be based clinically on a benign course and normal or hyperplastic myeloid maturation in the bone marrow. There is considerable overlap between AIN of infancy and "chronic benign neutropenia."

Treatment is not generally necessary because the disease is only rarely associated with severe infection and usually remits spontaneously. Low-dose filgrastim may be useful for severe infections, to promote wound healing following surgery, or to avert emergency room visits or hospitalizations for febrile illnesses. Longitudinal studies of infants with AIN demonstrate median durations of disease ranging from 7-30 mo. Affected children generally have no evidence or risk of other autoimmune diseases.

AIN in older children can occur as an isolated process, as a manifestation of other autoimmune diseases, or as a secondary complication of infection, drugs or malignancy. In primary AIN, low circulating neutrophil counts are the only hematologic finding, and associated diseases or other factors that cause neutropenia are absent. Secondary AIN associated with immune dysregulation or other factors is more commonly identified in older children and is less likely to spontaneously remit. AIN is distinguished from other forms of neutropenia by the demonstration of antineutrophil antibodies (with caveats discussed above) and myeloid hyperplasia on bone marrow examination. The

most common antineutrophil antibody targets are human neutrophil antigens 1a, 1b, and 2.

Treatment of AIN relies on management of any underlying disorders. In addition, judicious use of appropriate antibiotics for bacterial infections, and regular dental hygiene is generally beneficial. Infections tend to be less frequent in AIN than with the corresponding degree of neutropenia from other causes, probably because tissue delivery of neutrophils is greater than that in conditions resulting from impaired production. Prophylactic antibiotics may be helpful for the management of recurrent minor infections. For patients with serious or recurrent infections, filgrastim is generally effective at raising the ANC and preventing infection. Very low doses (<1-2 μg/kg/day) are usually effective, and administration of standard doses can lead to severe bone pain as a consequence of marrow expansion.

Neutropenia Secondary to Bone Marrow Replacement. Various acquired bone marrow disorders lead to neutropenia, usually accompanied by anemia and thrombocytopenia. Hematologic malignancies, including leukemia, lymphoma, and metastatic solid tumors suppress myelopoiesis by infiltrating the bone marrow with tumor cells. Neutropenia may also accompany aplastic anemia, myelodysplastic disorders or preleukemic syndromes, which are characterized by multiple cytopenias and often macrocytosis. Treatment requires management of the underlying disease.

Neutropenia Secondary to Reticuloendothelial Sequestration. Splenic enlargement resulting from intrinsic splenic disease (storage disease), portal hypertension, or systemic causes of splenic hyperplasia (inflammation or neoplasia) can lead to neutropenia. Most often the neutropenia is mild to moderate and is accompanied by corresponding degrees of thrombocytopenia and anemia. The reduced neutrophil survival corresponds to the size of the spleen, and the extent of the neutropenia is inversely proportional to bone marrow compensatory mechanisms. Usually the neutropenia may be corrected by successfully treating the underlying disease. In selected cases, splenectomy may be necessary to restore the neutrophil count to normal, but results in increased risk of infections by encapsulated bacterial organisms. Patients undergoing splenectomy should receive appropriate presplenectomy immunizations and may benefit from antibiotic prophylaxis postsplenectomy to help mitigate the risk of sepsis. Splenectomy should be avoided in patients with common variable immunodeficiency, autoimmune lymphoproliferative disease and other immunodeficiency syndromes because of the higher risk of sepsis.

Inherited Neutropenia

Intrinsic disorders of proliferation or maturation of myeloid precursor cells are rare. Table 131-6 presents a classification based on genetics and molecular mechanisms; selected disorders are discussed below.

Primary Disorders of Granulocytopoiesis. **Cyclic neutropenia** is a rare autosomal dominant congenital granulopoietic disorder occurring with an estimated incidence of 0.5-1 cases per 1 million population. The disorder is characterized by regular, periodic oscillations, with the ANC ranging from normal to <200/μL, mirrored by reciprocal cycling of monocytes. Cyclic neutropenia is sometimes termed *cyclic hematopoiesis* because of the secondary cycling of other blood cells, such as platelets and reticulocytes. The mean oscillatory period of the cycle is 21 days (± 4 days). During the neutropenic nadir, many patients suffer from malaise, fever, oral and genital ulcers, gingivitis, periodontitis, or pharyngitis, and occasionally lymph node enlargement. More serious infections may occasionally occur, including pneumonia, mastoiditis, and intestinal perforation with peritonitis leading to life-threatening clostridial sepsis. Prior to the availability of filgrastim, approximately 10% of patients developed fatal clostridial or Gram-negative infections. Cyclic neutropenia arises from a regulatory abnormality involving early hematopoietic precursor cells and is almost invariably associated with mutations in the neutrophil elastase gene, *ELANE*, that lead to accelerated apoptosis as a result of abnormal protein folding. Many patients experience abatement of symptoms with age. The cycles tend to become less noticeable in older patients, and the hematologic picture often begins to resemble that of chronic idiopathic neutropenia.

Cyclic neutropenia is diagnosed by obtaining blood counts 3 times/wk for 6-8 wk. The requirement for repeated blood counts is necessary because some of the elastase mutations overlap with those in patients who have **severe congenital neutropenia**. Demonstrating oscillation or a lack thereof in the blood counts helps to identify the patients risk for progression to myelodysplastic syndrome (MDS)/acute myelogenous leukemia (AML), a risk that is only associated with severe congenital neutropenia. The diagnosis can be confirmed with genetic studies demonstrating a mutation in the *ELANE* gene. Affected patients with neutrophil nadirs <200/μL are treated with filgrastim and their cycle of profound neutropenia changes from a 21-day period with at least 3-5 days of profound neutropenia to a 9-11 day interval with 1 day of less-profound neutropenia. The dose needed to maintain nadirs >500/μL is usually 2-4 μg/kg/day administered daily or every other day.

Severe congenital neutropenia (SCN) is a rare, genetically heterogeneous, congenital granulopoietic disorder with an estimated incidence of 1-2 cases per 1 million population. The disorder is characterized by an arrest in myeloid maturation at the promyelocyte stage in the bone marrow, resulting in ANCs consistently <200/μL and may occur sporadically, with autosomal dominant or recessive inheritance. The **dominant** form is caused most often by mutations in the *ELANE* gene, which accounts for 60-80% of SCN cases, while **recessive** forms arise from mutations in *HAX1* (the form also known as **Kostmann disease**) or *G6PC3* (encoding a myeloid-specific isoform of glucose-6-phosphatase). *HAX1* mutations may be associated with neurologic deficits, and *G6PC3* with heart defects, urogenital abnormalities, and venous angiectasia. In addition to severe neutropenia, peripheral blood counts generally show monocytosis and many also exhibit eosinophilia; chronic inflammation may lead to secondary anemia and thrombocytosis. Patients who have SCN experience frequent episodes of fever, skin infections (including omphalitis), oral ulcers, gingivitis, pneumonia and perirectal abscesses, typically appearing in the 1st few mo of life. Infections often disseminate to the blood, meninges and peritoneum, and are usually caused by *S. aureus*, *Escherichia coli,* and *Pseudomonas* species. Prior to the current era of filgrastim therapy, most patients died of infectious complications within the 1st 1-2 yr of life despite prophylactic antibiotics.

More than 95% of SCN patients respond to filgrastim treatment with an increase in the ANC and a decrease in infections. Doses required to achieve an ANC >1000/uL vary greatly. A starting dose of filgrastim 5 μg/kg/day is recommended; the dose should be gradually increased, if necessary, as high as 100 μg/kg/day to attain an ANC of 1,000-2,000/μL. The 5% of patients who do not respond to filgrastim or who require high doses (>8 μg/kg/day) should be considered for hematopoietic stem cell transplantation. Besides infections, patients with SCN are at risk for developing MDS associated with monosomy 7 and AML. For this reason, regular monitoring with blood counts and yearly bone marrow surveillance, including karyotyping and fluorescence in situ hybridization, should be performed on all SCN patients. Although clonal cytogenetic abnormalities may spontaneously remit, their appearance should be considered a strong indication for hematopoietic stem cell transplantation, which is much more likely to be successful prior to progression to MDS/AML.

Disorders of Molecular Processing. Shwachman-Diamond syndrome (SDS) is an autosomal recessive disorder classically characterized by neutropenia, pancreatic insufficiency, and short stature with skeletal abnormalities. SDS is caused by proapoptotic mutations of the *SBDS* gene, which encodes a protein that plays a role in ribosome biogenesis and RNA processing. The initial symptoms are usually steatorrhea and failure to thrive because of malabsorption, which usually develops by 4 mo of age, although the gastrointestinal symptoms may be subtle in some patients and go unrecognized. Patients have also been reported to have respiratory problems with frequent otitis media, pneumonia and eczema. Virtually all patients with SDS have neutropenia, with the ANC periodically <1000/μL. Some children have defects in chemotaxis or in the number or function of B, T, and natural killer (NK) cells that may contribute to the increased susceptibility to pyogenic infection. The diagnosis of SDS is based on clinical

Table 131-6 Intrinsic Disorders of Myeloid Precursor Cells

SYNDROME	INHERITANCE *(GENE)*	CLINICAL FEATURES (INCLUDING STATIC NEUTROPENIA UNLESS OTHERWISE NOTED)
PRIMARY DISORDERS OF MYELOPOIESIS		
Cyclic neutropenia	AD *(ELANE)*	Periodic oscillation (21-day cycles) in ANC
Severe congenital neutropenia	AD (primarily *ELANE*, also *GFI* and others)	Risk of MDS/AML
	AR *(G6PC3, HAX1)* (*HAX1* = Kostmann syndrome)	*G6PC3:* cardiac and urogenital anomalies, venous angiectasias; *HAX1:* neurologic abnormalities, risk of MDS/AML
	XL *(WAS)*	Neutropenic variant of Wiskott-Aldrich syndrome
DISORDERS OF MOLECULAR PROCESSING		
Shwachman-Diamond syndrome	Ribosomal defect: AR *(SBDS)*	Pancreatic insufficiency, metaphysical dysostosis, bone marrow failure, MDS/AML
Dyskeratosis congenita	Telomerase defects: XL *(DKC1)*, AD *(TERC)*, AR *(TERT)*	Nail dystrophy, leukoplakia, abnormal and carious teeth, lacey reticulated hyperpigmentation of the skin, bone marrow failure
DISORDERS OF VESICULAR TRAFFICKING		
Chédiak-Higashi syndrome	AR *(LYST)*	Partial albinism, giant granules in myeloid cells, platelet storage pool defect, impaired natural killer cell function, HLH
Griscelli syndrome, type II	AR *(RAB27a)*	Partial albinism, impaired natural killer cell function, neurological impairment, HLH
Cohen syndrome	AR *(COH1)*	Partial albinism, pigmentary retinopathy, developmental delay, facial dysmorphism
Hermansky-Pudlak syndrome, type II	AR *(AP3P1)*	Cyclic neutropenia, partial albinism, HLH
p14 deficiency	Probable AR *(MAPBPIP)*	Partial albinism, decreased B and T cells
VPS45 defects	AR *(VPS45)*	neutrophil dysfunction, bone marrow fibrosis, nephromegaly
DISORDERS OF METABOLISM		
Glycogen storage disease, type 1b	AR *(G6PT1)*	Hepatic enlargement, growth retardation, impaired neutrophil motility
Barth syndrome	XL *(TAZ1)*	Episodic neutropenia, dilated cardiomyopathy, methylglutaconic aciduria
Pearson syndrome	Mitochondrial (DNA deletions)	Episodic neutropenia, pancytopenia; defects in exocrine pancreas, liver, and kidneys
NEUTROPENIA IN DISORDERS OF IMMUNE FUNCTION		
Common variable immunodeficiency	Familial, sporadic *(TNFRSF13B)*	Hypogammaglobulinemia, other immune system defects
IgA deficiency	Unknown (Unknown or *TNFRSF13B*)	Decreased IgA
Severe combined immunodeficiency	AR, XL (multiple loci)	Absent humoral and cellular immune function
Hyper-IgM syndrome	XL *(HIGM1)*	Absent IgG, elevated IgM, autoimmune cytopenias
WHIM syndrome	AD *(CXCR4)*	Warts, hypogammaglobulinemia, infections, myelokathexis
Cartilage-hair hypoplasia	AR *(RMKP)*	Lymphopenia, short-limbed dwarfism, metaphyseal chondrodysplasia, fine sparse hair
Schimke immunoosseous dysplasia	Probable AR *(SMARCAL1)*	Lymphopenia, pancytopenia, spondyloepiphyseal dysplasia, growth retardation, renal failure
X-linked agammaglobulinemia	BTK	Agammaglobulinemia, neutropenia in ~25%

AD, autosomal dominant; AML, acute myelogenous leukemia; ANC, absolute neutrophil count; AR, autosomal recessive; HLH, hemophagocytic lymphohistiocytosis; Ig, immunoglobulin; MDS, myelodysplasia; XL, X-linked, BTK, Briton tyrosine kinase.

phenotype; approximately 90% of patients have mutations identified in the *SBDS* gene. SDS may progress to bone marrow hypoplasia or to MDS/AML; cytogenetic abnormalities, particularly isochromosome i(7q) and del(20q), often precede conversion to MDS, so bone marrow monitoring is warranted. Treatment includes pancreatic enzyme replacement, plus filgrastim in patients with severe neutropenia.

Dyskeratosis congenita, a disorder of telomerase activity, most often presents as bone marrow failure rather than isolated neutropenia. The classical phenotype also includes nail dystrophy, leukoplakia, malformed teeth, and reticulated hyperpigmentation of the skin, although many patients, particularly young ones, do not exhibit these clinical features.

Vesicular Trafficking Disorders. This group of very rare **primary immunodeficiency syndromes** (see Table 131-6) derives from autosomal recessive defects in the biogenesis or trafficking of lysosomes and related endosomal organelles. As a result, the syndromes share phenotypic characteristics including defects in melanosomes contributing to partial albinism, abnormal platelet function, and immunologic defects involving not only neutrophil number, but also the function of neutrophils, B lymphocytes, NK cells, and cytotoxic T lymphocytes. The syndromes share a high risk of hemophagocytic lymphohistiocytosis (HLH) as a result of defects in T and NK cells.

Chédiak-Higashi syndrome, best known for the characteristic giant cytoplasmic granules in neutrophils, monocytes, and lymphocytes, is a disorder of subcellular vesicular dysfunction caused by mutations in the *LYST* gene, with resultant giant granules in all granule-bearing cells. Patients have increased susceptibility to infections, mild bleeding diathesis, progressive peripheral neuropathy, and predisposition to life-threatening HLH. The only curative treatment is hematopoietic stem cell transplantation.

Griscelli syndrome type II also features neutropenia, partial albinism, and a high risk of HLH, but peripheral blood granulocytes do not show giant granules. Patients often have hypogammaglobulinemia. The disorder is caused by mutations in *RAB27a*, which encodes a small guanosine triphosphatase that regulates granule secretory pathways. The only curative treatment is hematopoietic stem cell transplantation.

Disorders of Metabolism. Recurrent infections with neutropenia are a distinctive feature of **glycogen storage disease (GSD)**

type Ib. As in classic von Gierke disease (GSDIa), glycogen storage in GSDIb causes massive hepatomegaly and severe growth retardation (see Chapter 87.1). Mutations in glucose-6-phosphate transporter 1, *G6PT1*, inhibit glucose transport in GSDIb, resulting in both defective neutrophil motility and increased apoptosis associated with neutropenia and recurrent bacterial infections. **Treatment** with filgrastim can correct the neutropenia but does not correct the underlying functional neutrophil defects.

Neutropenia in Disorders of Immune Dysfunction. Congenital immunologic disorders that have severe neutropenia as a clinical feature include X-linked agammaglobulinemia, common variable immunodeficiency, the severe combined immunodeficiencies, autoimmune lymphoproliferative syndrome, hyperimmunoglobulin M syndrome, WHIM (warts, hypogammaglobulinemia, infections, myelokathexis) syndrome, and a number of even rarer immunodeficiency disorders (see Table 131-6).

Unclassified Neutropenic Disorders. **Chronic benign neutropenia** of childhood represents a common group of disorders characterized by mild to moderate neutropenia that does not lead to an increased risk of pyogenic infections. Spontaneous remissions are often reported, although these may represent misdiagnosis of AIN of infancy, in which remissions occur commonly during childhood. Chronic benign neutropenia may be sporadic or inherited in either a dominant or recessive form. Because of the relatively low risk of serious infection, patients usually do not require any form of therapy.

Idiopathic chronic neutropenia is characterized by the onset of neutropenia after 2 yr of age, with no identifiable etiology. Patients with an ANC persistently <500/μL may be afflicted with recurrent pyogenic infections involving the skin, mucous membranes, lungs, and lymph nodes. Bone marrow examination reveals variable patterns of myeloid formation with arrest generally occurring between the myelocyte and band forms. The diagnosis overlaps with chronic benign and AINs.

Treatment

The management of acquired transient neutropenia associated with malignancies, myelosuppressive chemotherapy, or immunosuppressive chemotherapy differs from that of congenital or chronic forms of neutropenia. In the former situation, infections sometimes are heralded only by fever, and sepsis is a major cause of death. Early recognition and treatment of infections may be lifesaving (see Chapter 178). Therapy of severe chronic neutropenia is dictated by the clinical manifestations. Patients with benign neutropenia and no evidence of repeated bacterial infections or chronic gingivitis require no specific therapy. Superficial infections in children with mild to moderate neutropenia may be treated with appropriate oral antibiotics. In patients who have invasive or life-threatening infections, broad-spectrum intravenous antibiotics should be started promptly.

Subcutaneously administered filgrastim can provide effective treatment of severe chronic neutropenia including SCN, chronic symptomatic idiopathic neutropenia, and cyclic neutropenia. Treatment leads to dramatic increases in neutrophil counts, resulting in marked attenuation of infection and inflammation. Doses range from 2-5 μg/kg/day for cyclic, idiopathic, and autoimmune neutropenias, to 10-100 μg/kg/day for SCN. The long-term effects of filgrastim therapy include a propensity for the development of moderate splenomegaly, thrombocytopenia, and, rarely, vasculitis; only patients with SCN are at risk for MDS/AML.

Patients with SCN or SDS who develop MDS or AML respond only to hematopoietic stem cell transplantation; chemotherapy is ineffective. Hematopoietic stem cell transplantation is also the treatment of choice for aplastic anemia or HLH.

LYMPHOPENIA

The definition of **lymphopenia,** like neutropenia, is age-dependent and can be from acquired or inherited causes. **The absolute lymphocyte count (ALC)** is determined by multiplying the total WBC count by the percentage of total lymphocytes. For children younger than 12 mo old, lymphopenia is defined as an ALC <3,000 cells/μL. For older children and adults, an ALC <1,000 cells/μL is considered lymphopenia. In isolation, mild to moderate lymphopenia is generally a benign condition often detected only in the evaluation of other illnesses. However, severe lymphopenia can result in serious, life-threatening illness. Lymphocyte subpopulations can be measured by flow cytometry, which uses the pattern of lymphocyte antigen expression to quantitate and classify T, B, and NK cells.

Table 131-7 Causes of Lymphocytopenia

ACQUIRED	
Infectious diseases	AIDS, hepatitis, influenza, sepsis, tuberculosis, typhoid
Iatrogenic	Corticosteroids, cytotoxic chemotherapy, high-dose PUVA, immunosuppressive therapy, radiation, thoracic duct drainage
Systemic diseases	Hodgkin disease, lupus erythematosus, myasthenia gravis, protein-losing enteropathy, renal failure sarcoidosis
Other	Aplastic anemia, dietary deficiencies, thermal injury
INHERITED	
Aplasia of lymphopoietic stem cells	Cartilage-hair hypoplasia, ataxia-telangiectasia, SCID, thymoma, Wiskott-Aldrich syndrome

PUVA, psoralen and ultraviolet A irradiation; SCID, severe combined immunodeficiency.

Acquired Lymphopenia

Acute lymphopenia is most often a consequence of infection and/or is iatrogenic from lymphocyte-toxic medications and treatments (Table 131-7). Microbial causes include viruses (e.g., respiratory syncytial virus, cytomegalovirus, influenza, measles, and hepatitis) bacterial infections (e.g., tuberculosis, typhoid fever, histoplasmosis, and brucellosis) and malaria. The mechanisms behind infection-associated lymphopenia are not fully elucidated but probably include lymphocyte redistribution and accelerated apoptosis. Corticosteroids are a common cause of medication-induced lymphopenia, as are lymphocyte-specific immunosuppressive agents (e.g., antilymphocyte globulin, alemtuzumab, and rituximab) chemotherapy drugs, and radiation. In most cases, infectious and iatrogenic causes of acute lymphopenia are reversible, although full lymphocyte recovery from chemotherapy and lymphocyte-specific immunosuppressive agents may take several months to years. Prolonged lymphopenia (Table 131-7) may be caused by recurrent infection; persistent infections, mostly notably HIV; malnutrition; mechanical loss of lymphocytes through protein-losing enteropathy or thoracic duct leaks; or systemic diseases such as lupus erythematosus, rheumatoid arthritis, sarcoidosis, renal failure, lymphoma, and aplastic anemia.

Inherited Lymphopenia

Primary immunodeficiencies and bone marrow failure syndromes are the main cause of inherited lymphopenia in children (see Table 131-7). Primary immunodeficiency may result in a severe quantitative defect, as in X-linked agammaglobulinemia and severe combined immunodeficiency (SCID), or a qualitative or progressive defect as in Wiskott-Aldrich syndrome and common variable immunodeficiency. X-linked agammaglobulinemia is characterized by a near absence of mature B cells because of a mutation in *BTK* that results in a dysfunctional tyrosine kinase. SCIDs are a genetically heterogenous group of disorders characterized by abnormalities of thymopoiesis and T-cell maturation. Newborn screening for severe T-cell deficiency, via analysis of T-cell receptor excision circles from dried blood spot Guthrie cards, is available in many states to aid in the rapid identification and treatment of infants with SCID and other T-cell disorders. Quantitative defects in lymphocytes can also be appreciated in select forms of inherited bone marrow failure such as reticular dysgenesis, SCN secondary to *GFI1* mutation, and dyskeratosis congenita.

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Chapter 132

Leukocytosis

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Leukocytosis is an elevation in the total leukocyte or white blood cell (WBC) count that is 2 SD above the mean count for a particular age (see Chapter 727). To evaluate the patient with leukocytosis, it is critical to determine which class of WBC is elevated in conjunction with the duration and extent of the leukocytosis. For discussion of WBC elevation caused by immature leukocytes in acute and chronic leukemias, see Chapter 495.

A WBC count exceeding 50,000/μL is termed a **leukemoid reaction** because of the similarity to some features of leukemia. Leukemoid reactions are usually neutrophilic, and unlike true leukemia, show only small proportions of immature myeloid cells, consisting primarily of band forms, occasional metamyelocytes, and progressively rarer myelocytes, promyelocytes, and blasts. The process is most frequently associated with septicemia and severe bacterial infections, including shigellosis, salmonellosis, and meningococcemia.

A proportion of immature neutrophil cells >5%, termed a **left shift**, indicates rapid release of cells from the bone marrow, consisting primarily of band forms, which usually constitute 1-5% of circulating neutrophilic cells, or metamyelocytes and myelocytes, which are not usually found in the peripheral circulation. Higher degrees of left shift with more immature neutrophil precursors are indicative of serious bacterial infections and may be a dire sign of depletion of the bone marrow reserve pool of neutrophils. Marked left shift may occasionally be encountered with trauma, burns, surgery, acute hemolysis, or hemorrhage.

NEUTROPHILIA

Neutrophilia is an increase in the total number of blood neutrophils that is 2 SD above the mean count for age (see Chapter 727). Elevated absolute neutrophil counts represent disturbances of the normal equilibrium involving bone marrow neutrophil production, movement out of the marrow compartments into the circulation, and neutrophil destruction. Neutrophilia may arise either alone or in combination with enhanced mobilization into the **circulating pool** from either the bone marrow storage compartment or the peripheral blood **marginating pool,** by impaired neutrophil egress into tissues, or by expansion of the circulating neutrophil pool secondary to increased granulocytopoiesis. Myelocytes are not released to the blood except under extreme circumstances.

Acute Acquired Neutrophilia

Neutrophilia is usually an acquired, secondary finding associated with inflammation, infection, injury, or stress (Table 132-1). Acute or chronic bacterial infections, trauma, and surgery are among the most common causes encountered in clinical practice. Neutrophilia may also be associated with heatstroke, burns, diabetic ketoacidosis, or any other acute stress. Drugs commonly associated with neutrophilia include epinephrine, corticosteroids, and recombinant growth factors such as recombinant human granulocyte colony-stimulating factor (G-CSF; filgrastim) and recombinant human granulocyte-macrophage colony-stimulating factor.

Epinephrine causes release into the circulation of a sequestered pool of neutrophils that normally marginate along the vascular endothelium. Corticosteroids accelerate the release of neutrophils and bands from a large storage pool within the bone marrow and impair the migration of neutrophils from the circulation into tissues. Acute neutrophilia in response to inflammation and infections occurs because of release of neutrophils from the marrow storage pool. The postmitotic marrow neutrophil pools are approximately 10 times the size of the blood neutrophil pool, and about half of these cells are bands and segmented neutrophils. In neutrophil production disorders, such as those associated with malignancies and cancer chemotherapy, the size of this pool may be reduced and the capacity to develop neutrophilia remains impaired. Exposure of blood to foreign substances such as hemodialysis membrane activates the complement system and causes transient neutropenia followed by neutrophilia because of release of bone marrow neutrophils. G-CSF and granulocyte-macrophage colony-stimulating factor cause acute and chronic neutrophilia by mobilizing cells from the marrow reserves and by stimulating neutrophil production.

Table 132-1 Causes of Neutrophilia

TYPE	CAUSE	EXAMPLE
Acute acquired	Bacterial infections	
	Surgery	
	Acute stress	Burns, diabetic ketoacidosis, heat stroke, postneutropenia rebound, exercise
	Drugs	Corticosteroids, epinephrine, hematopoietic growth factors, lithium
Chronic acquired	Chronic inflammation	Inflammatory bowel disease, rheumatoid arthritis, vasculitis
	Persistent infection	Tuberculosis
	Persistent stress	Chronic blood loss, hypoxia, sickle cell and other chronic hemolytic anemias
	Drugs	Corticosteroids, lithium; rarely ranitidine, quinidine
	Other	Postsplenectomy, tumors, Hodgkin disease
Lifelong	Congenital asplenia	
	Hereditary disorders	Familial cold urticaria, hereditary neutrophilia, leukocyte adhesion deficiencies, periodic fever syndromes

Chronic Acquired Neutrophilia

Chronic acquired neutrophilia is usually associated with continued stimulation of neutrophil production resulting from persistent inflammatory reactions or chronic infections (e.g., tuberculosis), vasculitis, postsplenectomy states, Hodgkin disease, chronic myelogenous leukemia, chronic blood loss, sickle cell disease, some chronic hemolytic anemias, and prolonged administration of corticosteroids (see Table 132-1). Chronic neutrophilia can arise after expansion of cell production secondary to stimulation of cell divisions within the mitotic precursor pool, which consists of promyelocytes and myelocytes. Subsequently, the size of the postmitotic pool increases. These changes lead to an increase in the marrow reserve pool, which can be readily mobilized for release of neutrophils into the circulation. The neutrophil production rate can increase greatly in response to exogenously administered hemopoietic growth factors, such as G-CSF, with a maximum response taking at least 1 wk to develop.

Lifelong Neutrophilia

Congenital or acquired asplenia is associated with lifelong neutrophilia. Uncommon genetic disorders that present with neutrophilia include leukocyte function disorders such as leukocyte adhesion deficiency and Rac2 mutation (see Chapter 124), and systemic disorders such as familial cold urticarial, periodic fever syndromes, and familial myeloproliferative disease (see Table 132-1). Two kindreds have been reported with autosomal dominant hereditary neutrophilia, with 1 caused by an activating mutation in the G-CSF receptor gene that leads to an increased proliferation of neutrophil precursors and a heightened risk of myelodysplastic syndrome.

Table 132-2 Causes of Monocytosis

CAUSE	EXAMPLE
Infections	
Bacterial infections	Brucellosis, subacute bacterial endocarditis, syphilis, tuberculosis typhoid
Nonbacterial infections	Fungal infections, kala-azar, malaria, Rocky Mountain spotted fever, typhus
Hematologic disorders	Congenital and acquired neutropenias, hemolytic anemias
Malignant disorders	Acute myelogenous leukemia, chronic myelogenous leukemia, juvenile myelomonocytic leukemia, Hodgkin disease, non-Hodgkin lymphomas, preleukemia
Chronic inflammatory diseases	Inflammatory bowel disease, polyarteritis nodosa, rheumatoid arthritis, sarcoidosis, systemic lupus erythematosus
Miscellaneous	Cirrhosis, drug reaction, postsplenectomy, recovery from bone marrow suppression

Evaluation of persistent neutrophilia requires a careful history, physical examination, and laboratory studies to search for infectious, inflammatory, and neoplastic conditions. The leukocyte alkaline phosphatase score of circulating neutrophils can differentiate chronic myelogenous leukemia, in which the level is uniformly near zero, from reactive or secondary neutrophilia, which feature normal to elevated levels.

MONOCYTOSIS

The average absolute blood monocyte count varies with age, which must be considered in the assessment of monocytosis. Given the role of monocytes in antigen presentation and cytokine secretion and as effectors of ingestion of invading organisms, it is not surprising that many clinical disorders give rise to monocytosis (Table 132-2). Most commonly, monocytosis occurs in patients recovering from myelosuppressive chemotherapy and is a harbinger of the return of the neutrophil count to normal. Monocytosis is occasionally a sign of an acute bacterial, viral, protozoal, or rickettsial infection, and may also occur in some forms of chronic neutropenia and postsplenectomy states. Chronic inflammatory conditions can stimulate sustained monocytosis, as can preleukemia, chronic myelogenous leukemia, lymphomas, and occasionally Hodgkin disease.

Lymphocytosis

The most common cause of lymphocytosis is an acute viral illness, as part of the normal T-cell response to the infection. In infectious mononucleosis, the B cells are infected with the Epstein-Barr virus and the T cells react to the viral antigens present in the B cells, resulting in **atypical lymphocytes** with characteristic large, vacuolated morphology. Other viral infections classically associated with lymphocytosis are cytomegalovirus and viral hepatitis. Chronic bacterial infections such as tuberculosis and brucellosis may lead to a sustained lymphocytosis. Pertussis is accompanied by marked lymphocytosis in approximately 25% of infants infected before 6 mo of age. Thyrotoxicosis and Addison disease are endocrine disorders associated with lymphocytosis. Persistent or pronounced lymphocytosis suggests acute lymphocytic leukemia.

Basophilia

Basophilia is defined as an absolute basophil count >120 cells/μL. Basophilia is a nonspecific sign of a wide variety of disorders and is usually of limited diagnostic importance. Basophilia is most often present in hypersensitivity reactions and frequently accompanies the leukocytosis of chronic myeloid leukemia.

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Section 4

The Complement System

Chapter 133

The Complement System

Richard B. Johnston Jr.

Complement (C) was originally defined as the nonspecific, heat-labile complementary principal required with specific antibody to lyse bacteria. The 1st 4 components were numbered in the order of their discovery and are termed the classical pathway. Unfortunately, the components fix to the immune complex in a different order, C1423. Beyond this confusing start, complement is a logical, exquisitely balanced, and highly influential system that is fundamental to the clinical expression of host defense and inflammation. In addition, it is evolutionarily ancient, and as it coevolved with other physiologic systems, it developed the capacity to perform functions beyond just host defense. Among these, it promotes phagocytic removal of dying body cells, molecular debris, and synapses during brain formation. But it can also cause harm and has been implicated in more than 30 illnesses.

The complement system, an essential component of innate immunity, is broadly conceptualized as the **classical, lectin,** and **alternative pathways,** which interact and depend on each other for their full activity; the **membrane attack complex (C5b6789),** formed from activity of any pathway; cell membrane **receptors** that bind complement components or fragments to mediate complement activity; and a large array of serum and membrane regulatory proteins (Table 133-1,

Table 133-1 Constituents of the Complement System

SERUM COMPONENTS THAT ARE THE CORE OF THE COMPLEMENT SYSTEM
Classical pathway: C1q, C1r, C1s, C4, C2, C3
Alternative pathway: Factor B, Factor D
Lectin pathway: Mannose-binding lectin (MBL), ficolins 1/2/3, MBL-associated serine proteases (MASPs) 1/2/3
Membrane attack complex: C5, C6, C7, C8, C9
Regulatory protein, enhancing: properdin
Regulatory proteins, downregulating: C1 inhibitor (C1 INH), C4-binding protein (C4-bp), factor H, factor I, vitronectin, clusterin, carboxypeptidase N (anaphylatoxin inactivator)
MEMBRANE REGULATORY PROTEINS
CR1 (CD35), membrane cofactor protein (MCP; CD46), decay-accelerating factor (DAF, CD55), CD59 (membrane inhibitor of reactive lysis; protectin)
MEMBRANE RECEPTORS
CR1 (CD35), CR2 (CD21), CR3 (CD11b/CD18), CR4 (CD11c/CD18), C3a receptor, C5a receptor, C1q receptors, complement receptor of the immunoglobulin superfamily (CRIg)

Fig. 133-1). The circulating components and regulators together comprise approximately 15% of the globulin fraction and 4% of the total proteins in serum. The normal concentrations of serum complement components vary by age (see Chapter 727); newborn infants have mild to moderate deficiencies of all components.

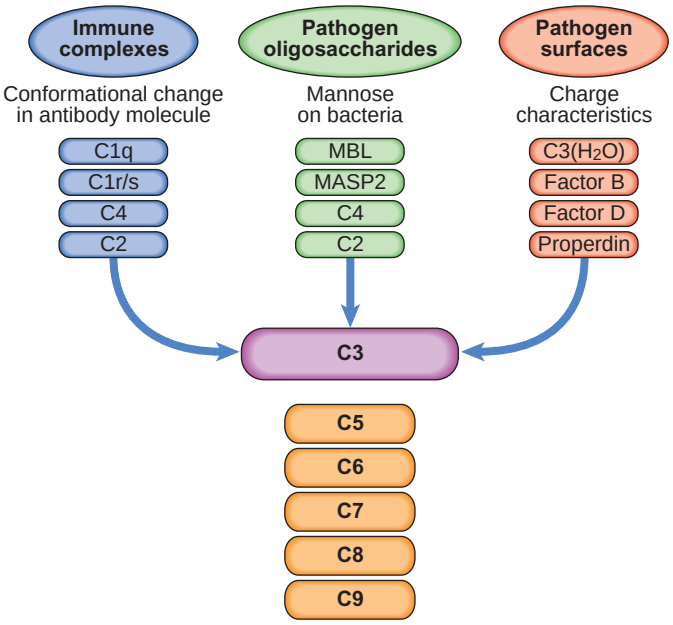


Figure 133-1 The complement cascade. The classical pathway is activated primarily by antibody while the mannose-binding lectin and alternative pathways are activated directly by pathogens. In each case, the activation arm leads to cleavage of C3. *(From Leung DYM, editor: Pediatric allergy principles and practice, ed 2, Philadelphia, 2010, WB Saunders, Fig. 11-1, p. 121.)*

After C1423, complement nomenclature is logical and consists of only a few rules. Fragments of components resulting from cleavage by other components acting as enzymes are assigned lowercase letters (a, b, c, d, e); with the exception of C2 fragments, the smaller piece that is released into surrounding fluids is assigned the lowercase letter *a,* and the major part of the molecule, bound to other components or to some part of the immune complex, is assigned letter *b*—for example, C3a and C3b. Components of the alternative pathway, B and D, have been assigned uppercase letters, as have the control proteins I and H, which downregulate both pathways. C3, and especially its major fragment C3b, is a component of both the classical and alternative pathways.

Complement is a system of interacting proteins. The biologic functions of the system depend on the interactions of individual components, which occur in sequential, cascade fashion. Activation of each component, except the 1st, depends on activation of the prior component or components in the sequence. Interaction occurs along 3 pathways (Fig. 133-2): the **classical pathway,** in the order antigen–antibody–C142356789; the **lectin** (carbohydrate-binding) **pathway**, in the order microbial carbohydrate–lectin (mannose-binding lectin [MBL] or ficolin)–MBL-associated serine protease–C42356789; and the **alternative pathway,** in the order activator–C3bBD–C356789. Antibody accelerates the rate of activation of the alternative pathway, but activation can occur on appropriate surfaces in the absence of antibody. The classical and the alternative pathways interact with each other through the ability of both to activate C3.

Activation of the early-acting components of complement (C1423) results in the generation of a series of active enzymes, C1, C42, and C423, on the surface of the immune complex or underlying cell. These enzymes cleave and activate the next component in the sequence. In contrast, the interaction among C5b, C6, C7, C8, and C9 is nonenzymatic and depends on changes in molecular configuration.

CLASSICAL AND LECTIN PATHWAYS

The classical pathway sequence begins with fixation of C1, by way of C1q, to the Fc, non–antigen-binding part of the antibody molecule after antigen–antibody interaction. The C1 tricomplex changes

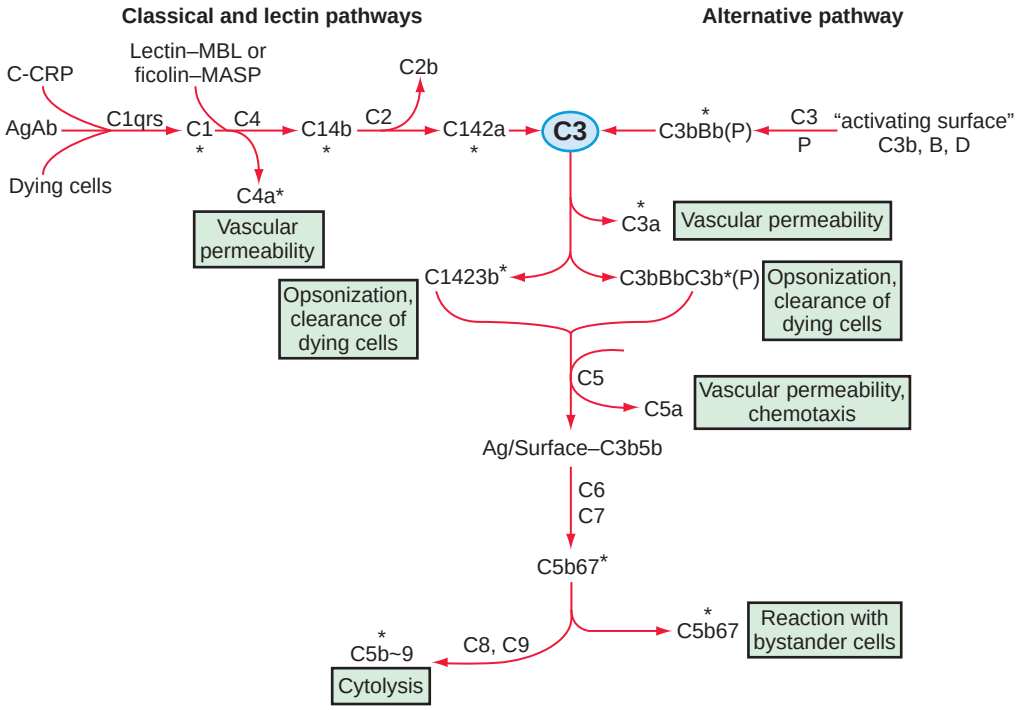


Figure 133-2 Sequence of activation of the components of the classical and lectin pathways of complement and interaction with the alternative pathway. Activation of C3 is the essential target. Functional activities generated during activation are enclosed in boxes. The multiple sites at which inhibitory regulator proteins (not shown) act are indicated by *asterisks,* emphasizing the delicate balance between action and control in this system that is essential for host defense yet capable of profound damage to host tissues. *Ab,* antibody (immunoglobulin G or M class); *Ag,* antigen (bacterium, virus, tumor or tissue cell); *B, D, I, P,* factors B, D, I, and properdin; *C-CRP,* carbohydrate–carbohydrate-reactive protein; *C4-bp,* C4-binding protein; *MASP,* MBL-associated serine protease; *MBL,* mannose-binding lectin.

configuration and the C1s subcomponent becomes an active enzyme, "C1 esterase." Certain bacteria, *Mycoplasma,* RNA viruses, and the lipid A component of bacterial endotoxin can activate C1q directly and trigger the full complement cascade.

As part of the innate immune response, broadly reactive "natural" antibodies and C-reactive protein, which reacts with carbohydrate from microorganisms and with dying cells, can substitute for specific antibody in the fixation of C1q and initiate reaction of the entire sequence. Endogenous agents, including uric acid crystals, amyloid deposits, DNA, and components of damaged cells such as apoptotic blebs and mitochondrial membranes, can activate C1q directly. But in this case, the ligand–C1q complex interacts strongly with the inhibitors C4-binding protein and factor H, allowing some C3-mediated opsonization and phagocytosis, but limiting the full inflammatory response typically triggered by microbes. C1q synthesized in the brain and retina enables the complement-dependent pruning of synapses that is essential for normal nervous system development.

There are 4 recognition molecules in the lectin pathway: MBL and ficolins 1, 2, and 3. MBL is the prototype of the collectin family of carbohydrate-binding proteins (lectins) that are believed to play an important part in innate, nonspecific immunity; its structure is homologous to that of C1q. These lectins, in association with MBL-associated serine proteases 1, 2, and 3 (MASPs 1/2/3), can bind to mannose, lipoteichoic acid, and other carbohydrates on the surface of bacteria, fungi, parasites, and viruses. MASPs then function there like C1s to cleave C4 and C2 and activate the complement cascade. The peptide C4a has weak "anaphylatoxin" activity and reacts with mast cells to release the chemical mediators of immediate hypersensitivity, including histamine. C3a and C5a, released later in the sequence, are potent anaphylatoxins, and C5a is also an important chemotactic factor. Fixation of C4b to the complex permits it to adhere to neutrophils, macrophages, B cells, dendritic cells, and erythrocytes. MASP-2 can activate clotting by generating thrombin from prothrombin, which could prevent microbial spread.

Cleavage of C3 and generation of C3b is the next step in the sequence. The serum concentration of C3 is the highest of any component, and its activation is the most crucial step in terms of biologic activity. Cleavage of C3 can be achieved through the **C3 convertase** of the classical pathway, C142, or of the alternative pathway, C3bBb. Once C3b is fixed to a complex or dead or dying host cell, it can bind to cells with receptors for C3b (complement receptor 1 [CR1]), including B lymphocytes, erythrocytes, and phagocytic cells (neutrophils, monocytes, and macrophages). Efficient **phagocytosis** of most microorganisms in vitro, especially by neutrophils, requires binding of C3 to the microbe. The severe pyogenic infections that commonly occur in C3-deficient patients indicate that phagocytosis in vivo is also inefficient without C3. The biologic activity of C3b is controlled by cleavage by **factor I** to iC3b, which promotes phagocytosis on binding to the **iC3b receptor (CR3)** on phagocytes. Further degradation of iC3b by factor I and proteases yields C3dg, then C3d; C3d binds to CR2 on B lymphocytes and thereby serves as a costimulator of antigen-induced B-cell activation.

ALTERNATIVE PATHWAY

The alternative pathway can be activated by C3b generated through classical pathway activity or proteases from neutrophils or the clotting system. It can also be activated by a form of C3 created by low-grade, spontaneous reaction of native C3 with a molecule of water, a "tick-over" that occurs constantly in plasma. Once formed, C3b or the hydrolyzed C3 can bind to any nearby cell or to factor B. Factor B attached to C3b in the plasma or on a surface can be cleaved to Bb by the protease factor D. The complex C3bBb becomes an efficient C3 convertase, which generates more C3b through an amplification loop. Properdin can bind to C3bBb, increasing stability of the enzyme and protecting it from inactivation by factors I and H, which modulate the loop and the pathway.

Certain "activating surfaces" promote alternative pathway activation if C3b is fixed to them, including bacterial teichoic acid or endotoxin, virally infected cells, antigen–immunoglobulin A complexes, and cardiopulmonary bypass and renal dialysis membranes. These surfaces act by protecting the C3bBb enzyme from the control otherwise exercised by factors I and H. Rabbit red blood cell membrane is such a surface, which serves as the basis for an assay of serum alternative pathway activity. Sialic acid on the surface of microorganisms or cells prevents formation of an effective alternative pathway C3 convertase by promoting activity of factors I and H. Nevertheless, significant activation of C3 can occur through the alternative pathway, and the resultant biologic activities are qualitatively the same as those achieved through activation by C142 (see Fig. 133-2).

MEMBRANE ATTACK COMPLEX

The sequence leading to cytolysis begins with the attachment of C5b to the C5-activating enzyme from the classical pathway, C4b2a3b, or from the alternative pathway, C3bBb3b. C6 is bound to C5b without being cleaved, stabilizing the activated C5b fragment. The C5b6 complex then dissociates from C423 and reacts with C7. C5b67 complexes must attach promptly to the membrane of the parent or a bystander cell, or they lose their activity. Next, C8 binds, and the C5b678 complex then promotes the addition of multiple C9 molecules. The C9 polymer of at least 3-6 molecules forms a transmembrane channel, and lysis ensues.

CONTROL MECHANISMS

Without control mechanisms acting at multiple points, there would be no effective complement system, and unbridled consumption of components would generate severe, potentially lethal damage to the host. At the 1st step, C1 inhibitor (C1 INH) inhibits C1r and C1s enzymatic activity and, thus, the cleavage of C4 and C2. C1 INH also inhibits MASP-2, factors XIa and XIIa of the clotting system, and kallikrein of the contact system. Activated C2 has a short half-life, and this relative instability limits the effective life of C42 and C423. The alternative pathway enzyme that activates C3, C3bBb, also has a short half-life, though it can be prolonged by the binding of properdin (P) to the enzyme complex. P can also bind directly to microbes and promote assembly of the alternative pathway C3 convertase.

Serum contains the enzyme carboxypeptidase N, which cleaves the N-terminus arginine from C4a, C3a, and C5a, thereby limiting their biologic activity. Factor I inactivates C4b and C3b; factor H accelerates inactivation of C3b by factor I; and an analogous factor, C4-binding protein (C4-bp), accelerates C4b cleavage by factor I, thus limiting assembly of the C3 convertase. Three protein constituents of cell membranes, CR1, membrane cofactor protein (MCP), and decay-accelerating factor (DAF), promote the disruption of C3 and C5 convertases assembled on those membranes. Another cell membrane-associated protein, CD59, can bind C8 or both C8 and C9 and thereby interfere with insertion of the membrane attack complex (C5b6789). The serum proteins vitronectin and clusterin can inhibit attachment of the C5b67 complex to cell membranes, bind C8 or C9 in a full membrane attack complex, or otherwise interfere with the formation or insertion of this complex. Vitronectin also promotes macrophage uptake of dying neutrophils. The genes for the regulatory proteins factor H, C4-bp, MCP, DAF, CR1, and CR2 are clustered on chromosome 1.

PARTICIPATION IN HOST DEFENSE

Neutralization of virus by antibody can be enhanced with C1 and C4 and further enhanced by the additional fixation of C3b through the classical or alternative pathway. Complement may, therefore, be particularly important in the early phases of a viral infection when antibody is limited. Antibody and the full complement sequence can also eliminate infectivity of at least some viruses by the production of typical complement "holes," as seen by electron microscopy. Fixation of C1q can opsonize (promote phagocytosis) through binding to the C1q receptor.

C4a, C3a, and C5a can bind to mast cells and thereby trigger release of histamine and other mediators, leading to vasodilation and the swelling and redness of inflammation. C5a can enhance macrophage phagocytosis of C3b-opsonized particles and induce macrophages to release the cytokines tumor necrosis factor and interleukin 1. C5a is a major chemotactic factor for neutrophils, monocytes, and eosinophils, which can efficiently phagocytize microorganisms opsonized with C3b

or cleaved C3b (iC3b). Further inactivation of cell-bound C3b by cleavage to C3d and C3dg removes its opsonizing activity, but it can still bind to B cells. Fixation of C3b to a target cell can enhance its lysis by natural killer cells or macrophages.

Insoluble immune complexes can be solubilized if they bind C3b, apparently because C3b disrupts the orderly antigen-antibody lattice. Binding C3b to a complex also allows it to adhere to C3 receptors (CR1) on red blood cells, which then transport the complexes to hepatic and splenic macrophages for removal. This phenomenon may at least partially explain the immune complex disease found in patients who lack C1, C4, C2, or C3.

The complement system serves to link the innate and adaptive immune systems. C4b or C3b coupled to immune complexes promotes their binding to antigen-presenting macrophages, dendritic cells, and B cells. Coupling of antigen to C3d allows binding to CR2 on B cells, which markedly reduces the amount of antigen needed to trigger an antibody response.

Neutralization of endotoxin in vitro and protection from its lethal effects in experimental animals require C1 INH and later-acting components of complement, at least through C6. Finally, activation of the entire complement sequence can result in lysis of virus-infected cells, tumor cells, and most types of microorganisms. Bactericidal activity of complement has not appeared to be important to host defense, except for the occurrence of *Neisseria* infections in patients lacking later-acting components of complement (see Chapter 134).

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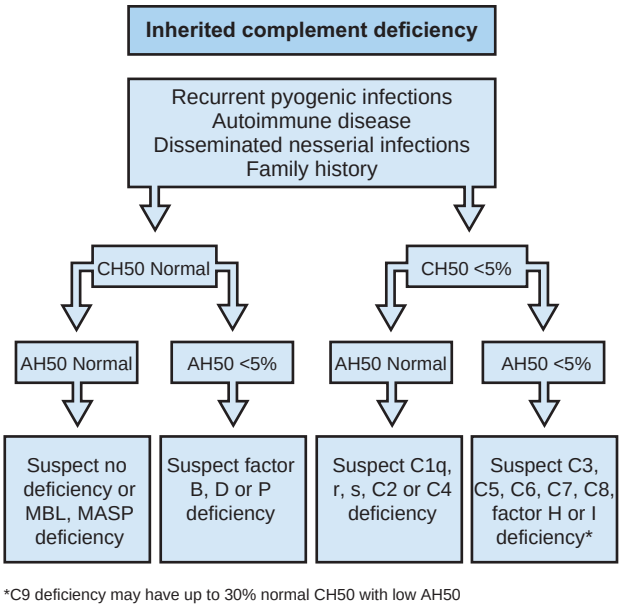


Figure 134-1 Flow chart for the evaluation of inherited complement deficiencies using hemolytic screening assays for the classical (CH_{50}) and alternative pathways (AH_{50}). For each assay, the entire activation pathway including the membrane attack complex (MAC) is required for lysis. *(Modified from Rich RR, Fleisher TA, Shearer WT, et al, editors, Clinical immunology: principles and practice, ed 4, Philadelphia, 2012, WB Saunders, Fig. 20-8, p. 262.)*

Chapter 134

Disorders of the Complement System

134.1 Evaluation of the Complement System

Richard B. Johnston Jr.

Testing for **total hemolytic complement activity (CH_{50})** effectively screens for most of the common diseases of the complement system. A normal result in this assay depends on the ability of all 11 components of the classical pathway and membrane attack complex to interact and lyse antibody-coated sheep erythrocytes. The dilution of serum that lyses 50% of the cells determines the end point. In **congenital deficiencies** of C1 through C8, the CH_{50} value is 0 or close to 0; in C9 deficiency, the value is approximately half-normal. Values in the acquired deficiencies vary with the type and severity of the underlying disorder. This assay does not detect deficiency of mannose-binding lectin (MBL), factors D or B of the alternative pathway, or properdin (Fig. 134-1). Deficiency of factors I or H permits consumption of C3, with partial reduction in the CH_{50} value. When clotted blood or serum sits at room temperature or warms, CH_{50} activity begins to decline, which leads to values that are falsely low but not zero. It is important to separate the serum and freeze it at −70°C (−94°F) by no more than 1 hr after blood draw.

In **hereditary angioedema,** depression of C4 and C2 during an attack significantly reduces the CH_{50}. Typically, C4 is low and C3 normal or slightly decreased. Concentrations of C1 inhibitor protein will be normal in 15% of cases; but C1 acts as an esterase, and the diagnosis can be established by showing increased capacity of patients' sera to hydrolyze synthetic esters.

A decrease in serum concentration of both C4 and C3 suggests activation of the **classical pathway** by immune complexes. Decreased C3 and normal C4 levels suggest activation of the **alternative pathway.** This difference is particularly useful in distinguishing nephritis secondary to immune complex deposition from that caused by NeF (nephritic factor). In the latter condition and in deficiency of factor I or H, factor B is consumed and C3 serum concentration is low. Alternative pathway activity can be measured with a relatively simple and reproducible hemolytic assay that depends on the capacity of rabbit erythrocytes to serve as both an activating (permissive) surface and a target of alternative pathway activity. This assay ($\mathbf{AP}_{50}$) detects deficiency of properdin, factor D, and factor B. Immunochemical methods can be used to quantify individual components of all 3 pathways, guided by results of the screening hemolytic assays. It is possible to analyze the genes encoding most of the components.

A defect of complement function should be considered in any patient with recurrent angioedema, autoimmune disease (especially systemic lupus erythematosus [SLE]), chronic nephritis, hemolytic-uremic syndrome, or partial lipodystrophy, or with recurrent pyogenic infections, disseminated meningococcal or gonococcal infection, or a second episode of bacteremia at any age. A previously well adolescent or young adult with meningococcal meningitis caused by an uncommon serotype (not A, B, or C) should undergo screening for a late-component or alternative pathway deficiency with CH_{50} and AP_{50} assays.

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134.2 Genetic Deficiencies of Complement Components

Richard B. Johnston Jr.

Congenital deficiencies of all 11 components of the classical-membrane attack pathway and of factor D and properdin of the alternative pathway are described in Table 134-1. All of the components of the

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Table 134-1 Genetic Deficiencies of Plasma Complement Components and Associated Clinical Findings

DEFICIENT COMPONENT	INFECTION*			AUTOIMMUNE/IMMUNE COMPLEX DISEASE*		
	VERY COMMON	COMMON	OCCASIONAL	VERY COMMON	COMMON	OCCASIONAL
CLASSICAL PATHWAY						
C1q			Pneumococcal B/M, other pyogenic	SLE	GN	DV/DLE
C1r, C1s, C1rs		Other pyogenic	Pneumococcal B/M, DGI	SLE	Other AD	GN
C4		Other pyogenic		SLE	GN, other AD	
C2		Other pyogenic, pneumococcal B/M, meningococcal M			SLE, GN, DV/DLE, other AD	
C3	Other pyogenic	Pneumococcal B/M, meningococcal M			GN, DV/DLE	SLE, other AD
C5	Meningococcal M	DGI	Other pyogenic			SLE, GN
C6	Meningococcal M	DGI	Other pyogenic			SLE, GN, other AD
C7	Meningococcal M		DGI, other pyogenic		SLE, other AD	
C8	Meningococcal M	DGI	Other pyogenic			SLE, GN
C9		Meningococcal M				
LECTIN PATHWAY						
MBL			Other pyogenic, fungal, HIV			SLE
MASP-2			Pneumococcal pneumonia			SLE
Ficolin-3			Other pyogenic			
ALTERNATIVE PATHWAY						
Factor D	DGI, meningococcal M, other pyogenic					
CONTROL PROTEINS						
C1 INH	Hereditary angioedema†					SLE
Factor I	Other pyogenic, meningococcal M	Pneumococcal B/M				
Factor H		Meningococcal B/M	Other pyogenic		GN, aHUS	SLE
Properdin		Meningococcal M	Pneumococcal B/M, other pyogenic		DV/DLE	
C4-binding protein						Other AD

*A finding was reported as "very common" if it occurred in 50% or more of reported cases, "common" if reported in approximately 5-50% of cases, and "occasional" if present in 1 or 2 cases or <5% of the more frequent deficiencies.

†Hereditary angioedema is not typically associated with infection or autoimmunity.

aHUS, atypical hemolytic-uremic syndrome; B/M, bacteremia and/or meningitis; DGI, disseminated gonococcal infection; DV/DLE, dermal vasculitis or typical discoid lupus erythematosus; GN, glomerulonephritis in various forms, often membranoproliferative; HIV, human immunodeficiency virus; M, meningitis; MASP, MBL-associated serine protease; MBL, mannose-binding lectin; other AD, autoimmune disease (almost all possible diagnoses have been reported); other pyogenic, serious deep or systemic infection caused by, or typically caused by, a pyogenic bacterium (abscess, osteomyelitis, pneumonia, bacteremia other than pneumococcal, meningitis other than meningococcal or pneumococcal, cellulitis, myopericarditis, and peritonitis); SLE, typical systemic lupus erythematosus or an SLE-like syndrome without characteristic serologic findings.

Data from Figueroa JE, Densen P: Infectious diseases associated with complement deficiencies, Clin Microbiol Rev *4:359–395, 1991; Ross SC, Densen P: Complement deficiency states and infection: epidemiology, pathogenesis and consequences of neisserial and other infections in an immune deficiency,* Medicine (Baltimore) *63:243–273, 1984; and other cases and series reported to date.*

classical and alternative pathways except properdin are inherited as autosomal recessive codominant traits. Each parent transmits a gene that codes for synthesis of half the serum level of the component. Deficiency results from inheritance of 1 null gene from each parent; the hemizygous parents typically have low normal CH_{50} levels and no consequences of the partial deficiency. Properdin deficiency is transmitted as an X-linked trait.

Most patients with primary **C1q deficiency** have SLE; some have an SLE-like syndrome without typical SLE serology, a chronic rash with underlying vasculitis, or membranoproliferative glomerulonephritis (MPGN). Some C1q-deficient children have serious infections, including septicemia and meningitis. Individuals with **C1r, C1s, combined C1r/C1s, C4, C2,** or **C3 deficiency** also have a high incidence of autoimmune syndromes (see Table 134-1), especially SLE or an SLE-like syndrome without an elevated antinuclear antibody level.

C4 is encoded by 2 genes, *C4A* and *C4B*. **C4 deficiency** represents absence of both gene products. Complete deficiency of only C4A, present in approximately 1% of the population, also predisposes to SLE, although C4 levels are only partially reduced. Patients with only C4B deficiency may be predisposed to infection. A few patients with **C5, C6, C7,** or **C8 deficiency** have SLE, but recurrent meningococcal infections are much more likely to be the major problem.

There are at least 2 possible reasons for the concurrence of complement component deficiencies, especially C1, C4, C2, or C3 deficiency, and autoimmune–immune complex diseases. First, deposition of C3 on autoimmune complexes facilitates their removal from the circulation through binding to complement receptor 1 (CR1) on erythrocytes and transport to the spleen and liver. Second, the early components, particularly C1q and C3, expedite the clearance of necrotic and apoptotic cells, which are sources of autoantigens.

Individuals with **C2 deficiency** carry the risk of life-threatening septicemic illnesses, most commonly caused by pneumococci. However, most have not had problems with increased susceptibility to infection, presumably because of the protective function of the alternative pathway. The genes for C2, factor B, and C4 are situated close to each other on chromosome 6, and a partial depression of factor B levels can occur in conjunction with C2 deficiency. Persons with a deficiency of both proteins may be at particular risk.

Because C3 can be activated by C142 or by the alternative pathway, a defect in the function of either pathway can be compensated for, at least to some extent. Without C3, however, opsonization of bacteria is inefficient, and the chemotactic fragment from C5 (C5a) is not generated. Some organisms must be well opsonized in order to be cleared, and genetic **C3 deficiency** has been associated with recurrent, severe pyogenic infections caused by pneumococci, *Haemophilus influenzae*, and meningococci.

More than half of the individuals reported to have congenital **C5, C6, C7,** or **C8 deficiency** have had meningococcal meningitis or extragenital gonococcal infection. Patients with **C9 deficiency**, which is most often reported in individuals of Japanese descent, retain about one-third normal CH_{50} titers; some of these patients have also had *Neisseria* disease. In studies of patients 10 yr of age and older with systemic meningococcal disease, 3-15% have had a genetic deficiency of C5, C6, C7, C8, C9, or properdin. Among patients with infections caused by the uncommon *Neisseria meningitidis* serogroups (X, Y, Z, W135, 29E, or nongroupable; not A, B, or C), 33-45% have an underlying complement deficiency. It is not clear why patients with a deficiency of 1 of the late-acting components suffer a particular predisposition to *Neisseria* infections. It may be that serum bacteriolysis is uniquely important in defense against this organism. Many persons with such a deficiency have no significant illness.

A few individuals have been identified with **deficiency of factor D** of the alternative pathway, all with recurrent infections, most often neisserial. Hemolytic complement activity and C3 levels in their serum were normal, but alternative pathway activity was markedly deficient or absent.

Mutations in the structural gene encoding MBL or polymorphisms in the promoter region of the gene result in pronounced interindividual variation in the level of circulating MBL. More than 90% of individuals with **MBL deficiency** do not express a predisposition to infection. Those with a very low level of MBL have a predisposition to recurrent respiratory infections in infancy and to serious pyogenic and fungal infections if there is another underlying defect of host defense. MBL-associated serine protease (**MASP)-2 deficiency** has been reported with SLE-like symptoms and recurrent pneumococcal pneumonia. Homozygous **ficolin-3 deficiency** is associated with repeated pneumonia since early childhood, cerebral abscesses, and bronchiectasis.

Bibliography is available at Expert Consult.

134.3 Deficiencies of Plasma, Membrane, or Serosal Complement Control Proteins

Richard B. Johnston Jr.

Congenital deficiencies of 5 plasma complement control proteins have been described (see Table 134-1). **Factor I deficiency** was reported originally as a deficiency of C3 resulting from hypercatabolism. The first patient described had suffered a series of severe pyogenic infections similar to those associated with agammaglobulinemia or congenital deficiency of C3. Factor I is an essential regulator of both pathways. Its deficiency permits prolonged existence of C3b as a part of the C3 convertase of the alternative pathway, C3bBb. This results in constant activation of the alternative pathway and cleavage of more C3 to C3b, in circular fashion. Intravenous infusion of plasma or purified factor I induced a prompt rise in serum C3 concentration in the patient and a return to normal of in vitro C3-dependent functions such as opsonization.

The effects of **factor H deficiency** are like those of factor I deficiency because factor H also assists in dismantling the alternative pathway C3 convertase. A trigger event such as infection initiates uninhibited continuous activation of the alternative pathway, which consumes C3, factor B, total hemolytic activity, and alternative pathway activity. Patients have sustained systemic infections due to pyogenic bacteria, particularly *N. meningitidis.* Many have had glomerulonephritis or atypical hemolytic uremic syndrome (aHUS) (see Chapter 518). Mutations in genes encoding membrane cofactor protein (MCP; CD46), factors I or B, C3, or the endothelial antiinflammatory protein thrombomodulin, or autoantibodies to factors H or B, also are associated with aHUS. The majority of patients with factor H deficiency and aHUS, typically younger than 2 yr of age, develop end-stage renal disease or die. The few patients thus far reported as having **C4-binding protein deficiency** have approximately 25% of the normal levels of the protein and no typical disease presentation, although 1 had angioedema and Behçet disease.

Persons with **properdin deficiency** have a striking predisposition to *N. meningitidis* meningitis. All reported patients have been male. The predisposition to infection in these patients demonstrates clearly the need for the alternative pathway in defense against bacterial infection. Serum hemolytic complement activity is normal in these patients, and if the patient has specific antibacterial antibody from immunization or prior exposure, the need for the alternative pathway and properdin is greatly reduced. Several patients have had dermal vasculitis or discoid lupus.

Hereditary angioedema occurs in persons unable to synthesize normal levels of active C1 inhibitor (C1 INH). In 85% of affected families, the patient has markedly reduced concentrations of inhibitor, averaging 30% of normal; the other 15% have normal or elevated concentrations of an immunologically cross-reacting but nonfunctional protein. Both forms of the disease are transmitted as autosomal dominant traits. C1 INH suppresses the complement proteases C1rs and MASP-2 and the activated proteases of the contact and fibrinolysis systems. In doing so, C1 INH is consumed as a "suicide inhibitor." In the absence of full C1 INH function, activation of any of these proteases tips the balance toward the protease. This activation leads to uncontrolled C1 and kallikrein activity with breakdown of C4 and C2 and release of bradykinin, which interacts with vascular endothelial cells to cause vasodilation, which produces localized, nonpitting edema. The biochemical triggers that induce attacks of angioedema in these patients are not well understood.

Swelling of the affected part progresses rapidly, without urticaria, itching, discoloration, or redness and often without severe pain. Swelling of the intestinal wall, however, can lead to intense abdominal cramping, sometimes with vomiting or diarrhea. Concomitant subcutaneous edema is often absent, and patients have undergone abdominal surgery or psychiatric examination before the true diagnosis was established. Laryngeal edema can be fatal. Attacks last 2-3 days and then gradually abate. They may occur at sites of trauma, especially dental, after vigorous exercise, or with menses, fever, or emotional stress. Attacks begin in the 1st 5 yr of life in almost half of patients, but are usually not severe until late childhood or adolescence. **Acquired C1 INH deficiency** can occur in association with B-cell cancer or autoantibody to C1 INH. SLE and glomerulonephritis have been reported in patients with the congenital disease.

Three of the membrane complement control proteins—CR1, MCP (CD46), and decay-accelerating factor (DAF)—prevent the formation of the full C3-cleaving enzyme, C3bBb, which is triggered by C3b deposition. CD59 (membrane inhibitor of reactive lysis) prevents the full development of the membrane attack complex that creates the "hole." **Paroxysmal nocturnal hemoglobinuria** (PNH) is a hemolytic anemia that occurs when DAF and CD59 are not expressed on the erythrocyte surface. The condition is acquired as a somatic mutation in a hematopoietic stem cell of the *PIG-A* gene on the X chromosome. The product of this gene is required for normal synthesis of a

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glycosyl-phosphatidylinositol molecule that anchors about 20 proteins to cell membranes, including DAF and CD59. One patient with **genetic isolated CD59 deficiency** had a mild PNH-like disease in spite of normal expression of membrane DAF. In contrast, **genetic isolated DAF deficiency** has not resulted in hemolytic anemia.

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134.4 Secondary Disorders of Complement

Richard B. Johnston Jr.

Partial deficiency of C1q has occurred in patients with severe combined immunodeficiency disease or hypogammaglobulinemia, apparently secondary to the deficiency of immunoglobulin (Ig) G, which normally binds reversibly to C1q and prevents its rapid catabolism.

Chronic MPGN can be caused by NeF, an IgG autoantibody to the C3-cleaving enzyme of the alternative pathway, C3bBb, which protects the enzyme from inactivation and promotes over activation of the alternative pathway. The result is increased consumption of C3 and decreased concentration of serum C3. Pyogenic infections, including meningitis, may occur if the serum C3 level drops to <10% of normal. This disorder has been found in children and adults with **partial lipodystrophy**. Adipocytes are the main source of factor D and synthesize C3 and factor B; exposure to NeF induces their lysis. An IgG NeF that binds to and inhibits the breakup of C42, the classical pathway C3 convertase, has been described in acute postinfectious nephritis and in SLE. The consumption of C3 that characterizes poststreptococcal nephritis and SLE could be caused by this factor, by complement activation by immune complexes, or by both.

Newborn infants have mild to moderate reductions in all plasma components of the complement system. Opsonization and generation of chemotactic activity in serum from full-term newborns can be markedly deficient through either the classical or alternative pathway. Complement activity is even lower in preterm infants. Patients with severe chronic cirrhosis of the liver, hepatic failure, malnutrition, or anorexia nervosa can have significant deficiency of complement components and functional activity. Synthesis of components is depressed in these conditions, and serum from some patients with malnutrition also contains immune complexes that could accelerate depletion.

Patients with **sickle cell disease** have normal activity of the classical pathway, but some have defective function of the alternative pathway in opsonization of pneumococci, in bacteriolysis and opsonization of *Salmonella,* and in lysis of rabbit erythrocytes. Deoxygenation of erythrocytes from patients with sickle cell disease alters their membranes to increase exposure of phospholipids that can activate the alternative pathway and consume its components. This activation is accentuated during painful crisis. Children with nephrotic syndrome may have decreased serum levels of factors B and D and subnormal serum opsonizing activity.

Immune complexes initiated by microorganisms or their by-products can induce complement consumption. Activation occurs primarily through fixation of C1 and initiation of the classical pathway. Formation of immune complexes and consumption of complement have been demonstrated in lepromatous leprosy, bacterial endocarditis, infected ventriculojugular shunts, malaria, infectious mononucleosis, dengue hemorrhagic fever, and acute hepatitis B. Nephritis or arthritis can develop as a result of deposition of immune complexes and activation of complement in these infections. In SLE, immune complexes activate C142, and C3 is deposited at sites of tissue damage, including kidneys and skin; depressed synthesis of C3 is also noted. The syndrome of recurrent urticaria, angioedema, eosinophilia, and hypocomplementemia secondary to activation of the classical pathway may be due to autoantibody to C1q and circulating immune complexes. Circulating immune complexes and decreased C3 have been reported in some patients with dermatitis herpetiformis, celiac disease, primary biliary cirrhosis, and Reye syndrome.

Circulating bacterial products in sepsis or tissue factors released after severe trauma can initiate activation of the classical and alternative pathways, leading to increased serum levels of C3a, C5a, and C5b-9 and systemic inflammatory response syndrome and multiple organ failure. C5a and its receptors, particularly on neutrophils, appear to be central to the pathogenesis of systemic inflammatory response syndrome. Intravenous injection of iodinated roentgenographic contrast medium can trigger a rapid and significant activation of the alternative pathway, which may explain the occasional reactions that occur in patients undergoing this procedure.

Burns can induce massive activation of the complement system, especially the alternative pathway, within a few hours after injury. Resulting generation of C3a and C5a stimulates neutrophils and induces their sequestration in the lungs, leading to shock lung. Cardiopulmonary bypass, extracorporeal membrane oxygenation, plasma exchange, or hemodialysis using cellophane membranes may be associated with a similar syndrome as a result of activation of plasma complement, with release of C3a and C5a. In patients with erythropoietic protoporphyria or porphyria cutanea tarda, exposure of the skin to light of certain wavelengths activates complement, generating chemotactic activity. This chemotactic activity leads to lysis of capillary endothelial cells, mast cell degranulation, and the appearance of neutrophils in the dermis.

Some tumor cells can avoid complement-mediated lysis by overexpressing DAF, MCP, CD59, CR1, or factor H, or by secreting proteases that cleave tumor-bound C3b. Microorganisms have evolved similar evasive mechanisms; for example, HIV-1 particles budding from infected cells acquire the membrane proteins DAF and CD59, and staphylococci can produce multiple complement inhibitors.

Bibliography is available at Expert Consult.

134.5 Treatment of Complement Disorders

Richard B. Johnston Jr.

No specific therapy is available at present for genetic deficiencies of the components of the classical, alternative, and lectin complement pathways. Much can be done, however, to protect patients with any of these disorders from serious complications; and specific treatment is available for 3 disorders caused by control-protein deficiencies, hereditary angioedema, aHUS, and PNH.

Management of hereditary angioedema starts with avoidance of precipitating factors, usually trauma. Infusion of C1 INH concentrate (nanofiltered C1-esterase inhibitor), an inhibitor of kallikrein (ecallantide) that blocks bradykinin production, and an antagonist of the bradykinin receptor (icatibant) are approved in the United States for use in adolescents and adults for long-term prophylaxis, preparation for surgery or dental procedures, or treatment of acute attacks. The synthetic androgen oxandrolone increases the level of functional C1 INH severalfold and is approved for cautious use in children. Antihistamines, adrenalin, and corticosteroids have no effect. Eculizumab, a humanized monoclonal antibody to C5, is an effective treatment for PNH and aHUS.

Effective supportive management is available for other primary diseases of the complement system, and identification of a specific defect in the complement system can have an important impact on management. Concern for the associated complications such as autoimmune disease and infection should encourage vigorous diagnostic efforts and earlier institution of therapy. Individuals with SLE and a complement defect generally respond as well to therapy as do those without complement deficiency. With the onset of unexplained fever, cultures should be obtained and antibiotic therapy instituted more quickly and with less stringent indications than in a normal child. The parent or patient should be given letters describing any predisposition to systemic bacterial infection or autoimmune disease associated with the patient's deficiency, along with the recommended approach to management, for possible use by school, camp, or emergency room physicians. The

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patient and close household contacts should be immunized against *H. influenzae, Streptococcus pneumoniae,* and *N. meningitidis*. High titers of specific antibody might opsonize effectively without the full complement system, and immunization of household members could reduce the risk of exposing patients to these particularly threatening pathogens. Repeat immunization of patients is advisable since complement deficiency can be associated with a blunted or shorter-lived antibody response than normal.

Considering the many conditions in which complement is a central mediator of disease, there is an intensive effort to develop therapeutic complement inhibitors. These include soluble CR1 and inhibitors of C5 convertase and C3a and C5a binding. Heparin, which inhibits both classical and alternative pathways, has been used to prevent "post-pump syndrome."

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Section 5

Hematopoietic Stem Cell Transplantation

Chapter 135

Principles and Clinical Indications of Hematopoietic Stem Cell Transplantation

Andrea Velardi and Franco Locatelli

Thousands of children have received an infusion of either **allogeneic** (from a donor) or **autologous** (from the same individual) hematopoietic stem cells to cure both malignant and nonmalignant disorders. **Autologous** transplantation is employed as a rescue strategy after delivering otherwise lethal doses of radiotherapy and chemotherapy in children with hematologic malignancies such as relapsed lymphoma or selected solid tumors (e.g., neuroblastoma, brain tumors). **Allogeneic** transplantation is used to treat children with genetic diseases of blood cells, such as thalassemia and primary immunodeficiency diseases, as well as hematologic malignancies, such as leukemia and myelodysplastic syndromes. Since 1968 and for many years, bone marrow has represented the only source of hematopoietic progenitors employed. Growth factor (granulocyte colony-stimulating factor)–mobilized peripheral blood hematopoietic stem cells and umbilical cord blood hematopoietic progenitors have been more recently introduced in the clinical practice to perform hematopoietic stem cell transplantation (HSCT).

An human leukocyte antigen (HLA)–matched sibling was once the only type of donor employed. Today, matched unrelated volunteers, full-haplotype mismatched family members, and unrelated cord blood donors have been largely employed to transplant patients lacking an HLA-identical relative.

Protocols for allogeneic HSCT consist of 2 parts: the preparative regimen and transplantation itself. During the **preparative conditioning regimen,** chemotherapy, often associated with irradiation, is administered to destroy the patient's hematopoietic system and to suppress the immune system, especially T cells, so that graft rejection is prevented. In patients with malignancies, the preparative regimen also serves to significantly reduce the tumor burden. The patient then receives an intravenous infusion of hematopoietic cells from the donor. Less-aggressive conditioning regimens, known as reduced intensity conditioning regimens, are also used in pediatric patients. These regimens are mainly immune-suppressive and aim at inducing a state of reduced immune competence of the recipient permitting to avoid the rejection of donor cells.

The immunology of HSCT is distinct from that of other types of transplant because, in addition to stem cells, the graft contains mature blood cells of donor origin, including T cells, B cells, natural killer cells, and dendritic cells. These cells repopulate the recipient's lymphohematopoietic system and give rise to a new immune system, which helps eliminate residual leukemia cells that survive the conditioning regimen. This effect is known as the **graft-versus-leukemia (GVL) effect.**

The donor immune system exerts its T-cell–mediated GVL effect through alloreactions directed against not shared recipient histocompatibility antigens displayed on recipient leukemia cells. Because some of these histocompatibility antigens are also displayed on tissues, however, T-cell–mediated alloreactions may ensue. Specifically, donor alloreactive cytotoxic CD8+ effector T cells may attack recipient tissues—in particular, the skin, gastrointestinal tract, and liver—causing acute graft-versus-host disease (GVHD), a condition of varying severity, that, in some cases, can be life-threatening or even fatal (see Chapter 137). Although the main benefit for allogeneic HSCT recipients with leukemia derives from the GVL effect displayed by immune-competent cells, disease recurrence remains the main cause of treatment failure. The risk of failing to eradicate leukemia is influenced by many variables, including disease phase, molecular lesions of tumor cells, and disparity for major or minor histocompatibility antigens in the donor/recipient pairs. Strategies for rescuing patients experiencing disease recurrence are mainly based on either second transplantation or infusion of donor leukocytes. To overcome the hurdle of tumor elusion caused by HLA-loss on malignant cells, the use of non-HLA–restricted chimeric antigen receptors (CARs) has been envisaged. This therapeutic strategy is based on genetic reprogramming of T cells through artificial immune receptors that reproducibly and efficiently redirect the antigen specificity of polyclonal T lymphocytes toward target antigens expressed by leukemic cells. When expressed by T cells, CARs mediate antigen recognition and tumor cytolysis in an major histocompatibility complex (MHC)–unrestricted fashion, and can target any molecule (protein, carbohydrate, or glycolipid) expressed on the surface of tumor cells, thus bypassing one of the major tumor escape mechanisms based on the down regulation of MHC molecules. CARs are composed of an extracellular specific antigen-binding moiety, obtained from the variable regions of a monoclonal antibody, linked together to form a single-chain antibody (scFv), and of an intracellular signaling component derived from the ζ chain of the T-cell–receptor–CD3 complex. The addition to the CAR gene construct of costimulation signals and cytokines promoting T-cell expansion and/or survival improves the antitumor efficiency of the engineered T cells and their survival in the tumor milieu. Gamma retrovirus and lentiviruses are usually used to transduce CARs into T lymphocytes to be employed in the clinical setting. These vectors have been shown to efficiently infect T lymphocytes, integrate into the host genome and produce robust expression of the gene in human T cells and their progeny.

The success of allogeneic HSCT is undermined by diversity between donors and recipients in major and minor histocompatibility antigens. MHC molecules, the HLA-A, HLA-B, and HLA-C MHC class I molecules, present peptides to CD8+ T cells, while the HLA-DR, HLA-DQ, and HLA-DP MHC class II molecules present peptides to CD4+ T cells. There are hundreds of variant forms of each class I and class II molecule, and even small differences can elicit alloreactive T-cell

responses that mediate graft rejection and/or GVHD. Disparities for HLA-A, -B, -C, or -DRB1 alleles in the donor–recipient pair are independent risk factors for both acute and chronic GVHD.

Minor histocompatibility antigens derive from differences between the HLA-matched recipient and donor in peptides that are presented by the same HLA allotype. They are a result of polymorphisms of non-HLA proteins, of differences in the level of expression of proteins, or of genetic differences between males and females. An example of the latter is represented by the H-Y antigens encoded by the Y chromosome, which can stimulate GVHD when a female donor is employed to transplant an HLA-identical male recipient. Thus, from this evidence, it is clear that GVHD may occur even when the donor and recipient are HLA identical.

The optimal donor for any patient undergoing HSCT is an HLA-identical sibling. Because polymorphic HLA genes are closely linked and usually constitute a single genetic locus, any pair of siblings has a 25% chance of being HLA identical. Thus, also in view of the limited family size in the developed countries, less than 25-30% of patients in need of an allograft can receive their transplant from an HLA-identical sibling. This percentage is even lower in patients with inherited disorders.

HEMATOPOIETIC STEM CELL TRANSPLANTATION FROM AN HLA-IDENTICAL SIBLING DONOR

Allogeneic HSCT from an HLA-compatible sibling is the treatment of choice for children with hematological malignancies and congenital diseases (Table 135-1). Best results are achieved in patients with congenital or acquired non-malignant disorders because the risk of disease recurrence is low and the cumulative transplantation-related mortality is lower than in children receiving transplants for hematologic malignancies.

ACUTE LYMPHOBLASTIC LEUKEMIA

Allogeneic HSCT is used for pediatric patients with acute lymphoblastic leukemia (ALL), either in the first complete remission when a child is considered to be at high risk of leukemia recurrence (such as, e.g., those carrying poor-risk cytogenetic characteristics or with high levels of minimal residual disease), or in second or further complete remission after previous marrow relapse. ALL is the most common indication for HSCT in childhood. Several patient-, donor-, disease-, and transplant-related variables may influence the outcome of patients with ALL given an allogeneic HSCT. The long-term probabilities of event-free survival for patients with ALL transplanted in the 1st or 2nd complete remission is 60–70% and 40-60%, respectively. Inferior results are obtained in patients receiving transplants in more advanced disease phases. The use of radiotherapy, total body irradiation, during the preparative regimen offers an advantage in terms of better event-free survival compared to a regimen consisting of cytotoxic drugs alone (Fig. 135-1), but it can induce more long-term side effects. Less-intensive GVHD prophylaxis is also associated with a better outcome. Bone marrow is still the preferred source of stem cells to be employed for transplantation.

ACUTE MYELOID LEUKEMIA

Allogeneic HSCT from an HLA-identical sibling is largely employed as postremission treatment of pediatric patients with acute myeloid leukemia (AML). In fact, many studies show that children with AML in 1st complete remission who are given allogeneic HSCT as consolidation therapy have a better probability of event-free survival than those treated with either chemotherapy alone or with autologous transplantation. Results obtained in patients given HSCT from an HLA-identical sibling after either a total body irradiation–containing or a chemotherapy-based preparative regimen are similar, the probability of event-free survival being in the order of 70%. Children with acute promyelocytic leukemia in molecular remission at the end of treatment with chemotherapy and all-*trans*-retinoic acid, or with AML and either translocation t(8;21) or inversion of chromosome 16 (inv16) are no longer considered eligible for allogeneic HSCT in 1st complete remission in view of their excellent prognosis with alternative treatments. Studies suggest restricting the use of HSCT to those patients with poor molecular lesions, such as FLT3-internal tandem duplication, or mixed lineage leukemia abnormalities, or with high levels of minimal residual disease at time the end of induction therapy. Approximately 40% of pediatric patients with AML in the second complete remission can be rescued by an allograft from an HLA-identical sibling.

Table 135-1 Indications for Allogeneic Hematopoietic Stem Cell Transplantation for Pediatric Diseases

- Acute lymphoblastic leukemia

First complete remission for patients at very high risk of relapse

- Translocation t(9;22) or t(4;11)
- Early thymocyte precursor phenotype
- Nonresponder after 1 wk of corticosteroid therapy and
  - T-immunophenotype or
  - >100,000 cells/μL at diagnosis
- Not in remission at the end of the induction phase
- Marked hypodiploidy (<43 chromosomes)
- High levels of minimal residual disease at the end of induction therapy

Second complete remission

Third or later complete remission

- Acute myeloid leukemia in 1st complete remission or in advanced disease phase
- Philadelphia chromosome–positive chronic myeloid leukemia
- Myelodysplastic syndromes
- Hodgkin and non-Hodgkin lymphomas
- Selected solid tumors
  - Metastatic neuroblastoma
  - Rhabdomyosarcoma refractory to conventional treatment
  - Very-high-risk Ewing sarcoma
- Severe acquired aplastic anemia
- Fanconi anemia
- Congenital dyskeratosis
- Diamond-Blackfan anemia
- Thalassemia major
- Sickle cell disease
- Variants of severe combined immunodeficiency
- Hyperimmunoglobulin M syndrome
- Leukocyte adhesion deficiency
- Omenn syndrome
- Wiskott-Aldrich syndrome
- Chédiak-Higashi syndrome
- Kostmann syndrome (infantile malignant agranulocytosis), chronic granulomatous disease and other severe neutrophil defects
- X-linked lymphoproliferative disease (Duncan syndrome)
- Hemophagocytic lymphohistiocytosis
- Selected severe variants of platelet function disorders (e.g., Glanzmann thromboasthenia, or congenital amegakaryocytic thrombocytopenia)
- Selected types of mucopolysaccharidosis (Hurler disease) or other liposomal/peroxisomal disorders (Krabbe disease, adrenoleukodystrophy)
- Infantile malignant osteopetrosis
- Life-threatening cytopenia unresponsive to conventional treatments

CHRONIC MYELOGENOUS LEUKEMIA

For many yr, allogeneic HSCT has been considered to be the only proven curative treatment for children with Philadelphia-positive (Ph+) chronic myelogenous leukemia. Leukemia-free survival of chronic myelogenous leukemia patients after an allograft is 45-80%, the phase of disease (chronic phase, accelerated phase, blast crisis), recipient age, type of donor employed (either related or unrelated), and time interval between diagnosis and HSCT being the main factors influencing the outcome. The best results are obtained in children transplanted during the chronic phase from an HLA-identical sibling within 1 year from diagnosis. Treatment with the specific BCR-ABL tyrosine protein kinase inhibitors (imatinib mesylate, dasatinib,

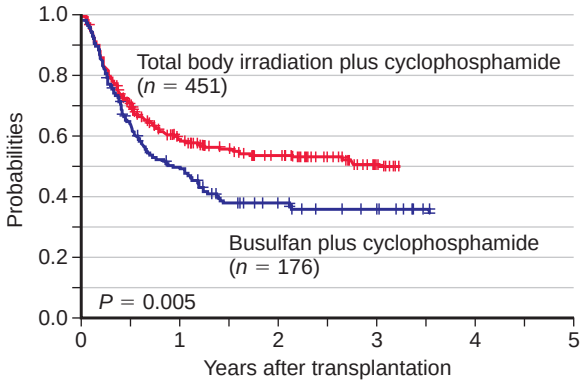


Figure 135-1 Cumulative probability of leukemia-free survival after HLA-identical sibling bone marrow transplantation for childhood acute lymphoblastic leukemia, by pretransplantation conditioning regimen of total body irradiation (TBI) plus cyclophosphamide (CY) *(upper line)* or busulfan (Bu) plus cyclophosphamide *(lower line)*. There was superior survival with the TBI plus cyclophosphamide regimen. *(From Davies S, Ramsay NK, Klein JP, et al: Comparison of preparative regimens in transplants for children with acute lymphoblastic leukemia.* J Clin Oncol *18:340–347, 2000.)*

nilotinib), targeting the enzymatic activity of the BCR-ABL fusion protein, could modify the natural history of the disease and, thus, the indications for transplantation. Infusion of donor leukocytes can re-induce a state of complete remission in a large proportion of patients experiencing leukemia relapse.

JUVENILE MYELOMONOCYTIC LEUKEMIA

This is a rare hematopoietic malignancy of early childhood, representing 2–3% of all pediatric leukemias. Juvenile myelomonocytic leukemia (JMML) is characterized by hepatosplenomegaly and organ infiltration, with excessive proliferation of cells of monocytic and granulocytic lineages. Hypersensitivity to granulocyte-macrophage colony-stimulating factor and pathologic activation of the RAS-RAF-MAP (mitogen-activated protein) kinase signaling pathway play an important role in the pathophysiology. JMML usually runs an aggressive clinical course, with a median duration of survival for untreated children of <12 mo from diagnosis. Rare patients with *CBL-1* or *N-RAS* mutations can survive for years without an allograft. HSCT is able to cure approximately 50-60% of patients with JMML. Patients who receive a transplant from an unrelated donor have comparable outcome to those given HSCT from an HLA-compatible related donor. Cord blood transplantation represents a suitable alternative option for those patients with either a related or an unrelated donor. Leukemia recurrence is the main cause of treatment failure in children with JMML after HSCT, the relapse rate being as high as 40-50%. Because children with JMML frequently have massive spleen enlargement, splenectomy has been performed before transplantation. Spleen size at the time of HSCT and splenectomy before HSCT do not appear to affect the post-transplantation outcome. Although donor leukocyte infusion is not useful to rescue patients experiencing disease recurrence, a second allograft can induce sustained remission in approximately one-third of children with JMML relapsing after a 1st HSCT.

MYELODYSPLASTIC SYNDROMES OTHER THAN JUVENILE MYELOMONOCYTIC LEUKEMIA

Myelodysplastic syndromes are a heterogeneous group of clonal disorders characterized by ineffective hematopoiesis leading to peripheral blood cytopenia and a propensity to evolve toward AML. HSCT is the treatment of choice for children with refractory anemia with excess of blasts (RAEB) and for those with RAEB in transformation (RAEB-t). The probability of survival without evidence of disease for these children is 60% if the donor is an HLA-identical sibling, whereas that of patients transplanted from an alternative donor is slightly lower. It is still unclear whether patients with myelodysplastic syndromes and a blast percentage >20% benefit from pretransplantation chemotherapy. HSCT from an HLA-identical sibling is also the preferred treatment for all children with refractory cytopenia. Transplantation from an alternative donor is also employed in children with refractory cytopenia associated with monosomy 7, complex karyotype, life-threatening infections, profound neutropenia, or transfusion-dependency. For children with refractory cytopenia, the probability of event-free survival after HSCT may be as high as 80%, disease recurrence being rarely observed. This observation has provided the rationale for testing reduced-intensity regimens in these patients.

NON-HODGKIN LYMPHOMA AND HODGKIN DISEASE

Childhood non-Hodgkin lymphoma (NHL) and Hodgkin disease (HD) are quite responsive to conventional chemoradiotherapy, but some of these patients are at high risk for relapse. HSCT can cure a proportion of patients with relapsed NHL and HD and should be offered early after relapse, while the disease is still sensitive to therapy. If an HLA-identical sibling is available, allogeneic transplantation should be offered to patients with NHL to take advantage of the GVL effect. Patients with sensitive disease and limited tumor burden have favorable outcomes, with event-free survival rates of 50-60%. Studies also suggest that patients with HD can benefit from a GVL effect when given an allograft.

ACQUIRED APLASTIC ANEMIA

HSCT from an HLA-identical sibling is the treatment of choice for children with the severe form of acquired aplastic anemia, defined as 2 of the following: platelet count <20,000/mm^3, absolute neutrophil count <500/mm^3, or reticulocyte count <1% when anemia is present, together with hypoplastic bone marrow (<20% total cellularity). The probability of survival with sustained donor engraftment for these patients is <85-90%, younger patients having even better outcomes. Every child diagnosed with severe acquired aplastic anemia should undergo HLA-typing as early as possible in order to identify a suitable HLA-compatible family donor. Graft rejection represents the most important cause of treatment failure. Blood transfusion should be avoided whenever possible because sensitization to blood products increases the likelihood of graft rejection. GVHD prophylaxis combining cyclosporine and short-term methotrexate is associated with a better outcome as compared to cyclosporine alone (Fig. 135-2). Some studies suggest that the addition of antithymocyte globulin to the classical conditioning regimen consisting of cyclophosphamide (200 mg/kg) can reduce the risk of graft rejection, particularly in patients with previous heavy sensitization to blood products. The use of granulocyte colony-stimulating factor mobilized peripheral blood progenitors has provided inferior results with respect to the infusion of bone marrow cells, since it is associated with an increased risk of chronic GVHD.

CONSTITUTIONAL APLASTIC ANEMIA

Fanconi anemia and **dyskeratosis congenita** are genetic disorders associated with a high risk of developing pancytopenia. Fanconi anemia is an autosomal recessive disease characterized by spontaneous chromosomal fragility, which is increased after exposure of peripheral blood lymphocytes to DNA crosslinking agents, including clastogenic compounds, such as diepoxybutane, mitomycin C, and melphalan. Patients with Fanconi anemia, besides being at risk of pancytopenia, show a high propensity to develop clonal disorders of hematopoiesis, such as myelodysplastic syndromes and AML. HSCT can rescue aplastic anemia and prevent the occurrence of clonal hematopoietic disorders. In view of their defects in DNA repair mechanisms, which are responsible for the chromosomal fragility, Fanconi anemia patients have an exquisite sensitivity to alkylating agents. Thus, they must be prepared for the allograft with reduced doses of cyclophosphamide. Many patients were once successfully transplanted after receiving low-dose cyclophosphamide and thoracoabdominal irradiation. However, the use of this regimen is associated with an increased incidence of

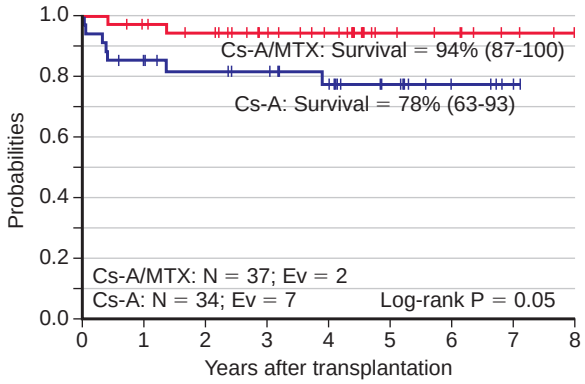


Figure 135-2 Cumulative probability of survival after HLA-identical sibling bone marrow transplantation (BMT) for aplastic anemia, by graft-versus-hostvs disease (GVHD) prophylaxis with cyclosporin alone *(dotted line)* or cyclosporine plus methotrexate *(continuous line)*. GVHD prophylaxis combining cyclosporin and short-term methotrexate is associated with superior outcome compared to cyclosporin alone. *EV,* number of events occurring in each arm of randomization; *N,* number of patients in each arm of randomization. *(From Locatelli F, Bruno B, Zecca M, et al: Cyclosporin A and short-term methotrexate versus cyclosporin A as graft versus host disease prophylaxis I patients with severe aplastic anemia given allogeneic bone marrow transplantation from an HLA-identical sibling: results of a GITMO/EMBT randomized trial.* Blood *96:1690–1697, 2000.)*



Figure 135-3 Kaplan-Meier estimates of survival and thalassemia-free survival and cumulative incidences of rejection and nonrejection mortality for 33 thalassemic patients younger than 17 yr of age. Survival was 93%, with incidence of recurrent thalassemia after transplantation of 8%. *(From Sodani P, Gaziev D, Polchi P, et al: New approach for bone marrow transplantation in patients with class 3 thalassemia aged younger than 17 years.* Blood *104:1201–1203, 2004.)*

posttransplantation head and neck cancers. Either reduced doses of cyclophosphamide alone or low-dose cyclophosphamide with fludarabine are currently employed for preparing Fanconi anemia patients to the allograft. Using these regimens, the success rate of HSCT from an HLA-identical sibling is on the order of 70-80%. Results of unrelated donor allograft have markedly improved over time and rival with those obtained using an HLA-identical sibling donor.

Allogeneic HSCT remains the only potentially curative approach for severe bone marrow failure associated with dyskeratosis congenita, a rare congenital syndrome characterized also by atrophy and reticular pigmentation of the skin, nail dystrophy, and leukoplakia of mucous membranes. Results of allograft in these patients have been relatively poor, due to occurrence of both early and late complications, reflecting increased sensitivity of endothelial cells to radiotherapy and alkylating agents.

THALASSEMIA

Conventional treatment (i.e., regular blood transfusion and iron-chelation therapy) has dramatically improved both the survival and quality of life of patients with thalassemia, changing a previously fatal disease with early death to a chronic, slowly progressive disease compatible with prolonged survival. However, HSCT remains the only curative treatment for patients with thalassemia. In patients with thalassemia, the risk of dying from transplant-related complications is primarily dependent on patient age, iron overload, and concomitant hepatic viral infections. Adults, especially when affected by chronic active hepatitis, have a poorer outcome than children. Among children, 3 classes of risk have been identified on the basis of 3 parameters, namely regularity of previous iron chelation, liver enlargement, and presence of portal fibrosis. In pediatric patients without liver disease who have received regular iron chelation (class 1 patients), the probability of survival with transfusion independence is >90%, whereas for patients with low compliance with iron chelation and signs of severe liver damage (class 3 patients), the probability of survival is 60% (Fig. 135-3). As in other nonmalignant disorders the most effective pharmacologic combinations (such as that including cyclosporine and methotrexate) should be employed to prevent GVHD. The outcome of patients transplanted from an unrelated donor has been reported to be similar to that of HLA-identical sibling recipients.

SICKLE CELL DISEASE

Disease severity varies greatly among patients with sickle cell disease, with 5-20% of the overall population suffering significant morbidity from vasoocclusive crises and pulmonary, renal, or neurologic damage. Despite the fact that hydroxyurea, an agent favoring the synthesis of fetal hemoglobin, reduces the frequency and severity of vasoocclusive crises and improves the quality of life for patients with sickle cell disease, allogeneic HSCT is the only curative treatment for this disease. Although HSCT can cure homozygous hemoglobin S disease, selecting appropriate candidates for transplantation is difficult. Patients with sickle cell disease may survive for decades, but some patients have a poor quality of life, with repeated hospitalizations for painful vasoocclusive crises and central nervous system infarcts. The main **indications for** performing HSCT in patients with sickle cell disease are history of strokes, magnetic resonance imaging of central nervous system lesions associated with impaired neuropsychologic function, failure to respond to hydroxyurea as shown by recurrent acute chest syndrome, and/or recurrent vasoocclusive crises and/or severe anemia and/or osteonecrosis. The results of HSCT are best when performed in children with an HLA-identical sibling, with a probability of cure of 80-90%. The use of antithymocyte globulin during the preparative regimen improves patient outcome, dramatically reducing the risk of graft failure.

IMMUNODEFICIENCY DISORDERS

HSCT is the **treatment of choice** for children affected by severe combined immunodeficiency, as well as for other inherited immunodeficiencies, including Wiskott-Aldrich Syndrome, leukocyte adhesion deficiency, and chronic granulomatous disease (see also Table 135-1 for details), among others. With an HLA-identical sibling, the probability of survival approaches 100%, with less-favorable results for patients transplanted from an HLA–partially matched relative. Some children with severe combined immunodeficiency, mainly those without residual natural killer activity or maternal T-cell engraftment, may be transplanted without receiving any preparative regimen, the donor lymphoid cells usually being the only elements that engraft. Sustained donor engraftment is more difficult to achieve in children with Omenn syndrome, hemophagocytic lymphohistiocytosis, or leukocyte adhesion deficiency. Life-threatening opportunistic fungal and viral infections occurring before the allograft adversely affect the patient's outcome after HSCT. Patients with the most severe immunodeficiencies must be transplanted as early as possible.

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Chapter 136

Hematopoietic Stem Cell Transplantation from Alternative Sources and Donors

Andrea Velardi and Franco Locatelli

Two-thirds of patients who need allogeneic hematopoietic stem cell transplantation (HSCT) do not have an available human leukocyte antigen (HLA)-identical sibling. Alternative donor/sources of hematopoietic stem cells are being increasingly used and include: matched unrelated donors, unrelated umbilical cord blood (UCB), and HLA-haploidentical relatives. Each of these 3 options has advantages and limitations, but rather than being considered competing alternatives, they should be regarded as complementary strategies to be chosen after a careful evaluation of the relative risks and benefits in the patient's best interest. The choice of the donor will depend on various factors related to urgency of transplantation, patient-, disease-, transplant-related factors and center experience. Physician preference is expected to influence this choice as well.

UNRELATED DONOR TRANSPLANTS

One of the most widely used strategies for children who need an allograft and do not have an available HLA-identical sibling is to identify an unrelated HLA-matched donor in a registry. Today, worldwide international registries include more than 20 million HLA-typed volunteer donors. HLA-A, -B, -C class I loci, and the DRB1 class II locus are the HLA loci most influencing outcome after HSCT from an unrelated volunteer. The roles played by other class II loci (namely, DQB1 and DP1 loci) on patient outcome remain controversial.

Data on serologic typing of HLA classes IA and IB loci are available for all donors, and there is information on DRB1 typing for approximately one-third of donors. Although in the past serologic (low-resolution) typing was used for HLA-A and -B loci, currently, the unrelated donors are selected using high-resolution (allelic) molecular typing of loci HLA-A, -B, -C, and -DRB1. The chance of finding an HLA-matched donor depends on the frequency of the HLA phenotype, which is closely linked to the ethnic origin of the registry donors and ranges from 60-70% for white patients to <10% for persons of other ethnic groups (Hispanic, black, etc).

Identifying a suitable unrelated donor is a complicated and lengthy process, the median time elapsing from the start of search to transplantation being 3-4 mo. During this period, a patient with acute leukemia may relapse and require further therapy, accumulating organ toxicity that unfavorably affects outcome. Moreover, for various different reasons, a relevant proportion of donors (sometimes reaching 10-20%) are either no longer available or refuse donation. Despite these limitations, many thousands of matched unrelated donor transplantations have been performed.

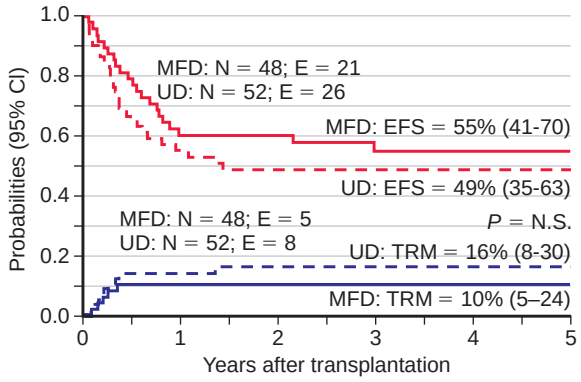
Initially, HLA polymorphism and the intrinsic limitations of conventional (i.e., serologic) HLA-typing techniques unfavorably affected the accuracy of matching, thus increasing rejection rates and the incidence of acute and chronic graft-versus-host disease (GVHD). Consequently, because the event-free survival of recipients of an unrelated donor allograft was worse than that observed when the donor was a compatible sibling transplant, there is no consensus on the use of unrelated donor transplants for nonmalignant diseases, such as thalassemia or primary immune deficiency syndromes other than severe combined immunodeficiency (SCID). DNA-based (i.e., high-resolution molecular) techniques for HLA typing have revealed an impressive number of new alleles within antigens that were previously defined by serology only. Matching by high-resolution DNA typing reduces the risk of immune complications, namely graft rejection and GVHD, but also the chance of finding a suitable donor. Nevertheless, the advent of both high-resolution molecular HLA classes I and II loci-typing coupled with progress in the prophylaxis and treatment of GVHD has resulted in a reduction of transplantation-related mortality and improvement of outcome. Indeed, outcomes from a fully matched unrelated volunteer donor are now similar to those of HSCT from an HLA-identical sibling, as indicated by results of unrelated donor transplantation in children with acute lymphoblastic leukemia in second complete remission, juvenile myelomonocytic leukemia, or thalassemia (Fig. 136-1).

Although a single locus disparity in patients with leukemia does not markedly affect the probability of event-free survival as the increased risk of toxic death may be compensated for by a reduction in the relapse rate, in patients with nonmalignant disorders optimal results are obtained only when a donor matched at the allelic level with the recipient is selected. In general, a single HLA disparity in the donor–recipient pair, irrespective of whether antigenic or allelic in nature, predicts a greater risk of nonleukemia mortality; multiple allelic disparities at different HLA loci have an additive detrimental effect and are associated with an even worse outcome. To reduce the risk of acute GVHD, **ex vivo T-cell depletion of the graft** has been employed, but has not significantly affected patient outcome, which is similar to that of patients given an unmanipulated graft and pharmacologic prophylaxis for GVHD.

The analyses on the outcome of unrelated donor HSCT include only patients who are transplanted; these numbers do not take into account patients for whom a donor is not found. For patients who urgently need a transplant, the time required to identify a suitable donor from a potential panel, establish eligibility, and harvest the cells may lead to relapse and failure to transplant. For patients who do not have a matched donor or who urgently need a transplant, attention has focused on unrelated cord blood and HLA-haploidentical, mismatched family donors.

UMBILICAL CORD BLOOD TRANSPLANTS

UCB transplantation (UCBT) is a viable option for children who need allogeneic HSCT. To date, several hundred children have been cured



No. of cases at risk:

MFD	48	28	25	19	14	9
UD	52	26	20	16	9	4

Figure 136-1 Kaplan-Meier estimates of event-free survival *(EFS) (upper lines)* and transplantation-related mortality *(TRM) (lower lines)* according to the type of donor used, matched family donor *(MFD)* or unrelated donor *(UD)*. Matched family donor was superior (55% EFS and 10% TRM) compared to unrelated donor (49% EFS and 16% TRM). *(From Locatelli F, Nöllke P, Zecca M, et al: Hematopoietic stem cell transplantation [HSCT] in children with juvenile myelomonocytic leukemia [JMML]: results of the EWOG-MDS/EBMT trial.* Blood *105:410–419, 2005.)*

through transplantation of either related or unrelated UCB units. UCBT offers the advantages of absence of risks to donors, reduced risk of transmitting infections, and, for transplants from unrelated donors, immediate availability of cryopreserved cells, the median time elapsing from start of search to transplantation being only 3-4 wk. In comparison to bone marrow transplantation (BMT), the advantages of UCBT are also represented by lower incidence and severity of GVHD, easier procurement and prompter availability of cord blood cells, and the possibility of using donors showing HLA disparities with the recipient. Despite these advantages, the large experience gained over the last 2 decades has clearly demonstrated that UCBT patients may be exposed to an increased risk of early fatal complications, mainly because of a lower engraftment rate of donor hematopoiesis, delayed kinetics of neutrophil recovery, and lack of adoptive transfer of pathogen-specific memory T-cells. In fact, transfer of donor-derived, memory T cells significantly contributes to early immunologic reconstitution of children after unmanipulated allogeneic bone marrow or peripheral blood stem cell transplantation.

Concerning the issues of engraftment and hematopoietic recovery, it has been unquestionably shown that an inverse correlation between the number of nucleated cord blood cells infused per kilogram recipient body weight and the risk of dying for transplantation-related causes exists. In particular, engraftment is a major concern when the nucleated cells are $<2.5 \times 10^7$/kg of recipient body weight. As a cord blood unit usually contains between 1×10^9 and 1.8×10^9 cells, it is not surprising that UCB transplantation has been less frequently employed for adolescents or adults with body weight >40 kg. Indeed, it can be estimated that only 30% of the UCB units available in the bank inventory could suffice for a 75 kg patient according to the recommended threshold cell dose (namely more than 2.5×10^7 total nucleated cells/kg recipient body weight before thawing the unit). In view of these findings, it is not surprising that efforts have been focused on approaches capable of increasing the number of UCB cells to be transplanted. Selection of the richest cord blood units, infusion of 2 units in the same recipient (i.e., double UCBT), and transplantation of ex vivo expanded progenitors have contributed to improve the results of UCBT, opening new scenarios for a wider application of the procedure. In particular, double UCBT is largely employed as it was demonstrated to be effective in adults, significantly increasing the engraftment rate, as compared to single-unit UCBT. In the majority of double UCBT, the 2 UCB units are partially HLA-matched with the recipient, as well as with each other, and sustained hematopoiesis after double UCBT is usually derived from a single donor. This technique is of interest to pediatricians for extending the applicability of UCBT also to adolescents or to patients with a body weight exceeding 40-50 kg.

Direct intrabone transplantation of UCB cells is also a feasible and safe approach, able to overcome the problem of graft failure, even when low numbers of HLA-mismatched cord-blood cells are transplanted, and to guarantee prompt platelet recovery.

Despite the low incidence of acute and chronic GVHD observed after UCB transplantation, the risk of recurrence of leukemia is not increased. The long-term results of UCB transplants are similar to those after transplantation from other sources of hematopoietic stem cells. In particular, several published reports have compared the outcome of UCBT and BMT from unrelated donors in children with hematologic malignancies. Recipients of UCBT were transplanted from donors with greater HLA-disparities, received 1-log fewer nucleated cells, had delayed neutrophil and platelet recovery, and showed reduced incidence of GVHD as compared to children given BMT. Nevertheless, both the relapse rate and the overall survival probability did not differ in unrelated UCBT or BMT pediatric recipients. The outcome of patients receiving a fully matched UCB unit is reported to be even better than that of patients who receive a transplant from an HLA-identical, unrelated volunteer. Thus, today, there is no doubt that, in the absence of an HLA-identical family donor, unrelated UCBT can be considered a suitable option for children with malignant and nonmalignant disorders. Results of UCBT have been of particular interest in children with Hurler syndrome or Krabbe disease transplanted with cord blood cells from an unrelated donor, as well as in children with hemoglobinopathies given a related UCB transplantation. It has to be emphasized that the lower risk of GVHD associated with UCBT is of particular importance in patients affected by nonmalignant disorders.

Approximately 5% of patients receiving UCB transplantation develop an autoimmune disorder. These disorders include autoimmune hemolytic anemia, autoimmune thrombocytopenia, Evans syndrome, and immune neutropenia. Less frequently, patients have developed Graves disease, glomerulonephritis, rheumatoid arthritis, or thyroiditis. Treatment for these post-UCB transplant-related autoimmune diseases has included steroids, rituximab, and cyclosporine, with only varying degrees of success.

HAPLOIDENTICAL TRANSPLANTS

HSCT from an HLA-haploidentical (haplo-HSCT) donor offers an immediate source of hematopoietic stem cells to almost all leukemia patients who fail to find a matched donor, whether related or unrelated, or a suitable cord blood unit. Indeed, almost all children have at least 1 haploidentical–3 loci mismatched family member who is promptly available as donor. Moreover, the few patients who reject the haploidentical transplant have the advantage of another immediately available donor within the family.

Efficient T-cell depletion of the graft has been demonstrated to prevent acute and chronic GVHD even when using haploidentical parental bone marrow differing at the 3 major HLA loci. The benefits of T-cell depletion were first demonstrated in transplantation of children with SCID. More than 300 transplants in SCID patients using haploidentical donors have been performed worldwide, with a high rate of long-term partial or complete immune reconstitution.

As patients with acute leukemia have a high chance of rejecting a haploidentical bone marrow graft, a "megadose" of granulocyte colony-stimulating factor–mobilized peripheral blood stem cells has been demonstrated to be crucial for overcoming the barrier of HLA incompatibility in the donor–recipient pair and for eluding residual antidonor cytotoxic T-lymphocyte precursor activity in the recipient. Indeed, in leukemia patients, the combination of high-intensity immune-suppressive/myeloablative conditioning regimens with the infusion of great numbers of highly purified, peripheral blood CD34+ cells has been demonstrated capable to (1) guarantee the successful and sustained engraftment of donor haematopoiesis across the HLA barrier, and (2) guarantee a very low incidence of grades II-IV acute GVHD without the need for any posttransplantation immune suppression as prophylaxis. The physical elimination of mature T cells from the graft, necessary for preventing GVHD occurrence in a context of great immune genetic disparity, leads to the consequence that recipients cannot benefit from the adoptive transfer of donor memory T lymphocytes that, through their peripheral expansion, are the main factor responsible for protection from infections in the 1st few mo after transplantation. A state of profound immune deficiency lasts for at least 4-6 mo after transplantation in haplo-HSCT recipients. Sophisticated strategies of adoptive infusions of T-cell lines or clones specific for the most common and life-threatening pathogens (namely Epstein-Barr virus, human cytomegalovirus, *Aspergillus*, and adenovirus) have been envisaged and successfully tested in a few pilot trials to protect the recipients in the early posttransplantation period. Selective approaches of graft manipulation have also been developed. In particular, promising results have been obtained through a negative depletion of T lymphocytes carrying the α/β chains of the T-cell receptor. B-lymphocytes are also depleted to prevent the occurrence of Epstein-Barr virus–related lymphoproliferative disease. Through this approach the patient can benefit from the adoptive transfer of committed hematopoietic progenitors, mature natural killer (NK) cells and γ/δ+ T cells, which can confer a protection against life-threatening infections.

The outcomes of haplo-HSCT have been more extensively reported in adults than in children. The reported probability of survival at 3-4 yr after a haplo-HSCT in children with acute leukemia ranged from 18-48%. Survival was influenced by many factors, the most important being the state of remission at time of transplantation, with poorer outcomes in children with myeloid leukemias than in those with lymphoid leukemia. It has been reported that in haplotype mismatched

parent-to-child HSCT, patients with acute leukemia grafted from the mother had reduced relapse rates as compared with recipients of paternal grafts, translating into better event-free survival.

For many years the absence of the T-cell mediated graft-versus-leukemia (GVL) effect has been considered rendering the recipients of a T-cell depleted allograft more susceptible to leukemia relapse. However, it has been demonstrated that a GVL effect displayed by donor NK cells can compensate for this lack of T-specific alloreactivity when an HLA-disparate NK alloreactive relative is employed as a donor.

DONOR VERSUS RECIPIENT NATURAL KILLER–CELL ALLOREACTIVITY

Donor vs recipient NK-cell alloreactivity is a biologic phenomenon that is unique to the mismatched transplant. It derives from a mismatch between donor NK clones, carrying specific inhibitory receptors for self–major histocompatibility complex (MHC) class I molecules, and MHC class I ligands on recipient cells. NK cells are primed to kill by several activating receptors, which play an important role in the NK cell-mediated GVL effect. Human NK cells discriminate allelic forms of MHC molecules via **killer cell immunoglobulin-like receptors (KIRs),** which are clonally distributed with each cell in the repertoire bearing at least 1 receptor that is specific for self-MHC class I molecules. Because NK cells coexpress inhibitory receptors for self-MHC class I molecules, autologous cells are not killed. When faced with mismatched allogeneic targets, NK cells sense the missing expression of self–class I alleles and mediate alloreactions. In mismatched transplants, there are many donor recipient pairs in which the donor NK inhibitory cells do not recognize the recipient's class I alleles as self. Consequently, the donor NK cells are not blocked and are activated to lyse the recipient's lymphohematopoietic cells.

Haplo-HSCT trials demonstrate that MHC class I mismatches, which generate an alloreactive NK cell response in the graft-versus-host direction, eradicate leukemia cells, improve engraftment, and protect from T-cell–mediated GVHD. Lack of an NK-alloreactive donor is the strongest independent risk factor for leukemia relapse after adjustment for disease status at transplantation. The potential for donor vs recipient NK cell alloreactivity, which can be predicted by standard HLA typing, is recommended when selecting the donor of choice from among the mismatched family members.

The chance of finding a "perfect mismatch" NK-alloreactive donors in the family is on the order of 50%. From a practical point of view, first, the transplantation candidate is HLA typed. Candidates expressing class I alleles belonging to the 3 class I groups recognized by KIRs (HLA-C group 1, HLA-C group 2, and HLA-Bw4 alleles) will block all NK cells from every donor and belong to the one-third of the population that is resistant to alloreactive NK killing. Patients who express only 1 or 2 of these allele groups may find NK-alloreactive donors.

Donor HLA typing identifies family members who do not express the class I group(s) expressed by the patient and, therefore, have the potential for NK alloreactivity. Not all inhibitory KIRs are present in 100% of the population. KIR2DL2/3, the receptor for HLA-C group 1, is present in all persons; KIR2DL1, the receptor for HLA-C group 2, is present in 97% of persons; and KIR3DL1, the receptor for HLA-Bw4 alleles, is present in ≈90%. Donor KIR genotyping ensures that the donor expresses the relevant NK cells.

In HLA-Bw4 mismatches, even when the KIR3DL1 gene is present, NK repertoire studies show alloreactive NK cells in approximately two-thirds of individuals. This may be because they occur in highly variable frequencies or because allelic KIR3DL1 variants may not allow receptor expression at the cell membrane. Therefore, for HLA-Bw4 mismatches, direct assessment of the donor NK repertoire is necessary.

AUTOLOGOUS HEMATOPOIETIC STEM CELL TRANSPLANTATION

Autologous transplantation, using the patient's own stored marrow, is associated with a low risk of life-threatening transplant-related complications, although the main cause of failure is disease recurrence resulting from a lack of the immune-mediated GVL effect. Bone marrow was once the only source of stem cells employed in patients given an autograft; in the past few years, the vast majority of patients treated with autologous HSCT receive hematopoietic progenitors mobilized in peripheral blood by either cytokines alone (mainly granulocyte colony-stimulating factor) or by cytokines plus cytotoxic agents. A CXCR4 antagonist (plerixafor) can be extremely effective in mobilizing hematopoietic progenitors in the periphery. When compared to bone marrow, the use of peripheral blood progenitors is associated with a faster hematopoietic recovery and a comparable outcome. A major concern in patients with malignancies given autologous HSCT is represented by the risk of reinfusing malignant cells with the graft; tumor progenitors contained in the graft can contribute to recurrence of the original malignant disease. This observation has provided the rational for **tumor purging** using elaborated strategies aimed at reducing or eliminating tumor contamination of the graft.

Table 136-1 Indications to Autologous Hematopoietic Stem Cell Transplantation for Pediatric Diseases

- Acute lymphoblastic leukemia after an isolated extramedullary relapse
- Relapsed Hodgkin or non-Hodgkin lymphoma
- Stage IV or relapsed neuroblastoma
- High-risk, relapsed, or resistant brain tumors
- Stage IV Ewing sarcoma
- Life-threatening autoimmune diseases resistant to conventional treatments

Autologous HSCT is employed primarily to prevent relapse in patients with acute myelogenous leukemia (AML) who achieve complete remission after induction therapy, and also for selected children with relapsed lymphomas and selected solid tumors (Table 136-1).

Randomized studies have not shown an advantage in terms of event-free survival for patients with AML in the 1st complete remission given an autologous HSCT as compared to those treated with chemotherapy alone. The probability of event-free survival for children with AML in the 1st complete remission given autologous HSCT is reported to range from 40-60%. Ex vivo purging of bone marrow cells with mafosfamide has been shown to reduce the risk of disease recurrence in children with AML in the 1st complete remission given an autologous transplantation.

Patients with sensitive lymphomas and little tumor burden have favorable outcomes after autologous HSCT, with disease-free survival rates of 50-60%, whereas high-risk patients with bulky tumor or poorly responsive disease have a dismal outcome, with survival rates of 10-20%.

Some studies suggest that, as compared to conventional chemotherapy and radiotherapy, autologous HSCT may offer an advantage in terms of event-free survival to children with acute lymphoblastic leukemia in the second complete remission after an isolated extramedullary relapse (i.e., central nervous system, testicular relapse).

Autologous HSCT in patients with high-risk neuroblastoma is associated with a better outcome compared to conventional chemotherapy. In these patients, posttransplantation infusion of a monoclonal antibody directed against a molecule (GD2) expressed on the surface of neuroblastoma cells confers a protection against the risk of tumor recurrence.

For children with brain tumors at high risk of relapse, or resistant to conventional chemotherapy and irradiation, the dose-limiting toxicity for intensifying therapy is myelosuppression, thus providing a role for stem cell rescue. Several studies provide encouraging results for patients with different histologic types of brain tumors treated with autologous HSCT.

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Chapter 137

Graft-Versus-Host Disease, Rejection, and Venoocclusive Disease

Andrea Velardi and Franco Locatelli

The major cause of mortality and morbidity after allogeneic hematopoietic stem cell transplantation (HSCT) is graft-versus-host disease (GVHD), which is caused by engraftment of immunocompetent donor T lymphocytes in an immunologically compromised host which show histocompatibility differences with the donor. These differences between the donor and the host may result in donor T-cell activation against either recipient major histocompatibility complex antigens or minor histocompatibility antigens. GVHD is usually subdivided in 2 forms: acute GVHD, which occurs within 3 mo after transplantation, and chronic GVHD, which, although related, is a different disease, occurring later and displaying some clinical and pathologic features that resemble those observed in selected autoimmune disorders (systemic sclerosis, Sjögren syndrome, etc.).

ACUTE GRAFT-VERSUS-HOST DISEASE

Acute GVHD is caused by the alloreactive, donor-derived T cells contained in the graft, which attack nonshared recipient's antigens on target tissues. A three-step process generates the clinical syndrome. First, conditioning-induced tissue damage activates recipient antigen-presenting cells, which present recipient alloantigens to the donor T cells transferred with the graft and secrete cytokines, such as interleukin 12, favoring the polarization of T-cell response in the type 1 direction. Second, in response to recipient antigens, donor T cells become activated, proliferate, expand, and generate cytokines such as tumor necrosis factor-α, interleukin (IL)-2, and interferon-γ. In the third step of the process, these cytokines cause tissue damage and promote differentiation of cytotoxic CD8+ T cells, which, together with macrophages, in turn, kill recipient cells and further disrupt tissues.

Acute GVHD usually develops from 2-8 wk posttransplantation. The primary **manifestations** are an erythematous maculopapular rash, persistent anorexia, vomiting and/or diarrhea, and liver disease with increased serum levels of bilirubin, alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase (Table 137-1). Diagnosis may benefit from skin, liver, or gastrointestinal biopsy for confirmation. Endothelial damage and lymphocytic infiltrates are seen in all affected organs. The epidermis and hair follicles of the skin are damaged, the hepatic small bile ducts show segmental disruption, and there is destruction of the crypts and mucosal ulceration of the gastrointestinal tract. Grade I acute GVHD (skin rash alone) has a favorable prognosis and often does not require treatment (Fig. 137-1). Grade II GVHD is a moderately severe multiorgan disease requiring immunosuppressive therapy. Grade III GVHD is a severe multiorgan disease, and grade IV GVHD is a life-threatening, often fatal condition. The standard **pharmacologic prophylaxis** of GVHD after an unmanipulated allograft relies mainly on posttransplant administration of immunosuppressive drugs, such as cyclosporine or tacrolimus or combinations of either with methotrexate or prednisone, anti–T-cell antibodies, mycophenolate mofetil, and other immunosuppressive agents. Infusion of cyclophosphamide on days +3 and +5 after transplantation has been proposed as a strategy to delete alloreactive donor T lymphocytes that become activated, and thus cycling, after exposure to recipient antigens. Pretransplantation infusion of either antithymocyte globulin or monoclonal antibodies such as alemtuzumab is largely used to modulate alloreactivity of donor T cells, in particular in patients given the allograft from either an unrelated donor or a partially matched relative. An alternative approach, which has been widely used in clinical practice, is the removal of T lymphocytes from the graft (T-cell depletion). Any form of GVHD prophylaxis in itself may impair posttransplantation immunologic reconstitution, increasing the risk of infection-related deaths. T-cell depletion of the graft is also associated with an increased risk of leukemia recurrence in patients transplanted from an human leukocyte antigen (HLA)-identical sibling or an unrelated volunteer.

Despite prophylaxis, significant acute GVHD develops in ≈30% of recipients of HSCT from matched siblings and in as many as 60% of HSCT recipients from unrelated donors. The risk of acute GVHD is increased by factors such as diagnosis of malignant disease, older donor and recipient ages, and, in patients given an unmanipulated allograft, GVHD prophylaxis including only 1 drug. However, the most important risk factor for acute GVHD is the present of disparities for HLA-molecules in the donor–recipient pair. Acute GVHD is usually initially treated with glucocorticoids; approximately 40-50% of patients show a complete response to steroids. The risk of transplantation-related mortality is much higher in patients who do not respond to

Table 137-1 Clinical Staging and Grading of Graft-Versus-Host Disease

STAGE	SKIN	LIVER	INTESTINAL TRACT
+	Maculopapular rash <25% of body surface	Bilirubin 2-3 mg/dL	>500 mL diarrhea/day
++	Maculopapular rash 25%–50% of body surface	Bilirubin 3-6 mg/dL	>1,000 mL diarrhea/day
+++	Generalized erythroderma	Bilirubin 6-15 mg/dL	>1,500 mL diarrhea/day
++++	Generalized erythroderma with bullous formation and desquamation	Bilirubin >15 mg/dL	Severe abdominal pain with or without ileus

GVHD GRADE	SKIN STAGE	LIVER STAGE	INTESTINAL TRACT STAGE	DECREASE IN CLINICAL PERFORMANCE
I	+ to ++	0	0	None
II	+ to +++	+	+	Mild
III	++ to +++	++ to ++++	++ to +++	Marked
IV	++ to ++++	++ to ++++	++ to ++++	Extreme

Adapted from Thomas ED, Storb R, Clift RA, et al: Bone marrow transplantation [in 2 parts]. N Engl J Med *292:832–843, 895–902, 1975.*



Figure 137-1 Acute graft-versus-host disease of the skin with ear, arm, shoulder, and trunk involvement. See also color plates. *(Courtesy of Evan Farmer, MD.)*

steroids than in those showing a complete response. Mofetil mycophenolate, extracorporeal photopheresis, pentostatin, or monoclonal antibodies targeting either molecules expressed on T cells or cytokines released during the inflammatory cascade, which underlies the physiopathology of GVHD, have been used in patients with steroid-resistant acute GVHD. There are no clear data showing the superiority of one of these approaches over the others. Promising results in children with steroid-resistant acute GVHD have been obtained using mesenchymal stromal cells, which are able to blunt the inflammatory response associated with acute GVHD.

CHRONIC GRAFT-VERSUS-HOST DISEASE

Chronic GVHD develops or persists >3 mo posttransplantation and is the most frequent late complication of allogeneic HSCT with an incidence of ≈25% in pediatric patients. Chronic GVHD is the major cause of nonrelapse mortality and morbidity in long-term HSCT survivors. Acute GVHD is recognized as the most important factor predicting the development of the chronic form of the disease. The use of matched unrelated volunteers as donors, and of peripheral blood as the stem cell source, has increased the incidence and severity of chronic GVHD. Other factors that predict occurrence of chronic GVHD include older donor and recipient ages, female donor for male recipient, diagnosis of malignancy, and use of total-body irradiation as part of the preparative regimen.

Chronic GVHD is a disorder of immune regulation characterized by autoantibody production, increased collagen deposition and fibrosis, and clinical symptoms similar to those seen in patients with autoimmune diseases. The predominant cytokines involved in the pathophysiology of chronic GVHD are usually type II cytokines such as IL-4, IL-5, and IL-13. IL-4 and IL-5 contribute to eosinophilia, B-cell hyperactivity with elevated immunoglobulin (Ig) M, IgG, and IgE titers. Associated monoclonal gammopathies indicate clonal dysregulation. Chronic GVHD is dependent on the development and persistence of donor T cells that are not tolerant to the recipient. Maturation of transplanted stem cells within a damaged thymus could lead to errors in negative selection and production of cells that have not been tolerized to recipient antigens and are, therefore, autoreactive or, more accurately, **recipient reactive.** This ongoing immune reactivity results in clinical features resembling a systemic autoimmune disease with lichenoid and sclerodermatous skin lesions, malar rash, sicca syndrome, arthritis, joint contractures, obliterative bronchiolitis, and bile duct degeneration with cholestasis.

Patients with chronic GVHD involving only the skin and liver have a favorable course (Fig. 137-2). Extensive multiorgan disease may be associated with a very poor quality of life, recurrent infections associated with prolonged immunosuppressive regimens to control GVHD, and a high mortality rate. Morbidity and mortality are highest in patients with a **progressive onset** of chronic GVHD that directly



Figure 137-2 Chronic graft-versus-host disease of the skin with sclerodermoid changes. *(Courtesy of Evan Farmer, MD.)*

follows acute GVHD, intermediate in those with a **quiescent onset** after resolution of acute GVHD, and lowest in patients with **de novo onset** in the absence of acute GVHD. Single-agent prednisone is standard treatment at present, although other agents, including extracorporeal photopheresis, mofetil mycophenolate, anti-CD20 monoclonal antibody, and pentostatin, have been employed with variable success. Treatment with imatinib mesylate, which inhibits the synthesis of collagen, has been shown to be effective in patients with chronic GVHD and sclerotic features. As a consequence of prolonged immunosuppression, patients with chronic GVHD are particularly susceptible to infections and should receive appropriate antibiotic prophylaxis, including trimethoprim-sulfamethoxazole. Chronic GVHD resolves in most pediatric patients but may require 1-3 yr of immunosuppressive therapy before the drugs can be withdrawn without the disease recurring. Chronic GVHD promotes also the development of secondary neoplasms, in particular in patients with Fanconi anemia.

Graft failure is a serious complication exposing patients to a high risk of fatal infection. **Primary graft failure** is defined as failure to achieve a neutrophil count of 0.2×10^9/L by 21 days posttransplantation. **Secondary graft failure** is loss of peripheral blood counts following initial transient engraftment of donor cells. Causes of graft failure after autologous and allogeneic transplantation include transplantation of an inadequate stem cell dose (more frequently observed in children given cord blood transplantation), and viral infections such as with cytomegalovirus or human herpesvirus type 6, which are often associated with activation of recipient macrophages. Graft failure after allogeneic transplantation, however, is mainly caused by immunologically mediated rejection of the graft by residual recipient-type T cells that survive the conditioning regimen. **Diagnosis** of graft failure resulting from immunologic mechanisms is based on examination of peripheral blood and marrow aspirate and biopsy, along with molecular analysis of chimerism status. Persistence of lymphocytes of host origin in allogeneic transplant recipients with graft failure indicates immunologic

rejection. The risk of immune-mediated graft rejection is higher in patients given HLA-disparate, T-cell–depleted grafts, reduced-intensity conditioning regimens, and transplantation of low numbers of stem cells, and in recipients who are sensitized toward HLA antigens or, less frequently, minor histocompatibility antigens. Allosensitization develops as a consequence of preceding blood product transfusions and is observed particularly in recipients with aplastic anemia, sickle cell disease, and thalassemia. In HSCT for nonmalignant diseases, such as mucopolysaccharidoses, graft failure is also facilitated by the absence of previous treatment with cytotoxic and immunosuppressive drugs. In thalassemia, graft failure is promoted by expansion of recipient hematopoietic cells. GVHD prophylaxis with methotrexate, an antimetabolite, and antiinfective prophylaxis with trimethoprim-sulfamethoxazole or ganciclovir may also delay engraftment.

Treatment of graft failure usually requires removing all potentially myelotoxic agents from the treatment regimen and attempting a short trial of hematopoietic growth factors, such as granulocyte colony-stimulating factor. A second transplant, usually preceded by a highly immune-suppressive regimen, is frequently employed to rescue patients experiencing graft failure. High-intensity regimens are generally tolerated poorly if administered within 100 days from a 1st transplant because of cumulative toxicities.

VENOOCCLUSIVE DISEASE

Hepatic venoocclusive disease, also known as sinusoidal obstruction syndrome, presents with hepatomegaly, right upper quadrant tenderness, jaundice, and weight gain from fluid retention and ascites. Onset is usually within 30 days of transplantation, with an incidence of approximately 15%, depending on the intensity of the conditioning protocol. Risk factors include young age, prior hepatic disease (fibrosis, cirrhosis), abdominal radiation, repeated transplantations, neuroblastoma, osteopetrosis and familial hemophagocytic lymphohistiocytosis. The severe form of venoocclusive disease has a high mortality rate; treatment results for severe disease are poor.

Prophylaxis has traditionally used heparin and ursodeoxycholic acid; however, only defibrotide has demonstrated some efficacy in preventing venoocclusive disease. Defibrotide is a combination of porcine oligodeoxyribonucleotides that reduces procoagulant activity and enhances fibrinolytic properties of endothelial cells.

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Chapter 138

Infectious Complications of Hematopoietic Stem Cell Transplantation

Andrea Velardi and Franco Locatelli

Hematopoietic stem cell transplantation (HSCT) recipients experience a transient but profound state of immune deficiency. Immediately after transplantation, because neutrophils are absent or markedly reduced, patients are particularly susceptible to bacterial and fungal infections. Consequently, most centers start prophylactic antibiotic or antifungal treatment during the conditioning regimen. Despite these prophylactic measures, most patients will develop fever and signs of infection in the early posttransplantation period. The common pathogens include enteric bacteria and fungi such as *Candida* and *Aspergillus.* An indwelling central venous line, routinely employed in all children given HSCT, is a significant risk factor for bacterial and fungal infections, staphylococcal species and *Candida* being the most frequent pathogens in catheter-related infections (see Chapter 178). Emergence of multidrug resistant strains of *Pseudomonas aeruginosa* and *Klebsiella pneumoniae* has become a serious problem, being associated with a high case : fatality ratio.

HSCT recipients remain at increased risk of developing severe infections even after the neutrophil count has normalized, because T-cell number and function remain below normal for months after transplantation. Unrelated donor transplant recipients are at increased risk of developing graft-versus-host disease (GVHD), which is itself an additional risk factor for fungal and viral opportunistic infections, as are the associated immunosuppressive treatments. After cord blood transplantation, infections are the consequence of both the slow neutrophil engraftment and donor T-cell naïveté. In haploidentical transplantation, the increased risk of infection observed in the 1st 4-6 mo after the allograft is the consequence of T-cell depletion of the graft. Indeed, patients given this type of transplantation, as well as those receiving cord blood transplantation, cannot benefit from the adoptive transfer of donor-derived, antigen-experienced T cells.

Among HSCT recipients, invasive aspergillosis, cytomegalovirus (CMV) infection, disseminated adenovirus infections, and Epstein-Barr virus (EBV)–related lymphoproliferative disorders represent peculiar, life-threatening complications that significantly affect patient's outcome.

Invasive **aspergillosis** remains a significant cause of infectious morbidity and mortality in HSCT recipients. Despite prompt and aggressive administration of potent antifungal agents, proven cases of aspergillosis remain difficult to treat, with case-fatality rates of 80-90%. The annual incidence of invasive aspergillosis has risen with use of stem cells from alternative sources. The incidence is 7.3% in recipients of an human leukocyte antigen (HLA)-matched related donor transplant and 10.5% in patients given the allograft from either an HLA-mismatched family donor or an unrelated donor volunteer. Most cases of aspergillosis are diagnosed from 40-180 days after HSCT, with 30% diagnosed <40 days before and 17% more than 6 mo after transplantation. The risk of developing aspergillosis is mainly influenced by the duration of neutropenia, GVHD occurrence, use of corticosteroid therapy, posttransplant CMV infection, viral respiratory tract infections, advanced disease status, older age, and T-cell depletion of the graft. Patients with a previous history of invasive aspergillosis are at particular risk.

Aspergillus infection often originates from the upper airway mucosa. Early lesions in the nose should be sought in patients with neutropenia who have fever and minimal epistaxis. Rapid extension into the adjacent paranasal sinuses, orbit, or face is usual, with or without the appearance of lung lesions. In the lung, invasive aspergillosis generally presents as an acute, rapidly progressive, densely consolidated pulmonary infiltrate. Infection progresses by direct extension across tissue and by hematogenous dissemination to brain and other organs. The earliest CT finding is one or more small pulmonary nodules. As a nodule enlarges, the dense central core of infarcted tissue becomes surrounded by edema or hemorrhage, forming a hazy rim, the **halo sign.** This rim disappears in a few days as the dense core enlarges. In neutropenic patients, when bone marrow function recovers, the infarcted central core cavitates, creating the **crescent sign.** Repeated positivity for serum galactomannan represents a useful biomarker for confirming/suspecting a diagnosis of invasive aspergillosis. Antifungal prophylaxis includes isolation of the patient in a laminar air flow or positive pressure room. Liposomal amphotericin B, azole compounds (itraconazole, voriconazole, posaconazole) and echinocandins (caspofungin, micafungin, anidulafungin) are useful for both preventing and treating the fungal infection. Voriconazole represents the treatment of choice for patients with invasive pulmonary and brain aspergillosis. However, often, aspergillosis does not respond satisfactorily to antifungal agents alone, and patients remain at risk until T-cell counts and function recover. This observation provides the rationale

for developing strategies to accelerate the recovery of pathogen-specific immune responses.

CMV infection remains the most common and potentially severe viral complication in patients given allogeneic HSCT. Seropositivity for CMV is an independent risk factor for mortality, even in recipients of matched sibling or unrelated donor transplants. CMV is itself immunosuppressive, as it impairs dendritic cell and T-lymphocyte function. Moreover, ganciclovir, the most frequently used anti-CMV agent, may cause leukopenia and T-cell immune suppression.

The period of maximal risk for CMV infection is 1-4 mo after transplantation. Until CMV-specific T-cell responses develop months after transplant, CMV infection may result in a variety of syndromes including fever, leukopenia, thrombocytopenia, hepatitis, pneumonitis, retinitis, esophagitis, gastritis, and colitis. CMV pneumonia, the most life-threatening complication related to viral infection, has been reported to occur in up to 15-20% of bone marrow transplant recipients, with a case fatality rate of 85%. The risk is greatest between 5 and 13 wk after transplantation. Risk factors include T-cell depletion of the graft, donor seronegative status together with recipient seropositive status, acute GVHD, and patient older age.

Tachypnea, hypoxia, and unproductive cough signals respiratory involvement. Chest x-ray often reveals bilateral interstitial or reticulonodular infiltrates, which begin in the periphery of the lower lobes and spread centrally and superiorly. The differential diagnosis includes infection with *Pneumocystis jiroveci* or other viral, bacterial, or fungal pathogens, pulmonary hemorrhage, and injury secondary to irradiation or to treatment with cytotoxic drugs. Gastrointestinal CMV involvement may lead to ulcers of the esophagus, stomach, small intestine, and colon that may result in bleeding or perforation.

Fatal CMV infections are often associated with persistent viremia and multiorgan involvement. In the 1980s, antiviral treatment was deferred until overt clinical symptoms of CMV infection developed, which led to a high incidence of fatal events. CMV disease has largely been **prevented** through prophylaxis and a preemptive approach. Prophylaxis is based on administration of antiviral drugs to all transplanted patients for a median duration of 3 mo after transplantation. The major drawbacks of this approach refer to drug toxicity, occurrence of late CMV disease, mainly pneumonia, after withdrawal of prophylaxis, treatment of patients who do not need antiviral therapy as they would not have reactivated CMV infection, and low cost-effectiveness. Preemptive, or presymptomatic, therapy aims at treating only patients who experience CMV reactivation and, thus, are at risk of developing overt disease; it starts only upon detection of CMV in blood by any assay. The most widely used assay is CMV detection of CMV DNA in blood, which have been used to decide inception of treatment when it either becomes positive or reaches a predetermined threshold. Although in the past treatment usually started after this assay became positive, nowadays therapy is usually initiated when a certain viral load is reached. Moreover, quantification of CMV DNA in blood provides a reliable approach for deciding interruption of treatment. The major drawback of this strategy is the need of serial monitoring that is required for the period in which patients are at risk of developing CMV disease. In this regard, approaches to reliably prove the restoration of virus-specific immunity have been developed. Generally, ganciclovir, or less frequently foscarnet, is usually used for prophylaxis and preemptive treatment of CMV infection. Treatment is usually discontinued when repeated negative controls have been obtained.

Disseminated adenovirus infection is a life-threatening complication of HSCT recipients. Clinical manifestations include fever, hepatitis, enteritis, meningoencephalitis, and pneumonia. Young children are at particular risk of developing this complication. Diagnosis is based on the demonstration of high levels of adenovirus DNA in blood or on recovery of virus in tissue biopsies. Pharmacologic treatment of adenovirus infections is based on the use of cidofovir, which has significant renal toxicity and sometimes is unable to control viral replication. Recovery of immune system function is associated with a greater chance to survive adenovirus disseminated infection.

EBV-related **lymphoproliferative** disease (EBV-LPD) is a major complication in HSCT and solid-organ transplantation. In patients given HSCT, selective procedures of T-cell-depletion–sparing B lymphocytes, as well as the use of HLA partially matched family and unrelated donors, are risk factors for the development of EBV-LPD. These disorders usually present in the 1st 4-6 mo after transplantation as high-grade diffuse large-cell B-cell lymphomas, which are oligoclonal or monoclonal, express the full array of EBV antigens, and are of donor origin. High levels of EBV-DNA in blood and in vitro spontaneous growth of EBV-lymphoblastoid cell lines predict development of EBV-LPD.

In immunocompromised hosts, EBV-LPD originates from a deficiency of virus-specific cytotoxic T lymphocytes (CTLs), which control outgrowth of EBV-infected B cells. This finding provided the rationale for developing strategies of adoptive cell therapy to restore EBV-specific immune competence. Unselected donor leukocyte infusion, the first attempt at EBV-directed adoptive immunotherapy in humans, can induce EBV-LPD remission but exposes patients to a high risk of developing clinically relevant GVHD and is not suitable for patients transplanted from an HLA-mismatched donor. A safer approach is infusion of in vitro generated EBV-specific CTL lines of donor origin containing both CD8+ and CD4+ T lymphocytes. These CTL lines prevent lymphoproliferative disorders in patients considered at high risk, such as patients given T-cell depleted HSCT from HLA-disparate donors, and cure clinically overt LPD. Infusion of EBV-specific CTLs from third-party donors sharing HLA-class I molecules with the recipient can be also useful. In recent years, use of monoclonal antibodies directed against CD20, a molecule expressed on B cells, has significantly contributed to reduce the incidence and severity of EBV-related LPD, although it can be associated with the emergence of neoplasms in which cells are CD19+ but CD20 negative, thus rendering patients no longer susceptible to the treatment with the monoclonal antibody.

Chapter 139

Late Effects of Hematopoietic Stem Cell Transplantation

Andrea Velardi and Franco Locatelli

Many children given hematopoietic stem cell transplantation (HSCT) become long-term survivors. Besides chronic graft-versus-host disease (GVHD), long-term complications that may develop in pediatric transplant recipients include impaired growth, neuroendocrine dysfunction, delayed puberty, infertility, second malignancies, cataracts and other ocular complications, leukoencephalopathy, and cardiac and pulmonary dysfunction.

Children given HSCT before puberty may develop **growth impairment,** precluding achievement of the genetic target for adult height. The decrease in growth velocity is similar for boys and girls and is more frequently observed in patients given total-body irradiation (TBI) as part of the preparative regimen. Fractionation of irradiation has a less-adverse impact on height than does single-dose TBI, whereas the use of craniospinal radiotherapy before transplantation plays a synergistic detrimental role with TBI in favoring growth impairment. A study of 175 children younger than 6 yr of age, 6-12 yr of age, or 12-15 yr of age receiving TBI-based regimens and not treated with growth hormone reported a mean final adult height of 3.49, 1.92, and 0.37 SD below average, respectively. Chronic GVHD and its treatment with corticosteroids may also contribute to growth impairment. Serial studies of children given a busulfan-based preparative regimen indicate busulfan

has much less impact on growth but produces the same gonadal failure as TBI-based regimens. Preparative regimens using only cyclophosphamide for children transplanted for aplastic anemia have little, if any, detrimental effect on growth and development.

Growth impairment of patients given TBI is mainly a result of direct damage of cartilage plates and to the effect of TBI on the hypothalamic–pituitary axis, which leads to an inappropriately low production of growth hormone (GH). GH deficiency is susceptible to at least partial correction through administration of hormonal replacement therapy. Annual growth evaluation should be performed in all children after HSCT. Children showing a decreased growth velocity should be further investigated through evaluation of bone age and secretion of GH in response to pharmacologic stimulus. Current studies are aimed at identifying children with GH deficiencies at an earlier age and administering hormonal replacement therapy. Initial concerns about potential risks of favoring disease recurrence or promoting development of second malignancies in GH substitute therapy have not been confirmed and GH replacement therapy is widely employed.

The use of TBI during the preparative regimen involves the thyroid gland in the irradiation field and may result in **hypothyroidism.** Some children who have received single-dose TBI develop either compensated (28-56%) or overt (9-13%) hypothyroidism. The use of fractionated TBI reduces the incidence of both compensated (10-14%) and overt (<5%) hypothyroidism. Children younger than 7 yr old at the time of allograft are at greater risk of developing hypothyroidism. Chemotherapy-only preparative regimens have far fewer adverse effects on normal thyroid function. The site of injury by irradiation is at the level of the thyroid gland rather than at the pituitary or hypothalamus. Therapy with thyroxine is very effective for overt hypothyroidism, but treatment of compensated hypothyroidism is more controversial, although there is evidence that hormonal replacement therapy may reduce the risk of thyroid carcinoma through a suppression of thyroid-stimulating hormone. Despite treatment of hypothyroidism, the incidence of thyroid carcinoma is not negligible. An annual echo of the thyroid gland is indicated for timely identification of nodules in the thyroid gland suspected to be of neoplastic origin. When a nodule with echo characteristics suggestive for a carcinoma is identified, a needle biopsy is indicated to clarify the histologic nature of the nodule. The cumulative incidence of hypothyroidism increases over time, underscoring the importance of annual thyroid function studies.

Gonadal hormones are essential for normal pubertal growth, as well as for development of secondary sexual characteristics. A significant proportion of patients receiving TBI-containing preparative regimens show **delayed development of secondary sexual characteristics,** resulting from primary ovarian or testicular failure. Laboratory evaluation of these patients reveals elevated follicle-stimulating hormone and luteinizing hormone levels with depressed estradiol and testosterone serum levels. These patients benefit from careful follow-up with evaluation of annual Tanner scores and endocrine function. Supplementation of gonadal hormones is useful for primary gonadal failure and is administered with GH to promote pubertal growth. The incidence of sex hormone deficiency is lower in patients given a busulfan-based regimen, while infertility during adulthood is a common problem of these children, as well as of those prepared to the allograft with TBI. The use of reduced-intensity regimens can have the advantage of sparing fertility in a large proportion of patients.

The overall risk of developing a **secondary form of cancer** is significantly higher after HSCT than in the general population. Although few studies have specifically analyzed pediatric patients, available evidence indicates that the cumulative incidence of second malignancies shows a slight, but continuous, tendency to increase over time. Several types of secondary tumors have been identified in patients given HSCT. The most frequently diagnosed neoplasms are thyroid carcinoma, brain tumors, and epithelial cancers. Young age, male gender, use of TBI during the preparative regimen, chronic GVHD, and an intrinsic genetic predisposition to develop cancer (Fanconi anemia) have been reported to be risk factors for development of secondary malignancies after HSCT.

Cataracts mainly occur in children given a radiotherapy-based preparative regimen. The incidence of cataracts is particularly high if TBI is delivered as a single-fraction (800-1,000 cGy). The introduction of fractionated TBI has led to a marked reduction of this complication to ≈10-20% of patients, one-third of whom require surgical intervention. Corticosteroids, frequently employed for treating GVHD, also promote development of cataracts. A dry eye syndrome, or keratoconjunctivitis sicca, may also affect HSCT recipients. It is often related to chronic GVHD and postradiotherapy fibrosis of the lacrimal gland and is treated with artificial tears and lubricants.

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Allergic Disorders

PART XV

Chapter 140

Allergy and the Immunologic Basis of Atopic Disease

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Allergic or atopic patients have an altered state of reactivity to common environmental and food antigens that do not cause clinical reactions in unaffected people. Patients with clinical allergy usually produce immunoglobulin (Ig) E antibodies to the antigens that trigger their illness. The term *allergy* represents the clinical expression of IgE-mediated allergic diseases that have a familial predisposition and that manifest as hyperresponsiveness in target organs such as the lung, skin, gastrointestinal tract, and nose. There has been a significant increase in the prevalence of allergic diseases during the last few decades. This increase is attributed to changes in environmental factors (exposure to tobacco smoke, air pollution, indoor and outdoor allergens, respiratory viruses, obesity and perhaps a decline in certain infectious diseases [hygiene hypothesis]).

KEY ELEMENTS OF ALLERGIC DISEASES

Allergens

Allergens are almost always proteins, but not all proteins are allergens. For a protein antigen to display allergenic activity, it must induce IgE production, which must lead to a type 1 hypersensitivity response upon subsequent exposure to the same protein. Biochemical properties of the allergen, stimulating factors of the innate immune response around the allergen substances at the time of exposure, stability of the allergen in the tissues, digestive system, skin, or mucosa, and the dose and time of stay in lymphatic organs during the interaction with the immune system are all factors that may cause an antigen to become an allergen. This is distinguished from general antigen responses, which induce a state of immune responsiveness without associated IgE production.

Most allergens are proteins of 10-70 kDa molecular weight; molecules <10 kDa do not bridge adjacent IgE antibody molecules on the surfaces of mast cells or basophils; most molecules >70 kDa do not pass through mucosal surfaces, a feature needed to reach antigen-presenting cells (APCs) for stimulation of the immune system. Allergens frequently contain proteases, which promote barrier dysfunction and increase allergen penetration into host tissues. Low-molecular-weight moieties, such as drugs, can become allergens by reacting with serum proteins or cell membrane proteins to be recognized by the immune system. Carbohydrate structures can also be allergens and are most relevant with the increasing use of biologics in clinical practice; patients with cetuximab-induced anaphylaxis have IgE antibodies specific for galactose-α-1,3-galactose (see Chapter 151).

T Cells

Everyone is exposed to potential allergens. Atopic individuals respond to allergen exposure with rapid expansion of **T-helper type 2 (Th2)** cells that secrete cytokines, such as interleukin (IL)-4, IL-5, and IL-13, favoring IgE synthesis and eosinophilia. Allergen-specific IgE antibodies associated with atopic response are detectable by serum testing or positive immediate reactions to allergen extracts on prick skin testing (see Chapter 141). The Th2 cytokines IL-4 and IL-13 play a key role in immunoglobulin isotype switching to IgE (Fig. 140-1). IL-5 and IL-9 are important in differentiation and development of eosinophils. The combination of IL-3, IL-4, and IL-9 contributes to mast cell activation. Th2 cytokines are important effector molecules in the pathogenesis of asthma and allergic diseases; acute allergic reactions are characterized by infiltration of Th2 cells into affected tissues. In addition, IL-25, IL-33, and thymic stromal lymphopoietin (TSLP) contribute to Th2 response and eosinophilia.

A fraction of the immune response to allergen results in proliferation of **T helper type 1 (Th1)** cells. Th1 cells are typically involved in the eradication of intracellular organisms, such as mycobacteria, because of the ability of Th1 cytokines to activate phagocytes and promote the production of opsonizing and complement-fixing antibodies. The Th1 component of allergen-specific immune response contributes to chronicity and the effector phase in allergic disease. Activation and apoptosis of epithelial cells induced by Th1 cell–secreted interferon-γ (IFN-γ), tumor necrosis factor-α (TNF-α), and Fas ligand constitute an essential pathogenetic event for the formation of eczematous lesions in atopic dermatitis and bronchial epithelial cell shedding in asthma.

Chronic lesions of allergic reactions are characterized by infiltration of Th1 and **Th17 cells**. This is important because Th1 cytokines such as IFN-γ can potentiate the function of allergic inflammatory effector cells such as eosinophils and thereby contribute to disease severity. Th17 and Th22 cells link the immune response to tissue inflammation; IL-17A and IL-17F and IL-22 are their respective prototype cytokines. Although both T-helper cell subsets play roles in immune defense to extracellular bacteria, IL-17 augments inflammation, whereas IL-22 plays a tissue-protective role. Cytokines in the IL-17 family act on multiple cell types, including epithelial cells and APCs, to cause the release of chemokines, antimicrobial peptides, and proinflammatory cytokines to enhance inflammation and antimicrobial responses. In addition, recently identified Th9 cells produce IL-9, but not other typical Th1, Th2, and Th17 cytokines, and constitute a distinct population of effector T cells that promotes tissue inflammation. Figure 140-2 depicts the complex cytokine cascades involving Th1, Th2, Th9, Th17 and Th22 cells.

T-regulatory (Treg) cells are a subset of T cells thought to play a critical role in expression of allergic and autoimmune diseases. These cells have the ability to suppress effector T cells of either the Th1 or Th2 phenotypes (Fig. 140-3). Treg cells express $CD4^+CD25^+$ surface molecules and immunosuppressive cytokines such as IL-10 and transforming growth factor-β (TGF-β_1). The forkhead box/winged-helix transcription factor gene *FOXP3* is expressed specifically by $CD4^+CD25^+$ Treg cells and programs their development and function. Adoptive transfer of Treg cells inhibits the development of airway eosinophilia and protects against airway hyperreactivity in animal models of asthma. T-cell response to allergens in healthy individuals shows a wide range, from no detectable response to involvement of active peripheral tolerance mechanisms mediated by different subsets of Treg cells. Individuals who are not allergic even though they are exposed to high doses of allergens, such as beekeepers and cat owners, show a detectable allergen-specific IgG4 response accompanied by IL-10–producing Treg cells. It is thought that $CD4^+CD25^+$ Treg cells play an important role in mitigating the allergic immune response and that the lack of such cells may predispose to the development of allergic diseases. Patients with mutations in the human *FOXP3* gene lack $CD4^+CD25^+$ Treg cells and develop severe immune dysregulation, with polyendocrinopathy, food allergy, and high serum IgE levels (XLAAD/

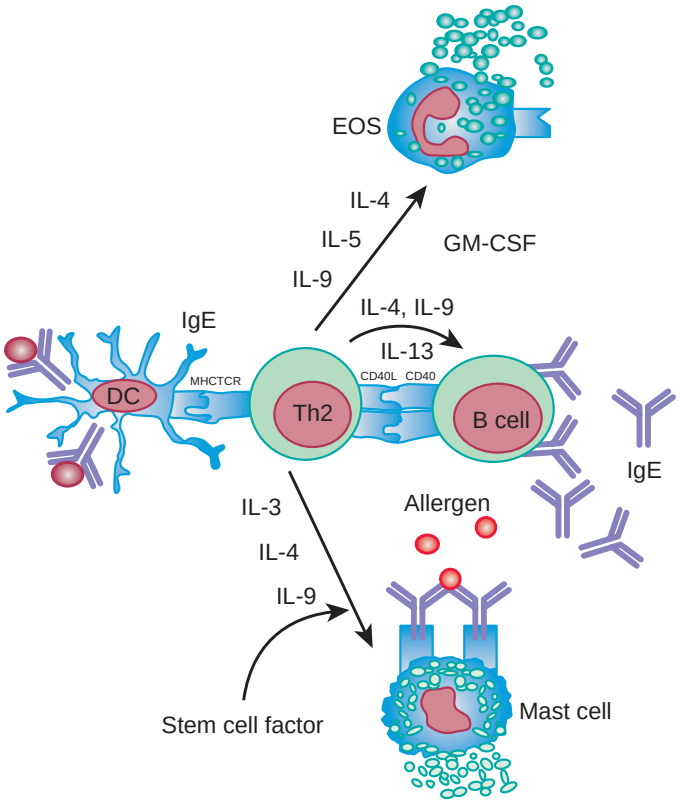


Figure 140-1 Role of Th2 cytokines in allergic cascade. DC, dendritic cell; EOS, eosinophil; GM-CSF, granulocyte-macrophage colony-stimulating factor; IL, interleukin; Th2, T-helper type 2 cell.

IPEX disease) (see Chapter 126). In addition to Treg cells, IL-10 secreting and allergen-specific Breg cells that increase during allergen-specific immunotherapy, and may play a role in allergen tolerance were recently demonstrated.

Antigen-Presenting Cells

Dendritic cells, Langerhans cells, monocytes, and macrophages have the ability to present allergens to T cells and thereby modulate allergic inflammation by controlling the type of T-cell development. APCs are a heterogeneous group of cells that share the property of antigen presentation in the context of the major histocompatibility complex (MHC) and are found primarily in lymphoid organs and the skin. Dendritic cells (DCs) and Langerhans cells are unique in their ability to prime naïve T cells and are responsible for the primary immune response, or the **sensitization phase** of allergy. Monocytes and macrophages are thought to contribute to activating memory T-cell responses upon reexposure to allergen, which characterizes the **elicitation phase** of allergy.

Peripheral DCs residing in sites such as the skin, intestinal lamina propria, and lung are relatively immature. These immature DCs take up antigens in tissues and then migrate to the T-cell areas in locally draining lymph nodes. The DCs undergo phenotypic and functional changes during migration, characterized by increased expression of MHC class I, MHC class II, and costimulatory molecules that react with CD28 expressed on T cells. In the lymph nodes, they directly present processed antigens to resting T cells to induce their proliferation and differentiation.

Mature DCs have been designated as myeloid DC or plasmacytoid DC on the basis of their ability to favor Th1 or Th2 differentiation, respectively. The critical factor for polarization to Th1 cells is the level of IL-12 produced by myeloid DC. By contrast, plasmacytoid DC have low levels of IL-12. Plasmacytoid DC particularly play a role in antiviral immunity by rapid production of high amounts of interferon

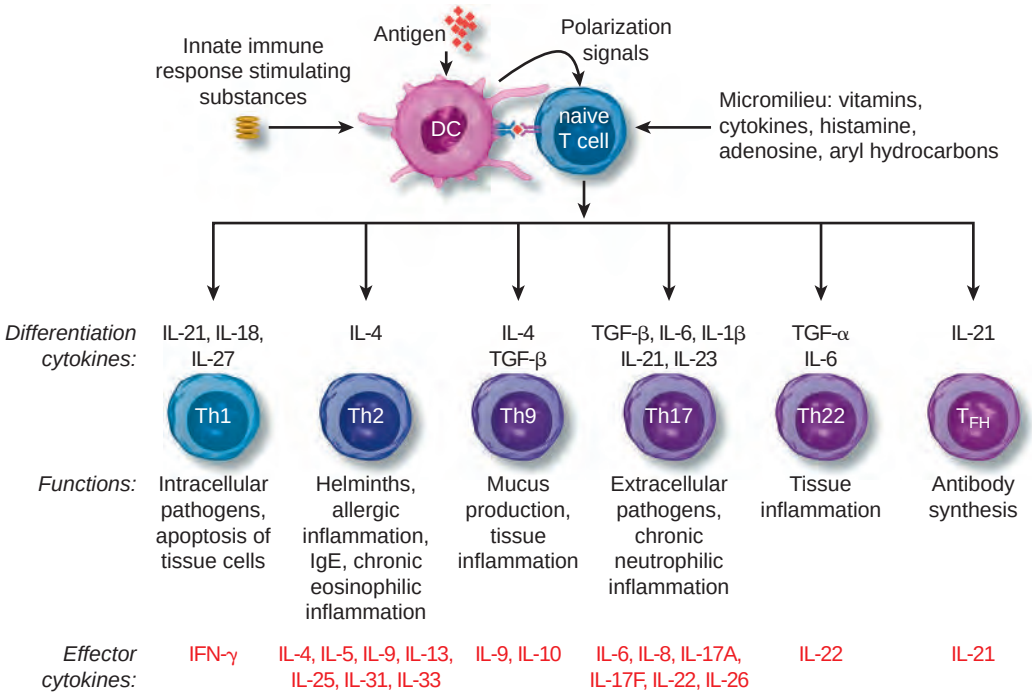


Figure 140-2 Effector T-cell subsets. Following antigen presentation by dendritic cells (DCs), naïve T cells differentiate into Th1, Th2, Th9, Th17, Th22, and follicular helper TFH effector subsets. Their differentiation requires cytokines and other cofactors that are released from dendritic cells and also expressed in the micromilieu. T-cell activation in the presence of interleukin-4 (IL-4) enhances differentiation and clonal expansion of Th2 cells, perpetuating the allergic response. IFN-γ, interferon-γ; TGF-β, transforming growth factor-β. *(From Akdis M, Palomares O, van de Veen W, van Splunter M, Akdis CA. TH17 and TH22 cells: a confusion of antimicrobial response with tissue inflammation versus protection,* J Allergy Clin Immunol *129:1438–1449, 2012.)*

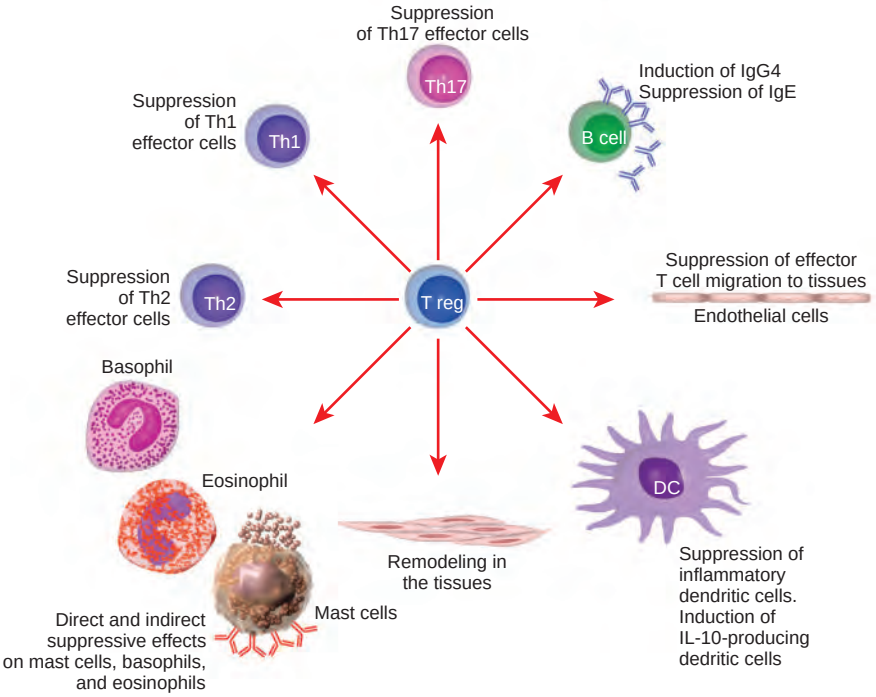


Figure 140-3 FoxP3$^+$, CD4$^+$, CD25$^+$, and Tr1 cells contribute to the control of allergen-specific immune responses in several major ways: Suppression of dendritic cells that support the generation of effector T-cells; suppression of Th1, Th2, and Th17 cells; suppression of allergen-specific IgE, and induction of IgG_4 and/or IgA; suppression of mast cells, basophils, and eosinophils; interaction with resident tissue cells and remodeling, and suppression of effector T-cell migration to tissues. IL-10, interleukin 10. *(From Akdis CA, Akdis M: Mechanisms and treatment of allergic disease in the big picture of regulatory T cells,* J Allergy Clin Immunol *123:735–746, 2009.)*

(IFN)-α and also help B cells for antibody production. There is considerable interest in the role of TSLP, which is overexpressed in the mucosal surfaces and skin of atopic individuals. TSLP enhances Th2 cell differentiation by inducing expression of OX40L on immature myeloid DCs in the absence of IL-12 production.

Presence of allergen-specific IgE on the cell surfaces of APCs is a unique feature of atopy. Importantly, the formation of high-affinity IgE receptor I (FcεRI)/IgE/allergen complexes on APC cell surfaces markedly facilitates allergen uptake and presentation. The clinical importance of this phenomenon is supported by the observation that FcεRI-positive Langerhans cells bearing IgE molecules are a prerequisite for skin-applied, aeroallergen provocation of eczematous lesions in patients with atopic dermatitis. The role of the low-affinity IgE receptor II (FcεRII, CD23) on monocytes-macrophages is less clear, although it appears that under certain conditions it can also facilitate antigen capture. Cross-linking of FcεRII, as well as FcεRI, on monocytes-macrophages leads to the release of inflammatory mediators. There is a critical role for DCs in induction of oral tolerance; tolerogenic DCs are compartmentalized within the mucosa and present antigen through a mechanism designed to produce a Th1/Treg–suppressive response that ablates allergen-specific T cells.

Immunoglobulin E and its Receptors

The acute allergic response depends on IgE and its ability to bind selectively to the α chain of the high-affinity FcεRI or the low-affinity FcεRII (CD23). Cross-linking of receptor-bound IgE molecules by allergen initiates a complex intracellular signaling cascade followed by the release of various mediators of allergic inflammation from mast cells and basophils. The FcεRI molecule is also found on the surface of antigen-presenting DCs (e.g., Langerhans cells), but differs from the structure found on mast cells/basophils in that the FcεRI molecule found on DCs lacks the β chain. CD23 is found on B cells, eosinophils, platelets, and DCs. Cross-linking and FcεRI aggregation on mast cells and basophils can also lead to anaphylaxis (see Chapter 149). Differential expression of tyrosine kinases responsible for positive and negative regulation of mast cell/basophil degranulation are thought to be responsible for this aberrant allergic response.

The induction of IgE synthesis requires 2 major signals. The first signal (signal 1) initiates IL-4 or IL-13 activation of germline transcription at the ε Ig locus, which dictates isotype specificity. The second signal (signal 2) involves the engagement of CD40 on B cells by CD40 ligand expressed on T cells. This engagement results in activation of the recombination machinery, resulting in DNA switch recombination. Interactions between several costimulatory molecule pairs (CD28 and B7; lymphocyte function–associated antigen-1 and intercellular adhesion molecule-1; CD2 and CD58) can further amplify signal 1 and signal 2 to enhance IgE synthesis. Factors that inhibit IgE synthesis include Th1-type cytokines (IL-12, IFN-α, IFN-γ) and microbial DNA containing CpG (cytosine-phosphate-guanine) repeats.

Eosinophils

Allergic diseases are characterized by peripheral blood and tissue eosinophilia. Eosinophils participate in both innate and adaptive immune responses and, like mast cells, contain dense intracellular granules that are sources of inflammatory proteins. These granule proteins include major basic protein, eosinophil-derived neurotoxin, peroxidase, and cationic protein. Eosinophil granule proteins damage epithelial cells, induce airway hyperresponsiveness, and cause degranulation of basophils and mast cells. Major basic protein released from eosinophils can bind to an acidic moiety on the M2 muscarinic receptor and block its function, thereby leading to increased acetylcholine levels and the development of increased airway hyperreactivity. Eosinophils are also a rich source of prostaglandins and leukotrienes; in particular, cysteinyl leukotriene C4 contracts airway smooth muscle and increases vascular permeability. Other secretory products of eosinophils include cytokines (IL-4, IL-5, TNF-α), proteolytic enzymes, and reactive oxygen intermediates, all of which significantly enhance allergic tissue inflammation.

Several cytokines regulate the function of eosinophils in allergic disease. Eosinophils develop and mature in the bone marrow from myeloid precursor cells activated by IL-3, IL-5, and granulocyte-macrophage colony-stimulating factor (GM-CSF). Allergen exposure of allergic patients causes resident hematopoietic CD34 cells to express the IL-5 receptor. The IL-5 receptor activation induces eosinophil maturation, causing eosinophils to synthesize granule proteins, prolonging their survival, potentiating degranulation of eosinophils, and stimulating release of eosinophils from the bone marrow. GM-CSF also enhances proliferation, cell survival, cytokine production, and degranulation of eosinophils. Certain chemokines, such as RANTES (regulated upon activation, normal T-cell expressed and secreted),

macrophage inflammatory protein-1α (MIP-1α), and eotaxins, are important for recruiting eosinophils into local allergic tissue inflammatory reactions. Eotaxins mobilize IL-5–dependent eosinophil colony–forming progenitor cells from the bone marrow. These progenitors are rapidly cleared from the blood and either return to the bone marrow or are recruited to inflamed tissue sites.

Mast Cells

Mast cells are derived from CD34 hematopoietic progenitor cells that arise in bone marrow. Upon entering the circulation, they travel to peripheral tissue, where they undergo tissue-specific maturation. Mast cell development and survival relies on interactions between the tyrosine kinase receptor c-kit expressed on the surface of mast cells and the fibroblast-derived c-kit ligand stem cell factor. Unlike mature basophils, mature mast cells do not typically circulate in the blood. They are, instead, widely distributed throughout connective tissues, where they often lie adjacent to blood vessels and beneath epithelial surfaces that are exposed to the external environment, such as the respiratory tract, gastrointestinal tract, and skin. So placed, mast cells are positioned anatomically to participate in allergic reactions. At least 2 subpopulations of human mast cells are recognized: mast cells with tryptase and mast cells with both tryptase and chymase. Mast cells with tryptase are the predominant type found in the lung and small intestinal mucosa, whereas mast cells with both tryptase and chymase are the predominant type found in skin, the gastrointestinal submucosa, and blood vessels.

Mast cells contain, or produce on appropriate stimulation, a diverse array of mediators that have different effects on allergic inflammation and organ function. They include preformed granule-associated mediators (histamine, serine proteases, proteoglycans) and membrane-derived lipid, cytokine, and chemokine mediators arising from de novo synthesis and release. The most important mast cell-derived lipid mediators are the cyclooxygenase and lipoxygenase metabolites of arachidonic acid, which have potent inflammatory activities. The major cyclooxygenase product of mast cells is prostaglandin D_2, and the major lipoxygenase products are the sulfidopeptide leukotrienes (LTs): LTC_4 and its peptidolytic derivatives LTD_4 and LTE_4. Mast cells also can produce cytokines that promote Th2-type responses (IL-4, IL-13, GM-CSF) and inflammation (TNF-α, IL-6), and regulate tissue remodeling (TGF, vascular endothelial cell growth factor). Immunologic activation of mast cells and basophils typically begins with cross-linkage of IgE bound to the FcεRI with multivalent allergen. Mast cell surface FcεRI is increased by IL-4 and IgE. Surface levels of FcεRI decrease in subjects receiving treatment with anti-IgE antibody that lowers serum IgE, which is of potential therapeutic interest.

MECHANISMS OF ALLERGIC TISSUE INFLAMMATION

IgE-mediated immune responses can be classified chronologically according to 3 reaction patterns. The **early-phase response** is the immediate response after allergen is introduced into target organs. This response is characterized by mast cell degranulation and release of preformed mediators, occurring within an immediate time frame of between 1 and 30 min after allergen exposure and resolving within 1-3 hr. Acute reactions are associated with increased local vascular permeability, which leads to leakage of plasma proteins, tissue swelling, and increased blood flow, as well as itching, sneezing, wheezing, and acute abdominal cramps in the skin, nose, lung, and gastrointestinal tract, respectively, depending on the targeted organ.

A second, **late-phase response** can occur within hours of allergen exposure, reaching a maximum at 6-12 hr and resolving by 24 hr. Late-phase responses are characterized in the skin by edema, redness, and induration; in the nose by sustained nasal blockage; and in the lung by airway obstruction and persistent wheezing. In general, late-phase responses are associated with early infiltration of neutrophils and eosinophils followed by basophils, monocytes, macrophages, and Th2-type cells. Recruitment of inflammatory cells from the circulation requires increased expression of adhesion molecules on their cell surfaces and expression of their ligand on endothelial cells, which are under the control of cytokines. Several hours after allergen exposure, TNF-α released by activated mast cells induces the vascular endothelial expression of cell adhesion molecules, and this change leads to transendothelial migration of various inflammatory cells. Preferential accumulation of eosinophils occurs through interactions between selective adhesion molecules on the eosinophil cell surface (e.g., $\alpha_4\beta_1$ integrin or very late antigen-4); vascular cell adhesion molecule-1 surface expression can be enhanced by IL-4 and IL-13 on endothelial cells.

Chemokines are chemotactic cytokines that play a central role in tissue-directed migration of inflammatory cells. RANTES, MIP-1α, monocyte chemotactic protein (MCP)-3, and MCP-4 are chemoattractants for eosinophils and mononuclear cells, whereas eotaxins are relatively selective for eosinophils. These chemoattractants have been detected in epithelium, macrophages, lymphocytes, and eosinophils at sites of late-phase responses and allergic tissue inflammation. Blockade of these chemokines leads to significant reduction in tissue-directed migration of allergic effector cells.

In the third reaction pattern, **chronic allergic disease,** tissue inflammation can persist for days to years. Several factors contribute to persistent tissue inflammation, including recurrent exposure to allergens and microbial agents. The repeated stimulation of allergic effector cells such as mast cells, basophils, eosinophils, and Th2 cells contributes to unresolved inflammatory conditions. Additionally, Th2-type cytokines (IL-3, IL-5, GM-CSF) secreted during allergic reactions can prolong survival of allergic effector cells by delaying apoptosis. Local differentiation of tissue-infiltrating eosinophil precursors induced by IL-5 results in self-generation of eosinophils, further sustaining damage of local tissue. Tissue remodeling leading to irreversible changes in target organs is also a feature of chronic allergic disease. In asthma, **remodeling** involves thickening of the airway walls and submucosal tissue, as well as smooth muscle hypertrophy and hyperplasia, which are associated with a decline in lung function. This is an unexpected role for eosinophils in airway remodeling as well as chronic inflammation. In atopic dermatitis, lichenification is an obvious manifestation of skin remodeling.

Th2 cytokines can not only maintain allergic inflammation but also influence tissue remodeling by activating resident cells in target organs; IL-4, IL-9, and IL-13 induce mucus hypersecretion and metaplasia of mucus cells; IL-4 and IL-13 stimulate fibroblast growth and synthesis of extracellular matrix proteins; and IL-5 and IL-9 increase subepithelial fibrosis. TGF-β produced by eosinophils and fibroblasts can enhance subepithelial fibrosis. IL-11 expressed by eosinophils and epithelial cells also contributes to subepithelial fibrosis, in addition to enhancing deposition of collagen and the accumulation of fibroblasts. Additional interleukins released from epithelial cells and DCs, such as IL-25, IL-31, and IL-33, also contribute to the Th2 and eosinophilic inflammation in the affected tissues. The resulting tissue injury amplifies further epithelial injury through proinflammatory cytokine release, extracellular matrix deposition in target organs, and angiogenesis. Genetic predisposition to aberrant injury-repair responses may contribute to chronicity of illness. Once the allergic immune response is established, it can be self-perpetuating and can lead to chronic disease in genetically predisposed individuals. The subsequent infiltration of Th1 cells and Th17 cells enhances the inflammatory potential of allergic effector cells and contributes to chronic tissue inflammatory responses through the release of proinflammatory cytokines and chemokines. In addition, an autoimmune response might be playing a causative role in allergic inflammation resulting from possible mechanisms through IgE autoantibodies, IgG autoantibodies, and Th1 cell and Th17 cell autoreactivity.

GENETIC BASIS OF ATOPY

Allergic diseases are complex genetic conditions susceptible to environmental triggers. Several major groups of genes are associated with allergic diseases: genes that regulate systemic expression of atopy (increased IgE synthesis, eosinophilia, mast cell responses) that are commonly expressed among various allergic diseases, genes that control barrier function in specific target organs (e.g., the skin in atopic

dermatitis, the lung in asthma, the gastrointestinal tract in food allergy), and genes encoding pattern-recognition receptors of the innate immune system that engage microbial pathogens and influence adaptive immune responses. Once allergic responses have been initiated, a genetic predisposition to chronic allergic inflammation and aberrant injury-repair responses contribute to tissue remodeling and persistent disease.

Atopic diseases have a strong familial predisposition, with approximately 60% heritability found in twin studies of asthma and atopic dermatitis. The 5q23-35 region comprises several genes implicated in allergic disease pathogenesis, including genes coding for Th2 cytokines (IL-3, IL-4, IL-5, IL-9, IL-13, GM-CSF). Among these, *IL4* is a well-studied potential candidate gene. A nucleotide change at position 589 of the *IL4* promoter region is associated with the formation of a unique binding site for NF-AT (**n**uclear **f**actor for **a**ctivated **T** cells) transcription factor, increased IL-4 gene transcription, higher NF-AT binding affinity, and increased IgE production. Similarly, *IL13* coding region variants have been associated with asthma and atopic dermatitis. An association between atopy and a gain-of-function polymorphism on chromosome 16, which codes for the α subunit of the IL-4R, has been found. This finding is consistent with the important role of IL-4, IL-13, and their receptors in the immunopathogenesis of allergic diseases.

Genome-wide searches have also linked atopy to chromosome region 11q13. The gene encoding the β subunit of FcεRI-β has been proposed to be the candidate gene in this region. The β subunit gene modifies the FcεRI activity on mast cells, and several genetic variants of FcεRI-β are associated with asthma and atopic dermatitis. Chromosome 6 contains genes coding for human leukocyte antigen class I and class II molecules, which regulate the specificity and intensity of the immune responses to specific allergens. IgE responses to specific allergens, such as ragweed antigen Amb a V and mite allergen *Der p* I, have been linked to specific MHC class II loci. TNF-α, a key cytokine that contributes to the influx of inflammatory cells, is also located on chromosome 6. TNF-α polymorphisms are associated with asthma.

Barrier dysfunction has a key role in the pathogenesis of allergic diseases. Genetic linkage studies of atopic dermatitis have demonstrated the importance of chromosome 1q21, which contains a cluster of genes involved in epidermal differentiation. Filaggrin is a protein that is essential in the formation of the stratum corneum. Null mutations of the filaggrin gene are strongly associated with early onset and severe atopic dermatitis. Mutations in the gene encoding the serine protease inhibitor SPINK5 has been shown to cause **Netherton disease**, a single-gene disorder associated with erythroderma, food allergy, and high serum IgE levels. A common polymorphism in SPINK5 (in particular, Glu420Lys) increases the risk of developing atopic dermatitis and asthma. SPINK5 is expressed in the outer epidermis and is thought to be critical to neutralizing the proteolytic activity of *Staphylococcus aureus* and common allergens such as *Der p* I, which use these proteases to penetrate the skin to induce allergic responses. Barrier dysfunction is involved in other allergic diseases, such as asthma and rhinosinusitis, but likely involves other barrier genes, such as those encoding gap junctions.

Candidate genes associated with asthma susceptibility have been identified by positional cloning: *GPRA* (G-protein coupled receptor for asthma susceptibility on chromosome 7p14), *ADAM-33* (a disintegrin and metalloproteinase 33 on chromosome 20p), and *DPP10* (dipeptidyl peptidase 10 on chromosome 2q14). The functions of these genes do not fit into classical pathways of atopy and therefore provide new insights into asthma pathogenesis. *GPRA* encodes a G-protein coupled receptor, with isoforms expressed in bronchial epithelial cells and smooth muscle in asthmatic persons, suggesting an important role for these tissues in asthma. *ADAM-33* is expressed in bronchial smooth muscle and has been linked to bronchial hyperresponsiveness. *DPP10* encodes a dipeptidyl dipeptidase that can remove the terminal 2 peptides from certain proinflammatory chemokines, a change that may modulate allergic inflammation.

Pattern-recognition receptors of the innate immune system, which are expressed by epithelial cells and DCs, are associated with disease susceptibility. These receptors recognize specific microbial components. Polymorphisms in CD14 (engages endotoxin), Toll-like receptor 2 (which engages *S. aureus*), and T-cell immunoglobulin domain and mucin domain (which engage hepatitis A virus) correlate with asthma and/or atopic dermatitis susceptibility. Dysregulation of these frontline immune defense systems would permit abnormal response to common environmental allergens.

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Chapter 141

Diagnosis of Allergic Disease

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ALLERGY HISTORY

Obtaining a complete history from the allergic patient involves eliciting a description of all symptoms along with their timing and duration, exposure to common allergens, and responses to previous therapies. Because patients often suffer from more than 1 allergic disease, the presence or absence of other allergic diseases, including allergic rhinoconjunctivitis, asthma, food allergy, eosinophilic esophagitis, atopic dermatitis, and drug allergy should be determined. A family history of allergic disease is common and is one of the most important factors predisposing a child to the development of allergies. The risk of allergic disease in a child approaches 50% when 1 parent is allergic and 66% when both parents are allergic, with maternal history of atopy having a greater effect than paternal history.

Several characteristic behaviors are often seen in allergic children. Because of nasal pruritus and rhinorrhea, children with allergic rhinitis often perform the **allergic salute** by rubbing their nose upward with the palm of their hand. This repeated maneuver may give rise to the **nasal crease,** a horizontal wrinkle over the bridge of the nose. Characteristic vigorous **grinding** of the eyes with the thumb and side of the fist is frequently observed in children with allergic conjunctivitis. The **allergic cluck** is produced when the tongue is placed against the roof of the mouth to form a seal and withdrawn rapidly in an effort to scratch the palate. The presence of other symptoms, such as fever, unilateral nasal obstruction, and purulent nasal discharge, suggests other diagnoses.

The timing of onset and the progression of symptoms are relevant. The onset of recurrent or persistent nasal symptoms coinciding with placement in a daycare center might suggest recurrent infection rather than allergy. When patients present with a history of episodic acute symptoms, it is important to review the setting in which symptoms occur as well as the activities and exposures that immediately precede their onset. Symptoms associated with lawn mowing suggest allergy to grass pollen or fungi, whereas if symptoms occur in homes with pets, animal dander sensitivity is an obvious consideration. Reproducible reactions after ingestion of a specific food raise the possibility of food allergy. When symptoms wax and wane but evolve gradually and are more chronic in duration, a closer look at whether the timing and progression of symptoms correlate with exposure to a seasonal aeroallergen is warranted.

Aeroallergens, such as pollens and fungal spores, the concentrations of which in outdoor air fluctuate seasonally, are prominent causes of allergic disease. Correlating symptoms with seasonal pollination patterns of geographically relevant plants and trees along with information provided by local pollen counts can aid in identifying the allergen. Throughout most of the United States, trees pollinate in the early spring, grasses pollinate in the late spring and early summer, and

weeds pollinate in late summer through the fall. The presence of fungal spores in the atmosphere follows a seasonal pattern in the northern United States with spore counts rising with the onset of warmer weather and peaking in late summer months, only to recede again with the first frost through the winter. In warmer regions of the southern United States, fungal spores and grass pollens may cause symptoms on a perennial basis.

Rather than experiencing seasonal symptoms, some patients suffer allergic symptoms year-round. In these patients, sensitization to perennial allergens usually found indoors, such as dust mites, animal dander, cockroaches, and fungi, warrants consideration. Species of certain fungi, such as *Aspergillus* and *Penicillium,* are found indoors whereas *Alternaria* is found in both indoor and outdoor environments. Cockroach allergens are often problematic in inner city environments. Patients sensitive to perennial allergens often also become sensitized to seasonal allergens and experience baseline symptoms year-round with worsening during the pollen seasons.

The age of the patient is an important consideration in identifying potential allergens. Infants and young children are first sensitized to allergens that are in their environment on a continuous basis, such as dust mites, animal dander, and fungi. Sensitization to seasonal allergens usually takes several seasons of exposure to develop and is thus unlikely to be a significant trigger of symptoms in infants and toddlers.

Food allergies are more common in infants and young children, resulting primarily in cutaneous, gastrointestinal, and, less frequently, respiratory symptoms. Symptoms of immediate or immunoglobulin (Ig) E-mediated hypersensitivity food reactions develop within minutes to 2 hr after ingestion of the offending food. Symptoms of non–IgE-mediated food allergies are often delayed or chronic (see Chapter 151).

Complete information from previous evaluations and prior treatments for allergic disease should be reviewed, including impact of changes in local environment (e.g., home vs. school), response to medications, elimination diets, and duration and impact of allergen immunotherapy (if applicable). Improvement in symptoms with medications or avoidance strategies used to treat allergic disease provides additional evidence for an allergic process.

A thorough environmental survey should be performed, focusing on potential sources of allergen and/or irritant exposure, particularly when respiratory symptoms (upper and/or lower) are reported. The age and type of the dwelling, how it is heated and cooled, the use of humidifiers or air filtration units, and any history of water damage should be noted. Forced air heating may stir up dust mite, fungi, and animal allergens. The irritant effects of wood-burning stoves, fireplaces, and kerosene heaters may provoke respiratory symptoms. Increased humidity or water damage in the home is often associated with greater exposure to dust mites and fungi. Carpeting serves as a reservoir for dust mites, fungi, and animal dander. The number of domestic pets and their movements about the house should be ascertained. Special attention should be focused on the bedroom, where a child spends a significant proportion of time. The age and type of bedding, the number of stuffed animals, type of window treatments, and the accessibility of pets to the room should be reviewed. The number of smokers in the home and where they smoke is useful information. Activities that might result in exposure to allergens or respiratory irritants such as paint fumes, cleansers, sawdust, or glues should be identified. Similar information should be obtained in regard to other environments where the child spends large portions of time, such as a relative's home or school setting.

PHYSICAL EXAMINATION

In patients with **asthma,** spirometry should be performed. If respiratory distress is observed, pulse oximetry should be performed.

The child presenting with a chief complaint of rhinitis or rhinoconjunctivitis should be observed for mouth breathing, paroxysms of sneezing, sniffing/snorting, throat clearing, and rubbing of the nose and eyes (representing pruritus). Infants should be observed during feeding for nasal obstruction severe enough to interfere with feeding or for more obvious signs of aspiration or gastroesophageal reflux. The frequency and nature of coughing that occurs during the interview and any positional increase in coughing or wheezing should be noted. Children with asthma should be observed for congested or wet cough, tachypnea at rest, retractions, and audible wheezes, which may worsen with crying. Patients with atopic dermatitis should be monitored for repetitive scratching and the extent of skin involvement.

Because children with severe asthma as well as those receiving chronic or frequent oral corticosteroids may suffer growth suppression, an accurate height should be plotted at regular intervals. However, long-term follow-up studies suggest that use of inhaled glucocorticoids in prepubertal children is associated with a small initial decrease in attained height (~1 cm) that may persist as a reduction in adult height that is not progressive or cumulative. Poor weight gain in a child with chronic chest symptoms should prompt consideration of cystic fibrosis. Anthropometric measures are also important to monitor in those on restricted diets because of multiple food allergies or eosinophilic esophagitis. Blood pressure should be measured to evaluate for steroid-induced hypertension. The patient with acute asthma may present with **pulsus paradoxus,** defined as a drop in systolic blood pressure during inspiration >10 mm Hg. Moderate to severe airways obstruction is indicated by a decrease of >20 mm Hg. An increased heart rate may be the result of an asthma flare or the use of a β-agonist or decongestant. Fever is not caused by allergy alone and should prompt consideration of an infectious process, which may exacerbate asthma.

Parents are often concerned about blue-gray to purple discolorations beneath their child's lower eyelids, which can be attributed to venous stasis and are referred to as **allergic shiners.** They are found in up to 60% of allergic patients and almost 40% of patients *without* allergic disease. Thus, "shiners" may suggest, but are not diagnostic of, allergic disease. In contrast, the **Dennie-Morgan folds** (Dennie lines) are a feature of atopic dermatitis. These are prominent infraorbital skin folds that extend in an arc from the inner canthus beneath and parallel to the lower lid margin.

In patients with **allergic conjunctivitis,** involvement of the eyes is bilateral. Examination of the conjunctiva reveals varying degrees of lacrimation, conjunctival injection, and edema. In severe cases, periorbital edema involving primarily the lower eyelids or **chemosis** (conjunctival edema that is gelatinous in appearance) may be observed. The classic discharge associated with allergic conjunctivitis is usually described as "stringy" or "ropy." In children with vernal conjunctivitis, a more severe, chronic phenotype, examination of the tarsal conjunctiva may reveal cobblestoning. **Keratoconus,** or protrusion of the cornea, may occur in patients with vernal conjunctivitis or periorbital atopic dermatitis as a result of repeated trauma produced by persistent rubbing of the eyes. Children treated with high-dose or chronic corticosteroids are at risk for development of posterior subcapsular cataracts.

The external ear should be examined for eczematous changes in patients with atopic dermatitis, including the postauricular area and base of the earlobe. Because otitis media with effusion is common in children with allergic rhinitis, pneumatic otoscopy should be performed to evaluate for the presence of fluid in the middle ear and to exclude infection.

Examination of the nose in allergic patients may reveal the presence of a nasal crease. Nasal patency should be assessed, and the nose examined for structural abnormalities affecting nasal airflow, such as septal deviation, turbinate hypertrophy, and nasal polyps. Decrease or absence of the sense of smell should raise concern about chronic sinusitis or nasal polyps. Nasal polyps in children should raise concerns of cystic fibrosis. The nasal mucosa in allergic rhinitis is classically described as pale to purple in comparison with the beefy red mucosa of patients with nonallergic rhinitis. Allergic nasal secretions are typically thin and clear. Purulent secretions suggest another cause of rhinitis. The frontal and maxillary sinuses should be palpated to identify tenderness to pressure that might be associated with acute sinusitis.

Examination of the lips may reveal cheilitis caused by drying of the lips from continuous mouth breathing or repeated licking of the lips in an attempt to replenish moisture and relieve discomfort (**lip licker's dermatitis**). Tonsillar and adenoidal hypertrophy along with a history of impressive snoring raises the possibility of obstructive

sleep apnea. The posterior pharynx should be examined for the presence of postnasal drip and posterior pharyngeal lymphoid hyperplasia ("cobblestoning").

Chest findings in asthmatic children vary significantly and may depend on disease duration, severity, and activity. In a child with well-controlled asthma, the chest should appear entirely normal on examination between asthma exacerbations. Examination of the same child during an acute episode of asthma may reveal hyperinflation, tachypnea, use of accessory muscles, wheezing, and decreased air exchange with a prolonged expiratory time. Tachycardia may be caused by the asthma exacerbation or accompanied by jitteriness after treatment with β-agonists. Decreased airflow or rhonchi and wheezes over the right chest may be noted in children with mucus plugging and right middle lobe atelectasis. The presence of cyanosis indicates severe respiratory compromise. Unilateral wheezing after an episode of coughing and choking in a small child without a history of previous respiratory illness suggests **aspiration of a foreign body.** Wheezing limited to the larynx in association with inspiratory stridor may be seen in older children and adolescents with **vocal cord dysfunction.** Digital clubbing is rarely seen in patients with uncomplicated asthma and should prompt further evaluation to rule out other potential chronic diagnoses, such as cystic fibrosis.

The skin of the allergic patient should be examined for evidence of urticaria/angioedema or atopic dermatitis. **Xerosis,** or dry skin, is the most common skin abnormality of allergic children. **Keratosis pilaris**, often found on facial cheeks and extensor surfaces of the upper arms and thighs, is a benign condition characterized by skin-colored or slightly pink papules caused by keratin plugs lodged in the openings of hair follicles. Examination of the skin of the palms and soles may reveal thickened skin and exaggerated palmar and plantar creases (hyperlinearity) in children with moderate-to-severe atopic dermatitis.

DIAGNOSTIC TESTING

In Vitro Tests

Allergic diseases are often associated with increased numbers of eosinophils circulating in the peripheral blood and invading the tissues and secretions of target organs. Eosinophilia, defined as the presence of >500 eosinophils/μL in peripheral blood, is the most common hematologic abnormality of allergic patients. Seasonal increases in the number of circulating eosinophils may be observed in sensitized patients after exposure to allergens such as tree, grass, and weed pollens. The number of circulating eosinophils can be suppressed by certain infections and systemic corticosteroids. In certain pathologic conditions, such as drug reactions, eosinophilic pneumonias, and eosinophilic esophagitis, significantly increased numbers of eosinophils may be present in the target organ in the absence of peripheral blood eosinophilia. Increased numbers of eosinophils are observed in a wide variety of disorders in addition to allergy (Table 141-1; see Chapter 129). Eosinophil counts >1500 without an identifiable etiology should suggest 1 of the 2 hypereosinophilic syndromes (Table 141-1; see Chapter 129).

Nasal and bronchial secretions may be examined for the presence of eosinophils. The presence of eosinophils in the sputum of asthmatic patients is classic. An increased number of eosinophils in a smear of nasal mucus with Hansel stain is a more sensitive indicator of nasal allergies than peripheral blood eosinophilia and can aid in distinguishing allergic rhinitis from other causes of rhinitis. An elevated IgE value is often found in the serum of allergic patients, because IgE is the primary antibody associated with immediate hypersensitivity reactions. IgE values are measured in international units (IU), with 1 IU equal to 2.4 ng of IgE. Maternal IgE (unlike IgG) does not cross the placenta. Serum IgE levels gradually rise over the first years of life to peak in the teen years and decrease steadily thereafter. Additional factors, such as genetic influences, race, gender, certain diseases, and exposure to cigarette smoke and allergens, also affect serum IgE levels. Total serum IgE levels may increase 2- to 4-fold during and immediately after the pollen season and then gradually decline until the next pollen season. Comparison of total IgE levels among patients with allergic diseases reveals that those with atopic dermatitis tend to have the highest levels while patients with allergic asthma generally have higher levels than those with allergic rhinitis. Although average total IgE levels are higher in populations of allergic patients than in comparable populations without allergic disease, the overlap in levels is such

Table 141-1 Differential Diagnosis of Childhood Eosinophilia

PHYSIOLOGIC
Prematurity
Infants receiving hyperalimentation
Hereditary
INFECTIOUS
Parasitic (with tissue-invasive helminths, e.g., trichinosis, strongyloidiasis, pneumocystosis, filariasis, cysticercosis, cutaneous and visceral larva migrans, echinococcosis)
Bacterial (brucellosis, tularemia, cat-scratch disease, *Chlamydia*)
Fungal (histoplasmosis, blastomycosis, coccidioidomycosis, allergic bronchopulmonary aspergillosis)
Mycobacterial (tuberculosis, leprosy)
Viral (HIV-1, HTLV-1, hepatitis A, hepatitis B, hepatitis C, Epstein-Barr virus)
PULMONARY
Allergic (rhinitis, asthma)
Churg-Strauss syndrome
Loeffler syndrome
Hypersensitivity pneumonitis
Eosinophilic pneumonia (chronic, acute)
Pulmonary interstitial eosinophilia
DERMATOLOGIC
Atopic dermatitis
Pemphigus
Dermatitis herpetiformis
Infantile eosinophilic pustular folliculitis
Eosinophilic fasciitis (Schulman syndrome)
Eosinophilic cellulitis (Wells syndrome)
Kimura disease (angiolymphoid hyperplasia with eosinophilia)
HEMATOLOGIC/ONCOLOGIC
Neoplasm (lung, gastrointestinal, uterine)
Leukemia/lymphoma
Myelofibrosis
Myeloproliferative (FIP1L1-PDGFRA–positive) hypereosinophilic syndrome
Lymphatic hypereosinophilic syndrome
Systemic mastocytosis
IMMUNOLOGIC
T-cell immunodeficiencies
Hyperimmunoglobulin E (Job) syndrome
Wiskott-Aldrich syndrome
Graft-versus-host disease
Drug hypersensitivity
Postirradiation
Postsplenectomy
ENDOCRINE
Addison disease
Hypopituitarism
CARDIOVASCULAR
Loeffler disease (fibroplastic endocarditis)
Congenital heart disease
Hypersensitivity vasculitis
Eosinophilic myocarditis
GASTROINTESTINAL
Benign proctocolitis
Inflammatory bowel disease
Eosinophilic gastrointestinal diseases (EGID)

FIP1L1-PDGFRA, FIP1-like 1–platelet-derived growth factor receptor α.

that the diagnostic value of a total IgE level is poor. Approximately one-half of patients with allergic disease have total IgE levels in the normal range. However, measurement of total IgE is indicated when the diagnosis of **allergic bronchopulmonary aspergillosis** is suspected because total serum IgE concentration >1,000 ng/mL is a criterion for diagnosis of this disorder (see Chapter 237.1). Total serum IgE may also be elevated in several nonallergic diseases (Table 141-2; see Chapter 126).

The presence of IgE specific for a particular allergen can be documented in vivo by skin testing or in vitro by the measurement of **allergen-specific IgE (sIgE)** levels in the serum (Table 141-3). The first test for documenting the presence of sIgE was called the radioallergosorbent test because it used a radiolabeled anti-IgE antibody. The radioallergosorbent test has been replaced by an improved generation of automated enzymatic sIgE immunoassays. These assays use solid-phase supports to which allergens of an individual allergen extract are bound. A small amount of the patient's serum is incubated with the allergen-coated support. The allergen-coated support bound to the patient's sIgE is then incubated with enzyme-conjugated antihuman IgE. Incubation of this sIgE–antihuman IgE complex with a fluorescent substrate of the conjugated enzyme results in the generation of fluorescence that is proportional to the amount of sIgE in the serum sample. The amount of sIgE in the serum sample is calculated by interpolation from a standard calibration curve and reported in arbitrary mass units (kilo-IU of allergen-specific antibody per unit volume of sample [kU_A/L]). Laboratory reports may specify classes, counts, or units, but quantification of results in kU_A/L is most useful. There are 3 commercial detection systems approved by the U.S. Food and Drug Administration that have excellent performance characteristics, but the individual systems do not measure sIgE antibodies with comparable efficiencies and thus are not interchangeable. **Component testing** refers to emerging diagnostic tests where sIgE is measured to specific proteins that comprise allergens (e.g., Ara h 2 from peanut or Bet v 1 from birch pollen), rather than to a mixture of the allergens extracted from the source. Testing sIgE to component allergens may add additional diagnostic value by differentiating immune responses that are directed toward clinically relevant allergenic proteins.

Table 141-2 Nonallergic Diseases Associated with Increased Serum IgE Concentrations

PARASITIC INFESTATIONS
Ascariasis
Capillariasis
Echinococcosis
Fascioliasis
Filariasis
Hookworm
Onchocerciasis
Malaria
Paragonimiasis
Schistosomiasis
Strongyloidiasis
Trichinosis
Visceral larva migrans
INFECTIONS
Allergic bronchopulmonary aspergillosis
Candidiasis, systemic
Coccidioidomycosis
Cytomegalovirus mononucleosis
Human immunodeficiency virus type 1 infections
Infectious mononucleosis (Epstein-Barr virus)
Leprosy
Pertussis
Viral respiratory infections
IMMUNODEFICIENCY
Autosomal dominant hyperimmunoglobulin E syndrome (*STAT3* mutations)
Autosomal recessive hyperimmunoglobulin E syndrome (*DOCK8, TYK2* mutations)
IgA deficiency, selective
Nezelof syndrome (cellular immunodeficiency with immunoglobulins)
Thymic hypoplasia (DiGeorge anomaly)
Wiskott-Aldrich syndrome
NEOPLASTIC DISEASES
Hodgkin disease
IgE myeloma
Bronchial carcinoma
OTHER DISEASES AND DISORDERS
Alopecia areata
Bone marrow transplantation
Burns
Cystic fibrosis
Dermatitis, chronic acral
Erythema nodosum, streptococcal infection
Guillain-Barré syndrome
Kawasaki disease
Liver disease
Medications
Nephritis, drug-induced interstitial
Nephrotic syndrome
Pemphigus, bullous
Polyarteritis nodosa, infantile
Primary pulmonary hemosiderosis
Rheumatoid arthritis

In Vivo Tests

Allergen skin testing is the primary in vivo procedure for the diagnosis of allergic disease. Mast cells with sIgE antibodies attached to high-affinity receptors on their surfaces reside in the skin of allergic patients. The introduction of minute amounts of an allergen into the skin of the sensitized patient results in cross-linking of IgE antibodies on the mast cell surface, thereby triggering local mast cell activation. Once activated, these mast cells release a variety of preformed and newly generated mediators that act on surrounding tissues. Histamine is the mediator most responsible for the immediate wheal and flare reactions observed in skin testing. Examination of the site of a positive skin test result reveals a pruritic wheal surrounded by erythema. The time course of these reactions is rapid in onset, reaching a peak within 10-20 min and usually resolving over the next 30 min.

Skin testing is performed using the **prick/puncture technique.** With this technique, a small drop of allergen is applied to the skin surface, and a tiny amount is introduced into the epidermis by lightly pricking or puncturing the outer layer of skin through the drop of extract with a small needle or other device. When the **skin prick test**

Table 141-3 Determination of Specific IgE by Skin Testing Versus In Vitro Testing

VARIABLE	SKIN TEST*	sIgE ASSAY
Risk of allergic reaction	Yes (especially ID)	No
Relative sensitivity	High	High
Affected by antihistamines	Yes	No
Affected by corticosteroids	Usually not	No
Affected by extensive dermatitis or dermographism	Yes	No
Broad selection of antigens	Fewer	Yes
Immediate results	Yes	No
Expensive	No	Yes
Lability of allergens	Yes	No
Results evident to patient	Yes	No

*Skin testing may be the prick test or intradermal (ID) injection.

(SPT) result is negative but the history suggestive, selective skin testing (for vaccines, venom, drugs, and aeroallergens) using the **intradermal technique** may be performed. This technique involves using a 26-gauge needle to inject 0.01-0.02 mL of an allergen extract diluted 1,000- to 100-fold into the dermis of the arm. Intradermal skin tests are *not recommended for use with food allergens* because of the risk of triggering anaphylaxis. Irritant rather than allergic reactions can occur with intradermal skin testing if higher concentrations of extracts are used. Although skin prick testing is less sensitive than intradermal skin testing, positive SPT results tend to correlate better with clinical symptoms.

The number of skin tests performed should be individualized, with the allergens suggested by the history taken into account. A positive and negative control SPT, using histamine and saline, respectively, is performed with each set of skin tests. A negative control is necessary to assess for dermatographism, in which reactions are caused merely by applying pressure to overly sensitive skin. A positive control is necessary to establish the presence of a cutaneous response to histamine. Medications with antihistaminic properties in addition to adrenergic agents such as ephedrine and epinephrine suppress skin test responses and should be avoided for appropriate intervals (≈5 half-lives) prior to skin testing. Prolonged courses of systemic corticosteroids may suppress cutaneous reactivity by decreasing the number of tissue mast cells as well as their ability to release mediators.

Whether identified via serologic or skin testing, detection of sIgE denotes a sensitized state (i.e., atopy or a tendency toward development of allergic disease) but is not equivalent to a clinically relevant allergic diagnosis. *Many children with positive tests have no clinical symptoms upon exposure to the allergen*. Increasingly strong tests (higher serum sIgE results or larger SPT wheal sizes) generally correlate with increasing likelihood of clinical reactivity (but not severity). The limitations of these test modalities underscore the need for the clinician to obtain a detailed medical history that can guide the selection and interpretation of test results. Large panels of indiscriminately performed screening tests may, therefore, provide misleading information.

Both serum sIgE tests and SPT are sensitive and have similar diagnostic properties. The benefits of the serologic immunoassays are that performance is not limited by presence of skin disease (i.e., active atopic dermatitis) or medication use (i.e., antihistamines). Advantages of skin testing are that they provide rapid results to the patient/family during the clinic visit, do not require venipuncture, and are less costly.

Under certain circumstances, **provocation testing** is performed to examine the association between allergen exposure and the development of symptoms. The bronchial provocation test most frequently performed clinically is the methacholine challenge, which causes potent bronchoconstriction of asthmatic but not of normal airways. **Methacholine challenge testing** is performed to document the presence and degree of bronchial hyperreactivity in a patient in whom asthma is suspected. After baseline spirometry values are obtained, increasing concentrations of nebulized methacholine are inhaled until a drop occurs in lung function, specifically a 20% decrease in FEV_1 (forced expiratory volume in the first second of expiration), or the patient is able to tolerate the inhalation of a set concentration of methacholine, typically 25 mg/mL.

Oral **food challenges** are performed to determine whether a specific food causes symptoms or whether a suspected food can be added to the diet. Food challenges are performed for those foods incriminated by the history and results of skin tests and/or immunoassays for sIgE. These challenges may be performed in an open, single-blind, double-blind, or double-blind placebo-controlled fashion and involve the ingestion of gradually increasing amounts of the suspected food at set time intervals until the patient either experiences a reaction or tolerates a normal portion (i.e., 1 serving size) of the food openly. Because of the potential for significant allergic reactions, these challenges should be performed only in an appropriately equipped facility with personnel experienced in the performance of food challenges and the treatment of anaphylaxis, including cardiopulmonary resuscitation.

Upper gastrointestinal **endoscopy** is required to confirm the diagnosis of eosinophilic esophagitis. One or more biopsy specimens from the proximal and distal esophagus must show eosinophil-predominant inflammation. With few exceptions, 15 eosinophils/hpf (high power field) (peak value) is considered a minimum threshold for the diagnosis.

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Chapter 142

Principles of Treatment of Allergic Disease

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The basic principles of the treatment of allergic disease include the avoidance of exposure to allergens and irritants that trigger symptoms and the pharmacologic management of symptoms caused by unavoidable acute and chronic allergen exposures. In selected patients, allergen immunotherapy may be considered.

ENVIRONMENTAL CONTROL MEASURES

Children spend the majority of their time in indoor environments, including the home. In an effort to save energy, houses and buildings have been built more tightly and with more insulation with limited air exchange. These factors have led to an increase in indoor humidity and higher concentrations of allergens and irritants. Examination of indoor environments suggests that house dust mite, cat, and cockroach allergens are the most common significant triggers of allergic disease in these settings; exposures to allergens from other pets, pests, mold, and respiratory irritants such as cigarette smoke are also a problem.

More than 30,000 species of mites have been identified, but the term *dust mites* usually refers to the pyroglyphid mites *Dermatophagoides pteronyssinus, Dermatophagoides farinae,* and *Euroglyphus maynei,* which are the major sources of allergen in house dust. Respiration and water vapor exchange occur through the skin of dust mites, rendering them sensitive to humidity and temperature extremes. The regular use of humidifiers promotes dust mite survival. Mites do not survive with relative humidity <50%. They feed on animal and human skin scales and other debris, which is why they exist in large numbers in mattresses and bedding, carpet, and upholstered furniture. They may also be found in flour and mixes for baked goods. Anaphylaxis has been reported following the ingestion of baked goods, such as waffles and pancakes, prepared with flour infested with dust mites ("pancake syndrome"). Dust mite fecal pellets are a major source of allergens. They consist of partially digested food combined with digestive enzymes encased in a permeable membrane, which keeps the fecal pellets intact. These fecal pellets have been likened to pollen grains, given their similarities in size (10-40 μm), the amount of allergen they contain, and their ability to release allergens rapidly on contact with moist mucous membranes. Mites can persist in imported furnishings for at least 2 yr; mite allergens have been shown to remain stable under domestic conditions for periods of at least 4 yr. Dust mite allergens become airborne during normal household activities; a vigorous disturbance, such as vacuuming without a vacuum bag, shaking a bed sheet, or a pillow fight, can launch significant amounts of dust mite allergens into the air. Once airborne, dust mite allergen particles settle out of the air relatively rapidly because of their size and weight. Nonetheless, dust mite allergen exposure likely occurs during sleep on mite-infested pillows and mattresses and during normal household activities when dust mite concentrations in the home are high. Levels of dust mite allergens as

Table 142-1 Environmental Control of Allergen Exposure

ALLERGEN	CONTROL MEASURES
Dust mites	Encase bedding in airtight, allergen-impermeable covers Wash bedding weekly in water at temperatures >54.4°C (130°F) Remove wall-to-wall carpeting Replace curtains with blinds Remove upholstered furniture Reduce indoor humidity Minimize bedroom and living room clutter
Animal dander	Avoid furred pets Keep animals out of patient's bedroom
Cockroaches	Control available food and water sources Keep kitchen/bathroom surfaces dry and free of standing water Seal cracks in walls Use professional extermination services; safe pesticide should be used in baits
Mold	Repair moisture-prone areas Avoid high humidity in patient's bedroom Use high-efficiency particulate air (HEPA) filters in living areas Repair water leaks Replace carpets with hardwood floors Regularly check basements, attics, and crawl spaces for standing water and mold
Pollen	Keep automobile and house windows closed Control timing of outdoor exposure Restrict camping, hiking, and leaf raking Drive in an air-conditioned automobile Air-condition the home Install portable HEPA filters

Modified from Leung DYM, Sampson HA, Geha RS, et al: Pediatric allergy principles and practice, *St. Louis, 2010, Mosby, p. 297.*

low as 2 μg/g of house dust can lead to sensitization, whereas levels of 10 μg/g of house dust are associated with symptoms.

Appropriate environmental control measures can significantly reduce exposure to dust mite allergens (Table 142-1). Major emphasis should be placed on reducing exposure to dust mite allergens in the bedroom and living areas in which the child spends a large amount of time. Encasements impermeable to dust mite allergens should be placed on all pillows, the mattress, and the box spring. Dust should be removed from the surfaces of these covers and the bed frame by vacuuming weekly. The sheets and mattress pad should be washed weekly in hot water at a temperature of >54.4°C (130°F). Minimizing the number of items in the room that collect dust, such as books, drapes, toys, stuffed animals, and any clutter, is recommended. Major reservoirs of dust mite allergen that are often more difficult to deal with include the carpet and upholstered furniture, which should be vacuumed weekly with an efficient double-thickness-bagged vacuum cleaner. The actual benefit of applying acaricides or denaturing agents to carpets and upholstered furniture remains unclear, and the amount of effort required may be more than most families are willing to invest. If possible, carpet removal, at least in the bedroom, may prove a better choice for eliminating a large reservoir of dust mite allergen. Other measures for dust mite allergen control include maintaining the indoor relative humidity at <50% and keeping the air conditioning set at the lowest level during the warmer months.

In many countries, more than half of the households have pets, the most common of which are cats and dogs. The major sources of allergens from cats, dogs, and horses are hair, dander, and saliva, whereas the major source of allergens from rodents is urine. Studies of airborne cat allergen have shown that a significant portion is found on small particles. As much as 30% of airborne cat allergen may reside on particles <5 μm. Particles this small may not be adequately filtered by the nose and could potentially be deposited in the airways. Their small size enables these particles to remain airborne for longer periods and to be suspended repeatedly by air currents from heating and ventilation systems or just by walking across the carpet or sitting in an upholstered chair. **Fel d 1,** the major cat allergen, is a highly charged protein that readily sticks to a variety of surfaces, including walls, carpeting, and upholstered furniture. Owing to this adhesiveness, cat allergens bind to the cat owner's clothing and are routinely transported to public buildings, including schools, where they have been measured in moderately high amounts. From these sites, significant amounts of cat allergen can subsequently be carried into homes without cats. Analysis of house dust from homes with cats reveals levels of Fel d 1 ranging from 8 μg to 1.5 mg/g of house dust. Levels of Fel d 1 in homes without cats vary from 0.2 to 80 μg/g of house dust. Sensitization to cat allergen is associated with levels ranging from 1 to 8 μg/g of house dust. Carpets, upholstered furniture, and bedding serve as reservoirs of cat allergens, resulting in the persistence of significant amounts in the home for months after a cat has been removed. Complete avoidance of cat allergen is virtually impossible, although significant reduction in exposure to cat allergens is achievable.

Removing the pet from the home is obviously the most effective means of reducing exposure to animal allergens, although it has been demonstrated that without other interventions, such as removing carpeting and upholstered furniture and wiping down walls, it takes 6 mo or more for the levels of cat allergen to drop to a level found in houses without a cat. As a result, cat owners who remove their pets from their homes should be informed not to expect immediate results. Unfortunately, advice to remove a pet from the home or keep it outdoors is often ignored. In contrast to dust mite allergens, cat allergen is light and remains suspended in the air for long periods. As a result, **air cleaners with high-efficiency particulate air (HEPA) filters** are helpful in reducing the amount of airborne cat allergen. Other suggested methods include washing the cat regularly and maintaining a cat allergen–free bedroom from which the cat is excluded and where mattress covers and air-filtering devices are used. The cat should also be restricted from other living areas where the sensitized child spends large amounts of time, such as the family room and other play areas (see Table 142-1). Regular vacuuming with a HEPA-filtered and double-thickness bag vacuum cleaner is also encouraged. Similar measures are suggested for the control of exposure to other animal allergens, although whether these measures reduce exposure to levels resulting in clinical improvement as demonstrated by decreased symptoms, improved peak flows, or decreases in bronchial hyperreactivity remains to be documented by appropriately controlled studies.

Infestation of the home by insects and other pests, such as mice and rats, is another potential source of significant indoor allergen exposure. Studies have identified exposure to cockroach allergens as a major risk factor for the development of asthma in inner-city children. Once sensitized, inner-city cockroach-sensitive asthmatic children with continued exposure to high levels of cockroach allergens in their bedrooms are at higher risk for urgent care visits and hospitalization than are inner-city asthmatic children who are not allergic to cockroaches. Recommended methods to decrease cockroach allergen exposure include reducing cockroaches' access to the home by sealing cracks in the flooring and walls and removing sources of food and water by repairing leaky pipes, putting away food in sealed containers, and frequent cleaning (see Table 142-1). Regular extermination using baits or chemical treatment of infested areas is also advised.

Efforts to improve indoor air quality should also encompass reducing exposure to respiratory irritants. Passive exposure to environmental tobacco smoke worsens asthma and increases nasal symptoms in patients with allergic nasal disease. Smoking cessation should be repeatedly encouraged, and smoking indoors should never be permitted. The use of wood-burning stoves, fireplaces, and kerosene heaters should also be discouraged.

Although exposure to pollens and molds occurs primarily outdoors, these allergens are detectable indoors during the warmer months,

when their indoor levels often reflect their prevalence in the outdoor environment. During the winter, when the outdoor levels of other molds are lowest, the indoor molds *Aspergillus* and *Penicillium* are the most prevalent. Molds are often found in damp basements and thrive in conditions associated with increased moisture in the home, such as water leaks, flooding, and increased humidity promoted by the excessive use of humidifiers or swamp coolers. Exposure to indoor mold allergens can be reduced by maintaining the indoor relative humidity at <50%, removing contaminated carpets, and wiping down washable surfaces prone to fungal growth, such as shower stalls, shower curtains, sinks, drip trays, and garbage pails, with the use of solutions of detergent and 5% bleach (see Table 142-1). Dehumidifiers should be placed in damp basements. Standing water at any site in the home should be eliminated, and the cause addressed. Removing all items from the home that are prone to mold contamination is also encouraged. Keeping the windows and doors closed and using air conditioning to filter outdoor air can keep both indoor pollen and mold levels to a minimum during the warmer months, when outdoor levels of these allergens are at their peak. The use of window or attic fans is to be avoided. Laundry should be dried in a dryer rather than on a clothesline. Measures to avoid pollens and mold spores when out of the house include closing the windows and using the air conditioner when traveling in the car, avoiding moldy vegetation, and wearing a mask when these materials cannot be avoided. Outdoor activities during periods of high pollen counts should be kept to a minimum. Pollen travels best on warm, dry, breezy days but counts are lowest during chilly, wet periods. Someone other than the sensitized patient should mow the lawn and rake leaves. Hand washing after outdoor play is suggested to avoid transferring pollens from the hands to the eyes and nose. At the end of the day, showering and shampooing are suggested to avoid contamination of the bed with allergens.

PHARMACOLOGIC THERAPY

Adrenergic Agents

Adrenergic agents exert their effects through the stimulation of cell surface α- and β-adrenergic receptors in a variety of target tissues. In general, α-adrenergic receptor stimulation results in excitatory responses such as vasoconstriction, whereas β-adrenergic stimulation leads to inhibitory responses such as bronchodilation. The α-adrenergic receptors have been classified into α_1- and α_2-adrenergic receptors. There are 3 subtypes of α_1-adrenergic receptors and 3 subtypes of α_2-adrenergic receptors. The β-adrenergic receptors are further divided into 3 subtypes: β_1, β_2, and β_3. Each of these adrenergic receptors exhibits a distinctive tissue distribution. The physiologic response in a given tissue to the administration of an adrenergic agent depends on the specific receptor-binding characteristics of the drug as well as the numbers and distribution of the various types of adrenergic receptors in the tissue. Epinephrine remains the drug of choice for the treatment of anaphylaxis because of its combined α- and β-adrenergic effects. Epinephrine autoinjectors are prescribed for ease of administration and are available in 2 dosages: 0.15 mg for children who weigh <30 kg, and 0.30 mg for children who weigh ≥30 kg, according to manufacturer recommendations. Consider prescribing the 0.15 mg dose for children who weigh ≥25 kg to avoid under-dosing.

The α-adrenergic agents are effective in the treatment of allergic nasal disease because of their decongestant effects (see Tables 143-4 and 143-5). In the nose, stimulation of α_1-adrenergic receptors on postcapillary venules and of α_2-adrenergic receptors on precapillary arterioles leads to vasoconstriction, resulting in a reduction in nasal congestion. The oral decongestants currently in clinical use include pseudoephedrine and phenylephrine. These medications are available individually or in combination with antihistamines in liquid and tablet forms, including sustained-release preparations. Pseudoephedrine is rapidly and thoroughly absorbed, whereas phenylephrine, the less effective of the 2 drugs, is incompletely absorbed, resulting in a significantly lower bioavailability of ≈38%. Peak plasma concentrations of these drugs are reached between 30 min and 2 hr of administration, but the decongestant effect has not been directly correlated to the plasma concentration. Pseudoephedrine is excreted essentially unchanged by the kidney. The use of oral decongestants should be avoided in patients <6 yr of age and in patients with hypertension, coronary artery disease, glaucoma, or metabolic disorders, such as diabetes and hyperthyroidism. Reported **adverse effects** of oral decongestants include excitability, headache, nervousness, palpitations, tachycardia, arrhythmias, hypertension, nausea, vomiting, and urinary retention. Decongestants available as topical nasal sprays include phenylephrine, oxymetazoline, naphthazoline, tetrahydrozoline, and xylometazoline. Given their efficacy and rapid onset of action, the potential for excessive use of topical nasal decongestants resulting in rebound nasal congestion (rhinitis medicamentosa) is high and patients should be carefully counseled to prevent dependency on the product. Thus, limiting the use of these sprays to 2-3 days is generally recommended.

Drugs that stimulate β-adrenergic receptors have been used for years in the treatment of asthma because of their potent bronchodilator effects (see Table 144-16). The subclassification of β-adrenergic receptors into β_1 and β_2 subtypes led to the development of drugs selective for the β_2-adrenergic receptor, such as albuterol, levalbuterol, and pirbuterol, that have the advantage of producing significant bronchodilation with less cardiac stimulation. *The long-acting inhaled β_2-adrenergic agonists (LABAs) salmeterol and formoterol,* with a 12-hr duration of action, are approved for use in children ≥4 yr of age. LABAs are not recommended for the treatment of acute asthma exacerbations because of their relatively slow onset of action. Concern about an increased risk of asthma-related adverse events is why LABAs are not recommended as monotherapy for the long-term control of persistent asthma, but are promoted as best used in conjunction with an inhaled steroid. Dry powder inhaled and metered-dose inhaler preparations combining a *LABA with an inhaled corticosteroid have had significant impact on treatment of moderate persistent asthma.* In addition to their bronchodilating effects, β_2-adrenergic agonists have been reported to improve mucociliary clearance, decrease microvascular permeability, inhibit cholinergic nerve transmission, and reduce mediator release in mast cells, basophils, and eosinophils. Although β-adrenergic agonists can be delivered orally, by inhalation, or by injection, the inhaled route is preferred because of the rapid onset of action and fewer adverse effects. Reported **adverse effects** of β-adrenergic agents include tremor, palpitations, tachycardia, arrhythmias, central nervous system stimulation, hyperglycemia, hypokalemia, hypomagnesemia, and a transient increase in hypoxia, which is attributed to an increase in perfusion to inadequately ventilated areas of the asthmatic lung.

Anticholinergic Agents

Anticholinergic drugs inhibit vagally mediated reflexes by antagonizing the action of acetylcholine at muscarinic receptors. Of the available anticholinergic agents, **ipratropium bromide** is the most commonly used. It is a quaternary amine that is poorly absorbed across mucosal surfaces and does not readily cross the blood–brain barrier. As a bronchodilator, it has a slower onset of action than short-acting inhaled β_2-agonists and takes longer to reach maximal effect, making it less effective as a rescue medication. There is increasing support, particularly in children, for combination therapy using ipratropium bromide and β-agonist therapy in more severe asthma exacerbations. Multiple doses of combined therapy can decrease risk of hospitalization in children by 25%. Ipratropium is available by prescription as a metered-dose inhaler delivering 17 μg/spray and as a 0.02% nebulized solution (500 μg/2.5 mL).

Ipratropium given as a nasal spray (0.03-0.06%) is effective in the reduction of rhinorrhea resulting from perennial nonallergic rhinitis, the common cold, and vasomotor rhinitis. The use of ipratropium is suboptimal in the treatment of moderate to severe allergic rhinitis because it does not alter other common allergic nasal symptoms, such as sneezing, nasal congestion, and pruritus. Nasal dryness and epistaxis are occasionally encountered with use of the nasal spray.

Antihistamines

The release of histamine and its effects on surrounding tissues is central to the development of symptoms classically associated with the allergic response. Histamine exerts its effects through binding with 1 of its 4

receptors, as H_1-, H_2-, H_3-, or H_4-receptor. Histamine effects triggered through H_1-receptor binding are those most relevant to allergic inflammation, and include pain, pruritus, vasodilation, increased vascular permeability, smooth muscle contraction, mucus production, and the stimulation of parasympathetic nerve endings and reflexes. The antimuscarinic effect of some of the early H_1-type antihistamines may be explained by the reported 45% homology of the H_1-receptor with the human muscarinic receptor. The H_1-type antihistamines prevent the effects of H_1-receptor activation through reversible, competitive inhibition of histamine by binding to the H_1-receptor. Antihistamines work best in preventing rather than reversing the actions of histamine and are most effective when given at doses and dosing intervals resulting in the persistent saturation of target organ tissue histamine receptors.

The H_1-type antihistamines are traditionally divided into 6 classes on the basis of differences in their chemical structures (Tables 142-2 and 143-3). These antihistamines are further divided into first-generation antihistamines, which, because of their lipophilicity, cross the blood–brain barrier to exert effects on the central nervous system, and second-generation antihistamines, which exert minimal, if any, central nervous system effects because of their inability to cross the blood-brain barrier owing to their size, charge, and lipophilicity. The sedative effects and cognitive impairment associated with the use of first-generation antihistamines are well documented. Thus, a primary advantage of second-generation antihistamines is that they are nonsedating or much less sedating than first-generation antihistamines. Although fexofenadine is considered the least sedating of the available nonprescription antihistamines (0% occupation of central nervous system H_1-receptors), cetirizine has the most potential for sedation (26-30%). Both first- and second-generation antihistamines are available in oral preparations. Many first-generation and second-generation antihistamines are available in nonprescription form, including diphenhydramine, loratadine, fexofenadine, and cetirizine. Other antihistamines require a prescription, such as hydroxyzine and cyproheptadine. Antihistamines available as an intranasal spray are azelastine and olopatadine, the latter also functioning as a mast cell stabilizer. The benefit of this form of administration is the potential for a rapid onset of action, within 15 min. Azelastine, which is systemically absorbed and can cross the blood–brain barrier, has the potential for central nervous system effects in some patients and is not currently approved for use in children <12 yr of age. Patients often experience a bitter metallic taste in their mouths when using azelastine, which is a common reason for nonadherence.

Orally administered antihistamines are well absorbed and reach peak serum concentrations within ~2 hr. High tissue concentrations of antihistamines are usually achieved, likely accounting for the sustained suppression of wheal and flare reactions even after serum levels have significantly declined. Most antihistamines are metabolized by the hepatic cytochrome P450 enzyme system. Elimination of antihistamines may be reduced in patients with hepatic impairment or by the simultaneous ingestion of inhibitors of this pathway, such as erythromycin and other macrolide antibiotics, ciprofloxacin, ketoconazole, itraconazole, and certain antidepressants, such as nefazodone and fluvoxamine. Some antihistamines, such as hydroxyzine and loratadine, are converted to clinically active metabolites. Clearance of fexofenadine and cetirizine is reduced in patients with impaired renal function. Cetirizine clearance is also reduced in patients with hepatic dysfunction. Fruit juices (apple, orange, grapefruit) are organic anion transporter inhibitors and interfere with the absorption of fexofenadine: juices should be avoided 4 hr before or 1-2 hr after taking fexofenadine.

Table 142-2 Classification of Antihistamines (H_1-Antagonists)

CLASS	EXAMPLES
ETHYLENEDIAMINES	
First-generation	Antazoline, pyrilamine, tripelennamine
TYPE II ETHANOLAMINES	
First-generation	Carbinoxamine, clemastine, diphenhydramine
TYPE III ALKYLAMINES	
First-generation	Brompheniramine, chlorpheniramine, triprolidine
Second-generation	Acrivastine
TYPE IV PIPERAZINES	
First-generation	Cyclizine, hydroxyzine, meclizine
Second-generation	Cetirizine, levocetirizine
TYPE V PIPERIDINES	
First-generation	Azatadine, cyproheptadine, ketotifen
Second-generation	Fexofenadine, loratadine, desloratadine
TYPE VI PHENOTHIAZINES	
First-generation	Methdilazine, promethazine

The efficacy of antihistamines in the treatment of seasonal and perennial allergic rhinoconjunctivitis is well documented (see Chapter 143). Compared with other medications in regard to the relief of allergic nasal symptoms, antihistamines are more effective than cromolyn sodium, but significantly less effective than intranasal corticosteroids. Improvement in symptom relief in patients with allergic rhinitis has been reported when an antihistamine is given in combination with a decongestant or with an intranasal steroid. Numerous formulations combining antihistamines and decongestants are available. Antihistamines have also been shown to be beneficial in the treatment of acute and chronic urticaria/angioedema. With regard to asthma, a significant clinical effect of antihistamines at conventional doses is difficult to document, other than the possible improvement offered by better control of allergic nasal symptoms.

Second-generation antihistamines are preferable over first-generation antihistamines for the treatment of allergic disease in children because of negligible sedative and anticholinergic effects without a sacrifice in efficacy. Most second-generation antihistamines are effective with convenient once-daily dosing, which may improve therapy adherence. The widespread availability of first-generation antihistamines and their lower cost account for their continued use. The **adverse effects** most often encountered with second-generation agents include the performance impairment and anticholinergic effects noted with first-generation antihistamines although generally to a lesser degree. The anticholinergic adverse effects encountered may include drying of the mouth and eyes, urinary retention, constipation, excitation, nervousness, palpitations, and tachycardia. Prolongation of the QT interval and ventricular tachycardia (torsades de pointes) has been noted in older no longer available second-generation antihistamines; current antihistamines are not associated with concerning cardiac effects.

Chromones

Cromolyn sodium and nedocromil sodium are the 2 chromones used to treat allergic disorders. Neither cromolyn nor nedocromil is absorbed well orally, with only 1% of the swallowed dose absorbed. These drugs must be applied topically to the mucosal surface of the target organ to be effective. Both drugs inhibit mast cell degranulation and mediator release. They suppress the activation of a variety of cells, such as eosinophils, neutrophils, macrophages, and epithelial cells. They also suppress the activity of afferent C-type sensory nerve fibers of the nonadrenergic, noncholinergic nervous system. Both drugs inhibit the intracellular increase in free calcium after mast cell activation and phosphorylate a mast cell protein resembling moesin, which is thought to be involved in terminating mediator release.

Cromolyn and nedocromil prevent early- and late-phase allergic responses when administered before allergen exposure. They block allergen-induced increases in bronchial hyperresponsiveness, as well as seasonal increases in nonspecific bronchial hyperresponsiveness. With prolonged use, both drugs are capable of reducing bronchial hyperresponsiveness. These drugs have no bronchodilator properties but can inhibit the bronchoconstrictive effects of a variety of stimuli, such as allergen challenge, exercise, hyperventilation with cold air,

ultrasonically nebulized distilled water, and exposure to atmospheric and industrial pollutants.

Cromolyn and nedocromil are used as alternative, but not preferred, therapy for the treatment of mild persistent asthma. Because of their lack of bronchodilator properties, neither drug is useful for the treatment of acute asthma, although both may be used as preventive treatment before vigorous exercise or unavoidable known allergen exposure. Nedocromil is the more potent of the two, but no formulation of nedocromil is currently available for asthma in the United States. Cromolyn is available for the treatment of asthma by prescription as a 1% solution (20 mg/2 mL) for nebulization. The suggested dose for the treatment of asthma is 20 mg of cromolyn 2-4 times/24 hr by nebulization. In numerous studies, cromolyn has been found useful in the treatment of allergic rhinitis and allergic conjunctivitis. Preparations for the nasal and ocular administration of cromolyn are available without a prescription. The suggested dose for the treatment of allergic rhinitis is one spray in each nostril 3 to 4 times daily of a nasal spray containing 5.2 mg of cromolyn per spray (see Table 143-5). For the treatment of allergic conjunctivitis, the suggested dose is 1 drop in each eye 4-6 times a day of a 4% ophthalmic solution. A 2% solution of nedocromil is available by prescription for the treatment of allergic conjunctivitis at a suggested dose of 1-2 drops in each eye twice daily.

The safety of these drugs, even with prolonged administration, is well documented. Because of their favorable safety profile, the chromones are often chosen for use during pregnancy.

Glucocorticoids

Glucocorticoids are widely used in the treatment of allergic disorders because of their potent antiinflammatory properties. The diverse antiinflammatory actions of glucocorticoids are mediated via the glucocorticoid receptor, which is present in all inflammatory effector cells, as well as by direct inhibition of cytokines and mediators. Glucocorticoids are administered topically in ophthalmic preparations, nasal sprays, creams and ointments, metered-dose inhalers, and as a solution for nebulization. Systemic administration is accomplished orally or parenterally. The proper use and efficacy of glucocorticoids in the treatment of allergic disease along with the adverse effects associated with their use are presented in discussions of individual allergic diseases (see Chapters 142-152).

Leukotriene-Modifying Agents

Drugs that alter the leukotriene pathway exert their clinical effects either by inhibiting leukotriene production or by blocking receptor binding. These agents possess mild antiinflammatory properties and exhibit bronchodilator effects. In addition to inhibiting the early- and late-phase allergic responses to inhaled allergen, they diminish bronchoconstriction induced by exercise and exposure to allergen, aspirin, and cold air. Leukotriene-modifying agents have some use in the treatment of asthma (see Chapter 144) and are modestly effective in the treatment of allergic rhinitis (see Chapter 143).

Theophylline

Because of its bronchodilating effects, theophylline (1,3-dimethylxanthine) had been used for yr for the treatment of acute and chronic asthma. The bronchodilator effect of theophylline is likely caused by its action as a phosphodiesterase inhibitor, whereas its ability to antagonize adenosine receptors may play a role in other effects, such as the attenuation of diaphragmatic muscle fatigue and diminishing adenosine-enhanced mast cell mediator release. Theophylline inhibits the immediate- and late-phase pulmonary responses to allergen challenge and exhibits modest protective effects. The therapeutic and toxic effects of theophylline are related to the serum concentration, with the incidence of toxic effects significantly increasing as the serum levels approach and exceed 20 μg/mL. A variety of conditions and medications are capable of increasing or decreasing theophylline metabolism. The **toxic effects** of theophylline, ranging from mild nausea, insomnia, irritability, tremors, and headache to cardiac arrhythmias, seizures, and death, necessitate the routine monitoring of theophylline serum levels. Because of the introduction of other effective therapies for the treatment of acute and chronic asthma, the need to monitor drug serum levels routinely, and the potential for significant toxicity, the role of theophylline in the treatment of asthma has contracted significantly (see Chapter 144).

Lodoxamide Tromethamine

A mast cell stabilizer, lodoxamide tromethamine is more effective than topical cromolyn sodium in alleviating signs and symptoms of allergic ocular disease (see Chapter 147). It is used in children >2 yr of age for vernal keratoconjunctivitis, vernal conjunctivitis, and vernal keratitis. Occasional adverse effects have included transient burning or stinging after instillation.

Combination Mast Cell Stabilizer and Antihistamine

Olopatadine, epinastine, and ketotifen are examples of combination mast cell stabilizers and H_1-receptor antagonists effective in relieving signs and symptoms of allergic conjunctivitis after topical instillation, although all H_1-antihistamines likely have some mast cell stabilizing activity. Dosing is typically twice per day, except of olopatadine, which is dosed once daily.

Antiimmunoglobulin E

Monoclonal antiimmunoglobulin E antibodies (anti-IgE) bind to circulating IgE at a site that prevents its subsequent attachment to the high-affinity receptors for IgE on the mast cell surface. The parenteral administration of anti-IgE reduces free serum IgE concentrations, inhibits skin test responses in allergic patients, suppresses early- and late-phase responses to allergens, and decreases sputum eosinophilia in asthmatic persons. Anti-IgE has a beneficial effect in the treatment of patients with asthma, allergic rhinitis, and urticaria. An anti-IgE preparation **(omalizumab)** is available for the treatment of children ≥12 yr of age with documented allergen-induced asthma that is inadequately controlled by inhaled corticosteroids. Although this agent is usually well tolerated, local reactions at the injection site and rare episodes of anaphylaxis have been reported. Anti-IgE may also be beneficial in the treatment of other allergic disorders, such as anaphylaxis and food allergy, but more studies are needed. One monoclonal antibody preparation of anti-IgE used in the treatment of adults with peanut allergy resulted in a significant increase in the symptom threshold dose of peanuts. The cost of anti-IgE therapy and need for regular injections requires careful patient selection, special consideration being given to those patients with persistent symptoms despite aggressive pharmacotherapy, significant adverse effects of current therapy, and more than 1 allergic disorder.

Nasal Saline Irrigation

Irrigation with nasal saline can improve symptoms for those with mild allergic rhinitis. Nasal saline irrigation can be used alone or before topical medication. Squeeze bottle kits for this purpose are available over the counter, and typically about 200 mL are irrigated through the nares. Patients may make their own irrigation solutions or buy commercially-prepared solutions. Patients should use boiled or distilled water, as cases of sinus infection with amoebas found in tap water have been reported.

New Therapies

Recombinant soluble interleukin (IL)-4 receptor antagonists exert their effects by binding to and inactivating IL-4 before it can attach to its cell surface receptor. Although initial studies of an inhaled soluble IL-4 receptor in patients with moderate asthma requiring inhaled corticosteroids suggested a beneficial clinical effect, subsequent clinical studies of the effects of anti–IL-4 drugs in the treatment of asthma revealed these therapies to be safe, but clinical efficacy was lacking. Clinical trials of humanized monoclonal anti–IL-5 antibodies administered by injection to asthmatic patients revealed a decrease in circulating eosinophils and sputum eosinophilia, but a lesser reduction of eosinophils from the bronchial submucosa, and this effect was

unaccompanied by a reduction in methacholine reactivity or a suppression of the early- or late-phase response to allergen.

The use of cytokines with antiinflammatory effects in the treatment of allergic disorders is under investigation. Unfortunately, initial studies have not demonstrated a beneficial effect of IL-10 or interferons in the treatment of asthma. Although studies have documented that IL-12 administration is associated with a decrease in eosinophil accumulation in response to allergen challenge, inhibition of early- and late-phase responses to allergen and decreases in bronchial hyperreactivity have not been observed. In addition, the high incidence of significant adverse effects encountered with IL-12 administration limits its potential as a viable therapeutic option.

ALLERGEN IMMUNOTHERAPY

Allergen immunotherapy involves administering gradually increasing doses of allergens to a person with allergic disease for the purpose of reducing or eliminating the patient's adverse clinical response to subsequent natural exposure to those allergens. When properly administered to an appropriate candidate, allergen immunotherapy is a safe, effective form of therapy capable not only of reducing or preventing symptoms but also of potentially altering the natural history of the disease by minimizing disease duration and preventing disease progression. Conventional allergen immunotherapy is given subcutaneously under the direction of an experienced allergist. Sublingual immunotherapy (SLIT) is widely used in Europe for aeroallergens but is not yet FDA-approved in the United States. Sublingual and oral immunotherapy (OIT) for foods are being investigated and are also not FDA-approved.

Indications and Contraindications

Allergen immunotherapy is reserved for patients with an allergic disease demonstrated to respond to this form of therapy, such as seasonal or perennial allergic rhinoconjunctivitis, asthma triggered by allergen exposures, and insect venom sensitivity. Proof of the efficacy of conventional allergen immunotherapy for the treatment of food allergy, atopic dermatitis, latex allergy, and acute or chronic urticaria is lacking; consequently, conventional allergen immunotherapy is not recommended for the treatment of these disorders. Before allergen immunotherapy is considered, sensitivity of the patient to the allergens to be administered should be documented by a positive skin test result or an in vitro test revealing an increased serum level of allergen-specific IgE. The clinical relevance of these allergens should be supported by a history of symptoms upon known exposure or a timing of symptoms that correlates well with suspected allergen exposure, such as the presence of allergic nasal and ocular symptoms throughout the late summer and fall in a child with a positive ragweed skin test response. The duration and severity of the patient's symptoms, as well as the patient's preferences, should warrant the expense, effort, and risk associated with the administration of allergen immunotherapy. The presence of disabling symptoms in spite of a trial of allergen avoidance and appropriate medications at a suitable dose should be documented. Venom immunotherapy (VIT) is indicated in children <16 yr of age who have experienced respiratory or cardiovascular symptoms following a sting. For those ≥16 yr, VIT is indicated for any systemic reaction, including those limited to skin but not contiguous from the site of the sting (see Chapter 146).

Other factors that may affect the decision to institute allergen immunotherapy include quality-of-life issues, such as the amount of school missed or medical resource utilization, the age of the patient, and other logistical factors. With the exception of VIT, few data for the efficacy of allergen immunotherapy in children <5 yr of age are available. Allergen immunotherapy is not recommended for children <5 yr of age because of their increased risk of systemic reactions, the special expertise required to treat anaphylaxis in this age group, their potential inability to communicate clearly with the physician in the event of an allergic reaction, and their age-related potential for emotional distress with frequent injections. Other important logistic factors include the willingness of the patient to comply with a schedule of frequent injections over the course of several yr, cost considerations, and the availability of an appropriate medically supervised setting for administering allergen immunotherapy.

Allergen immunotherapy is **contraindicated** in children undergoing β-blocker therapy as well as those with certain immunologic or autoimmune disorders, allergic bronchopulmonary aspergillosis, hypersensitivity pneumonitis, severe psychiatric disturbance, or a medical condition that would impair the ability to survive an allergic reaction. Pregnancy is a contraindication to the initiation of allergen immunotherapy or dosing increases, although a pregnant adolescent can continue to receive her usual maintenance dose. Patients with unstable asthma should not be started on allergen immunotherapy because of their increased risk for anaphylaxis. Allergen immunotherapy is not used for the treatment of allergic bronchopulmonary aspergillosis or hypersensitivity pneumonitis because it has no benefit. Children receiving β-blockers and angiotensin-converting enzyme-inhibitors are not ideal candidates for allergen immunotherapy because of an increased intensity of allergic reactions and a poor response of conventional therapy to these reactions with β-blocker therapy. Allergen immunotherapy is usually avoided in patients with autoimmune disorders because of the theoretical concern for stimulation of the immune system (formation of antigen–antibody complexes), which might result in disease activation.

Allergen Extracts

The potency of the aqueous extracts used in allergen immunotherapy is affected by numerous factors. Allergens from weed and grass pollens are more easily extracted in aqueous solutions and, as a result, are more potent than extracts obtained from other sources, such as molds, tree pollens, and dust mites. Owing to their complexity, allergen extracts from mold allergens are more variable than extracts from pollen allergens. Refrigeration and appropriate handling of allergen extracts used in allergen immunotherapy are important because degradation of many allergen extracts, such as those from tree, grass, weed pollens, and dust mites, may occur at higher temperatures. Dilute extracts are more susceptible to loss of potency resulting from adherence of allergen to the glass vial than are more concentrated extracts. To combat this effect, preservatives such as 0.03% human serum albumin or 10-50% glycerin may be added to dilute allergen extracts. Some allergen extracts, such as those from cockroaches, dust mites, and molds, contain proteases capable of degrading other allergens in the extract. It is often recommended that these allergens not be mixed with those from tree, grass, and weed pollens. Insect venoms are never mixed with other allergens. When available, the use of standardized allergen extracts is preferred to ensure consistency in dosing and to avoid the variability in allergen content encountered with nonstandardized allergen extracts.

Allergen Extract Administration

The goal of allergen immunotherapy is to increase gradually the dose of allergen extract administered until the injection of an "optimal" maintenance dose containing 4-12 μg of each major allergen in the extract is reached. The mixture of allergen extracts administered during the course of allergen immunotherapy is individually formulated for each patient on the basis of the patient's documented sensitivities. Although various dosing schedules are used, initial injections are most often given at 5-10–day intervals year-round. Schedules of allergen administration are selected according to the sensitivity of the patient to the allergens in the extract. The most sensitive patients are advanced to a maintenance dose more gradually. Doses of allergen immunotherapy are increased according to a set schedule, although the reaction to the previous injection is also taken into account. A systemic reaction to the previous dose would result in a significant reduction in the next dose, whereas reducing the dose solely on the basis of a large local reaction does not reduce the rate of systemic reactions. Usually 5-6 mo of weekly injections is required to reach the maintenance dose, although it may take longer in highly sensitive patients. Unique schedules for the administration of insect venoms, which differ from those for the administration of other allergens (see Chapter 146), are used. Once the maintenance dose is reached and well tolerated, the interval between injections is increased to a few weeks

or a month. Because allergen extracts gradually lose potency, the first dose from a fresh replacement vial of maintenance allergen extract is reduced by 25-75% and is then increased in increments weekly until the usual maintenance dose is reached. The recommended length for a course of allergen immunotherapy is 3-5 yr. Insect VIT may be continued indefinitely in patients with a history of life-threatening anaphylaxis. Patients who have not shown improvement after 1 year of receiving maintenance doses of an appropriate allergen extract are unlikely to benefit, and allergen immunotherapy should be discontinued. Most patients enjoy a sustained improvement after allergen immunotherapy whereas others experience a gradual return of symptoms. Those who experience a relapse would be expected to respond upon resuming immunotherapy.

Rush immunotherapy is the administration of multiple injections either in a single day or over several days in an attempt to reach maintenance dose more rapidly. The risk of adverse reactions, including systemic reactions, is higher than with traditional allergen immunotherapy schedules. Patients to undergo rush immunotherapy are often pretreated with antihistamines and corticosteroids. Children are at even greater risk for adverse reactions with rush immunotherapy; thus the benefits and risks should be fully considered. Preadministration of omalizumab (anti-IgE therapy) reduces the incidence of systemic reactions associated with the use of this form of immunotherapy.

Although allergen immunotherapy is regarded as safe, the potential for anaphylaxis always exists when patients are injected with extracts containing allergens to which they are sensitized. Allergen immunotherapy should be offered in only medical settings where a physician with access to emergency equipment and medications required for the treatment of anaphylaxis is available (see Chapter 149). Allergen injections should never be given at home or by untrained personnel. The patient should remain in the office for 30 min after the injection because most reactions to allergen immunotherapy begin within this time frame. Fatal anaphylaxis triggered by allergen immunotherapy, although rare, is estimated to occur at an incidence of 1 per 2 million injections. The risk of an adverse reaction is increased by dosage errors and the use of rush immunotherapy schedules. Particular caution is warranted when injections from a new vial are given. Patients with exquisite sensitivity or unstable asthma and those experiencing exacerbations of allergic rhinitis or asthma are also at increased risk for adverse reactions to allergen immunotherapy. Precautions to reduce significant adverse reactions include using standardized extracts, having extract vials personalized for each patient, allowing only trained personnel to administer injections, paying careful attention to detail when giving injections, ensuring beforehand that the patient is medically stable, having appropriate medications and equipment available, and requiring the patient to remain in the office for 30 min after each injection. Checking peak flow or spirometry before an injection is advisable for some asthmatic patients. It is also prudent to advise patients to carry self-injectable epinephrine for 24 hr following each injection. While uncommon, delayed systemic reactions have been reported following immunotherapy injections.

Other approaches to immunotherapy are under investigation; they include chemical or genetic manipulation of the allergen and linking of the principle allergenic moiety of a relevant allergen to a highly active adjuvant, such as an immunostimulatory sequence mimicking patterns of bacterial DNA.

Local nasal immunotherapy is administered by having the patient spray allergen solutions into the nose at scheduled intervals. Although symptom amelioration has been noted, a lack of a significant systemic immunologic response has decreased interest in pursuing this form of therapy. SLIT involves the sublingual administration of high-dose allergen, which is then swallowed. SLIT is now FDA-approved for a limited number of pollens, and its use is expected to increase given its favorable safety profile and convenience of administration.

Efficacy

The positive impact of allergen immunotherapy on seasonal or perennial allergic rhinitis or rhinoconjunctivitis is well documented. In regard to the treatment of allergic rhinitis, birch, mountain cedar, grass, ragweed, and *Cladosporium* are allergens for which allergen immunotherapy has been effective. Effectiveness of allergen immunotherapy with other allergens commonly used for the treatment of allergic rhinitis is inconclusive. Most of the controlled trials examining the effects of allergen immunotherapy on seasonal or perennial allergic asthma also report favorable results. A meta-analysis of 20 trials examining the effects of allergen immunotherapy on allergic asthma revealed a significant increase in the odds for improvement after treatment along with fewer symptoms, improved pulmonary functions, less need for medication, and a reduction in bronchial hyperreactivity. The most convincing data for the benefit of allergen immunotherapy in the treatment of allergic asthma are available for birch, mountain cedar, grass, ragweed, and dust mite with less conclusive but suggestive data available for *Cladosporium, Alternaria,* and cat allergens. Studies examining the effects of allergen immunotherapy in the treatment of patients with allergic rhinitis and allergic asthma have documented increases in circulating allergen-specific IgG and decreases in allergen-specific IgE after treatment. Reductions in sensitivity to administered allergens have been demonstrated in nasal and bronchial challenges. These studies have often shown that the late-phase response after allergen challenge is ablated or significantly reduced. The protective benefit as well as the safety of VIT in patients with sensitivity to *Hymenoptera* venoms has also been well documented in several large studies. The efficacy of allergen immunotherapy for the treatment of urticaria and latex allergy has not been documented. Dust mite allergen immunotherapy may be helpful in patients with atopic dermatitis. Studies using OIT, involving the oral administration of gradually increasing doses of a food allergen under close medical observation followed by a prolonged maintenance phase of daily fixed-dose food allergen administration at home, has been shown to desensitize patients but has not yet proven to induce tolerance. Although still under investigation, OIT and perhaps SLIT are promising therapeutic approaches to the treatment of food allergy in the future.

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Chapter 143

Allergic Rhinitis

Henry Milgrom and Scott H. Sicherer

Allergic rhinitis (AR) is an inflammatory disorder of the nasal mucosa marked by nasal congestion, rhinorrhea, and itching, often accompanied by sneezing and conjunctival inflammation. Its recognition as a major chronic respiratory disease of children rests largely on its high prevalence, detrimental effects on quality of life and school performance, and comorbidities. Children with AR often have related conjunctivitis, sinusitis, otitis media, serous otitis, hypertrophic tonsils and adenoids, and eczema. Childhood AR is associated with a 3-fold increase in risk for asthma at an older age. Over the past 50 yr an upsurge in AR has been observed throughout the world, particularly in areas where its prevalence previously had been low. In prosperous societies, 20-40% of children suffer from AR. The symptoms may appear in infancy; with the diagnosis generally established by the time the child reaches age 6 yr. The prevalence peaks late in childhood.

Risk factors include family history of atopy and serum immunoglobulin (Ig) E higher than 100 IU/mL before age 6 yr. Early life exposures and/or their absence have a profound influence on the development of the allergic phenotype. The risk increases in children whose mothers smoke heavily, even before delivery and especially before the infants are 1 yr old, and those with heavy exposure to indoor allergens. A critical period exists early in infancy when the genetically susceptible individual is at greatest risk of sensitization. Delivery by

cesarean section is associated with AR and atopy in children with a parental history of asthma or allergies. This association may be explained by the lack of exposure to maternal vaginal/fecal flora during delivery. Children between 2 and 3 yr old who have elevated anticockroach and antimouse IgE are at increased risk of wheezing, AR, and atopic dermatitis. The occurrence of 3 or more episodes of rhinorrhea in the first year of life is associated with AR at age 7 yr. Intriguingly, the exposure to dogs, cats, and endotoxin early in childhood protects against the development of atopy. Prolonged breastfeeding is beneficial, but it does not need to be exclusive There is also a decreased risk of asthma, AR, and atopic sensitization with early introduction to wheat, rye, oats, barley, fish and eggs.

ETIOLOGY AND CLASSIFICATION

Two factors necessary for expression of AR are sensitivity to an allergen and the presence of the allergen in the environment. AR classification as **seasonal** or **perennial** is giving way to the designations **intermittent** and **persistent.** The 2 sets of terms are based on different suppositions, but inhalant allergens are the main cause of all forms of AR irrespective of terminology. AR may also be categorized as **mild-intermittent, moderate-severe intermittent, mild-persistent,** and **moderate-severe persistent** (Fig. 143-1). The symptoms of intermittent AR occur on <4 days per week or for <4 consecutive weeks. In persistent AR symptoms occur on >4 days per week and/or for >4 consecutive weeks. The symptoms are considered mild when they are not troublesome, the sleep is normal, there is no impairment in daily activities, and no incapacity at work or school. Severe symptoms result in sleep disturbance, and impairment in daily activities and school (Fig. 143-1).

In temperate climates, airborne pollen responsible for exacerbation of intermittent AR appear in distinct phases: trees pollinate in the spring, grasses in the early summer, and weeds in the late summer. In temperate climates, mold spores persist outdoors only in the summer, but in warm climates throughout the year. Symptoms of intermittent AR typically cease with the appearance of frost. Knowledge of the time of occurrence of symptoms, of the regional patterns of pollination and mold sporulation, and of the patient's specific IgE is necessary for the recognition of the cause of intermittent AR. Persistent AR is most often associated with the indoor allergens: house dust mites, animal danders, mice, and cockroaches. Cat and dog allergies are of major importance in the United States. The allergens from saliva and sebaceous secretions may remain airborne for a prolonged time. The ubiquitous major cat allergen, Fel d 1, may be carried on cat owners' clothing into such "cat-free" settings as schools and hospitals.

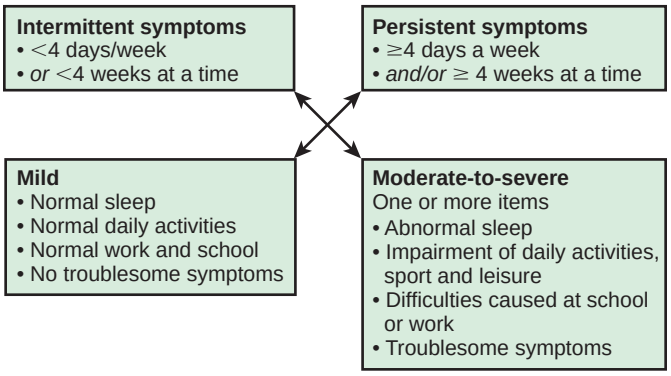


Figure 143-1 ARIA classification of allergic rhinitis. Every box can be subclassified further into seasonal or perennial on the basis of timing of symptoms or when causative and allergen therapeutic factors are considered. For example, a UK patient with grass pollen allergy might have moderate-to-severe persistent seasonal rhinitis in June and July and be suitable for specific allergen immunotherapy. *(From Scadding GK, Durham SR, Mirakian R, et al: BASCI guidelines for the management of allergic and non-allergic rhinitis.* Clin Exp Allergy *38:19-42, 2008 [Fig 2, p. 22].)*

PATHOGENESIS

The exposure of an atopic host to an allergen leads to specific IgE production. The clinical reactions on reexposure to the allergen have been designated as early-phase and late-phase allergic responses. Bridging of the IgE molecules on the surface of mast cells by allergen initiates early-phase allergic response, characterized by degranulation of mast cells and release of preformed and newly generated inflammatory mediators including histamine, prostaglandin 2, and the cysteinyl leukotrienes. Late-phase allergic response appears 4-8 hr following allergen exposure. Inflammatory cells, including basophils, eosinophils, neutrophils, mast cells, and mononuclear cells, infiltrate the nasal mucosa. Eosinophils release proinflammatory mediators, including cysteinyl leukotrienes, cationic proteins, eosinophil peroxidase, and major basic protein, and serve as a source of interleukin (IL)-3, IL-5, granulocyte-macrophage colony-stimulating factor, and IL-13. Repeated intranasal introduction of allergens causes "priming"—a more brisk response even with a lesser provocation. Over the course of an allergy season a multifold increase in submucosal mast cells takes place. These cells, once thought to have a role exclusively in the early-phase allergic response, have an important function in sustaining chronic allergic disease. Allergens, autoantigens, and components of superimposed infectious agents activate the immune system.

CLINICAL MANIFESTATIONS

Symptoms of AR may be ignored or mistakenly attributed to a respiratory infection. Older children blow their noses, but younger children tend to sniff and snort. Nasal itching brings on grimacing, twitching, and picking of the nose that may result in epistaxis. Children with AR often perform the allergic salute, an upward rubbing of the nose with an open palm or extended index finger. This maneuver relieves itching and briefly unblocks the nasal airway. It also gives rise to the nasal crease, a horizontal skin fold over the bridge of the nose. The diagnosis of AR is based on symptoms in the absence of an upper respiratory tract infection and structural abnormalities. Typical complaints include intermittent nasal congestion, itching, sneezing, clear rhinorrhea, and conjunctival irritation. Symptoms increase with greater exposure to the responsible allergen. The patients may lose their sense of smell and taste. Some experience headaches, wheezing, and coughing. Nasal congestion is often more severe at night, causing mouth breathing and snoring, interfering with sleep, and arousing irritability.

Signs on physical exam include abnormalities of facial development, dental malocclusion, and the "allergic gape" or continuous open-mouth breathing, chapped lips, "allergic shiners" (dark circles under the eyes), and the transverse nasal crease. Conjunctival edema, itching, tearing, and hyperemia are frequent findings. A nasal exam performed with a source of light and a speculum may reveal clear nasal secretions; edematous, boggy, and bluish mucus membranes with little or no erythema; and swollen turbinates that may block the nasal airway. It may be necessary to use a topical decongestant to perform an adequate examination. Thick, purulent nasal secretions indicate the presence of infection.

DIFFERENTIAL DIAGNOSIS

Evaluation of AR calls for a thorough history, including details of the patient's environment and diet and family history of allergic conditions such as eczema, asthma, and AR, physical examination, and laboratory evaluation. The history and laboratory findings provide clues to the provoking factors. Symptoms that include sneezing, rhinorrhea, nasal itching, and congestion and the laboratory findings of elevated IgE, specific IgE antibodies, and positive allergy skin test results typify AR. Intermittent AR differs from persistent AR by history and skin test results. Nonallergic rhinitides cause sporadic symptoms. Their causes are often unknown. Nonallergic inflammatory rhinitis with eosinophils imitates AR in presentation and response to treatment, but without elevated IgE antibodies. Vasomotor rhinitis is characterized by excessive responsiveness of the nasal mucosa to physical stimuli. Other nonallergic conditions, such as infectious rhinitis; structural problems, including nasal polyps and septal deviation; rhinitis medicamentosa (caused by the overuse of topical vasoconstrictors); hormonal rhinitis

Table 143-1 Causes of Nonallergic Rhinitis

Structural/mechanical factors:
- Deviated septum/septal wall anomalies
- Hypertrophic turbinates
- Adenoidal hypertrophy
- Foreign bodies

Nasal tumors:
- Benign
- Malignant
- Choanal atresia

Infectious:
- Acute
- Chronic

Inflammatory/immunologic:
- Granulomatosis with polyangiitis
- Sarcoidosis
- Midline granuloma
- Systemic lupus erythematosus
- Sjögren syndrome
- Nasal polyposis

Physiologic:
- Ciliary dyskinesia syndrome
- Atrophic rhinitis

Hormonally induced:
- Hypothyroidism
- Pregnancy
- Oral contraceptives
- Menstrual cycle
- Exercise
- Atrophic

Drug induced:
- Rhinitis medicamentosa
- Oral contraceptives
- Antihypertensive therapy
- Aspirin
- Nonsteroidal antiinflammatory drugs

Reflex induced:
- Gustatory rhinitis
- Chemical or irritant induced
- Posture reflexes
- Nasal cycle
- Environmental factors:
- Odors
- Temperature
- Weather/barometric pressure
- Occupational
- Nonallergic rhinitis with eosinophilia syndrome
- Perennial nonallergic rhinitis (vasomotor rhinitis)
- Emotional factors

From Leung DYM, Sampson HA, Geha RS, et al: Pediatric allergy principles and practice, *St. Louis, 2003, Mosby, p. 290.*

associated with pregnancy or hypothyroidism; neoplasms; vasculitides; and granulomatous disorders may mimic AR (Table 143-1, Fig. 143-2). Occupational risks for rhinitis include exposure to allergens (grain dust, insects, latex, enzymes) and irritants (wood dust, paint, solvents, smoke, cold air).

COMPLICATIONS

AR is frequently associated with complications and comorbid conditions. Children with AR experience frustration over their appearance. Allergic conjunctivitis, characterized by itching, redness and swelling of the conjunctivae, has been reported in at least 20% of the population and in more the 70% of patients with AR, most frequently in older children and young adults. The 2 conditions share pathophysiologic mechanisms and epidemiologic characteristics (see Chapter 147). Chronic sinusitis is a common complication of AR, sometimes associated with purulent infection, but most patients have negative bacterial cultures despite marked mucosal thickening, and sinus opacification. The inflammatory process is characterized by marked eosinophilia. Allergens, possibly fungal, are the inciting agents. The sinusitis of triad asthma (asthma, sinusitis with nasal polyposis, and aspirin sensitivity) often responds poorly to therapy. Patients who undergo repeated endoscopic surgery derive diminishing benefit with each successive procedure.

Rhinitis that coexists with asthma may be taken too lightly or completely overlooked. Up to 78% of patients with asthma have AR, and 38% of patients with AR have asthma. Aggravation of AR coincides with exacerbation of asthma, and treatment of nasal inflammation reduces bronchospasm, asthma-related emergency department visits, and hospitalizations. Postnasal drip associated with AR commonly causes persistent or recurrent cough. Eustachian tube obstruction and middle ear effusion are frequent complications. Chronic allergic inflammation causes hypertrophy of adenoids and tonsils that may be associated with eustachian tube obstruction, serous effusion, otitis media, and obstructive sleep apnea. AR is linked to snoring in children. The association between rhinitis and sleep abnormalities and subsequent daytime fatigue is well documented.

The Pediatric Rhinoconjunctivitis Quality of Life Questionnaire (PRQLQ) is suitable for children 6-12 yr old, and the Adolescent Rhinoconjunctivitis Quality of Life Questionnaire (ARQLQ) is appropriate for patients 12-17 yr of age. Children with rhinitis have anxiety and physical, social, and emotional issues that affect learning and the ability to integrate with peers. The disorder contributes to headaches and fatigue, limits daily activities, and interferes with sleep. There is evidence of impaired cognitive functioning and learning that may be exacerbated by the adverse effects of sedating medications. Rhinitis is an important cause of lost school attendance, resulting in more than 2 million days of absence in the United States annually.

LABORATORY FINDINGS

Epicutaneous skin tests provide the best method for detection of allergen-specific IgE (positive predictive value of 48.7% for the epidemiologic diagnosis of AR). They are inexpensive and sensitive, and the risks and discomfort are minimal. Responses to seasonal respiratory allergens are rare before 2 seasons of exposure, and children <1 yr seldom display positive skin test responses to these allergens. To avoid false-negative results, montelukast should be withheld for 1 day, most sedating antihistamine preparations for 3-4 days, and nonsedating antihistamines for 5-7 days. Serum immunoassays for specific IgE to allergens provide a suitable alternative (positive predictive value 43.5%) for patients with dermatographism or extensive dermatitis, those taking medications that interfere with mast cell degranulation, others at high risk for anaphylaxis, and some who cannot cooperate with the procedure. Presence of eosinophils in nasal smear supports the diagnosis of AR, and of neutrophils infectious rhinitis. Eosinophilia and measurements of total serum IgE concentrations have relatively low sensitivity.

TREATMENT

Safe and effective prevention and/or relief of symptoms are the current goals of treatment. Specific measures to limit indoor allergen exposure may reduce the risk of sensitization and symptoms of allergic respiratory disease. Sealing the patient's mattress, pillow, and covers in allergen-proof encasings reduces the exposure to mite allergen. Bed linen and blankets should be washed every week in hot water (>54.4°C [130°F]). The only effective measure for avoiding animal allergens in the home is the removal of the pet. Avoidance of pollen and outdoor molds can be accomplished by staying in a controlled environment. Air conditioning allows for keeping windows and doors closed, reducing the pollen exposure. High-efficiency particulate air filters lower the counts of airborne mold spores.

Oral antihistamines help reduce sneezing, rhinorrhea and ocular symptoms. Administered as needed they provide acceptable treatment for mild-intermittent disease. Antihistamines have been classified as first generation (relatively sedating) or second generation (relatively nonsedating). Antihistamines usually are administered by mouth, but they are also available for topical ophthalmic and intranasal use. Both first- and second-generation antihistamines are available as nonprescription drugs. Second-generation antihistamines are preferred

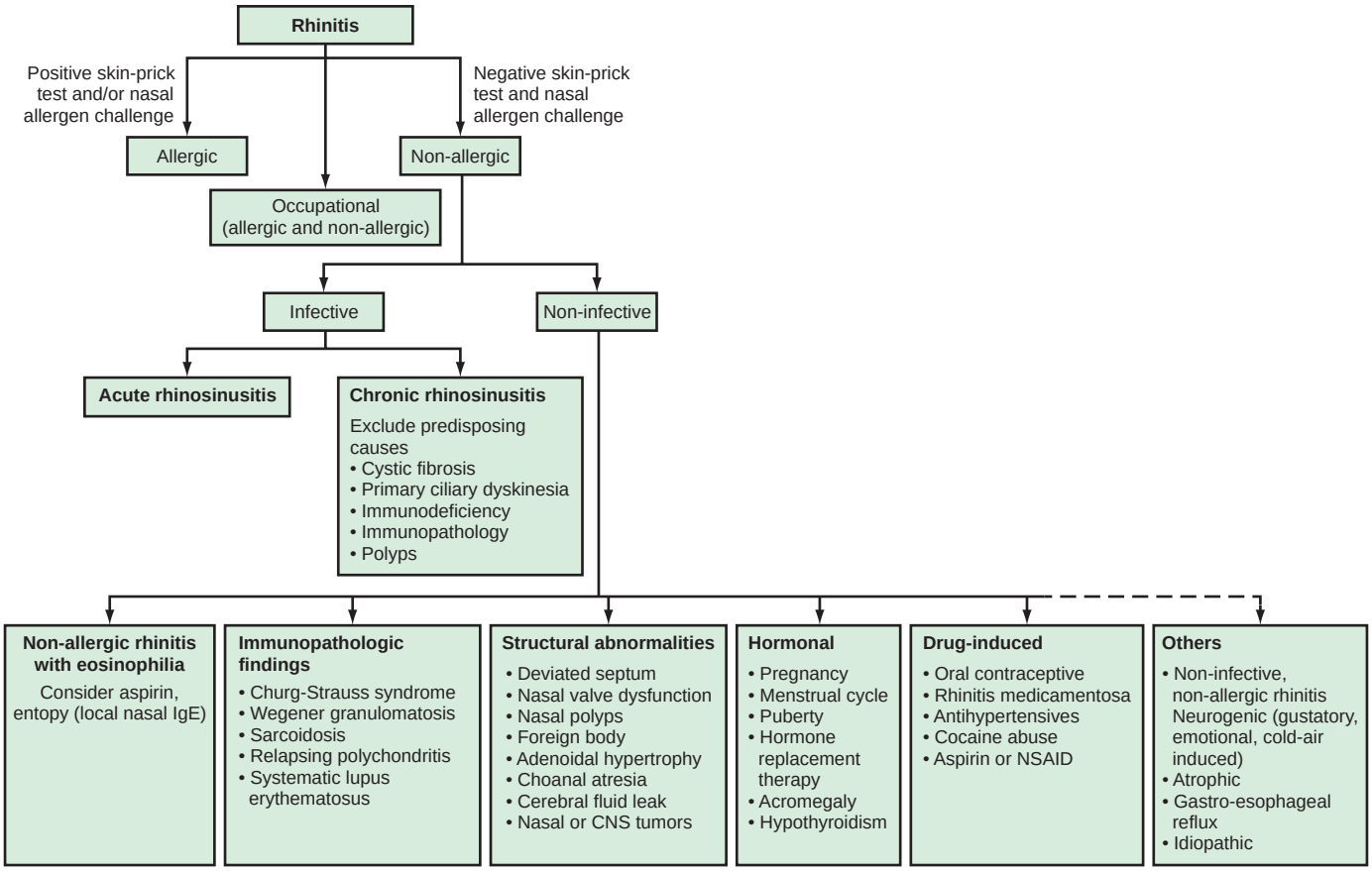


Figure 143-2 Diagnostic algorithm for rhinitis. Nasal allergen challenge is a research procedure and is not undertaken routinely. Causes likely to be seen in children are highlighted in italics. NSAID, nonsteroidal antiinflammatory drug. *(From Greiner AN, Hellings PW, Rotiroti G, Scadding GK: Allergic rhinitis. Lancet 378:2112-2120, 2011 [Fig. 3, p. 2116].)*

because they cause less sedation. Preparations containing pseudoephedrine, typically in combination with other agents, are used for relief of nasal and sinus congestion and pressure and other symptoms such as rhinorrhea, sneezing, lacrimation, itching eyes, oronasopharyngeal itching, and cough. Pseudoephedrine is available without prescription (generally in fixed combination with other agents such as first-generation antihistamines: brompheniramine, chlorpheniramine, triprolidine; second-generation antihistamines: desloratadine, fexofenadine, loratadine; antipyretics: acetaminophen, ibuprofen; antitussives: guaifenesin, dextromethorphan; anticholinergic: methscopolamine). Pseudoephedrine is an oral vasoconstrictor disfavored for causing irritability and insomnia and for its association with infant mortality. Because younger children (2-3 yr of age) are at increased risk of overdosage and toxicity, some manufacturers of oral nonprescription cough and cold preparations have voluntarily revised their product labeling to warn against the use of preparations containing pseudoephedrine for children younger than 4 yr. Pseudoephedrine is misused as a starting material for the synthesis of methamphetamine and methcathinone. Oral agents for treatment of AR are shown in Tables 143-2, 143-3, and 143-4.

The anticholinergic nasal spray ipratropium bromide is effective for the treatment of serous rhinorrhea (Table 143-5). Intranasal decongestants (oxymetazoline and phenylephrine) should be used for less than 5 days, not to be repeated more than once a month in order to avoid rebound nasal congestion. Sodium cromoglycate (available as nonprescription drug) is effective but requires frequent administration, q4h. Leukotriene-modifying agents have a modest effect on rhinorrhea and nasal blockage (see Chapter 144 for additional indications and side effects). Nasal saline irrigation is a good adjunctive option with all other treatments of AR. Patients with more persistent, severe symptoms require intranasal corticosteroids, the most effective therapy for AR, a treatment that may be beneficial also for concomitant allergic conjunctivitis (Table 143-6). These agents reduce the symptoms of AR with eosinophilic inflammation, but not those of rhinitis associated with neutrophils or free of inflammation. Beclomethasone, triamcinolone, and flunisolide are absorbed from the gastrointestinal tract, as well as from the respiratory tract; budesonide, fluticasone, mometasone, and ciclesonide offer greater topical activity with lower systemic exposure. More severely affected patients may benefit from simultaneous treatment with oral antihistamines and intranasal corticosteroids.

Allergy immunotherapy is an effective treatment for AR and allergic conjunctivitis. In addition to reducing symptoms, it may change the course of allergic disease and induce allergen-specific immune tolerance. Immunotherapy administered by subcutaneous injection should be considered for children in whom IgE-mediated allergic symptoms cannot be adequately controlled by avoidance and medication, especially in the presence of comorbid conditions. Sublingual immunotherapy has been used successfully in Europe and South America. Sublingual immunotherapy is considered investigational in the United States, and there are no extracts for sublingual administration licensed by the FDA. Omalizumab (anti-IgE antibody) given subcutaneously has a dose-dependent effect on seasonal AR; its role compared with standard therapy has yet to be determined.

Typically, treatment of AR with oral antihistamines and inhaled corticosteroids provides sufficient relief for most cases of coexisting allergic conjunctivitis. If it fails, additional therapies directed primarily to allergic conjunctivitis may be added (see Chapter 147). Intranasal corticosteroids are of some value for the treatment of ocular symptoms, but ophthalmic corticosteroids remain the most potent pharmacologic agents for ocular allergy. They carry the risk of adverse effects, such as delayed wound healing, secondary infection, elevated intraocular

Table 143-2 Oral Allergic Rhinitis Treatments (Prescription, Examples)

GENERIC/BRAND	STRENGTH	FORMULATIONS	DOSING
SECOND-GENERATION ANTIHISTAMINES			
Desloratadine			
Clarinex Reditabs*	2.5 mg, 5 mg	Orally disintegrating tablet	Children 6-11 mo of age: 1 mg once daily
Clarinex Tablets	5 mg	Tabs	Children 12 mo-5 yr of age: 1.25 mg once daily
Clarinex Syrup	0.5 mg/mL	Syrup	Children 6-11 yr of age: 2.5 mg once daily Adults and adolescents ≥12 yr of age: 5 mg once daily
Levocetirizine dihydrochloride			
Xyzal Oral Solution	0.5 mg/mL	Solution	6 mo-5 yr: max 1.25 mg once daily in the P.M. 6-11 yr: max 2.5 mg once daily in the P.M.
LEUKOTRIENE ANTAGONIST			
Montelukast			
Singulair	10 mg	Tablets	6 mo-5 yr: 4 mg daily
Singulair Chewables*	4 mg, 5 mg	Chewable tablets	6-14 yr: 5 mg daily
Singulair Oral Granules	4 mg/packet	Oral granules	>14 yr: 10 mg daily

*Contains phenylalanine.
Dosing recommendations taken in part from Arcara K, Tschudy M for the Johns Hopkins Hospital: The Harriet Lane Handbook, *ed 19. Philadelphia, 2012 Mosby.*

Table 143-3 Oral Allergic Rhinitis Treatments (Nonprescription, Examples)

GENERIC/BRAND	STRENGTH	FORMULATIONS	DOSING
FIRST-GENERATION H_1 ANTAGONISTS			
Chlorpheniramine maleate			
Chlor-Trimeton	4 mg	Tablets	2-5 yr: 1 mg every 4-6 hr (maximum 6 mg/day)
Chlor-Trimeton Syrup	2 mg/5 mL	Syrup	6-11 yr: 2 mg every 4-6 hr (maximum 12 mg/day) >12 yr 4 mg every 4-6 hr (maximum 24 mg/day)
SECOND-GENERATION H_1 ANTAGONISTS			
Cetirizine			
Children's Zyrtec Allergy Syrup	1 mg/mL	Syrup	6-12 mo: 2.5 mg once daily
Children's Zyrtec Chewable	5 mg, 10 mg	Chewable tablets	12-23 mo: initial: 2.5 mg once daily; dosage may be increased to 2.5 mg twice daily
Zyrtec tablets	5 mg, 10 mg	Tablets	2-5 yr: 2.5 mg/day; may be increased to a maximum of 5 mg/day given either as a single dose or divided into 2 doses
Zyrtec Liquid Gels	10 mg	Liquid-filled gels	≥6 yr: 5-10 mg/day as a single dose or divided into 2 doses
Fexofenadine HCl			
Children's Allegra	30 mg	Tablet	
Children's Allegra ODT*	30 mg	Orally disintegrating tablets	6 mo-<2 yr: 15 mg (2.5 mL) every 12 hr
Children's Allegra Oral Suspension	30 mg/5 mL	Suspension	>2-11 yr: 30 mg every 12 hr
Allegra	Tabs 30, 60, 180 mg	Tablet	>12 yr-adult: 60 mg every 12 hr; 180 mg once daily
Loratadine			
Alavert ODT*	10 mg	Orally disintegrating tablets	2-5 yr: 5 mg once daily.
	10 mg	Tablets	>6 yr: 10 mg once daily or 5 mg twice daily
	10 mg	Liquid-filled caps	
	5 mg	Chewable tablets	
	1 mg/mL	Syrup	

*Contains phenylalanine.
Dosing recommendations taken in part from Arcara K, Tschudy M for the Johns Hopkins Hospital: The Harriet Lane Handbook, *ed 19, Philadelphia, 2012, Mosby.*

Table 143-4 Combined Antihistamine + Sympathomimetic (Examples)

GENERIC	STRENGTH	FORMULATIONS	DOSING
Chlorpheniramine maleate Phenylephrine HCl Sudafed Sinus & Allergy	4 mg 10 mg	Tablets	>12 yr: 1 tablet every 4 hr not to exceed 6 tablets per day
Cetirizine + pseudoephedrine Zyrtec-D 12 hour	5 mg cetirizine + 120 mg pseudoephedrine	Extended release tablet	>12 yr: 1 tablet every 12 hr

Dosing recommendations taken in part from Arcara K, Tschudy M for the Johns Hopkins Hospital: The Harriet Lane Handbook, *ed 19, Philadelphia, 2012, Mosby.*

Table 143-5 Miscellaneous Intranasal Sprays

DRUG	INDICATIONS (I), MECHANISM(s) OF ACTION (M), AND DOSING	COMMENTS, CAUTIONS, ADVERSE EVENTS, AND MONITORING
Ipratropium bromide: Atrovent nasal spray (0.06%)	*I:* Symptomatic relief of rhinorrhea *M:* Anticholinergic Colds (symptomatic relief of rhinorrhea): 5-12 yr: 2 sprays in each nostril 3 times/day ≥12 yr and adults: 2 sprays in each nostril 3-4 times/day	Atrovent inhalation aerosol is contraindicated in patients with hypersensitivity to soy lecithin Safety and efficacy of use beyond 4 days in patients with the common cold have not been established *Adverse effects:* Epistaxis, nasal dryness, nausea
Azelastine: Astelin	*I:* Treatment of rhinorrhea, sneezing, and nasal pruritus *M:* Antagonism of histamine H_1-receptor 6-12 yr: 1 spray bid >12 yr: 1-2 sprays bid	May cause drowsiness *Adverse effects:* Headache, somnolence, bitter taste
Cromolyn sodium: NasalCrom	*I:* AR. *M:* Inhibition of mast cell degranulation >2 yr: 1 spray tid-qid; max ×6 /day	Not effective immediately; requires frequent administration
Oxymetazoline: Afrin, Nostrilla	*I:* Symptomatic relief of nasal mucosal congestion *M:* Adrenergic agonist, vasoconstricting agent 0.05% solution: instill 2-3 sprays into each nostril twice daily; therapy should not exceed 3 days	Excessive dosage may cause profound central nervous system (CNS) depression Use in excess of 3 days may result in severe rebound nasal congestion Do not repeat more than once a month Use with caution in patients with hyperthyroidism, heart disease, hypertension, and diabetes *Adverse effects:* Hypertension, palpitations, reflex bradycardia, nervousness, dizziness, insomnia, headache, CNS depression, convulsions, hallucinations, nausea, vomiting, mydriasis, elevated intraocular pressure, blurred vision
Phenylephrine: Neo-Synephrine	*I:* Symptomatic relief of nasal mucosal congestion *M:* Adrenergic, vasoconstricting agent 2-6 yr: 1 drop every 2-4 hr of 0.125% solution as needed. *Note:* Therapy should not exceed 3 continuous days 6-12 yr: 1-2 sprays or 1-2 drops every 4 hr of 0.25% solution as needed. *Note:* Therapy should not exceed 3 continuous days >12 yr: 1-2 sprays or 1-2 drops every 4 hr of 0.25% to 0.5% solution as needed; 1% solution may be used in adults with extreme nasal congestion. *Note:* Therapy should not exceed 3 continuous days	Use in excess of 3 days may result in severe rebound nasal congestion Do not repeat more than once a month 0.16% and 0.125% solutions are not commercially available *Adverse effects:* Reflex bradycardia, excitability, headache, anxiety, and dizziness

Table 143-6 Intranasal Inhaled Corticosteroids

DRUG	INDICATIONS (I), MECHANISM(s) OF ACTION (M), AND DOSING	COMMENTS, CAUTIONS, ADVERSE EVENTS, AND MONITORING
Beclomethasone: Beconase AQ (42 μg/spray) Qnasl (80 μg/spray)	*I:* AR *M:* Antiinflammatory, immune modulator 6-12 yr: 1 spray in each nostril bid; may increase if needed to 2 sprays in each nostril bid >12 yr: 1 or 2 sprays in each nostril bid	Shake container before use; blow nose; occlude 1 nostril, administer dose to the other nostril *Adverse effects:* Burning and irritation of nasal mucosa, epistaxis Monitor growth
Flunisolide	6-14 yr: 1 spray each nostril 3 times daily *or* 2 sprays in each nostril twice daily; not to exceed 4 sprays/day in each nostril ≥15 yr: 2 sprays each nostril twice daily (morning and evening); may increase to 2 sprays 3 times daily; maximum dose: 8 sprays/day in each nostril (400 μg/day)	Shake container before use; blow nose; occlude 1 nostril, administer dose to the other nostril *Adverse effects:* Burning and irritation of nasal mucosa, epistaxis Monitor growth

Continued

Table 143-6 Intranasal Inhaled Corticosteroids—cont'd

DRUG	INDICATIONS (I), MECHANISM(s) OF ACTION (M), AND DOSING	COMMENTS, CAUTIONS, ADVERSE EVENTS, AND MONITORING
Triamcinolone Nasacort AQ (55 µg/spray)	*I:* AR *M:* Antiinflammatory, immune modulator 2-6 yr; 1 spray in each nostril qd 6-12 yr: 1-2 sprays in each nostril qd ≥12 yr: 2 sprays in each nostril qd	Shake container before use; blow nose; occlude 1 nostril, administer dose to the other nostril *Adverse effects:* Burning and irritation of nasal mucosa, epistaxis Monitor growth
Fluticasone propionate (available as a generic preparation): Flonase (50 µg/spray)	*I:* AR *M:* Antiinflammatory, immune modulator ≥4 yr: 1-2 sprays in each nostril qd	Shake container before use; blow nose; occlude 1 nostril, administer dose to the other nostril Ritonavir significantly increases fluticasone serum concentrations and may result in systemic corticosteroid effects Use fluticasone with caution in patients receiving ketoconazole or other potent cytochrome P450 3A4 isoenzyme inhibitor *Adverse effects:* Burning and irritation of nasal mucosa, epistaxis Monitor growth
Fluticasone furoate: Veramyst (27.5 µg/spray)	2-12 yr: Initial dose: 1 spray (27.5 µg/spray) per nostril once daily (55 µg/day) Patients who do not show adequate response may use 2 sprays per nostril once daily (110 µg/day) Once symptoms are controlled, dosage may be reduced to 55 µg once daily Total daily dosage should not exceed 2 sprays in each nostril (110 µg)/day ≥12 yr and adolescents: Initial dose: 2 sprays (27.5 µg/spray) per nostril once daily (110 µg/day) Once symptoms are controlled, dosage may be reduced to 1 spray per nostril once daily (55 µg/day) Total daily dosage should not exceed 2 sprays in each nostril (110 µg)/day	
Mometasone: Nasonex (50 µg/spray)	*I:* AR *M:* Antiinflammatory, immune modulator 2-12 yr: 1 spray in each nostril qd >12 yr: 2 sprays in each nostril qd	Mometasone and its major metabolites are undetectable in plasma after nasal administration of recommended doses Preventive treatment of seasonal AR should begin 2-4 wk prior to pollen season Shake container before use; blow nose; occlude 1 nostril, administer dose to the other nostril *Adverse effects:* Burning and irritation of nasal mucosa, epistaxis Monitor growth
Budesonide: Rhinocort Aqua (32 µg/spray)	*I:* AR *M:* Antiinflammatory, immune modulator 6-12 yr: 2 sprays in each nostril qd >12 yr: up to 4 sprays in each nostril qd (maximum dose)	Shake container before use; blow nose; occlude 1 nostril, administer dose to the other nostril *Adverse effects:* Burning and irritation of nasal mucosa, epistaxis Monitor growth
Ciclesonide: Omnaris Zetonna (50 µg/spray)	*I:* AR *M:* Antiinflammatory, immune modulator 2-12 yr: 1-2 sprays in each nostril qd >12 yr: 2 sprays in each nostril qd	Prior to initial use, gently shake, then prime the pump by actuating 8 times If the product is not used for 4 consecutive days, gently shake and reprime with 1 spray or until a fine mist appears
Azelastine/fluticasone (137 µg azelastine/50 µg fluticasone) Dymista	>12 yr: 1 spray in each nostril bid	Shake bottle gently before using. Blow nose to clear nostrils. Keep head tilted downward when spraying. Insert applicator tip ¼ to ½ inch into nostril, keeping bottle upright, and close off the other nostril. Breathe in through nose. While inhaling, press pump to release spray

pressure, and formation of cataracts. These agents are only suited for the treatment of allergic conjunctivitis that does not respond to the medications discussed above. Sound practice calls for the assistance of an ophthalmologist.

PROGNOSIS

Therapy with nonsedating antihistamines and topical corticosteroids, when taken faithfully, significantly improves health-related quality-of-life measures in patients. The reported rates of remission among children are between 10% and 23%. Pharmacotherapy that will target cells and cytokines involved in inflammation and treat allergy as a systemic process is on the horizon, and more selective targeting of drugs based on the development of specific biomarkers and genetic profiling may soon be realized.

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Chapter 144

Childhood Asthma

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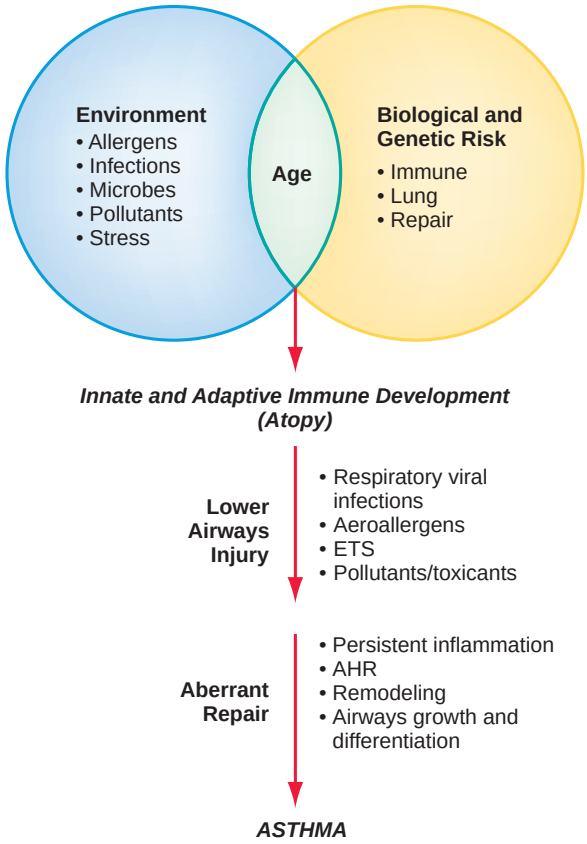


Figure 144-1 Etiology and pathogenesis of asthma. A combination of environmental and genetic factors in early life shape how the immune system develops and responds to ubiquitous environmental exposures. Respiratory microbes, inhaled allergens, and toxins that can injure the lower airways target the disease process to the lungs. Aberrant immune and repair responses to airways injury underlie persistent disease. AHR, airways hyperresponsiveness; ETS, environmental tobacco smoke.

Asthma is a chronic inflammatory condition of the lung airways resulting in episodic airflow obstruction. This chronic inflammation heightens the twitchiness of the airways—airways hyperresponsiveness (AHR)—to provocative exposures. Asthma management is aimed at reducing airways inflammation by minimizing proinflammatory environmental exposures, using daily controller antiinflammatory medications, and controlling comorbid conditions that can worsen asthma. Less inflammation typically leads to better asthma control, with fewer exacerbations and decreased need for quick-reliever asthma medications. Nevertheless, exacerbations can still occur. Early intervention with systemic corticosteroids greatly reduces the severity of such episodes. Advances in asthma management and, especially, pharmacotherapy enable all but the uncommon child with difficult asthma to live normally.

ETIOLOGY

Although the cause of childhood asthma has not been determined, a combination of environmental exposures and inherent biologic and genetic susceptibilities has been implicated (Fig. 144-1). In the susceptible host, immune responses to common airways exposures (e.g., respiratory viruses, allergens, tobacco smoke, air pollutants) can stimulate prolonged, pathogenic inflammation and aberrant repair of injured airways tissues. Lung dysfunction (AHR, reduced airflow) and airway remodeling develop. These pathogenic processes in the growing lung during early life adversely affect airways growth and differentiation, leading to altered airways at mature ages. Once asthma has developed, ongoing inflammatory exposures appear to worsen it, driving disease persistence and increasing the risk of severe exacerbations.

Genetics

To date, more than 100 genetic loci have been linked to asthma, although relatively few have consistently been linked to asthma in different study cohorts. Replicating variants include genetic loci containing proallergic, proinflammatory genes. Because epigenetic marks are heritable, are responsive to environmental exposures, and can result in rapid and persistent changes in gene expression it is conceivable that epigenetic modification of genes play a role in the transmission of asthma.

Environment

Recurrent wheezing episodes in early childhood are associated with common respiratory viruses, especially common cold rhinoviruses, and also respiratory syncytial virus, influenza virus, adenovirus, parainfluenza virus, and human metapneumovirus. This association implies that host features affecting immunologic host defense, inflammation, and the extent of airways injury from ubiquitous viral pathogens underlie susceptibility to recurrent wheezing in *early* childhood. Other airways exposures can also exacerbate ongoing airways inflammation, increase disease severity, and drive asthma persistence. Home allergen exposures in sensitized individuals can initiate airways inflammation and hypersensitivity to other irritant exposures, and are strongly linked to disease severity and persistence. Consequently, eliminating the offending allergen(s) can lead to resolution of asthma symptoms and can sometimes cure asthma. Environmental tobacco smoke and common air pollutants can aggravate airways inflammation and increase asthma severity. Cold, dry air, hyperventilation from physical play or exercise, and strong odors can trigger bronchoconstriction. Although many exposures that trigger and aggravate asthma are well recognized, the causal environmental features underlying the development of host susceptibilities to the various common airway exposures are not well defined.

EPIDEMIOLOGY

Asthma is a common chronic disease, causing considerable morbidity. In 2011, more than 10 million children (14% of U.S. children) had ever been diagnosed with asthma, with 70% of this group reporting current asthma. Male gender and living in poverty are demographic risk factors for having childhood asthma in the U.S. Fifteen percent of boys

compared to 13% of girls have had asthma; and 18% of all children living in poor families (incomes less than $25,000 per year), compared to 12% of children in families not classified as poor, have had asthma.

Childhood asthma is among the most common causes of childhood emergency department visits, hospitalizations, and missed school days. In the United States in 2006, childhood asthma accounted for 593,000 emergency department visits, 155,000 hospitalizations, and 167 deaths. A disparity in asthma outcomes links high rates of asthma hospitalization and death with poverty, ethnic minorities, and urban living. In the past 2 decades, black children have had 2-7 times more emergency department visits, hospitalizations, and deaths as a result of asthma than nonblack children. Although current asthma prevalence is higher in black than in nonblack U.S. children (in 2011, 16.5% vs 8.1% for white and 9.8% for Latino children), prevalence differences cannot fully account for this disparity in asthma outcomes.

Worldwide, childhood asthma appears to be increasing in prevalence, despite considerable improvements in our management and pharmacopeia to treat asthma. Numerous studies conducted in different countries have reported an increase in asthma prevalence of approximately 50% per decade. Globally, childhood asthma prevalence varies widely in different locales. A study of childhood asthma prevalence in 233 centers in 97 countries (International Study of Asthma and Allergies in Childhood, Phase 3) found a wide range in the prevalence of current wheeze in 6-7 yr (2.4-37.6%) and 13-14 yr old children (0.8-32.6%). Asthma prevalence correlated well with reported allergic rhinoconjunctivitis and atopic eczema prevalence. Childhood asthma seems more prevalent in modern metropolitan locales and more affluent nations, and is strongly linked with other allergic conditions. In contrast, children living in rural areas of developing countries and farming communities with domestic animals are less likely to experience asthma and allergy.

Approximately 80% of all asthmatic patients report disease onset prior to 6 yr of age. However, of all young children who experience recurrent wheezing, only a minority go on to have persistent asthma in later childhood. Early childhood risk factors for persistent asthma have been identified (Table 144-1) and have been described as major (parent asthma, eczema, inhalant allergen sensitization) and minor (allergic rhinitis, wheezing apart from colds, ≥4% peripheral blood eosinophils, food allergen sensitization) risk factors. Allergy in young children with recurrent cough and/or wheeze is the strongest identifiable factor for the persistence of childhood asthma.

Types of Childhood Asthma

There are 2 common types of childhood asthma based on different natural courses: (1) **recurrent wheezing** in *early* childhood, primarily triggered by common respiratory viral infections, usually resolves during the preschool/lower school years; and (2) **chronic asthma** associated with allergy that persists into later childhood and often adulthood (Table 144-2). School-age children with mild-moderate persistent asthma generally improve as teenagers, with some (~40%) developing intermittent disease. Milder disease is more likely to remit. Inhaled corticosteroid controller therapy for children with persistent asthma does not alter the likelihood of outgrowing asthma in later childhood; however, because children with asthma generally improve with age, their need for controller therapy subsequently lessens and often resolves. Progressive decline in lung function can be a feature of severe, persistent disease.

Asthma is also classified by disease severity (e.g., intermittent or persistent [mild, moderate, or severe]) or control (e.g., well, not well, or very poorly controlled), especially for asthma management purposes. Because most children with asthma can be well controlled with conventional management guidelines, children with asthma can also be characterized according to treatment response and medication requirements as being: (1) easy-to-treat: well controlled with low

Table 144-1 Early Childhood Risk Factors for Persistent Asthma

Parental asthma
Allergy:
- Atopic dermatitis (eczema)
- Allergic rhinitis
- Food allergy
- Inhalant allergen sensitization
- Food allergen sensitization

Severe lower respiratory tract infection:
- Pneumonia
- Bronchiolitis requiring hospitalization

Wheezing apart from colds
Male gender
Low birthweight
Environmental tobacco smoke exposure
Reduced lung function at birth

Table 144-2 Asthma Patterns in Childhood, Based on Natural History and Asthma Management

TRANSIENT NONATOPIC WHEEZING
Common in early preschool years
Recurrent cough/wheeze, primarily triggered by common respiratory viral infections
Usually resolves during the preschool and lower school years, without increased risk for asthma in later life
Reduced airflow at birth, suggestive of relatively narrow airways. AHR near birth. Improves by school age

PERSISTENT ATOPY-ASSOCIATED ASTHMA
Begins in early preschool years
Associated with atopy in early preschool years:
- Clinical (e.g., atopic dermatitis in infancy, allergic rhinitis, food allergy)
- Biologic (e.g., early inhalant allergen sensitization, increased serum immunoglobulin E, increased blood eosinophils)
- Highest risk for persistence into later childhood and adulthood

Lung function abnormalities:
- Those with onset before 3 yr of age acquire reduced airflow by school age
- Those with later onset of symptoms, or with later onset of allergen sensitization, are less likely to experience airflow limitation in childhood

ASTHMA WITH DECLINING LUNG FUNCTION
Children with asthma with progressive increase in airflow limitation
Associated with hyperinflation in childhood, male gender

ASTHMA MANAGEMENT TYPES
(From national and international asthma management guidelines)
SEVERITY CLASSIFICATION*
- Intrinsic disease severity while not on asthma medications

Intermittent
Persistent:
- Mild
- Moderate
- Severe

CONTROL CLASSIFICATION*
- Clinical assessment while asthma being managed and treated

Well controlled
Not well controlled
Very poorly controlled
MANAGEMENT PATTERNS
- **Easy-to-treat:** well controlled with low levels of daily controller therapy
- **Difficult-to-treat:** well controlled with multiple and/or high levels of controller therapies
- **Exacerbators:** despite being well controlled, continue to have severe exacerbations
- **Refractory:** continue to have poorly controlled asthma despite multiple and high levels of controller therapies

*From National Asthma Education and Prevention Program's Expert Panel Report 3 (EPR3): *Guideline for the diagnosis and management of asthma.* NIH Publication No. 07-4051. Bethesda, MD, 2007, U.S. Department of Health and Human Services; National Institutes of Health, National Heart, Lung, and Blood Institute; National Asthma Education and Prevention Program. http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm.
AHR, airways hyperresponsiveness.

levels of controller therapy; (2) difficult-to-treat: well controlled with multiple and/or high levels of controller therapies; (3) exacerbators: despite being well controlled, continue to have severe exacerbations; and (4) refractory asthma: continue to have poorly controlled asthma despite multiple and high levels of controller therapies (Table 144-2). Different airways pathologic processes, causing airways inflammation, AHR, and airways congestion and blockage, are believed to underlie these different types of asthma.

PATHOGENESIS

Airflow obstruction in asthma is the result of numerous pathologic processes. In the small airways, airflow is regulated by smooth muscle encircling the airway lumen; bronchoconstriction of these bronchiolar muscular bands restricts or blocks airflow. A cellular inflammatory infiltrate and exudates distinguished by eosinophils, but also including other inflammatory cell types (neutrophils, monocytes, lymphocytes, mast cells, basophils), can fill and obstruct the airways and induce epithelial damage and desquamation into the airways lumen. Helper T lymphocytes and other immune cells that produce proallergic, proinflammatory cytokines (interleukin [IL]-4, IL-5, IL-13), and chemokines (eotaxins) mediate this inflammatory process. Pathogenic immune responses and inflammation may also result from a breach in normal immune regulatory processes (such as regulatory T lymphocytes that produce IL-10 and transforming growth factor-β) that dampen effector immunity and inflammation when they are no longer needed. Hypersensitivity or susceptibility to a variety of provocative exposures or triggers (Table 144-3) can lead to airways inflammation, AHR, edema, basement membrane thickening, subepithelial collagen deposition, smooth muscle and mucous gland hypertrophy, and mucus hypersecretion—all processes that contribute to airflow obstruction.

Table 144-3 Asthma Triggers

Common viral infections of the respiratory tract Aeroallergens in sensitized asthmatic patients
INDOOR ALLERGENS • Animal dander • Dust mites • Cockroaches • Molds
SEASONAL AEROALLERGENS • Pollens (trees, grasses, weeds) • Seasonal molds
AIR POLLUTANTS • Environmental tobacco smoke • Ozone • Nitrogen dioxide • Sulfur dioxide • Particulate matter • Wood- or coal-burning smoke • Mycotoxins • Endotoxin • Dust
STRONG OR NOXIOUS ODORS OR FUMES • Perfumes, hairsprays • Cleaning agents
OCCUPATIONAL EXPOSURES • Farm and barn exposures • Formaldehydes, cedar, paint fumes
Cold dry air Exercise Crying, laughter, hyperventilation
COMORBID CONDITIONS • Rhinitis • Sinusitis • Gastroesophageal reflux
DRUGS • Aspirin and other nonsteroidal antiinflammatory drugs • β-Blocking agents • Sulfiting agents • Tartrazine

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Intermittent dry coughing and expiratory wheezing are the most common chronic symptoms of asthma. Older children and adults report associated shortness of breath and chest congestion and tightness; younger children are more likely to report intermittent, nonfocal chest pain. Respiratory symptoms can be worse at night, associated with sleep, especially during prolonged exacerbations triggered by respiratory infections or inhalant allergens. Daytime symptoms, often linked with physical activities (exercise-induced) or play, are reported with greatest frequency in children. Other asthma symptoms in children can be subtle and nonspecific, including self-imposed limitation of physical activities, general fatigue (possibly resulting from sleep disturbance), and difficulty keeping up with peers in physical activities. Asking about previous experience with asthma medications (bronchodilators) may provide a history of symptomatic improvement with treatment that supports the diagnosis of asthma. Lack of improvement with bronchodilator and corticosteroid therapy is inconsistent with underlying asthma and should prompt more vigorous consideration of asthma-masquerading conditions.

Asthma symptoms can be triggered by numerous common events or exposures: physical exertion and hyperventilation (laughing), cold or dry air, and airways irritants (see Table 144-3). Exposures that induce airways inflammation, such as infections with common respiratory pathogens (rhinovirus, respiratory syncytial virus, metapneumovirus, parainfluenza virus, influenza virus, adenovirus, *Mycoplasma pneumoniae, Chlamydia pneumoniae*), and inhaled allergens in sensitized children, also increase AHR to dry cold air and irritant exposures. An environmental history is essential for optimal asthma management (see Chapter 141).

The presence of risk factors, such as a history of other allergic conditions (allergic rhinitis, allergic conjunctivitis, atopic dermatitis, food allergies), parental asthma, and/or symptoms apart from colds, supports the diagnosis of asthma. During routine clinic visits, children with asthma commonly present without abnormal signs, emphasizing the importance of the medical history in diagnosing asthma. Some may exhibit a dry, persistent cough. The chest findings are often normal. Deeper breaths can sometimes elicit otherwise undetectable wheezing. In clinic, quick resolution (within 10 min) or convincing improvement in symptoms and signs of asthma with administration of a short-acting inhaled β-agonist (SABA; e.g., albuterol) is supportive of the diagnosis of asthma.

During asthma exacerbations, expiratory wheezing and a prolonged exhalation phase can usually be appreciated by auscultation. Decreased breath sounds in some of the lung fields, commonly the right lower posterior lobe, are consistent with regional hypoventilation caused by airways obstruction. Rhonchi and crackles (or rales) can sometimes be heard, resulting from excess mucus production and inflammatory exudate in the airways. The combination of segmental crackles and poor breath sounds can indicate lung segmental atelectasis that is difficult to distinguish from bronchial pneumonia and can complicate acute asthma management. In severe exacerbations, the greater extent of airways obstruction causes labored breathing and respiratory distress, which manifests as inspiratory and expiratory wheezing, increased prolongation of exhalation, poor air entry, suprasternal and intercostal retractions, nasal flaring, and accessory respiratory muscle use. In extremis, airflow may be so limited that wheezing cannot be heard (Table 144-4).

DIFFERENTIAL DIAGNOSIS

Many childhood respiratory conditions can present with symptoms and signs similar to those of asthma (Table 144-5). Besides asthma, other common causes of chronic, intermittent coughing include gastroesophageal reflux (GER) and rhinosinusitis. Both GER and chronic sinusitis can be challenging to diagnose in children. Often, GER is clinically silent in children, and children with chronic sinusitis do not report sinusitis-specific symptoms, such as localized sinus pressure and

Table 144-4 Formal Evaluation of Asthma Exacerbation Severity in the Urgent or Emergency Care Setting*

	MILD	MODERATE	SEVERE	SUBSET: RESPIRATORY ARREST IMMINENT
SYMPTOMS				
Breathlessness	While walking	While at rest (infant—softer, shorter cry, difficulty feeding)	While at rest (infant—stops feeding)	
	Can lie down	Prefers sitting	Sits upright	
Talks in	Sentences	Phrases	Words	
Alertness	May be agitated	Usually agitated	Usually agitated	Drowsy or confused
SIGNS				
Respiratory rate†	Increased	Increased	Often >30 breaths/min	
Use of accessory muscles; suprasternal retractions	Usually not	Commonly	Usually	Paradoxical thoracoabdominal movement
Wheeze	Moderate; often only end-expiratory	Loud; throughout exhalation	Usually loud; throughout inhalation and exhalation	Absence of wheeze
Pulse rate (beats/min)‡	<100	100-120	>120	Bradycardia
Pulsus paradoxus	Absent <10 mm Hg	May be present 10-25 mm Hg	Often present >25 mm Hg (adult) 20-40 mm Hg (child)	Absence suggests respiratory muscle fatigue
FUNCTIONAL ASSESSMENT				
Peak expiratory flow (value predicted or personal best)	≥70%	Approx. 40-69% or response lasts <2 hr	<40%	<25%§
Pao_2 (breathing air)	Normal (test not usually necessary)	≥60 mm Hg (test not usually necessary)	<60 mm Hg; possible cyanosis	
and/or				
PCO_2	<42 mm Hg (test not usually necessary)	<42 mm Hg (test not usually necessary)	≥42 mm Hg; possible respiratory failure	
SaO_2 (breathing air) at sea level	>95% (test not usually necessary)	90-95% (test not usually necessary)	<90%	
	Hypercapnia (hypoventilation) develops more readily in young children than in adults and adolescents			

*Notes:
- The presence of several parameters, but not necessarily all, indicates the general classification of the exacerbation.
- Many of these parameters have not been systematically studied, especially as they correlate with each other. Thus, they serve only as general guides.
- The emotional impact of asthma symptoms on the patient and family is variable but must be recognized and addressed and can affect approaches to treatment and follow-up.

†Normal breathing rates in awake children by age: <2 mo, <60 breaths/min; 2-12 mo, <50 breaths/min; 1-5 yr, <40 breaths/min; 6-8 yr, <30 breaths/min.
‡Normal pulse rates in children by age: 2-12 mo, <160 beats/min; 1-2 yr, <120 beats/min; 2-8 yr, <110 beats/min.
§Peak expiratory flow testing may not be needed in very severe attacks.
Modified from EPR–3. Expert panel report 3: guidelines for the diagnosis and management of asthma, *NIH Publication No. 07-4051, Bethesda, MD, 2007, U.S. Department of Health and Human Services; National Institutes of Health, National Heart, Lung, and Blood Institute; National Asthma Education and Prevention Program.* http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm.

tenderness. In addition, both GER and rhinosinusitis are often comorbid with childhood asthma and, if not specifically treated, may make asthma difficult to manage.

In early life, chronic coughing and wheezing can indicate recurrent aspiration, tracheobronchomalacia, a congenital anatomic abnormality of the airways, foreign-body aspiration, cystic fibrosis, or bronchopulmonary dysplasia.

In older children and adolescents, vocal cord dysfunction (VCD) can manifest as intermittent daytime wheezing (Table 144-6). In this condition, the vocal cords involuntarily close inappropriately during inspiration and sometimes exhalation, producing shortness of breath, coughing, throat tightness, and often audible laryngeal wheezing and/or stridor. In most cases of VCD, spirometric lung function testing reveals "truncated" and inconsistent inspiratory and expiratory flow-volume loops, a pattern that differs from the reproducible pattern of airflow limitation in asthma that improves with bronchodilators. VCD can coexist with asthma. Flexible rhinolaryngoscopy in the patient with symptomatic VCD can reveal paradoxical vocal cord movements with anatomically normal vocal cords. This condition can be well managed with specialized speech therapy training in the relaxation and control of vocal cord movement. Furthermore, treatment of underlying causes of vocal cord irritability (e.g., high GER/aspiration, allergic rhinitis, rhinosinusitis, asthma) can improve VCD. During acute VCD exacerbations, in addition to relaxation breathing techniques in conjunction with inhalation of heliox (a mixture of 70% helium and 30% oxygen) can relieve vocal cord spasm and VCD symptoms.

Exercise-induced laryngeal obstruction must be considered in children with a presumptive diagnosis of exercise-induced asthma. The diagnosis is confirmed by continuous video laryngoscopy during exercise.

In some locales, hypersensitivity pneumonitis (farming communities, homes of bird owners), pulmonary parasitic infestations (rural areas of developing countries), or tuberculosis may be common causes of chronic coughing and/or wheezing. Rare asthma-masquerading conditions in childhood include bronchiolitis obliterans, interstitial lung diseases, primary ciliary dyskinesias, humoral immune deficiencies, allergic bronchopulmonary mycoses, congestive heart failure, mass lesions in or compressing the larynx, trachea, or bronchi, and coughing and/or wheezing that is an adverse effect of medication. *Chronic pulmonary diseases often produce clubbing, but clubbing is a very unusual finding in childhood asthma.*

LABORATORY FINDINGS

Lung function tests can help to confirm the diagnosis of asthma and to determine disease severity.

Pulmonary Function Testing

Forced expiratory airflow measures are helpful in diagnosing and monitoring asthma and in assessing efficacy of therapy. Lung function testing is particularly helpful in children with asthma who are poor perceivers of airflow obstruction or when physical signs of asthma do not occur until airflow obstruction is severe.

Table 144-5 Differential Diagnosis of Childhood Asthma

UPPER RESPIRATORY TRACT CONDITIONS
Allergic rhinitis*
Chronic rhinitis*
Sinusitis*
Adenoidal or tonsillar hypertrophy
Nasal foreign body
MIDDLE RESPIRATORY TRACT CONDITIONS
Laryngotracheobronchomalacia*
Laryngotracheobronchitis (e.g., pertussis)*
Laryngeal web, cyst, or stenosis
Exercise-induced laryngeal obstruction
Vocal cord dysfunction*
Vocal cord paralysis
Tracheoesophageal fistula
Vascular ring, sling, or external mass compressing on the airway (e.g., tumor)
Foreign body aspiration*
Chronic bronchitis from environmental tobacco smoke exposure*
Toxic inhalations
LOWER RESPIRATORY TRACT CONDITIONS
Bronchopulmonary dysplasia (chronic lung disease of preterm infants)
Viral bronchiolitis*
Gastroesophageal reflux*
Causes of bronchiectasis:
Cystic fibrosis
Immune deficiency
Allergic bronchopulmonary mycoses (e.g., aspergillosis)
Chronic aspiration
Immotile cilia syndrome, primary ciliary dyskinesia
Bronchiolitis obliterans
Interstitial lung diseases
Hypersensitivity pneumonitis
Pulmonary eosinophilia, Churg-Strauss vasculitis
Pulmonary hemosiderosis
Tuberculosis
Pneumonia
Pulmonary edema (e.g., congestive heart failure)
Medications associated with chronic cough:
Acetylcholinesterase inhibitors
β-Adrenergic antagonists
Angiotensin-converting enzyme inhibitors

*More common asthma masqueraders.

Table 144-6 Similarities and Differences Between Vocal Cord Dysfunction and Asthma

VOCAL CORD DYSFUNCTION	ASTHMA
Extrathoracic	Intrathoracic
Rare (?never) hypoxemia	+ Hypoxemia
No hypercapnia/acidosis	+ Hypercapnia/acidosis
Normal expiratory spirometry	Reduced expiratory flow
Abnormal inspiratory loop (in some)	Normal inspiratory loop
Start/stop abruptly; few symptoms between episodes	Persistent symptoms
Frequent emergency department/office visits	Frequent emergency department/office visits
Multiple medications	Multiple medications

From Noyes BE, Kemp JS: Vocal cord dysfunction in children. Paediat Respir Rev *8:155–163, 2007 (Table 2, p. 159).*

Table 144-7 Lung Function Abnormalities in Asthma

Spirometry (in clinic):
• Airflow limitation:
• Low FEV_1 (relative to percentage of predicted norms)
• FEV_1:FVC ratio <0.80
Bronchodilator response (to inhaled β-agonist):
• Improvement in FEV_1 ≥12% and ≥200 mL*
Exercise challenge:
• Worsening in FEV_1 ≥15%*
Daily peak flow or FEV_1 monitoring: day to day and/or A.M.-to-P.M. variation ≥20%*

*Main criteria consistent with asthma.
FEV_1, forced expiratory volume in 1 sec; FVC, forced vital capacity.

Many asthma guidelines promote spirometric measures of airflow and lung volumes during forced expiratory maneuvers as standard for asthma assessment. **Spirometry** is a helpful objective measure of airflow limitation (Fig. 144-2). Spirometry is an essential assessment tool in children who are at risk for severe asthma exacerbations and those who have poor perception of asthma symptoms. Knowledgeable personnel are needed to perform and interpret findings of spirometry tests. Valid spirometric measures depend on a patient's ability to properly perform a full, forceful, and prolonged expiratory maneuver, usually feasible in children >6 yr of age (with some younger exceptions). Reproducible spirometric efforts are an indicator of test validity; i.e., the **FEV_1** (forced expiratory volume in 1 sec) should be reproducible within 5% on 3 measurements, and the *highest* value taken as the reported measure effort of the 3 is used. This standard utilization of the highest of 3 reproducible efforts is indicative of the effort dependence of reliable spirometric testing.

In asthma, airways blockage results in reduced airflow with forced exhalation (see Fig. 144-2). Because asthmatic patients typically have hyperinflated lungs, FEV_1 can be simply adjusted for full expiratory lung volume—the forced vital capacity (FVC)—with an FEV_1:FVC ratio. Generally, an FEV_1:FVC ratio <0.80 indicates significant airflow obstruction (Table 144-7). Normative values for FEV_1 have been determined for children on the basis of height, gender, and ethnicity. Abnormally low FEV_1 as a percentage of predicted norms is 1 of 6 criteria used to determine asthma severity and control in asthma management guidelines sponsored by the U.S. National Institutes of Health (NIH) and the Global Initiative for Asthma (GINA).

Such measures of airflow alone are not diagnostic of asthma, because numerous other conditions can cause airflow reduction. Bronchodilator response to an inhaled β-agonist (e.g., albuterol) is greater in asthmatic patients than nonasthmatic persons; an improvement in FEV_1 ≥12% or >200 mL is consistent with asthma. Bronchoprovocation challenges can be helpful in diagnosing asthma and optimizing asthma management. Asthmatic airways are hyperresponsive and therefore more sensitive to inhaled methacholine, mannitol, and cold or dry air. The degree of AHR to these exposures correlates to some extent with asthma severity and airways inflammation. Although bronchoprovocation challenges are carefully dosed and monitored in an investigational setting, their use is rarely practical in general practice. Exercise challenges (aerobic exertion or "running" for 6-8 min) can help to identify children with exercise-induced bronchospasm. Although the airflow response of nonasthmatic persons to exercise is to increase functional lung volumes and improve FEV_1 slightly (5-10%), exercise often provokes airflow obstruction in persons with inadequately treated asthma. Accordingly, in asthmatic patients, FEV_1 typically decreases during or after exercise by >15% (see Table 144-7). The onset of exercise-induced bronchospasm is usually within 15 min after a vigorous exercise challenge and can spontaneously resolve within 30-60 min. Studies of exercise challenges in school-age children typically identify an additional 5-10% with exercise-induced bronchospasm and previously unrecognized asthma. There are 2 caveats regarding exercise challenges: first,

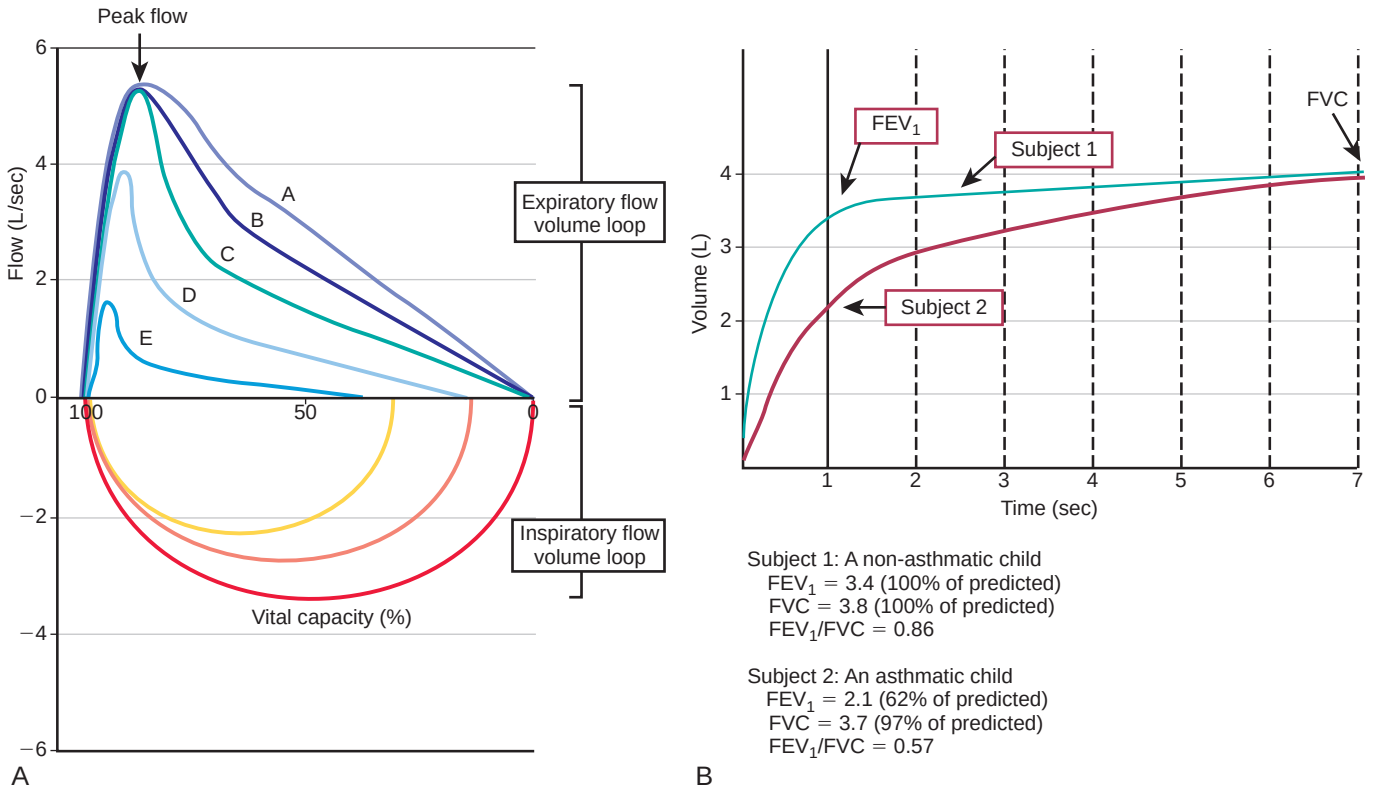


Figure 144-2 Spirometry. *A,* Spirometric flow-volume loops. A is an expiratory flow-volume loop of a nonasthmatic person without airflow limitation. B through E are expiratory flow-volume loops in asthmatic patients with increasing degrees of airflow limitation (B is mild; E is severe). Note the "scooped" or concave appearance of the asthmatic expiratory flow-volume loops; with increasing obstruction, there is greater "scooping." *B,* Spirometric volume-time curves. Subject 1 is a nonasthmatic person; subject 2 is an asthmatic patient. Note how the FEV_1 and FVC lung volumes are obtained. The FEV_1 is the volume of air exhaled in the 1st sec of a forced expiratory effort. The FVC is the total volume of air exhaled during a forced expiratory effort, or forced vital capacity. Note that subject 2's FEV_1 and FEV_1:FVC ratio are smaller than subject 1's, demonstrating airflow limitation. Also, subject 2's FVC is very close to what is expected.

treadmill challenges in the clinic are not completely reliable and can miss exertional asthma that can be demonstrated on the playing field; and second, exercise challenges can induce severe exacerbations in at-risk patients. Careful patient selection for exercise challenges and preparedness for severe asthma exacerbations are required.

Measuring **exhaled nitric oxide** (FE_{NO}), a marker of airway inflammation in allergy-associated asthma, may possibly help adjust antiinflammatory management and confirm the diagnosis of asthma.

Peak expiratory flow (PEF) monitoring devices provide simple and inexpensive home-use tools to measure airflow and can be helpful in a number of circumstances (Fig. 144-3). Similarly to spirometry in clinics, poor perceivers of asthma can benefit by monitoring PEFs at home to assess their airflow as an indicator of asthma control or problems. PEF devices vary in the ability to detect airflow obstruction: they are generally less sensitive and reliable than spirometry to detect airflow obstruction such that, in some patients, PEF values decline only when airflow obstruction is severe. Therefore, PEF monitoring should be started by measuring morning and evening PEFs (best of 3 attempts) for several weeks for patients to practice the technique, to determine diurnal variation and a "personal best," and to correlate PEF values with symptoms (and ideally spirometry). Diurnal variation in PEF >20% is consistent with asthma (see Fig. 144-3 and Table 144-7).

Radiology

The findings of chest radiographs (posteroanterior and lateral views) in children with asthma often appear to be normal, aside from subtle and nonspecific findings of hyperinflation (e.g., flattening of the diaphragms) and peribronchial thickening (Fig. 144-4). Chest radiographs can help identify abnormalities that are hallmarks of asthma masqueraders (aspiration pneumonitis, hyperlucent lung fields in bronchiolitis obliterans) and complications during asthma exacerbations (atelectasis, pneumomediastinum, pneumothorax). Some lung abnormalities can be better appreciated with high-resolution, thin-section chest CT scans. Bronchiectasis, which is sometimes difficult to appreciate on chest radiograph but is clearly seen on CT scan, implicates an asthma masquerader such as cystic fibrosis, allergic bronchopulmonary mycoses (aspergillosis), ciliary dyskinesias, or immune deficiencies.

Other tests, such as allergy testing to assess sensitization to inhalant allergens, help with the management and prognosis of asthma. In a comprehensive U.S. study of 5-12 yr old asthmatic children (Childhood Asthma Management Program [CAMP]), 88% of the subjects had inhalant allergen sensitization according to results of allergy prick skin testing.

TREATMENT

The NIH-sponsored *National Asthma Education and Prevention Program's Expert Panel Report 3 (EPR3): Guidelines for the Diagnosis and Management of Asthma 2007* is available online (www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm). Similar guidelines *From the Global Strategy for Asthma Management and Prevention,* GINA 2012, are also available online (www.ginaasthma.org). The key components to optimal asthma management are specified (Fig. 144-5). **Management** of asthma should have the following components: (1) assessment and monitoring of disease activity; (2) education to enhance patient and family knowledge and skills for self-management; (3) identification and management of precipitating factors and comorbid conditions that worsen asthma; and (4) appropriate selection of medications to address the patient's needs. The long-term goal of asthma management is attainment of optimal asthma control.

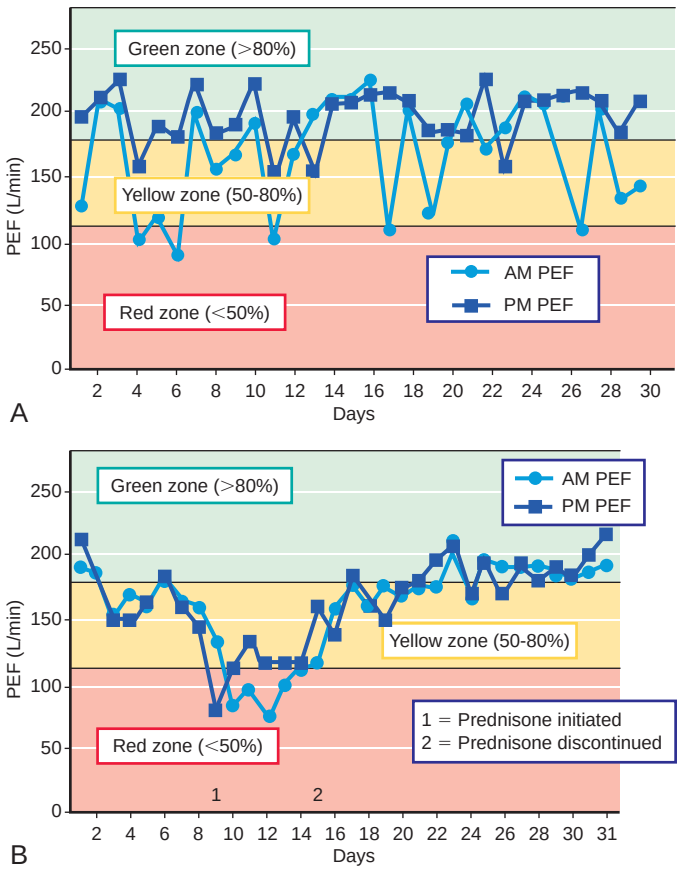


Figure 144-3 An example of the role of peak flow monitoring in childhood asthma. *A*, PEFs performed and recorded twice daily, in the morning (A.M.) and evening (P.M.), over 1 mo in an asthmatic child. This child's "personal best" PEF value is 220 L/min; therefore, the green zone (>80-100% of best) is 175-220 L/min; the yellow zone (50-80%) is 110-175 L/min; and the red zone (<50%) is <110 L/min. Note that this child's P.M. PEF values are almost always in the green zone, whereas his A.M. PEFs are often in the yellow or red zone. This pattern illustrates the typical diurnal A.M.-to-P.M. variation of inadequately controlled asthma. *B*, PEFs performed twice daily, in the morning (A.M.) and evening (P.M.), over 1 mo in an asthmatic child in whom an asthma exacerbation developed from a viral respiratory tract infection. Note that the child's PEF values were initially in the green zone. A viral respiratory tract infection led to asthma worsening, with a decline in PEF to the yellow zone that continued to worsen until PEF values were in the red zone. At that point, a 4-day prednisone course was administered, followed by improvement in PEF back to the green zone.

Component 1: Regular Assessment and Monitoring

Regular assessment and monitoring are based on the concepts of asthma severity, asthma control, and responsiveness to therapy. **Asthma severity** is the intrinsic intensity of disease, and assessment is generally most accurate in patients not receiving controller therapy. Hence, assessing asthma severity directs the initial level of therapy. The 2 general categories are **intermittent** asthma and **persistent** asthma, the latter being further subdivided into **mild, moderate,** and **severe.** In contrast, **asthma control** refers to the degree to which symptoms, ongoing functional impairments, and risk of adverse events are minimized, and goals of therapy are met. In children receiving controller therapy, assessment of asthma control is important in adjusting therapy and is categorized in 3 levels: well-controlled, not well-controlled, and very poorly controlled. **Responsiveness to therapy** is the ease or difficulty with which asthma control is attained by treatment.

Classification of asthma severity and control is based on the domains of **impairment** and **risk.** These domains may not correlate with each other and may respond differently to treatment. In some children with asthma, day-to-day impairment is well controlled, but the risk of severe exacerbations remains. The NIH guidelines have distinct criteria for 3 childhood age groups—0-4 yr, 5-11 yr, and ≥12 yr—for the evaluation of both severity (Table 144-8) and control (Table 144-9). The level of asthma severity or control is based on the most severe impairment or risk category. In assessing asthma severity, **impairment** consists of an assessment of the patient's recent symptom frequency (daytime and nighttime, with subtle differences in numeric cutoffs between the 3 age groups), SABA usage for quick relief, ability to engage in normal or desired activities, and airflow compromise evaluated by spirometry in children 5 yr and older. **Risk** refers to the likelihood of developing severe asthma exacerbations. Of note, in the absence of frequent symptoms, persistent asthma should be considered, and therefore long-term controller therapy should be initiated for infants or children who have risk factors for asthma (see earlier) and 4 or more episodes of wheezing over the past year that lasted longer than 1 day and affected sleep, or 2 or more exacerbations in 6 mo requiring systemic corticosteroids.

Asthma management can be optimized through regular clinic visits every 2-6 wk until good asthma control is achieved. For children already on controller medication therapy, management is tailored to the child's level of control. The NIH guidelines provide tables for evaluating asthma control for the 3 age groups (see Table 144-9). In evaluation of asthma control, as in severity assessment, impairment includes an assessment of the patient's symptom frequency (daytime and nighttime), SABA usage for quick relief, ability to engage in normal or desired activities, and, for older children, airflow measurements. Furthermore, with respect to risk assessment, besides considering severity and frequency of exacerbations requiring systemic corticosteroids, tracking of lung growth in older children and monitoring adverse effects of medications is also warranted. The degree of impairment and presence of risk are used to determine the patient's level of asthma control as well-controlled, not well-controlled, or very poorly controlled. Children with *well-controlled asthma* have daytime symptoms ≤2 days/wk and need a rescue bronchodilator ≤2 days/wk; an FEV_1 of >80% of predicted (and an FEV_1:FVC ratio >80% for children 5-11 yr of age); no interference with normal activity; and <2 exacerbations in the past year. The impairment criteria vary slightly depending on age group: there are different thresholds in the frequency of nighttime awakenings; addition of FEV_1:FVC ratio criteria for children 5-11 yr old and addition of validated impairment questionnaires (e.g., Asthma Control Test [ACT] for ages ≥12 yr, Childhood ACT for ages 4-11 yr). Children whose status does not meet all of the criteria defining well-controlled asthma are determined to have either not-well-controlled or very poorly controlled asthma, which is determined by the single criterion with the poorest rating.

Two to 4 asthma checkups per year are recommended for reassessing and maintaining good asthma control. Lung function testing (spirometry) is recommended at least annually and more often if asthma is poorly perceived, inadequately controlled and/or lung function is abnormally low. PEF monitoring at home can be helpful in the assessment of asthmatic children with poor symptom perception, other causes of chronic coughing in addition to asthma, moderate to severe asthma, or a history of severe asthma exacerbations. PEF monitoring is feasible in children as young as 4 yr who are able to master this skill. Use of a **stoplight zone system** tailored to each child's "personal best" PEF values can optimize effectiveness and interest (see Fig 144-3): The green zone (80-100% of personal best) indicates good control; the yellow zone (50-80%) indicates less-than-optimal control and necessitates increased awareness and treatment; the red zone (<50%) indicates poor control and greater likelihood of an exacerbation, requiring immediate intervention. In actuality, these ranges are approximate and may need to be adjusted for many asthmatic children by raising the ranges that indicate inadequate control (in the yellow zone, 70-90%). Once-daily PEF monitoring is preferable in the morning when peak flows are typically lower.

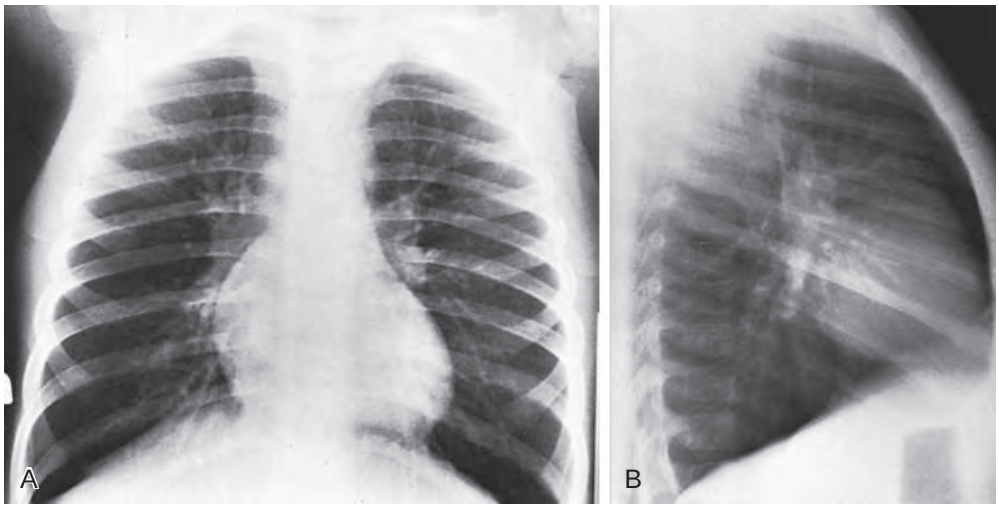


Figure 144-4 A 4-year-old boy with asthma. Frontal *(A)* and lateral *(B)* radiographs show pulmonary hyperinflation and minimal peribronchial thickening. No asthmatic complication is apparent.

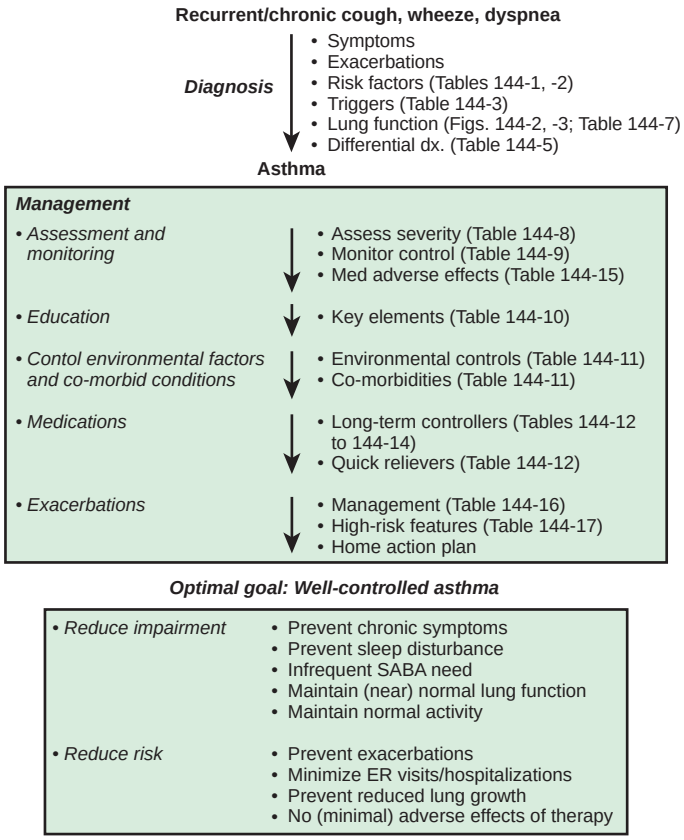


Figure 144-5 The key elements to optimal asthma management. SABA, short-acting β-agonist.

Component 2: Patient Education

Specific educational elements in the clinical care of children with asthma are believed to make an important difference in home management and in adherence of families to an optimal plan of care and eventually impacting patient outcomes (Table 144-10). Every visit presents an important opportunity to educate the child and family, allowing them to become knowledgeable partners in asthma management, because optimal management depends on their daily assessments and implementation of any management plan. Effective communications take into account sociocultural and ethnic factors of children and their families, provide an open forum for concerns about asthma and its treatment to be raised and addressed, and include patients and families as active participants in the development of treatment goals and selection of medications. Self-management skills should be reevaluated regularly (e.g., inhaler medication technique).

During initial patient visits, a basic understanding of the pathogenesis of asthma (chronic inflammation and AHR underlying a clinically intermittent presentation) can help children with asthma and their parents understand the importance of recommendations aimed at reducing airways inflammation to achieve and maintain good asthma control. It is helpful to specify the expectations of good asthma control resulting from optimal asthma management (see Fig. 144-5). Addressing concerns about potential adverse effects of asthma pharmacotherapeutic agents, especially their risks relative to their benefits, is essential in achieving long-term adherence with asthma pharmacotherapy and environmental control measures.

Children with asthma and their families, particularly patients with moderate or severe persistent or poorly controlled asthma and patients who have had severe exacerbations, benefit from a written asthma management plan. This plan has 2 main components: (1) a daily "routine" management plan describing regular asthma medication use and other measures to keep asthma under good control; and (2) an action plan to manage worsening asthma, describing indicators of impending exacerbations, identifying what medications to take, and specifying when and how to contact the regular physician and/or obtain urgent/emergency medical care.

Regular follow-up visits are recommended to help to maintain optimal asthma control. In addition to determining disease control level and revising daily and exacerbation management plans accordingly, follow-up visits are important teaching opportunities to encourage open communication of concerns with asthma management recommendations (e.g., daily administration of controller medications). Reassessing patients' and parents' understanding of the role of different medications in asthma management and control, and their technique in using inhaled medications, can be insightful and can help guide teaching to improve adherence to a management plan that might not have been adequately or properly implemented.

ADHERENCE

Asthma is a chronic condition that is usually best managed with daily controller medication. However, symptoms wax and wane, severe exacerbations are infrequent, and when asthma is asymptomatic, a natural tendency is to reduce or discontinue daily controller therapies. As such, adherence to a daily controller regimen is commonly suboptimal;

Table 144-8 Assessing Asthma Severity and Initiating Treatment for Patients Who Are Not Currently Taking Long-Term Control Medications*

	CLASSIFICATION OF ASTHMA SEVERITY			
		PERSISTENT		
	Intermittent	Mild	Moderate	Severe
COMPONENTS OF SEVERITY				
Impairment				
Daytime symptoms	≤2 days/wk	>2 days/wk but not daily	Daily	Throughout the day
Nighttime awakenings:				
Age 0-4 yr	0	1-2×/mo	3-4×/mo	>1×/wk
Age ≥5 yr	≤2×/mo	3-4×/mo	>1×/wk but not nightly	Often 7×/wk
Short-acting β_2-agonist use for symptoms (not for prevention of exercise-induced bronchospasm)	≤2 days/wk	>2 days/wk but not daily, and not more than 1× on any day	Daily	Several times per day
Interference with normal activity	None	Minor limitation	Some limitation	Extreme limitation
Lung function:				
FEV_1 % predicted, age ≥5 yr	Normal FEV_1 between exacerbations >80% predicted	≥80% predicted	60-80% predicted	<60% predicted
FEV_1:FVC ratio†:				
Age 5-11 yr	>85%	>80%	75-80%	<75%
Age ≥12 yr	Normal	Normal	Reduced 5%	Reduced >5%
Risk				
Exacerbations requiring systemic corticosteroids:				
Age 0-4 yr	0-1/yr (see notes)	≥2 exacerbations in 6 mo requiring systemic corticosteroids **or** ≥4 wheezing episodes/yr lasting >1 day *and* risk factors for persistent asthma		
Age ≥ 5 yr	0-1/yr (see notes)	≥2/yr (see notes)	≥2/yr (see notes)	≥2/yr (see notes)
Consider severity and interval since last exacerbation. Frequency and severity may fluctuate over time for patients in any severity category. Relative annual risk of exacerbations may be related to FEV_1.				
RECOMMENDED STEP FOR INITIATING THERAPY				
All ages	Step 1	Step 2		
Age 0-4 yr			Step 3	Step 3
Age 5-11 yr			Step 3, medium-dose ICS option	Step 3, medium-dose ICS option **or** Step 4
Age ≥12 yr			Consider a short course of systemic corticosteroids	Consider a short course of systemic corticosteroids
In 2-6 wk, evaluate level of asthma control that is achieved and adjust therapy accordingly. If no clear benefit is observed within 4-6 wk, consider adjusting therapy or alternative diagnoses.				

*Notes:
- The stepwise approach is meant to assist, not replace, the clinical decision-making required to meet individual patient needs.
- Level of severity is determined by both impairment and risk. Assess impairment domain by patient's/caregiver's recall of previous 2-4 wk. Symptom assessment for longer periods should reflect a global assessment, such as inquiring whether a patient's asthma is better or worse since the last visit. Assign severity to the most severe category in which any feature occurs.
- At present, there are inadequate data to correspond frequencies of exacerbations with different levels of asthma severity. For treatment purposes, patients who had ≥2 exacerbations requiring oral systemic corticosteroids in the past 6 mo, or ≥4 wheezing episodes in the past year, and who have risk factors for persistent asthma may be considered the same as patients who have persistent asthma, even in the absence of impairment levels consistent with persistent asthma.

†Normal FEV_1:FVC: 8-19 yr, 85%; 20-39 yr, 80%.

FEV_1, forced expiratory volume in 1 sec; FVC, forced vital capacity; ICS, inhaled corticosteroids.

Adapted from the National Asthma Education and Prevention Program: Expert Panel Report 3 (EPR 3): Guidelines for the diagnosis and management of asthma—summary report 2007, J Allergy Clin Immunol *120(Suppl):S94–S138, 2007*.

inhaled corticosteroids (ICSs) are underused 60% of the time. In one study, children with asthma who required an oral corticosteroid course for an asthma exacerbation had used their daily controller ICS 15% of the time. Misconceptions about controller medication time to onset, efficacy, and safety often underlie poor adherence and can be addressed by asking about such concerns at each visit.

Component 3: Control of Factors Contributing to Asthma Severity

Controllable factors that can worsen asthma can be generally grouped as (1) environmental exposures and (2) comorbid conditions (Table 144-11).

Eliminating and Reducing Problematic Environmental Exposures

The majority of children with asthma have an allergic component to their disease; steps should be taken to investigate and minimize allergen exposures in sensitized asthmatic patients. The medical history should address potential allergen triggers (see below), but often patients have chronic symptoms and cannot identify potential triggers. Therefore, allergy testing should be considered for at least those with persistent asthma. For asthmatic patients who are allergic to allergens in their homes, reducing or eliminating these home allergen exposures can decrease asthma symptoms, medication requirements, AHR, severe exacerbations, and disease persistence. Common home allergen

Table 144-9 Assessing Asthma Control and Adjusting Therapy in Children*

	CLASSIFICATION OF ASTHMA CONTROL		
	Well-Controlled	**Not Well-Controlled**	**Very Poorly Controlled**
COMPONENTS OF CONTROL			
Impairment			
Symptoms	≤2 days/wk but not more than once on each day	>2 days/wk or multiple times on ≤2 days/wk	Throughout the day
Nighttime awakenings:			
Age 0-4 yr	≤1×/mo	>1×/mo	>1×/wk
Age 5-11 yr	≤1×/mo	≥2×/mo	≥2×/wk
Age ≥12 yr	≤2×/mo	1-3×/wk	≥4×/wk
Short-acting β_2-agonist use for symptoms (not for exercise-induced bronchospasm pretreatment)	≤2 days/wk	>2 days/wk	Several times per day
Interference with normal activity	None	Some limitation	Extremely limited
Lung function:			
Age 5-11 yr:			
FEV_1 (% predicted or peak flow)	>80% predicted or personal best	60-80% predicted or personal best	<60% predicted or personal best
FEV_1/FVC:	>80%	75-80%	<75%
Age ≥ 12 yr:			
FEV_1 (% predicted or peak flow)	>80% predicted or personal best	60-80% predicted or personal best	<60% predicted or personal best
Validated questionnaires†:			
Age ≥ 12 yr:			
ATAQ	0	1-2	3-4
ACQ	≤0.75	≤1.5	N/A
ACT	≥20	16-19	≤15
Risk			
Exacerbations requiring systemic corticosteroids:			
Age 0-4 yr	0-1/yr	2-3/yr	>3/yr
Age ≥5 yr	0-1/yr	≥2/yr (see notes)	
Consider severity and interval since last exacerbation.			
Treatment-related adverse effects	Medication side effects can vary in intensity from none to very troublesome and worrisome. The level of intensity does not correlate to specific levels of control but should be considered in the overall assessment of risk.		
Reduction in lung growth *or* progressive loss of lung function	Evaluation requires long-term follow-up care.		
RECOMMENDED ACTION FOR TREATMENT			
	Maintain current step. Regular follow-up every 1-6 mo to maintain control. Consider step down if well-controlled for at least 3 mo.	Step up‡ (1 step) and reevaluate in 2-6 wk. If no clear benefit in 4-6 wk, consider alternative diagnoses or adjusting therapy. For side effects, consider alternative options.	Consider short course of oral corticosteroids. Step up§ (1-2 steps) and reevaluate in 2 wk. If no clear benefit in 4-6 wk, consider alternative diagnoses or adjusting therapy. For side effects, consider alternative options.

*Notes:
- The stepwise approach is meant to assist, not replace, the clinical decision making required to meet individual patient needs.
- The level of control is based on the most severe impairment or risk category. Assess impairment domain by caregiver's recall of previous 2-4 wk. Symptom assessment for longer periods should reflect a global assessment such as inquiring whether the patient's asthma is better or worse since the last visit.
- At present, there are inadequate data to correspond frequencies of exacerbations with different levels of asthma control. In general, more frequent and intense exacerbations (e.g., requiring urgent, unscheduled care, hospitalization, or intensive care unit admission) indicate poorer disease control. For treatment purposes, patients who had ≥2 exacerbations requiring oral systemic corticosteroids in the past year may be considered the same as patients who have not-well-controlled asthma, even in the absence of impairment levels consistent with not-well-controlled asthma.

†Validated questionnaires for the impairment domain (the questionnaires do not assess lung function or the risk domain) and definition of minimal important difference (MID) for each:
- ATAQ, Asthma Therapy Assessment Questionnaire; MID = 1.0
- ACQ, Asthma Control Questionnaire; MID = 0.5
- ACT, Asthma Control Test; MID not determined

‡ACQ values of 0.76-1.40 are indeterminate regarding well-controlled asthma.

§Before step-up therapy: (a) review adherence to medications, inhaler technique, and environmental control; (b) if alternative treatment option was used in a step, discontinue it and use preferred treatment for that step.

FEV_1, forced expiratory volume in 1 sec; FVC, forced vital capacity.

Adapted from the National Asthma Education and Prevention Program: Expert Panel Report 3 (EPR 3): Guidelines for the diagnosis and management of asthma—summary report 2007, J Allergy Clin Immunol *120(Suppl):S94–S138, 2007*.

Table 144-10 Key Elements of Productive Clinic Visits for Asthma

Specify goals of asthma management
Explain basic facts about asthma:
- Contrast normal vs asthmatic airways
- Link airways inflammation, "twitchiness," and bronchoconstriction
- Long-term-control and quick-relief medications
- Address concerns about potential adverse effects of asthma pharmacotherapy

Teach, demonstrate, and have patient show proper technique for:
- Inhaled medication use (spacer use with metered-dose inhaler)
- Peak flow measures

Investigate and manage factors that contribute to asthma severity:
- Environmental exposures
- Comorbid conditions

Create written 2-part asthma management plan:
- Daily management
- Action plan for asthma exacerbations

Regular follow-up visits:
- Twice yearly (more often if asthma not well-controlled)
- Monitor lung function annually

Table 144-11 Control of Factors Contributing to Asthma Severity

ELIMINATE OR REDUCE PROBLEMATIC ENVIRONMENTAL EXPOSURES:

Environmental tobacco smoke elimination or reduction in home and automobiles

Allergen exposure elimination or reduction in sensitized asthmatic patients:
- Animal danders: pets (cats, dogs, rodents, birds)
- Pests (mice, rats)
- Dust mites
- Cockroaches
- Molds

Other airway irritants:
- Wood- or coal-burning smoke
- Strong chemical odors and perfumes (e.g., household cleaners)
- Dusts

TREAT COMORBID CONDITIONS:
- Rhinitis
- Sinusitis
- Gastroesophageal reflux

exposures include furred or feathered animals as pets (cats, dogs, rodents, birds) or as pests (mice, rats), and occult indoor allergens, such as dust mites, cockroaches, and molds. Although some sensitized children may report an increase in asthma symptoms on exposure to the allergen source, improvement from allergen avoidance may not become apparent without a sustained period of days to weeks away from the offending exposure. Tobacco, wood and coal smoke, dusts, strong odors, and noxious air pollutants can all aggravate asthma. These airways irritants should be eliminated from or reduced in the homes and automobiles used by children with asthma. School classrooms and daycare settings can also be sites of environmental exposures that worsen asthma. Eliminating or minimizing these exposures (e.g., furred or feathered pets in classrooms of sensitized children with asthma) can reduce asthma symptoms, disease severity, and the amount of medication needed to achieve good asthma control. Annual influenza vaccination continues to be recommended for all children with asthma, although influenza is not responsible for the large majority of virus-induced asthma exacerbations experienced by children.

Aspirin-exacerbated respiratory disease, formerly called aspirin-induced asthma, is also associated with chronic eosinophilic rhinitis and nasal polyposis. Inhibition of cyclooxygenase by aspirin and other nonsteroidal antiinflammatory drugs (including cyclooxygenase [COX]-2 inhibiting agents) is thought to be the primary mechanism, which leads to exacerbations of disease, predominantly in patients with moderate to severe persistent asthma. Acetaminophen, a weak COX-1 inhibitor, is safe in low doses, but may produce symptoms if high doses are taken. The incidence is between 5% and 10% of predominantly adolescents with asthma; it is rare in children <10 yr of age. Following ingestion of the drug, symptoms may appear between 30 and 120 min and include profuse rhinorrhea, nasal congestion, and tearing, accompanied by bronchospasm. Vocal cord spasm and an anaphylactic-like reaction are rare complications. Aspirin and related drugs should be avoided in these patients; an alternative approach is aspirin desensitization by an allergist.

Treating Comorbid Conditions

Rhinitis, sinusitis, and GER often accompany asthma and worsen disease severity. They can also mimic asthma symptoms and lead to misclassification of asthma severity and control. Indeed, these conditions with asthma are the most common causes of chronic coughing. Effective management of these comorbid conditions may improve asthma symptoms and disease severity, such that less asthma medication is needed to achieve good asthma control.

GER is observed in 43% of children with persistent asthma. GER may worsen asthma through 2 postulated mechanisms: (1) aspiration of refluxed gastric contents (micro- or macro-aspiration); and (2) vagally mediated reflex bronchospasm. Occult GER should be suspected in individuals with difficult-to-control asthma, especially patients who have prominent asthma symptoms while eating or sleeping (in a horizontal position) or who prop themselves up in bed to reduce nocturnal symptoms. GER can be demonstrated by reflux of barium into the esophagus during a barium swallow procedure or by esophageal probe monitoring. Because radiographic studies lack sufficient sensitivity and specificity, extended esophageal monitoring is the method of choice for diagnosing GER. If significant GER is noted, reflux precautions should be instituted (no food 2 hr before bedtime, head of the bed elevated 6 in, avoidance of caffeinated foods and beverages) and medications such as proton pump inhibitors (omeprazole, lansoprazole) or H_2-receptor antagonists (cimetidine, ranitidine) administered for 8-12 wk. Proton pump inhibition did not improve asthma control in a study of children with persistent, poorly controlled asthma and GER.

Rhinitis is usually comorbid with asthma, detected in ≈90% of children with asthma. Rhinitis can be seasonal and/or perennial, with allergic and nonallergic components. Rhinitis complicates and worsens asthma via numerous direct and indirect mechanisms. Nasal breathing may improve asthma and reduce exercise-induced bronchospasm by humidifying and warming inspired air and filtering out allergens and irritants that can trigger asthma and worsen airway inflammation. Reduction of nasal congestion and obstruction can help the nose to perform these humidifying, warming, and filtering functions. In asthmatic patients, improvement in rhinitis is also associated with improvement in AHR, lower airways inflammation, asthma symptoms, and asthma medication use. Optimal rhinitis management in children is similar to asthma management in regard to the importance of interventions to reduce nasal inflammation (see Chapter 143).

Radiographic evidence for **sinus disease** is common in patients with asthma. There is usually significant improvement in asthma control in patients diagnosed and treated for sinus disease. A coronal, "screening" or "limited" CT scan of the sinuses is the gold standard test for sinus disease and can be helpful if recurrent sinusitis has been suspected and repeatedly treated without such evidence. In comparison, sinus X-rays are inaccurate. If the patient with asthma has clinical and radiographic evidence for sinusitis, topical therapy to include nasal saline irrigations, intranasal corticosteroids, and a 2-3–wk course of antibiotics should be considered.

Component 4: Principles of Asthma Pharmacotherapy

The current version of NIH asthma guidelines (2007) provides treatment recommendations that vary by age groups and are based on current evidence (Table 144-12). The goals of therapy are to achieve a well-controlled state by reducing the components of both impairment (e.g., preventing chronic and troublesome symptoms, allowing infrequent need of quick-reliever medications, maintaining "normal" lung function, maintaining normal activity levels including physical activity and school attendance, meeting families' expectations and satisfaction

Table 144-12 Stepwise Approach for Managing Asthma in Children*

AGE	THERAPY†	INTERMITTENT ASTHMA	PERSISTENT ASTHMA: DAILY MEDICATION				
			STEP DOWN if possible (and asthma is well controlled at least 3 months)	ASSESS CONTROL	STEP UP if needed (first check inhaler technique, adherence, environmental control, and comorbid condition)		
		Step 1	Step 2	Step 3	Step 4	Step 5	Step 6
0-4 yr	Preferred	SABA prn	Low-dose ICS	Medium-dose ICS	Medium-dose ICS *+ either* LABA *or* LTRA	High-dose ICS + *either* LABA *or* LTRA	High-dose ICS + *either* LABA *or* LTRA *and* Oral corticosteroid
	Alternative		Cromolyn or montelukast				
5-11 yr	Preferred	SABA prn	Low-dose ICS	*Either* low-dose ICS ± LABA, LTRA, or theophylline *or* Medium-dose ICS	Medium-dose ICS + LABA	High-dose ICS + LABA	High-dose ICS + LABA *and* Oral corticosteroid
	Alternative		Cromolyn, LTRA, nedocromil, or theophylline		Medium-dose ICS *+ either* LTRA *or* Theophylline	High-dose ICS + *either* LTRA *or* Theophylline	High-dose ICS + *either* LTRA *or* Theophylline *and* Oral corticosteroid
≥12 yr	Preferred	SABA prn	Low-dose ICS	Low-dose ICS + LABA *or* Medium-dose ICS	Medium-dose ICS + LABA	High-dose ICS + LABA *and* Consider omalizumab for patients with allergies	High-dose ICS + LABA + oral corticosteroid *and* Consider omalizumab for patients with allergies
	Alternative		Cromolyn, LTRA, nedocromil, or theophylline	Low-dose ICS + LTRA, theophylline, or zileuton	Medium-dose ICS + LTRA, theophylline, or zileuton		
Each step: Patient education, environmental control, and management of comorbidities.							
Age ≥5 yr: Steps 2-4: Consider subcutaneous allergen immunotherapy for patients who have allergic asthma.							
QUICK-RELIEF MEDICATION FOR ALL PATIENTS							
SABA as needed for symptoms. Intensity of treatment depends on severity of symptoms: up to 3 treatments at 20-min intervals as needed. Short course of oral systemic corticosteroids may be needed.							
Caution: Use of SABA >2 days/wk for symptom relief (not prevention of exercise-induced bronchospasm) generally indicates inadequate control and the need to step up treatment.							
For ages 0-4 yr: With viral respiratory infection: SABA q4-6h up to 24 hr (longer with physician consult). Consider short course of systemic corticosteroids if exacerbation is severe or patient has history of previous severe exacerbations.							

*Notes:
- The stepwise approach is meant to assist, not replace, the clinical decision making required to meet individual patient needs.
- If alternative treatment is used and response is inadequate, discontinue it and use the preferred treatment before stepping up.
- If clear benefit is not observed within 4-6 wk and patient/family medication technique and adherence are satisfactory, consider adjusting therapy or alternative diagnosis.
- Studies on children age 0-4 yr are limited. The stepwise approach is meant to assist, not replace, the clinical decision-making required to meet individual patient needs.
- Clinicians who administer immunotherapy or omalizumab should be prepared and equipped to identify and treat anaphylaxis that may occur.
- Theophylline is a less desirable alternative because of the need to monitor serum concentration levels.
- Zileuton is less desirable alternative because of limited studies as adjunctive therapy and the need to monitor liver function.

†Alphabetical order is used when more than 1 treatment option is listed within *either* preferred or alternative therapy.

ICS, inhaled corticosteroid; LABA, inhaled long-acting β_2-agonist; LTRA, leukotriene receptor antagonist; prn, as needed; SABA, inhaled short-acting β_2-agonist.

Adapted from the National Asthma Education and Prevention Program: Expert Panel Report 3 (EPR 3): Guidelines for the diagnosis and management of asthma—summary report 2007, J Allergy Clin Immunol *120(Suppl):S94–S138, 2007.*

with asthma care) and risk (e.g., preventing recurrent exacerbations, reduced lung growth, and medications' adverse effects). The recommendations for initial therapy are based on assessment of asthma severity. For patients who are already using controller therapy, modification of treatment is based on assessment of asthma control and responsiveness to therapy. A major objective of this approach is to identify and treat all "persistent" and inadequately controlled asthma with antiinflammatory controller medication. Daily controller therapy is not recommended for children with "intermittent asthma." *Management of intermittent asthma is simply the use of a SABA as needed for symptoms and for pretreatment in those with exercise-induced bronchospasm (Step 1 therapy; see Table 144-12).*

The preferred treatment for all patients with persistent asthma is daily ICS therapy, as monotherapy or in combination with adjunctive therapy. The type(s) and amount(s) of daily controller medications to be used are determined by the asthma severity and control rating. Alternative medications for Step 2 therapy include a leukotriene receptor antagonist (montelukast), nonsteroidal antiinflammatory agents (cromolyn and nedocromil), and theophylline (for youths). For young children (≤4 yr) with moderate or severe persistent asthma, medium-dose ICS monotherapy is recommended (Step 3); combination therapy is recommended only as a Step 4 treatment for uncontrolled asthma.

Along with medium-dose ICSs, combination therapy with an ICS plus any of the following adjunctive therapies (depending on age group) is recommended as Steps 3 and 4 treatment for moderate persistent asthma, or as step-up therapy for uncontrolled persistent asthma: long-acting inhaled β_2-agonists (LABAs), leukotriene-modifying agents, chromones, and theophylline. In a study of children with uncontrolled asthma while on low-dose ICS, the addition of LABA provided more improvement than either adding a leukotriene receptor antagonist (LTRA) or increasing ICS dosage. However, some children had a good response to ICS or LTRA, justifying them as step-up controller therapy options.

Children with severe persistent asthma (treatment Steps 5 and 6) should receive high-dose ICS and LABA. Long-term administration of oral corticosteroids as controller therapy can be effective, but is rarely needed with the availability of potent ICS and LABA combination formulations in single devices. In addition, omalizumab can be used in children ≥12 yr old with severe allergic asthma. A rescue course of systemic corticosteroids may be necessary at any step. For children age ≥5 yr with allergic asthma requiring Steps 2-4 care, allergen immunotherapy can be considered.

"Step-Up, Step-Down" Approach

The NIH guidelines emphasize initiating higher-level controller therapy at the outset to establish prompt control, with measures to "step down" therapy once good asthma control is achieved. Initially, airflow limitation and the pathology of asthma may limit the delivery and efficacy of ICS such that stepping up to higher doses and/or combination therapy may be needed to gain asthma control. Furthermore, ICS requires weeks to months of daily administration for optimal efficacy to occur. Combination pharmacotherapy can achieve relatively immediate improvement while also providing daily ICS to improve long-term control and reduce exacerbation risk.

Asthma therapy can be stepped down after good asthma control has been achieved and ICS has had time to achieve optimal efficacy. By determining the lowest number or dose of daily controller medications that can maintain good control, the potential for medication adverse effects is reduced. If a child has had well-controlled asthma for at least 3 mo, the guidelines suggest decreasing the dose or number of the child's controller medication(s) to establish the minimum required medications to maintain well-controlled asthma. Regular follow-up is still emphasized because the variability of asthma's course is well recognized. In contrast, if a child has not-well-controlled asthma, the therapy level should be increased by 1 step and close monitoring is recommended. For a child with very poorly controlled asthma, the recommendations are that treatment go up 2 steps and/or a short course of oral corticosteroid therapy be given, with evaluation within 2 wk. As step-up therapy is being considered at any point, it is important to check inhaler technique and adherence, implement environmental control measures, and identify and treat comorbid conditions.

Referral to Asthma Specialist

Referral to an asthma specialist for consultation or co-management is recommended if there are difficulties in achieving or maintaining control. For children younger than 4 yr, referral is recommended for moderate persistent asthma or if the patient requires at least Step 3 care, and should be considered if the patient requires Step 2 care. For children 5 yr of age and older, consultation with a specialist is recommended if the patient requires Step 4 care or higher, and should be considered if Step 3 is required. Referral is also recommended if allergen immunotherapy or anti–immunoglobulin (Ig) E therapy is being considered.

Long-Term Controller Medications

All levels of persistent asthma should be treated with daily medications to improve long-term control (see Table 144-12). Such medications include ICSs, LABAs, leukotriene modifiers, nonsteroidal antiinflammatory agents, and sustained-release theophylline. An anti-IgE preparation, omalizumab (Xolair), is approved by the FDA for use as an add-on therapy in children ≥12 yr who have moderate to severe allergic asthma that is difficult to control. Corticosteroids are the most potent and most effective medications used to treat both the acute (administered systemically) and chronic (administered by inhalation) manifestations of asthma. They are available in inhaled, oral, and parenteral forms (Tables 144-13 and 144-14).

Inhaled Corticosteroids

The NIH guidelines recommend daily ICS therapy as the treatment of choice for all patients with persistent asthma (see Table 144-12). ICS therapy improves lung function as well as reduces asthma symptoms, AHR, and use of "rescue" medications; most importantly, it reduces urgent care visits, hospitalizations, and prednisone use for asthma exacerbations by approximately 50%. ICS therapy may lower the risk of death attributable to asthma. It can achieve all of the goals of asthma management and, as a result, is viewed as first-line treatment for persistent asthma.

Six ICSs are approved for use in children by the FDA, and the NIH guidelines provide an equivalence classification (see Table 144-14), although direct comparisons of efficacy and safety outcomes in children are lacking. ICSs are available in metered-dose inhalers (MDIs), in dry powder inhalers (DPIs), or in suspension for nebulization. Fluticasone propionate, mometasone furoate, ciclesonide, and, to a lesser extent, budesonide are considered "second-generation" ICSs, in that they have greater antiinflammatory potency and diminished systemic bioavailability for potential adverse effects, owing to extensive first-pass hepatic metabolism. The selection of the initial ICS dose is based on the determination of disease severity. A fraction of the initial ICS dose is often sufficient to maintain good control after this goal has been achieved.

Although ICS therapy has been widely used in adults with persistent asthma, its application in children has lagged because of concerns about the potential for adverse effects with long-term use. Generally, clinically significant adverse effects that occur with long-term systemic corticosteroid therapy have not been seen or have only very rarely been reported in children receiving ICSs in recommended doses. The risk of adverse effects from ICS therapy is related to the dose and frequency with which ICSs are given (Table 144-15). High doses (≥1,000 μg/day in children) and frequent administration (4 times/day) are more likely to have local and systemic adverse effects. Children who receive maintenance therapy with higher ICS doses are also likely to require systemic corticosteroid courses for asthma exacerbations, further increasing the risk of corticosteroid adverse effects.

The most commonly encountered **adverse effects** of ICSs are local: oral candidiasis (thrush) and dysphonia (hoarse voice). Thrush results from propellant-induced mucosal irritation and local immunosuppression. Dysphonia occurs from vocal cord myopathy. These effects are

Table 144-13 Usual Dosages for Long-Term Control Medications

Medication	AGE 0-4 yr	5-11 yr	≥12 yr
INHALED CORTICOSTEROIDS (see Table 144-13)			
Methylprednisolone: 2, 4, 8, 16, 32 mg tablets Prednisolone: 5 mg tablets; 5 mg/5 mL, 15 mg/5 mL Prednisone: 1, 2.5, 5, 10, 20, 50 mg tablets; 5 mg/mL, 5 mg/5 mL	• 0.25-2 mg/kg daily in single dose in A.M. or qod as needed for control • Short-course "burst": 1-2 mg/kg/day; maximum 30 mg/day for 3-10 days	• 0.25-2 mg/kg daily in single dose in A.M. or qod as needed for control • Short-course "burst": 1-2 mg/kg/day; maximum 60 mg/day for 3-10 days	• 7.5-60 mg daily in a single dose in A.M. or qod as needed for control • Short-course "burst" to achieve control: 40-60 mg/day as single or 2 divided doses for 3-10 days
Fluticasone/salmeterol: DPI: 100, 250, or 500 mg/50 mg HFA: 45 µg/21 µg, 115 µg/21 µg, 230 µg/21 µg	NA	1 inhalation bid; dose depends on level of severity or control	1 inhalation bid; dose depends on level of severity or control 2 inhalations bid; dose depends on level of severity or control
Budesonide/formoterol: HFA: 80 µg/4.5 µg, 160 µg/4.5 µg	NA		2 inhalations bid; dose depends on level of severity or control
Mometasone/formoterol HFA: 100 µg/5 µg, 200 µg/5 µg			2 inhalations bid; dose depends on level of severity or control
Cromolyn: Nebulizer 20 mg/ampule	1 ampule qid; NA <2 yr of age	1 ampule qid	1 ampule qid
Leukotriene receptor antagonists: Montelukast: 4 or 5 mg chewable tablet 4 mg granule packets 10 mg tablet	4 mg qhs (1-5 yr of age)	5 mg qhs (6-14 yr)	10 mg qhs
Zafirlukast: 10- or 20-mg tablet	NA	10 mg bid (7-11 yr)	40 mg daily (20 mg tablet bid)
5-Lipoxygenase inhibitor: Zileuton CR: 600-mg tablet	NA	NA	1,200 mg twice daily (give 2 tablets bid)
Theophylline: Liquids, sustained-release tablets, and capsules	Starting dose 10 mg/kg/day; usual max: • <1 yr of age: 0.2 (age in wk) + 5 = mg/kg/day • >1 yr of age: 16 mg/kg/day	Starting dose 10 mg/kg/day; usual maximum: 16 mg/kg/day	Starting dose 10 mg/kg/day up to 300 mg maximum; usual maximum 800 mg/day
Immunomodulators: Omalizumab (anti-IgE): Subcutaneous injection, 150 mg/1.2 mL after reconstitution with 1.4 mL sterile water for injection	NA	NA	150-375 mg SC q 2-4 wk, depending on body weight and pretreatment serum IgE level

bid, Twice a day; DPI, dry powder inhaler; HFA, hydrofluoroalkane Ig, immunoglobulin; MDI, metered-dose inhaler; q, every; qhs, every night; qid, 4 times a day; qod, every other day; SC, subcutaneous.

dose-dependent and are most common in individuals receiving high-dose ICS and/or oral corticosteroid therapy. The incidence of these local effects can be greatly minimized by using a spacer with an MDI ICS, because spacers reduce oropharyngeal deposition of the drug and propellant. Mouth rinsing using a "swish and spit" technique after ICS use is also recommended.

The potential for growth suppression and osteoporosis with long-term ICS use has been a concern. In the long-term, prospective NIH-sponsored CAMP study of children with mild to moderate asthma, after ≈4.3 yr of ICS therapy and 5 yr after the trial, there was a significant 1.7 cm decrease in height in girls, but not in boys. There was also a slight dose-dependent effect of ICS therapy on bone mineral accretion in boys, but not girls. A greater effect on bone mineral accretion was observed with increasing numbers of courses of oral corticosteroid burst therapy for asthma, as well as an increase in risk for osteopenia, again limited to boys. Although this study cannot predict a significant effect of ICS therapy in childhood on osteoporosis in later adulthood, improved asthma control with ICS therapy may result in a need for fewer courses of oral corticosteroid burst therapy over time. These findings were with use of budesonide at doses of about 400 µg/day; higher ICS doses, especially of agents with increased potency, have a greater potential for adverse effects. Hence, corticosteroid adverse effects screening and osteoporosis prevention measures are recommended for patients receiving higher ICS doses, as these patients are also likely to require systemic courses for exacerbations (see Table 144-15).

Systemic Corticosteroids

ICS therapy has allowed the large majority of children with asthma to maintain good disease control without maintenance oral corticosteroid therapy. Oral corticosteroids are used primarily to treat asthma exacerbations and, rarely, in patients with severe disease who remain symptomatic despite optimal use of other asthma medications. In these severely asthmatic patients, every attempt should be made to exclude any comorbid conditions and to keep the oral corticosteroid dose at ≤20 mg qod. Doses exceeding this amount are associated with numerous adverse effects (see Chapter 577). To determine the need for continued oral corticosteroid therapy, tapering of the oral corticosteroid

Table 144-14 Estimated Comparative Inhaled Corticosteroid Doses

	LOW DAILY DOSE BY AGE			MEDIUM DAILY DOSE BY AGE			HIGH DAILY DOSE BY AGE		
Drug	**0-4 yr**	**5-11 yr**	**≥12 yr**	**0-4 yr**	**5-11 yr**	**≥12 yr**	**0-4 yr**	**5-11 yr**	**≥12 yr**
Beclomethasone HFA, 40 or 80 µg/puff	NA	80-160 µg	80-240 µg	NA	>160-320 µg	>240-480 µg	NA	>320 µg	>480 µg
Budesonide DPI 90, 180, or 200 µg/inhalation	NA	180-400 µg	180-600 µg	NA	>400-800 µg	>600-1200 µg	NA	>800 µg	>1200 µg
Budesonide inhaled suspension for nebulization, 0.25, 0.5, and 1.0 mg dose	0.25-0.5 mg	0.5 mg	NA	>0.5-1.0 mg	1.0 mg	NA	>1.0 mg	2.0 mg	NA
Flunisolide, 250 µg/puff	NA	500-750 µg	500-1000 µg	NA	1000-1250 µg	>1000-2000 µg	NA	>1250 µg	>2000 µg
Flunisolide HFA, 80 µg/puff	NA	160 µg	320 µg	NA	320 µg	>320-640 µg	NA	≥640 µg	>640 µg
Fluticasone HFA/MDI: 44, 110, or 220 µg/puff	176 µg	88-176 µg	88-264 µg	>176-352 µg	>176-352 µg	>264-440 µg	>352 µg	>352 µg	>440 µg
Fluticasone DPI, 50, 100, or 250 µg/inhalation	NA	100-200 µg	100-300 µg	NA	>200-400 µg	>300-500 µg	NA	>400 µg	>500 µg
Mometasone DPI, 110 µg and 220 µg/inhalation	NA	NA	220 µg	NA	NA	440 µg	NA	NA	>440 µg
Triamcinolone acetonide, 75 µg/puff	NA	300-600 µg	300-750 µg	NA	>600-900 µg	>750-1500 µg	NA	>900 µg	>1500 µg

DPI, dry powder inhaler; HFA, hydrofluoroalkane; MDI, metered-dose inhaler; NA, not approved and no data available for this age group.

Adapted, from the National Asthma Education and Prevention Program: Expert Panel Report 3 (EPR 3): guidelines for the diagnosis and management of asthma—summary report 2007, J Allergy Clin Immunol *120(Suppl):S94–S138, 2007*.

Table 144-15 Risk Assessment for Corticosteroid Adverse Effects

	CONDITIONS	RECOMMENDATIONS
Low risk	(≤1 risk factor*) Low- to medium-dose ICS (see Table 144-11)	• Monitor blood pressure and weight with each physician visit • Measure height annually (stadiometry); monitor periodically for declining growth rate and pubertal developmental delay • Encourage regular physical exercise • Ensure adequate dietary calcium and vitamin D with additional supplements for daily calcium if needed • Avoid smoking and alcohol • Ensure TSH status if patient has history of thyroid abnormality
Medium risk	(If >1 risk factor,* consider evaluating as high risk) High-dose ICS (see Table 144-11) At least 4 courses oral corticosteroid/yr	As above, plus: • Yearly ophthalmologic evaluations to monitor for cataracts or glaucoma • Baseline bone densitometry (DEXA scan) • Consider patient at increased risk for adrenal insufficiency, especially with physiologic stressors (e.g., surgery, accident, significant illness)
High risk	Chronic systemic corticosteroids (>7.5 mg daily or equivalent for >1 mo) ≥ 7 oral corticosteroid burst treatments/year Very-high-dose ICS (e.g., fluticasone propionate ≥800 µg/day)	As above, plus: • DEXA scan: if DEXA Z score ≤1.0, recommend close monitoring (every 12 mo) • Consider referral to a bone or endocrine specialist • Bone age assessment • Complete blood count • Serum calcium, phosphorus, alkaline phosphatase determinations • Urine calcium and creatinine measurements • Measurements of testosterone in males, estradiol in amenorrheic premenopausal women, vitamin D (25-OH and 1,25-OH vitamin D), parathyroid hormone, and osteocalcin • Urine telopeptides for those receiving long-term systemic or frequent oral corticosteroid treatment • Assume adrenal insufficiency for physiologic stressors (e.g., surgery, accident, significant illness)

*Risk factors for osteoporosis: Presence of other chronic illness(es), medications (corticosteroids, anticonvulsants, heparin, diuretics), low body weight, family history of osteoporosis, significant fracture history disproportionate to trauma, recurrent falls, impaired vision, low dietary calcium and vitamin D intake, and lifestyle factors (decreased physical activity, smoking, and alcohol intake).

DEXA, dual-energy x-ray absorptiometry; ICS, inhaled corticosteroid; TSH, thyroid-stimulating hormone.

dose (over several weeks to months) should be considered, with close monitoring of the patient's symptoms and lung function.

When administered orally, prednisone, prednisolone, and methylprednisolone are rapidly and completely absorbed, with peak plasma concentrations occurring within 1-2 hr. Prednisone is an inactive prodrug that requires biotransformation via first-pass hepatic metabolism to prednisolone, its active form. Corticosteroids are metabolized in the liver into inactive compounds, with the rate of metabolism influenced by drug interactions and disease states. Anticonvulsants (phenytoin, phenobarbital, carbamazepine) increase the metabolism of prednisolone, methylprednisolone, and dexamethasone, with methylprednisolone most significantly affected. Rifampin also enhances the clearance of corticosteroids and can result in diminished therapeutic effect. Other medications (ketoconazole, oral contraceptives) can significantly delay corticosteroid metabolism. Macrolide antibiotics (erythromycin, clarithromycin, troleandomycin) delay the clearance of only methylprednisolone.

Children who require long-term oral corticosteroid therapy are at risk for development of associated adverse effects over time. Essentially all major organ systems can be adversely affected by long-term oral corticosteroid therapy (see Chapter 577). Some of these effects occur immediately (metabolic effects). Others can develop insidiously over several months to years (growth suppression, osteoporosis, cataracts). Most adverse effects occur in a cumulative dose- and duration-dependent manner. Children who require routine or frequent short courses of oral corticosteroids, especially with concurrent high-dose ICSs, should receive corticosteroid adverse effects screening (see Table 144-15) and osteoporosis preventive measures (see Chapter 707).

Long-Acting Inhaled β-Agonists

LABAs (salmeterol, formoterol) are considered to be daily controller medications, *not intended* for use as rescue medication for acute asthma symptoms or exacerbations, nor as monotherapy for persistent asthma. Controller formulations that combine an ICS with a LABA (fluticasone/salmeterol, budesonide/formoterol, mometasone/formoterol) are available and recommended, in lieu of separate inhaler delivery devices. Salmeterol has a prolonged onset of action, with maximal bronchodilation approximately 1 hr after administration, whereas formoterol has an onset of action within 5-10 min. Both medications have a prolonged duration of effect, at least 12 hr. Given their long duration of action, they are well suited for patients with nocturnal asthma and for individuals who require frequent SABA use during the day to prevent exercise-induced bronchospasm. Their major role is as an add-on agent in patients whose asthma is suboptimally controlled with ICS therapy alone. For those patients, the addition of a LABA to ICS therapy is superior to doubling the dose of ICS, especially on day and nocturnal symptoms. Of note, the FDA requires all LABA-containing medications to be labeled with a warning of an increase in severe asthma episodes associated with these agents. Some studies have reported a higher number of asthma-related deaths among patients receiving LABA therapy in addition to their usual asthma care than in patients not receiving LABAs. This notice reinforces the appropriate use of LABAs in the management of asthma. Specifically, *LABA products should not be initiated as first-line or sole asthma therapy without the concomitant use of an ICS,* used with worsening wheezing, or used for acute control of bronchospasm. LABAs should be stopped once asthma control is achieved, and the asthma should be maintained with the use of an asthma controller agent (ICS). Fixed-dose preparations (with an ICS) are recommended to ensure compliance with these guidelines.

Leukotriene-Modifying Agents

Leukotrienes are potent proinflammatory mediators that can induce bronchospasm, mucus secretion, and airways edema. Two classes of leukotriene modifiers have been developed: inhibitors of leukotriene synthesis and LTRAs. Zileuton, the only leukotriene synthesis inhibitor, is not approved for use in children <12 yr of age. Because zileuton can result in elevated liver function enzyme values in 2-4% of patients, and interacts with medications metabolized via the cytochrome P450 system, it is rarely prescribed for children with asthma.

LTRAs have bronchodilator and targeted antiinflammatory properties and reduce exercise-, aspirin-, and allergen-induced bronchoconstriction. *LTRAs are recommended as alternative treatment for mild persistent asthma and as add-on medication with ICS for moderate persistent asthma.* Two LTRAs are FDA-approved for use in children: montelukast and zafirlukast. Both medications improve asthma symptoms, decrease the need for rescue β-agonist use, and improve lung function. Montelukast is FDA-approved for use in children ≥1 yr of age and is administered once daily. Zafirlukast is FDA-approved for use in children ≥5 yr of age and is administered twice daily. Although incompletely studied in children with asthma, LTRAs appear to be less effective than ICSs in patients with mild persistent asthma. In general, ICSs improve lung function by 5-15%, whereas LTRAs improve lung function by 2-7.5%. LTRAs are not thought to have significant adverse effects, although case reports described a Churg-Strauss–like vasculitis (pulmonary infiltrates, eosinophilia, cardiomyopathy) in adults with corticosteroid-dependent asthma treated with LTRAs. It remains to be determined whether these patients have a primary eosinophilic vasculitis masquerading as asthma, which was "unmasked" as the oral corticosteroid dose was tapered, or whether the disease is a very rare adverse effect of LTRA. Montelukast has rarely been associated with mood changes and suicidality.

Nonsteroidal Antiinflammatory Agents

Cromolyn and nedocromil are nonsteroidal antiinflammatory agents that can inhibit allergen-induced asthmatic responses and reduce exercise-induced bronchospasm. Both drugs are considered alternative antiinflammatory drugs for children with mild persistent asthma. Although largely devoid of adverse effects, these medications must be administered frequently (2-4 times/day) and are not nearly as effective daily controller medications as ICSs and leukotriene-modifying agents. Because they inhibit exercise-induced bronchospasm, they can be used in place of SABAs, especially in children who develop unwanted adverse effects with β-agonist therapy (tremor and elevated heart rate). Cromolyn and nedocromil can also be used in addition to a SABA in a combination pretreatment for exercise-induced bronchospasm in patients who continue to experience symptoms with use of SABA pretreatment alone. Nedocromil has been taken off the market and cromolyn is only available in a solution for nebulization.

Theophylline

In addition to its bronchodilator effects, theophylline has antiinflammatory properties as a phosphodiesterase inhibitor, although the extent of its clinical relevance has not been clearly established. When used long-term, theophylline can reduce asthma symptoms and the need for rescue SABA use. Although it is considered an alternative monotherapy controller agent for older children and adults with mild persistent asthma, it is no longer considered a first-line agent for young children, in whom there is significant variability in the absorption and metabolism of different theophylline preparations, necessitating frequent dose monitoring (drug blood levels) and adjustments. Because theophylline may have some corticosteroid-sparing effects in individuals with oral corticosteroid–dependent asthma, it is still sometimes used in this group of asthmatic children. Theophylline has a narrow therapeutic window; therefore, when it is used, serum theophylline levels need to be routinely monitored, especially if the patient has a viral illness associated with a fever or is started on a medication known to delay theophylline clearance, such as a macrolide antibiotic, cimetidine, an oral antifungal agent, an oral contraceptive, a leukotriene synthesis inhibitor, or ciprofloxacin. Theophylline overdosage and elevated theophylline levels have been associated with headaches, vomiting, cardiac arrhythmias, seizures, and death.

Anti–Immunoglobulin E (Omalizumab)

Omalizumab is a humanized monoclonal antibody that binds IgE, thereby preventing its binding to the high-affinity IgE receptor and blocking IgE-mediated allergic responses and inflammation. Because it is unable to bind IgE that is already bound to high-affinity IgE

receptors, the risk of anaphylaxis via direct IgE cross linking by the drug is circumvented. It is FDA-approved for patients >12 yr old with moderate to severe asthma, documented hypersensitivity to a perennial aeroallergen, and inadequate disease control with inhaled and/or oral corticosteroids. Omalizumab is given every 2-4 wk subcutaneously, the dosage based on body weight and serum IgE levels. Asthmatic patients receiving omalizumab have fewer asthma exacerbations and symptoms while able to reduce their ICS and/or oral corticosteroid doses. This agent is generally well tolerated, although local injection site reactions can occur. Hypersensitivity reactions (including anaphylaxis) and malignancies have been very rarely associated with omalizumab use. The FDA requires packaging of omalizumab to contain a black box warning of potentially serious and life-threatening anaphylactic reactions with omalizumab treatment. On the basis of reports from approximately 39,500 patients, anaphylaxis following omalizumab treatment occurred in at least 0.1% of treated people. Although most of these reactions occurred within 2 hr of omalizumab injection, there are reports of serious delayed reactions 2-24 hr or even longer after injections. Anaphylaxis occurred after any omalizumab dose (including the first dose). Omalizumab-treated patients should be observed in the facility for an extended period after the drug is given, and medical providers who administer the injection should be prepared to manage life-threatening anaphylactic reactions. Patients who receive omalizumab should be fully informed about the signs and symptoms of anaphylaxis, their chance of development of delayed anaphylaxis following each injection, and how to treat it, including the use of autoinjectable epinephrine.

Mepolizumab, an anti–IL-5 antibody, has been shown to improve asthma control, reduce prednisone dose and lower sputum and blood eosinophil events in adults with prednisone-dependent asthma who also had sputum eosinophils. Dupilumab, an anti–IL-4 receptor antibody and another monoclonal antibody against IL-13, have also shown promise in adult studies.

Quick-Reliever Medications

Quick-reliever or "rescue" medications (SABAs, inhaled anticholinergics, and short-course systemic corticosteroids) are used in the management of acute asthma symptoms (Table 144-16).

Table 144-16 Management of Asthma Exacerbation (Status Asthmaticus)

RISK ASSESSMENT ON ADMISSION		
Focused history	• Onset of current exacerbation • Frequency and severity of daytime and nighttime symptoms and activity limitation • Frequency of rescue bronchodilator use • Current medications and allergies • Potential triggers • History of systemic steroid courses, emergency department visits, hospitalization, intubation, or life-threatening episodes	
Clinical assessment	• Physical examination findings: vital signs, breathlessness, air movement, use of accessory muscles, retractions, anxiety level, alteration in mental status • Pulse oximetry • Lung function (defer in patients with moderate to severe distress or history of labile disease)	
Risk factors for asthma morbidity and death	See Table 144-17	
TREATMENT		
Drug and Trade Name	**Mechanisms of Action and Dosing**	**Cautions and Adverse Effects**
Oxygen (mask or nasal cannula)	Treats hypoxia	• Monitor pulse oximetry to maintain O_2 saturation >92% • Cardiorespiratory monitoring
Inhaled short-acting β-agonists:	Bronchodilator	• During exacerbations, frequent or continuous doses can cause pulmonary vasodilation, $\dot{V}/\dot{Q}$ mismatch, and hypoxemia • Adverse effects: palpitations, tachycardia, arrhythmias, tremor, hypoxemia
Albuterol nebulizer solution (5 mg/mL concentrate; 2.5 mg/3 mL, 1.25 mg/3 mL, 0.63 mg/3 mL)	Nebulizer: 0.15 mg/kg (minimum: 2.5 mg) as often as every 20 min for 3 doses as needed, then 0.15-0.3 mg/kg up to 10 mg every 1-4 hr as needed, or up to 0.5 mg/kg/hr by continuous nebulization	• Nebulizer: when giving concentrated forms, dilute with saline to 3 mL total nebulized volume
Albuterol MDI (90 µg/puff)	2-8 puffs up to every 20 min for 3 doses as needed, then every 1-4 hr as needed	• For MDI: use spacer/holding chamber
Levalbuterol (Xopenex) nebulizer solution (1.25 mg/0.5 mL concentrate; 0.31 mg/3 mL, 0.63 mg/3 mL, 1.25 mg/3 mL)	0.075 mg/kg (minimum: 1.25 mg) every 20 min for 3 doses, then 0.075-0.15 mg/kg up to 5 mg every 1-4 hr as needed, or 0.25 mg/kg/hr by continuous nebulization	• Levalbuterol 0.63 mg is equivalent to 1.25 mg of standard albuterol for both efficacy and side effects
Systemic corticosteroids:	Antiinflammatory	• If patient has been exposed to chickenpox or measles, consider passive immunoglobulin prophylaxis; also, risk of complications with herpes simplex and tuberculosis • For daily dosing, 8 A.M. administration minimizes adrenal suppression • Children may benefit from dosage tapering if course exceeds 7 days • Adverse effects monitoring: Frequent therapy bursts risk numerous corticosteroid adverse effects (see Chapter 578); see Table 144-15 for adverse effects screening recommendations

Continued

Table 144-16 Management of Asthma Exacerbation (Status Asthmaticus)—cont'd

Prednisone: 1, 2.5, 5, 10, 20, 50 mg tablets Methylprednisolone (Medrol): 2, 4, 8, 16, 24, 32 mg tablets Prednisolone: 5 mg tablets; 5 mg/5 mL and 15 mg/5 mL solution Depo-Medrol (IM); Solu-Medrol (IV)	0.5-1 mg/kg every 6-12 hr for 48 hr, then 1-2 mg/kg/day bid (maximum: 60 mg/day) Short-course "burst" for exacerbation: 1-2 mg/kg/day qd or bid for 3-7 days	
Anticholinergics: Ipratropium: Atrovent (nebulizer solution 0.5 mg/2.5 mL; MDI 18 μg/inhalation) Ipratropium with albuterol: DuoNeb nebulizer solution (0.5 mg ipratropium + 2.5 mg albuterol/3 mL vial)	Mucolytic/bronchodilator Nebulizer: 0.5 mg q6-8h (tid-qid) as needed MDI: 2 puffs qid 1 vial by nebulizer qid	• Should not be used as first-line therapy; added to β_2-agonist therapy • Nebulizer: may mix ipratropium with albuterol
Injectable sympathomimetic epinephrine: Adrenalin 1 mg/mL (1:1000) EpiPen autoinjection device (0.3 mg; EpiPen Jr 0.15 mg)	Bronchodilator SC or IM: 0.01 mg/kg (max dose 0.5 mg); may repeat after 15-30 min	• For extreme circumstances (e.g., impending respiratory failure despite high-dose inhaled SABA, respiratory failure)
Terbutaline: Brethine 1 mg/mL	Continuous IV infusion (terbutaline only): 2-10 μg/kg loading dose, followed by 0.1-0.4 μg/kg/min Titrate in 0.1-0.2 μg/kg/min increments every 30 min, depending on clinical response	• Terbutaline is β-agonist–selective relative to epinephrine • Monitoring with continuous infusion: cardiorespiratory monitor, pulse oximetry, blood pressure, serum potassium • Adverse effects: tremor, tachycardia, palpitations, arrhythmia, hypertension, headaches, nervousness, nausea, vomiting, hypoxemia
RISK ASSESSMENT FOR DISCHARGE		
Medical stability	Discharge to home if there has been sustained improvement in symptoms and bronchodilator treatments are at least 3 hr apart, physical findings are normal, PEF >70% of predicted or personal best, and oxygen saturation >92% when breathing room air	
Home supervision	Capability to administer intervention and to observe and respond appropriately to clinical deterioration	
Asthma education	See Table 144-9	

IM, intramuscular; MDI, metered-dose inhaler; PEF, peak expiratory flow; SABA, short-acting β-agonist; SC, subcutaneous; $\dot{V}/\dot{Q}$, ventilation–perfusion.

Short-Acting Inhaled β-Agonists

Given their rapid onset of action, effectiveness, and 4-6 hr duration of action, SABAs (albuterol, levalbuterol, terbutaline, pirbuterol) are the drugs of choice for acute asthma symptoms ("rescue" medication) and for preventing exercise-induced bronchospasm. β-Agonists cause bronchodilation by inducing airway smooth muscle relaxation, reducing vascular permeability and airways edema, and improving mucociliary clearance. Levalbuterol, or the r-isomer of albuterol, is associated with less tachycardia and tremor, which can be bothersome to some asthmatic patients. Overuse of β-agonists is associated with an increased risk of death or near-death episodes from asthma. This is a major concern for some patients with asthma who rely on the frequent use of SABAs as a "quick fix" for their asthma, rather than using controller medications in a preventive manner. It is helpful to monitor the frequency of SABA use, in that use of at least 1 MDI/mo or at least 3 MDIs/year (200 inhalations/MDI) indicates inadequate asthma control and necessitates improving other aspects of asthma therapy and management.

Anticholinergic Agents

As bronchodilators, the anticholinergic agents (ipratropium bromide) are less potent than the β-agonists. Inhaled ipratropium is used primarily in the treatment of acute severe asthma. When used in combination with albuterol, ipratropium can improve lung function and reduce the rate of hospitalization in children who present to the emergency department with acute asthma. Ipratropium is the anticholinergic formulation of choice for children because it has few central nervous system adverse effects and it is available in both MDI and nebulizer formulations. Although widely used in children with asthma exacerbations of all ages, it is approved by the FDA for use in children >12 yr of age. A long-acting inhaled anticholinergic agent, tiotropium, is gaining interest as a potential add-on controller therapy (i.e., in addition to ICS with or without LABA) for adults with asthma.

Delivery Devices and Inhalation Technique

Inhaled medications are delivered in aerosolized form in a MDI, as a DPI formulation, or in a suspension or solution form delivered via a

nebulizer. In the past, MDIs, which require coordination and use of a spacer device, have dominated the market. MDIs are now using hydrofluoroalkane propellant for its ozone-friendly properties, rather than chlorofluorocarbon. Spacer devices, recommended for the administration of all MDI medications, are simple and inexpensive tools that: (1) decrease the coordination required to use MDIs, especially in young children; (2) improve the delivery of inhaled drug to the lower airways; and (3) minimize the risk of propellant-mediated adverse effects (thrush). Optimal inhalation technique for each puff of MDI-delivered medication is a slow (5 sec) inhalation, then a 5-10 sec breathhold. No waiting time between puffs of medication is needed. Young, preschool-age children cannot perform this inhalation technique. MDI medications can also be delivered with a spacer and mask, using a different technique: Each puff is administered with regular breathing for about 30 sec or 5-10 breaths, a tight seal must be maintained, and talking, coughing, or crying will blow the medication out of the spacer. This technique will not deliver as much medication per puff as the optimal MDI technique used by older children and adults.

DPI devices (e.g., Diskus, Flexhaler Autohaler, Twisthaler, Aerolizer) are popular because of their simplicity of use, albeit adequate inspiratory flow is needed. They are breath-actuated (the drug comes out only as it is breathed in) and spacers are not needed. Mouth rinsing is recommended after ICS use to rinse out ICS deposited on the oral mucosa and reduce the swallowed ICS and the risk of thrush.

Nebulizers have been the mainstay of aerosol treatment for infants and young children. An advantage of using nebulizers is the simple technique required of relaxed breathing. The preferential nasal breathing, small airways, low tidal volume, and high respiratory rate of infants markedly increase the difficulty of inhaled drug therapy targeting the lung airways. Disadvantages of nebulizers include need for a power source, inconvenience in that treatments take about 5 min, expense, and potential for bacterial contamination.

Asthma Exacerbations and Their Management

Asthma exacerbations are acute or subacute episodes of progressively worsening symptoms and airflow obstruction. Airflow obstruction during exacerbations can become extensive, resulting in life-threatening respiratory insufficiency. Often, asthma exacerbations worsen during sleep (between midnight and 8 A.M.), when airways inflammation and hyperresponsiveness are at their peak. Importantly, SABAs, which are first-line therapy for asthma symptoms and exacerbations, increase pulmonary blood flow through obstructed, unoxygenated areas of the lungs with increasing dosage and frequency. When airways obstruction is not resolved with SABA use, ventilation–perfusion mismatching can cause significant hypoxemia, which can perpetuate bronchoconstriction and further worsen the condition. Severe, progressive asthma exacerbations need to be managed in a medical setting, with administration of supplemental oxygen as first-line therapy and close monitoring for potential worsening. Complications that can occur during severe exacerbations include atelectasis and air leaks in the chest (pneumomediastinum, pneumothorax).

A severe exacerbation of asthma that does not improve with standard therapy is termed **status asthmaticus.** Immediate management of an asthma exacerbation involves a rapid evaluation of the severity of obstruction and assessment of risk for further clinical deterioration (see Tables 144-15 and 144-16). For most patients, exacerbations improve with frequent bronchodilator treatments and a course of systemic (oral or intravenous) corticosteroid. However, the optimal management of a child with an asthma exacerbation should include a more comprehensive assessment of the events leading up to the exacerbation and the underlying disease severity. Indeed, the frequency and severity of asthma exacerbations help define the severity of a patient's asthma. Whereas most children who experience life-threatening asthma episodes have moderate to severe asthma by other criteria, some children with asthma appear to have mild disease except when they suffer severe, even near-fatal exacerbations. The biologic, environmental, economic, and psychosocial risk factors associated with asthma morbidity and death can further guide this assessment (Table 144-17).

Table 144-17 Risk Factors for Asthma Morbidity and Mortality

BIOLOGIC
Previous severe asthma exacerbation (intensive care unit admission, intubation for asthma)
Sudden asphyxia episodes (respiratory failure, arrest)
Two or more hospitalizations for asthma in past year
Three or more emergency department visits for asthma in past year
Increasing and large diurnal variation in peak flows
Use of >2 canisters of short-acting β-agonists per month
Poor response to systemic corticosteroid therapy
Male gender
Low birthweight
Nonwhite (especially black) ethnicity
Sensitivity to *Alternaria*
ENVIRONMENTAL
Allergen exposure
Environmental tobacco smoke exposure
Air pollution exposure
Urban environment
ECONOMIC AND PSYCHOSOCIAL
Poverty
Crowding
Mother <20 yr old
Mother with less than high school education
Inadequate medical care:
Inaccessible
Unaffordable
No regular medical care (only emergency)
Lack of written asthma action plan
No care sought for chronic asthma symptoms
Delay in care of asthma exacerbations
Inadequate hospital care for asthma exacerbation
Psychopathology in the parent or child
Poor perception of asthma symptoms or severity
Alcohol or substance abuse

Asthma exacerbations characteristically vary among individuals but tend to be similar in the same patient. Severe asthma exacerbations, resulting in respiratory distress, hypoxia, hospitalization, and/or respiratory failure, are the best predictors of future life-threatening exacerbations or a fatal asthma episode. In addition to distinguishing such high-risk children, some experience exacerbations that come on over days, with airflow obstruction resulting from progressive inflammation, epithelial sloughing, and cast impaction of small airways. When such a process is extreme, respiratory failure as a result of fatigue can ensue, necessitating mechanical ventilation for numerous days. In contrast, some children experience abrupt-onset exacerbations that may result from extreme AHR and physiologic susceptibility to airways closure. Such exacerbations, when extreme, are asphyxial in nature, often occur outside medical settings, are initially associated with very high arterial partial pressure of carbon dioxide (P_{CO_2}) levels, and tend to require only brief periods of supportive ventilation. Recognizing the characteristic differences in asthma exacerbations is important for optimizing their early management.

Home Management of Asthma Exacerbations

Families of all children with asthma should have a **written action plan** to guide their recognition and management of exacerbations, along with the necessary medications and tools to manage them. Early recognition of asthma exacerbations in order to intensify treatment early can often prevent further worsening and keep exacerbations from becoming severe. A written home action plan can reduce the risk of asthma death by 70%. The NIH guidelines recommend immediate treatment with "rescue" medication (inhaled SABA, up to 3 treatments in 1 hr). A good response is characterized by resolution of symptoms within 1 hr, no further symptoms over the next 4 hr, and improvement in PEF value to at least 80% of personal best. The child's physician

should be contacted for follow-up, especially if bronchodilators are required repeatedly over the next 24-48 hr. If the child has an incomplete response to initial treatment with rescue medication (persistent symptoms and/or a PEF value <80% of personal best), a short course of oral corticosteroid therapy (prednisone 1-2 mg/kg/day [not to exceed 60 mg/day] for 4 days), in addition to inhaled β-agonist therapy, should be instituted. The physician should also be contacted for further instructions. Immediate medical attention should be sought for severe exacerbations, persistent signs of respiratory distress, lack of expected response or sustained improvement after initial treatment, further deterioration, or high-risk factors for asthma morbidity or mortality (previous history of severe exacerbations). For patients with severe asthma and/or a history of life-threatening episodes, especially if abrupt-onset in nature, providing an epinephrine autoinjector and, possibly, portable oxygen at home should be considered. Use of either of these extreme measures for home management of asthma exacerbations would be an indication to call 911 for emergency support services.

Emergency Department Management of Asthma Exacerbations

In the emergency department, the primary goals of asthma management include correction of hypoxemia, rapid improvement of airflow obstruction, and prevention of progression or recurrence of symptoms. Interventions are based on clinical severity on arrival, response to initial therapy, and presence of risk factors that are associated with asthma morbidity and mortality (see Table 144-17). Indications of a severe exacerbation include breathlessness, dyspnea, retractions, accessory muscle use, tachypnea or labored breathing, cyanosis, mental status changes, a silent chest with poor air exchange, and severe airflow limitation (PEF or FEV_1 value <50% of personal best or predicted values). Initial treatment includes supplemental oxygen, inhaled β-agonist therapy every 20 min for 1 hr, and, if necessary, systemic corticosteroids given either orally or intravenously (see Table 144-16). Inhaled ipratropium may be added to the β-agonist treatment if no significant response is seen with the first inhaled β-agonist treatment. An intramuscular injection of epinephrine or other β-agonist may be administered in severe cases. Oxygen should be administered and continued for at least 20 min after SABA administration to compensate for possible ventilation-perfusion abnormalities caused by SABAs.

Close monitoring of clinical status, hydration, and oxygenation are essential elements of immediate management. A poor response to intensified treatment in the 1st hr suggests that the exacerbation will not remit quickly. The patient may be discharged to home if there is sustained improvement in symptoms, normal physical findings, PEF >70% of predicted or personal best, an oxygen saturation >92% while the patient is breathing room air for 4 hr. Discharge medications include administration of an inhaled β-agonist up to every 3-4 hr plus a 3-7 day course of an oral corticosteroid. Optimizing controller therapy before discharge is also recommended. The addition of ICS to a course of oral corticosteroid in the emergency department setting reduces the risk of exacerbation recurrence over the subsequent month.

Hospital Management of Asthma Exacerbations

For patients with moderate to severe exacerbations that do not adequately improve within 1-2 hr of intensive treatment, observation and/or admission to the hospital, at least overnight, is likely to be needed. Other indications for hospital admission include high-risk features for asthma morbidity or death (see Table 144-17). Admission to an intensive care unit is indicated for patients with severe respiratory distress, poor response to therapy, and concern for potential respiratory failure and arrest.

Supplemental oxygen, frequent or continuous administration of an inhaled bronchodilator, and systemic corticosteroid therapy are the conventional interventions for children admitted to the hospital for status asthmaticus (see Table 144-16). Supplemental oxygen is administered because many children hospitalized with acute asthma have or eventually have hypoxemia, especially at night and with increasing SABA administration. SABAs can be delivered frequently (every 20 min to 1 hr) or continuously (at 5-15 mg/hr). When administered continuously, significant systemic absorption of β-agonist occurs and, as a result, continuous nebulization can obviate the need for intravenous β-agonist therapy. Adverse effects of frequently administered β-agonist therapy include tremor, irritability, tachycardia, and hypokalemia. Patients requiring frequent or continuous nebulized β-agonist therapy should have ongoing cardiac monitoring. Because frequent β-agonist therapy can cause ventilation–perfusion mismatch and hypoxemia, oximetry is also indicated. Inhaled ipratropium bromide is often added to albuterol every 6 hr if patients do not show a remarkable improvement, although there is little evidence to support its use in hospitalized children receiving aggressive inhaled β-agonist therapy and systemic corticosteroids. In addition to its potential to provide a synergistic effect with a β-agonist agent in relieving severe bronchospasm, ipratropium bromide may be beneficial in patients who have mucous hypersecretion or are receiving β-blockers.

Short-course systemic corticosteroid therapy is recommended for use in moderate to severe asthma exacerbations to hasten recovery and prevent recurrence of symptoms. Corticosteroids are effective as single doses administered in the emergency department, short courses in the clinic setting, and both oral and intravenous formulations in hospitalized children. Studies in children hospitalized with acute asthma have found corticosteroids administered orally to be as effective as intravenous corticosteroids. Accordingly, oral corticosteroid therapy can often be used, although children with sustained respiratory distress who are unable to tolerate oral preparations or liquids are obvious candidates for intravenous corticosteroid therapy.

Patients with persistent severe dyspnea and high-flow oxygen requirements require additional evaluations, such as complete blood cell counts, measurements of arterial blood gases and serum electrolytes, and chest radiograph, to monitor for respiratory insufficiency, comorbidities, infection, and/or dehydration. Hydration status monitoring is especially important in infants and young children, whose increased respiratory rate (insensible losses) and decreased oral intake put them at higher risk for dehydration. Further complicating this situation is the association of increased antidiuretic hormone secretion with status asthmaticus. Administration of fluids at or slightly below maintenance fluid requirements is recommended. Chest physical therapy, incentive spirometry, and mucolytics are **not** recommended during the early acute period of asthma exacerbations as they can trigger severe bronchoconstriction.

Despite intensive therapy, some asthmatic children remain critically ill and at risk for respiratory failure, intubation, and mechanical ventilation. Complications (air leaks) related to asthma exacerbations increase with intubation and assisted ventilation; every effort should be made to relieve bronchospasm and prevent respiratory failure. Several therapies, including parenterally administered epinephrine, β-agonists, methylxanthines, magnesium sulfate (25-75 mg/kg, maximum dose 2.5 g, given intravenously over 20 min), and inhaled heliox (helium and oxygen mixture) have demonstrated some benefit as adjunctive therapies in patients with severe status asthmaticus. Administration of either methylxanthine or magnesium sulfate requires monitoring of serum levels and cardiovascular status. Parenteral (subcutaneous, intramuscular, or intravenous) epinephrine or terbutaline sulfate may be effective in patients with life-threatening obstruction that is not responding to high doses of inhaled β-agonists, because in such patients, inhaled medication may not reach the lower airway.

Rarely, a severe asthma exacerbation in a child results in respiratory failure, and intubation and mechanical ventilation become necessary. Mechanical ventilation in severe asthma exacerbations requires the careful balance of enough pressure to overcome airways obstruction while reducing hyperinflation, air trapping, and the likelihood of barotrauma (pneumothorax, pneumomediastinum) (see Chapter 411). To minimize the likelihood of such complications, mechanical ventilation should be anticipated, and asthmatic children at risk for the development of respiratory failure should be managed in a pediatric ICU. Elective tracheal intubation with rapid-induction sedatives and paralytic agents is safer than emergency intubation. Mechanical ventilation aims to achieve adequate oxygenation while tolerating mild to

moderate hypercapnia (P_{CO_2} 50-70 mm Hg) to minimize barotrauma. Volume-cycled ventilators, using short inspiratory and long expiratory times, 10-15 mL/kg tidal volume, 8-15 breaths/min, peak pressures <60 cm H_2O, and without positive end-expiratory pressure are starting mechanical ventilation parameters that can achieve these goals. As measures to relieve mucous plugs, chest percussion and airways lavage are not recommended because they can induce further bronchospasm. One must consider the nature of asthma exacerbations leading to respiratory failure; those of rapid or abrupt onset tend to resolve quickly (hours to 2 days), whereas those that progress gradually to respiratory failure can require days to weeks of mechanical ventilation. Such prolonged cases are further complicated by muscle atrophy and, when combined with corticosteroid-induced myopathy, can lead to severe muscle weakness requiring prolonged rehabilitation. This myopathy should not be confused with the rare occurrence of an asthma-associated flaccid paralysis (Hopkins syndrome), which is of unknown etiology but prolongs the intensive care stay.

In children, management of severe exacerbations in medical centers is usually successful, even when extreme measures are required. Consequently, asthma deaths in children rarely occur in medical centers; most occur at home or in community settings before lifesaving medical care can be administered. This point highlights the importance of home and community management of asthma exacerbations, early intervention measures to keep exacerbations from becoming severe, and steps to reduce asthma severity. A follow-up appointment within 1-2 wk of a child's discharge from the hospital after resolution of an asthma exacerbation should be used to monitor clinical improvement and to reinforce key educational elements, including action plans and controller medications.

Special Management Circumstances

Management of Infants and Young Children. Recurrent wheezing episodes in preschool-age children are very common, occurring in as much as one-third of this population. Of them, most improve and even become asymptomatic during the prepubescent school-age years, whereas others have lifelong persistent asthma. All require management of their recurrent wheezing problems (see Tables 144-5, 144-7, and 144-12). The updated NIH guidelines recommend risk assessment to identify preschool-age children who are likely to have persistent asthma. One implication of this recommendation is that these at-risk children may be candidates for conventional asthma management, including daily controller therapy and early intervention with exacerbations (see Tables 144-8, 144-9, and 144-12). Nebulized budesonide and montelukast appear to be more effective than cromolyn. For young children with a history of moderate to severe exacerbations, nebulized budesonide is FDA approved, and its use as a controller medication could prevent subsequent exacerbations.

Using aerosol therapy in infants and young children with asthma presents unique challenges. There are 2 delivery systems for inhaled medications for this age group, the nebulizer and the MDI with spacer/holding chamber and face mask. Multiple studies demonstrate the effectiveness of both nebulized albuterol in acute episodes and nebulized budesonide in the treatment of recurrent wheezing in infants and young children. In such young children, inhaled medications administered via MDI with spacer and face mask may be acceptable, although perhaps not preferred owing to limited published information and lack of FDA approval for children <4 yr of age.

Asthma Management in Pregnancy. The goals of asthma management during pregnancy should include prevention of exacerbations and control of chronic symptoms through the use of medications that pose minimal risk to the mother and fetus because most drugs cross the placenta. It is considered safer for pregnant asthmatic women to be treated with controller medications than it is to have uncontrolled symptoms and severe exacerbations. Albuterol is the preferred SABA for use during pregnancy. There is reassuring efficacy and safety data from prospective cohort studies supporting ICS use in pregnant women with asthma. Budesonide is currently the preferred ICS for pregnant women, attaining an FDA Pregnancy Category B rating because of substantial reassuring safety data. Nonmedication approaches to improve asthma control are encouraged. A multidisciplinary approach with monthly evaluations (including pulmonary function tests when not contraindicated) and ongoing consultation with the obstetrician and asthma specialist is recommended. Frequent fetal and maternal surveillance is especially important for adolescents with suboptimal asthma control, those with moderate to severe asthma, and those with a recent exacerbation.

Asthma Management During Surgery. Patients with asthma are at risk from disease-related complications from surgery, such as bronchoconstriction and asthma exacerbation, atelectasis, impaired coughing, respiratory infection, and latex exposure, that may induce asthma complications in patients with latex allergy. All patients with asthma should be evaluated before surgery, and those who are inadequately controlled should allow time for intensified treatment in order to improve asthma stability before surgery if possible. A systemic corticosteroid course may be indicated for the patient who is having symptoms and/or FEV_1 or PEF values <80% of the patient's personal best. In addition, patients who have received >2 wk of systemic corticosteroid and/or moderate- to high-dose ICS therapy may be at risk for intraoperative adrenal insufficiency. For these patients, anesthesia services should be alerted to provide "stress" replacement doses of systemic corticosteroid for the surgical procedure and possibly the postoperative period if needed.

PROGNOSIS

Recurrent coughing and wheezing occurs in 35% of preschool-age children. Of these, approximately one-third continue to have persistent asthma into later childhood, and approximately two-thirds improve on their own through their teen years. Asthma severity by the ages of 7-10 yr is predictive of asthma persistence in adulthood. Children with moderate to severe asthma and with lower lung function measures are likely to have persistent asthma as adults. Children with milder asthma and normal lung function are likely to improve over time, with some becoming periodically asthmatic (disease-free for months to years); however, complete remission for 5 yr in childhood is uncommon.

PREVENTION

Although chronic airways inflammation may result in pathologic remodeling of lung airways, conventional anti-inflammatory interventions—the cornerstone of asthma control—do not help children outgrow their asthma. Although controller medications reduce asthma morbidities, most children with moderate to severe asthma continue to have symptoms into young adulthood. Investigations into the environmental and lifestyle factors responsible for the lower prevalence of childhood asthma in rural areas and farming communities suggest that early immunomodulatory intervention might prevent asthma development. A *hygiene hypothesis* purports that naturally occurring microbial exposures in early life might drive early immune development away from allergic sensitization, persistent airways inflammation, and remodeling. If these natural microbial exposures truly have an asthma-protective effect, without significant adverse health consequences, then these findings may foster new strategies for asthma prevention.

Several nonpharmacotherapeutic measures with numerous positive health attributes—avoidance of environmental tobacco smoke (beginning prenatally), prolonged breastfeeding (>4 mo), an active lifestyle, and a healthy diet—might reduce the likelihood of asthma development. Immunizations are currently not considered to increase the likelihood of development of asthma; therefore, all standard childhood immunizations are recommended for children with asthma, including varicella and annual influenza vaccines.

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Chapter 145

Atopic Dermatitis (Atopic Eczema)

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Atopic dermatitis (AD), or eczema, is the most common chronic relapsing skin disease seen in infancy and childhood. It affects 10-30% of children worldwide and frequently occurs in families with other atopic diseases, such as asthma, allergic rhinitis, and food allergy. Infants with AD are predisposed to development of allergic rhinitis and/or asthma later in childhood, a process called "the atopic march."

ETIOLOGY

AD is a complex genetic disorder that results in a defective skin barrier, reduced skin innate immune responses, and exaggerated T-cell responses to environmental allergens and microbes that lead to chronic skin inflammation.

PATHOLOGY

Acute AD skin lesions are characterized by **spongiosis,** or marked intercellular edema, of the epidermis. In AD, dendritic antigen-presenting cells in the epidermis, such as Langerhans cells, exhibit surface-bound immunoglobulin (Ig) E molecules. These antigen-presenting cells play an important role in cutaneous allergen presentation to T-helper type 2 (Th2) cells (see Chapter 140). There is a marked perivenular T-cell infiltrate with occasional monocyte-macrophages in acute AD lesions. Mast cells are found in normal numbers but in different stages of degranulation. Chronic, lichenified AD is characterized by a hyperplastic epidermis with hyperkeratosis, and minimal spongiosis. There are predominantly IgE-bearing Langerhans cells in the epidermis, and macrophages in the dermal mononuclear cell infiltrate. Mast cell and eosinophil numbers are increased, contributing to skin inflammation.

PATHOGENESIS

Two forms of AD have been identified. **Atopic eczema** is associated with IgE-mediated sensitization (at onset or during the course of eczema) and occurs in 70-80% of patients with AD. **Nonatopic eczema** is not associated with IgE-mediated sensitization and is seen in 20-30% of patients with AD. Both forms of AD are associated with eosinophilia. In atopic eczema, circulating T cells expressing the skin homing receptor **cutaneous lymphocyte-associated antigen** produce increased levels of Th2 cytokines, including interleukin (IL)-4 and IL-13, which induce isotype switching to IgE synthesis. Another cytokine, IL-5, plays an important role in eosinophil development and survival. Nonatopic eczema is associated with lower IL-4 and IL-13 production than is atopic eczema.

Compared with the skin of healthy subjects, both unaffected skin and acute skin lesions of patients with AD have an increased number of cells expressing IL-4 and IL-13. Chronic AD skin lesions, by contrast, have significantly fewer cells that express IL-4 and IL-13, but increased numbers of cells that express IL-5, granulocyte-macrophage colony-stimulating factor, IL-12, and interferon (IFN)-γ than acute AD lesions. Chronic AD is characterized by a shift from a Th2-dominant to a Th1-dominant profile. The infiltration of IL-22–expressing T cells correlates with severity of AD, blocks keratinocyte differentiation, and induces epidermal hyperplasia.

The development of AD skin lesions is orchestrated by local tissue expression of proinflammatory cytokines and chemokines, which play a central role in defining the nature of the inflammatory infiltrate in AD. The chemotactic protein, CCL27, is highly upregulated in AD and preferentially attracts cutaneous lymphocyte-associated antigen-positive T cells to the skin. Other C-C chemokines, RANTES (regulated on activation, normal T-cell expressed and secreted), monocyte chemotactic protein-4, and eotaxin are increased in AD skin lesions, resulting in chemotaxis of eosinophils, macrophages, and Th2 lymphocytes expressing their receptor (CCR3).

In healthy people, the skin acts as a protective barrier against external irritants, moisture loss, and infection. Proper function of the skin depends on adequate moisture and lipid content, functional immune responses, and structural integrity. **Severely dry skin is a hallmark of AD.** This results from compromise of the epidermal barrier, which leads to excess transepidermal water loss, allergen penetration, and microbial colonization. **Filaggrin**, a structural protein in the epidermis, and its breakdown products are critical to skin barrier function. Genetic mutations in the filaggrin gene family have been identified in up to 50% of patients with severe AD. Cytokines found in allergic inflammation, such as IL-4, IL-13, IL-22, IL-25, and tumor necrosis factor, can also reduce filaggrin expression. AD patients thereby have increased risk of bacterial, viral, and fungal infection related to impairment of innate immunity, including a loss of barrier function and impaired generation of antimicrobial peptides.

CLINICAL MANIFESTATIONS

AD typically begins in infancy. Approximately 50% of patients experience symptoms in the 1st yr of life, and an additional 30% are diagnosed between 1 and 5 yr of age. Intense **pruritus**, especially at night, and **cutaneous reactivity** are the cardinal features of AD. Scratching and excoriation cause increased skin inflammation that contributes to the development of more pronounced eczematous skin lesions. Foods (cow milk, egg, peanut, tree nuts, soy, wheat, fish, shellfish), aeroallergens (pollen, grass, animal dander, dust mites), infection (staphylococcus, herpes simplex, molluscum), reduced humidity, excessive sweating, and irritants (wool, acrylic, soaps, toiletries, fragrances, detergents) can exacerbate (trigger) pruritus and scratching.

Acute AD skin lesions are intensely pruritic with erythematous papules (Figs. 145-1 and 145-2). Subacute dermatitis manifests as erythematous, excoriated, scaling papules. In contrast, chronic AD is characterized by **lichenification** (Fig. 145-3), or thickening of the skin with accentuated surface markings, and **fibrotic papules.** In chronic AD, all



Figure 145-1 Atopic dermatitis, typical cheek involvement. *(From Eichenfield LF, Friedan IJ, Esterly NB:* Textbook of neonatal dermatology, *Philadelphia, 2001, WB Saunders, p. 242.)*



Figure 145-2 Crusted lesions of atopic dermatitis on the face. *(From Eichenfield LF, Friedan IJ, Esterly NB:* Textbook of neonatal dermatology, *Philadelphia, 2001, WB Saunders, p. 242.)*



Figure 145-3 Lichenification of the popliteal fossa from chronic rubbing of the skin in atopic dermatitis. *(From Weston WL, Lane AT, Morelli JG:* Color textbook of pediatric dermatology, *ed 2, St. Louis, 1996, Mosby, p. 33.)*

3 types of skin reactions may coexist in the same individual. Most patients with AD have dry, lackluster skin irrespective of their stage of illness. Skin reaction pattern and distribution vary with the patient's age and disease activity. AD is generally more acute in infancy and involves the face, scalp, and extensor surfaces of the extremities. The diaper area is usually spared. Older children and children with chronic AD have lichenification and localization of the rash to the flexural folds of the extremities. AD often goes into remission as the patient grows older, leaving an adolescent or adult with skin prone to itching and inflammation when exposed to exogenous irritants.

LABORATORY FINDINGS

There are no specific laboratory tests to diagnose AD. Many patients have peripheral blood eosinophilia and increased serum IgE levels. Serum IgE measurement or prick skin testing can identify the allergens to which patients are sensitized. The diagnosis of clinical allergy to these allergens requires confirmation by history and environmental challenges.

Table 145-1 Clinical Features of Atopic Dermatitis

MAJOR FEATURES
Pruritus
Facial and extensor eczema in infants and children
Flexural eczema in adolescents
Chronic or relapsing dermatitis
Personal or family history of atopic disease
ASSOCIATED FEATURES
Xerosis
Cutaneous infections (*Staphylococcus aureus*, group A streptococcus, herpes simplex, coxsackievirus, vaccinia, molluscum, warts)
Nonspecific dermatitis of the hands or feet
Ichthyosis, palmar hyperlinearity, keratosis pilaris
Nipple eczema
White dermatographism and delayed blanch response
Anterior subcapsular cataracts, keratoconus
Elevated serum immunoglobulin E levels
Positive results of immediate-type allergy skin tests
Early age at onset
Dennie lines (Dennie-Morgan infraorbital folds)
Facial erythema or pallor
Course influenced by environmental and/or emotional factors

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

AD is diagnosed on the basis of 3 major features: pruritus, an eczematous dermatitis that fits into a typical presentation, and a chronic or chronically relapsing course (Table 145-1). Associated features, such as a family history of asthma, hay fever, elevated IgE, and immediate skin test reactivity, are variably present.

Many inflammatory skin diseases, immunodeficiencies, skin malignancies, genetic disorders, infectious diseases, and infestations share symptoms with AD and should be considered and excluded before a diagnosis of AD is established (Table 145-2). Severe combined immunodeficiency syndrome (see Chapter 126.1) should be considered for infants presenting in the 1st yr of life with diarrhea, failure to thrive, generalized scaling rash, and recurrent cutaneous and/or systemic infection. Histiocytosis (see Chapter 507) should be excluded in any infant with AD and failure to thrive. Wiskott-Aldrich syndrome (see Chapter 126.2), an X-linked recessive disorder associated with thrombocytopenia, immune defects, and recurrent severe bacterial infections, is characterized by a rash almost indistinguishable from that in AD. One of the hyper-IgE syndromes (see Chapter 126.2) is characterized by markedly elevated serum IgE values, recurrent deep-seated bacterial infections, chronic dermatitis, and refractory dermatophytosis. Many of these patients have disease as a result of autosomal dominant STAT3 mutations. In contrast, some patients with hyper-IgE syndrome present with increased susceptibility to viral infections and an autosomal recessive pattern of disease inheritance. These patients may have a Dock 8 (Dedicator of cytokinesis 8) mutation. This diagnosis should be considered in young children with severe eczema, food allergy, and disseminated skin viral infections.

Adolescents who present with an eczematous dermatitis but no history of childhood eczema, respiratory allergy, or atopic family history may have allergic **contact dermatitis** (see Chapter 655.1). A contact allergen may be the problem in any patient whose AD does not respond to appropriate therapy. Sensitizing chemicals, such as parabens and lanolin, can be irritants for patients with AD and are commonly found as vehicles in therapeutic topical agents. Topical glucocorticoid contact allergy has been reported in patients with chronic dermatitis on topical corticosteroid therapy. Eczematous dermatitis has also been reported with HIV infection as well as with a variety of infestations such as scabies. Other conditions that can be confused with AD include psoriasis, ichthyoses, and seborrheic dermatitis.

Table 145-2 Differential Diagnosis of Atopic Dermatitis

CONGENITAL DISORDERS
Netherton syndrome
Familial keratosis pilaris
CHRONIC DERMATOSES
Seborrheic dermatitis
Contact dermatitis (allergic or irritant)
Nummular eczema
Psoriasis
Ichthyoses
INFECTIONS AND INFESTATIONS
Scabies
HIV-associated dermatitis
Dermatophytosis
Insect bites
Onchocerciasis
MALIGNANCIES
Cutaneous T-cell lymphoma (mycosis fungoides/Sézary syndrome)
Letterer-Siwe disease (Langerhans cell histiocytosis)
AUTOIMMUNE DISORDERS
Dermatitis herpetiformis
Pemphigus foliaceus
Graft-versus-host disease
Dermatomyositis
IMMUNODEFICIENCIES
Wiskott-Aldrich syndrome
Severe combined immunodeficiency syndrome
Hyperimmunoglobulin E syndromes (autosomal dominant and recessive types)
Immunodysregulation polyendocrinopathy enteropathy X-linked (IPEX) syndrome
METABOLIC DISORDERS
Zinc deficiency
Pyridoxine (vitamin B_6) and niacin
Multiple carboxylase deficiency
Phenylketonuria

Modified from Leung DYM, Sampson HA, Geha RS, et al: Pediatric allergy principles and practice, *St. Louis, 2003, Mosby, p. 562.*

TREATMENT

The treatment of AD requires a systematic, multifaceted approach that incorporates skin hydration, topical anti-inflammatory therapy, identification and elimination of flare factors (Table 145-3), and, if necessary, systemic therapy. Assessment of the severity also helps direct therapy (Table 145-4).

Cutaneous Hydration

Because patients with AD have impaired skin barrier function from reduced lipid levels, they present with diffuse, abnormally dry skin, or **xerosis.** *Moisturizers are first-line therapy.* Lukewarm soaking baths for 15-20 min followed by the application of an occlusive emollient to retain moisture provide symptomatic relief. Hydrophilic ointments of varying degrees of viscosity can be used according to the patient's preference. Occlusive ointments are sometimes not well tolerated because of interference with the function of the eccrine sweat ducts and may induce the development of folliculitis. In these cases, less occlusive agents should be used. Several prescription (classified as a medical device) "therapeutic moisturizers/barrier creams" are available, containing components such as ceramides and filaggrin acid metabolites intended to improve skin barrier function. There are little data demonstrating their efficacy over standard emollients.

Hydration by baths or wet dressings promotes transepidermal penetration of topical glucocorticoids. Dressings may also serve as effective barriers against persistent scratching, in turn promoting healing of excoriated lesions. Wet dressings are recommended for use on severely affected or chronically involved areas of dermatitis refractory to skin care. It is critical that wet dressing therapy be followed by topical emollient application to avoid potential drying and fissuring from the therapy. Wet dressing therapy can be complicated by maceration and secondary infection and should be closely monitored by a physician.

Topical Corticosteroids

Topical corticosteroids are the cornerstone of antiinflammatory treatment for acute exacerbations of AD. Patients should be carefully instructed on their use of topical glucocorticoids in order to avoid potential adverse effects. There are 7 classes of topical glucocorticoids, ranked according to their potency as determined by vasoconstrictor assays (Table 145-5). Because of their potential adverse effects, the

Table 145-3 List of Aggravating Factors and Counselling for AD Patients

Clothing: avoid skin contact with irritating fibers (wool, large-fiber textiles); do not use tight and too warm clothing to avoid excessive sweating. New nonirritating clothing designed for AD children is being evaluated
Tobacco: avoid exposure
Cool temperature in bedroom and avoid too many bed covers
Increase emollient use with cold weather
Avoid exposure to herpes sores; urgent visit if flare of unusual aspect
Vaccines: normal schedule in noninvolved skin, including egg-allergic patients (see text)
Sun exposure: no specific restriction. Usually helpful because of improvement of epidermal barrier. Encourage summer holidays in altitude or at beach resorts
Physical exercise, sports: no restriction. If sweating induces flares of AD, progressive adaptation to exercise. Shower and emollients after swimming pool
Food allergens
Maintain breast feeding until 4 mo if possible
Otherwise normal diet, unless an allergy work-up has proven the need to exclude a specific food
Indoor aeroallergens
House dust mites
Use adequate ventilation of housing; keep the rooms well aerated even in winter
Avoid wall-to-wall carpeting
Remove dust with a wet sponge
Vacuum floors and upholstery with an adequately filtered cleaner once a week
Avoid soft toys in bed (cradle), except washable ones
Wash bed sheets at a temperature higher than 55° every 10 days
Use bed and pillow encasings made of Gore-Tex or similar material
Furred pets: advise to avoid. If allergy is demonstrated, be firm on avoidance measures, such as pet removal
Pollen: close windows during peak pollen season on warm and dry weather and restrict, if possible, stays outdoors. Windows may be open at night and early in the morning or during rainy weather. Avoid exposure to risk situations (lawn mowing). Use pollen filters in car. Clothes and pets can vectorize aeroallergens, including pollen

From Darsow U, Wollenberg A, Simon D, et al: ETFAD/EADV eczema task force 2009 position paper on diagnosis and treatment of atopic dermatitis. J Eur Acad Dermatol Venereol *24:317–328, 2010 (Table 2, p. 321).*

Table 145-4 Categorization of Physical Severity of Atopic Eczema

Clear—Normal skin, with no evidence of atopic eczema
Mild—Areas of dry skin, infrequent itching (with or without small areas of redness)
Moderate—Areas of dry skin, frequent itching, redness (with or without excoriation and localized skin thickening)
Severe—Widespread areas of dry skin, incessant itching, redness (with or without excoriation, extensive skin thickening, bleeding, oozing, cracking, and alteration of pigmentation)

From Lewis-Jones S, Mugglestone MA; Guideline Development Group: Management of atopic eczema in children aged up to 12 years: summary of NICE guidance, BMJ *335:1263–1264, 2007.*

Table 145-5 Selected Topical Corticosteroid Preparations*

GROUP 1
Clobetasol propionate (Temovate) 0.05% ointment/cream
Betamethasone dipropionate (Diprolene) 0.05% ointment/lotion/gel
Fluocinonide (Vanos) 0.1% cream
GROUP 2
Mometasone furoate (Elocon) 0.1% ointment
Halcinonide (Halog) 0.1% cream
Fluocinonide (Lidex) 0.05% ointment/cream
Desoximetasone (Topicort) 0.25% ointment/cream
Betamethasone dipropionate (Diprolene) 0.05% cream
GROUP 3
Fluticasone propionate (Cutivate) 0.005% ointment
Halcinonide (Halog) 0.1% ointment
Betamethasone valerate (Valisone) 0.1% ointment
GROUP 4
Mometasone furoate (Elocon) 0.1% cream
Triamcinolone acetonide (Kenalog) 0.1% ointment/cream
Fluocinolone acetonide (Synalar) 0.025% ointment
GROUP 5
Fluocinolone acetonide (Synalar) 0.025% cream
Hydrocortisone valerate (Westcort) 0.2% ointment
GROUP 6
Desonide (DesOwen) 05% ointment/cream/lotion
Alclometasone dipropionate (Aclovate) 0.05% ointment/cream
GROUP 7
Hydrocortisone (Hytone) 2.5% , 1%, 0.5% ointment/cream/lotion

*Representative corticosteroids are listed by group from 1 (superpotent) through 7 (least potent).

Adapted from Stoughton RB: Vasoconstrictor assay-specific applications. In Malbach HI, Surber C, editors: Topical corticosteroids, *Basel, Switzerland, 1992, Karger, pp. 42–53.*

ultrahigh-potency glucocorticoids should not be used on the face or intertriginous areas and should be used only for very short periods on the trunk and extremities. Mid-potency glucocorticoids can be used for longer periods to treat chronic AD involving the trunk and extremities. Long-term control can be maintained with twice-weekly applications of topical fluticasone or mometasone to areas that have healed but are prone to relapse, once control of AD is achieved after a daily regimen of topical corticosteroids. Compared with creams, ointments have a greater potential to occlude the epidermis, resulting in enhanced systemic absorption. Adverse effects of topical glucocorticoids can be divided into local adverse effects and systemic adverse effects, the latter of which result from suppression of the hypothalamic–pituitary–adrenal axis. Local adverse effects include the development of striae and skin atrophy. Systemic adverse effects are related to the potency of the topical corticosteroid, site of application, occlusiveness of the preparation, percentage of the body surface area covered, and length of use. The potential for adrenal suppression from potent topical corticosteroids is greatest in infants and young children with severe AD requiring intensive therapy.

Topical Calcineurin Inhibitors

The nonsteroidal topical calcineurin inhibitors are effective in reducing AD skin inflammation. Pimecrolimus cream 1% (Elidel) is indicated for mild to moderate AD. Tacrolimus ointment 0.1% and 0.03% (Protopic) is indicated for moderate to severe AD. Both are approved for short-term or intermittent long-term treatment of AD in patients ≥2 yr whose disease is unresponsive to or who are intolerant of other conventional therapies or for whom these therapies are inadvisable owing to potential risks. Topical calcineurin inhibitors may be better than topical corticosteroids in the treatment of patients whose AD is poorly responsive to topical steroids, of patients with steroid phobia, and of patients with face and neck dermatitis, in which ineffective, low-potency topical corticosteroids are usually used because of fears of steroid-induced skin atrophy.

Tar Preparations

Coal tar preparations have antipruritic and antiinflammatory effects on the skin; however, the antiinflammatory effects are usually not as pronounced as those of topical glucocorticoids or calcineurin inhibitors. Tar preparations are useful in reducing the potency of topical glucocorticoids required in long-term maintenance therapy of AD. Tar shampoos can be particularly beneficial for scalp dermatitis. Adverse effects associated with tar preparations include skin irritation, folliculitis, and photosensitivity.

Antihistamines

Systemic antihistamines act primarily by blocking the histamine H_1 receptors in the dermis, thereby reducing histamine-induced pruritus. Histamine is only one of many mediators that induce pruritus of the skin, so patients may derive minimal benefit from antihistaminic therapy. Because pruritus is usually worse at night, sedating antihistamines (hydroxyzine, diphenhydramine) may offer an advantage with their soporific side effects when used at bedtime. Doxepin hydrochloride has both tricyclic antidepressant and H_1- and H_2-receptor blocking effects. Short-term use of a sedative to allow adequate rest may be appropriate in cases of severe nocturnal pruritus. Studies of newer nonsedating antihistamines have shown variable effectiveness in controlling pruritus in AD, although they may be useful in the small subset of patients with AD and concomitant urticaria.

Systemic Corticosteroids

Systemic corticosteroids are rarely indicated in the treatment of chronic AD. The dramatic clinical improvement that may occur with systemic corticosteroids is frequently associated with a severe rebound flare of AD after therapy discontinuation. Short courses of oral corticosteroids may be appropriate for an acute exacerbation of AD while other treatment measures are being instituted in parallel. If a short course of oral corticosteroids is given, it is important to taper the dosage and begin intensified skin care, particularly with topical corticosteroids and frequent bathing followed by application of emollients, to prevent rebound flaring of AD.

Cyclosporine

Cyclosporine is a potent immunosuppressive drug that acts primarily on T cells by suppressing cytokine gene transcription. Cyclosporine forms a complex with an intracellular protein, cyclophilin, and this complex, in turn, inhibits calcineurin, a phosphatase required for

activation of NFAT (nuclear factor of activated T cells), a transcription factor necessary for cytokine gene transcription. Cyclosporine (5 mg/kg/day) for short-term and long-term (1 yr) use has been beneficial for children with severe, refractory AD. Possible adverse effects include renal impairment and hypertension.

Antimetabolites

Mycophenolate mofetil is a purine biosynthesis inhibitor used as an immunosuppressant in organ transplantation that has been used for treatment of refractory AD. Aside from immunosuppression, herpes simplex retinitis and dose-related bone marrow suppression have been reported with its use. Of note, not all patients benefit from treatment. Therefore, the medication should be discontinued if the disease does not respond within 4-8 wk. Methotrexate is an antimetabolite with potent inhibitory effects on inflammatory cytokine synthesis and cell chemotaxis. Methotrexate has been used for patients with recalcitrant AD. In AD, dosing is more frequent than the weekly dosing used for psoriasis. Azathioprine is a purine analog with antiinflammatory and antiproliferative effects that has been used for severe AD. Myelosuppression is a significant adverse effect, and thiopurine methyl transferase levels may identify individuals at risk for it. Before any of these drugs is used, patients should be referred to an AD specialist who is familiar with treatment of severe AD to weigh relative benefits of alternative therapies.

Phototherapy

Natural sunlight is often beneficial to patients with AD as long as sunburn and excessive sweating are avoided. Many phototherapy modalities are effective for AD, including ultraviolet A-1, ultraviolet B, narrow-band ultraviolet B, and psoralen plus ultraviolet A. Phototherapy is generally reserved for patients in whom standard treatments fail. Maintenance treatments are usually required for phototherapy to be effective. Short-term adverse effects with phototherapy include erythema, skin pain, pruritus, and pigmentation. Long-term adverse effects include predisposition to cutaneous malignancies.

Unproven Therapies

Other therapies that may be considered in patients with refractory AD are as follows.

Interferon-γ

IFN-γ is known to suppress Th2-cell function. Several studies, including a multicenter, double-blind, placebo-controlled trial and several open trials, have demonstrated that treatment with recombinant human IFN-γ results in clinical improvement of AD. Reduction in clinical severity of AD correlated with the ability of IFN-γ to decrease total circulating eosinophil counts. Influenza-like symptoms are commonly observed side effects during the treatment course.

Omalizumab

Treatment of patients who have severe AD and elevated serum IgE values with monoclonal anti-IgE may be considered in those with allergen-induced flares of AD. However, there have been no published double-blind, placebo-controlled trials of its use. Most reports have been case studies and show inconsistent responses to anti-IgE.

Allergen Immunotherapy

In contrast to its acceptance for treatment of allergic rhinitis and extrinsic asthma, immunotherapy with aeroallergens in the treatment of AD is controversial. There are reports of both disease exacerbation and improvement. Studies suggest specific immunotherapy in patients with AD sensitized to dust mite allergen showed improvement in severity of skin disease, as well as reduction in topical steroid use.

Probiotics

Perinatal administration of the probiotic *Lactobacillus rhamnosus* strain GG has been shown to reduce the incidence of AD in at-risk children during the first 2 yr of life. The treatment response has been found to be more pronounced in patients with positive skin prick test results and elevated IgE values. Other studies have not demonstrated a benefit.

Chinese Herbal Medications

Several placebo-controlled clinical trials have suggested that patients with severe AD may benefit from treatment with traditional Chinese herbal therapy. The subjects had significantly reduced skin disease and decreased pruritus. The beneficial response of Chinese herbal therapy is often temporary, and effectiveness may wear off despite continued treatment. The possibility of hepatic toxicity, cardiac side effects, or idiosyncratic reactions remains a concern. The specific ingredients of the herbs also remain to be elucidated, and some preparations have been found to be contaminated with corticosteroids. At present, Chinese herbal therapy for AD is considered investigational.

Vitamin D

Vitamin D deficiency often accompanies severe AD. Vitamin D enhances skin barrier function, reduces corticosteroid requirements to control inflammation and augments skin antimicrobial function. Several small clinical studies suggest vitamin D can enhance antimicrobial peptide expression in the skin and reduce severity of skin disease especially in patients with low baseline vitamin D, for example, during the wintertime when exacerbation of AD often occurs. Patients with AD might benefit from supplementation with vitamin D, particularly if they have a documented low level or low vitamin D intake.

AVOIDING TRIGGERS

It is essential to identify and eliminate triggering factors, both during the period of acute symptoms and on a long-term basis to prevent recurrences (see Table 145-3).

Irritants

Patients with AD have a low threshold response to irritants that trigger their itch-scratch cycle. Soaps or detergents, chemicals, smoke, abrasive clothing, and exposure to extremes of temperature and humidity are common triggers. Patients with AD should use soaps with minimal defatting properties and a neutral pH. New clothing should be laundered before wearing to decrease levels of formaldehyde and other chemicals. Residual laundry detergent in clothing may trigger the itch-scratch cycle; using a liquid rather than powder detergent and adding a second rinse cycle facilitates removal of the detergent.

Every attempt should be made to allow children with AD to be as normally active as possible. A sport such as swimming may be better tolerated than others that involve intense perspiration, physical contact, or heavy clothing and equipment. Rinsing off chlorine immediately and lubricating the skin after swimming are important. Although ultraviolet light may be beneficial to some patients with AD, high sun protection factor sunscreens should be used to avoid sunburn.

Foods

Food allergy is comorbid in approximately 40% of infants and young children with moderate to severe AD (see Chapter 151). Undiagnosed food allergies in patients with AD may induce eczematous dermatitis in some patients and urticarial reactions, wheezing, or nasal congestion in others. Increased severity of AD symptoms and younger age correlate directly with the presence of food allergy. Removal of food allergens from the diet leads to significant clinical improvement but requires a great deal of education, because most common allergens (egg, milk, peanut, wheat, soy) contaminate many foods and are difficult to avoid.

Potential allergens can be identified by a careful history and performing selective skin prick tests or in vitro blood testing for allergen-specific IgE. Negative skin and blood test results for allergen-specific IgE have a high predictive value for excluding suspected allergens. Positive results of skin or blood tests using foods often do not correlate with clinical symptoms and should be confirmed with controlled food challenges and elimination diets. Extensive elimination diets, which can be nutritionally deficient, are rarely required. Even with multiple

positive skin test results, the majority of patients react to fewer than 3 foods under controlled challenge conditions.

Aeroallergens

In older children, AD flares can occur after intranasal or epicutaneous exposure to aeroallergens such as fungi, animal dander, grass, and ragweed pollen. Avoiding aeroallergens, particularly dust mites, can result in clinical improvement of AD. Avoidance measures for dust mite–allergic patients include using dust mite–proof encasings on pillows, mattresses, and box springs; washing bedding in hot water weekly; removing bedroom carpeting; and decreasing indoor humidity levels with air conditioning.

Infections

Patients with AD have increased susceptibility to bacterial, viral, and fungal skin infections. Antistaphylococcal antibiotics are very helpful for treating patients who are heavily colonized or infected with *Staphylococcus aureus.* Erythromycin and azithromycin are usually beneficial for patients who are not colonized with a resistant *S. aureus* strain; a first-generation cephalosporin (cephalexin) is recommended for macrolide-resistant *S. aureus*. Topical mupirocin is useful in the treatment of localized impetiginous lesions, with systemic antibiotics for widespread infections. Cytokine-mediated skin inflammation contributes to skin colonization with *S. aureus;* this fact indicates the importance of combining effective anti-inflammatory therapy with antibiotics for treating moderate to severe AD to avoid the need for repeated courses of antibiotics, which can lead to the emergence of antibiotic-resistant strains of *S. aureus.* Dilute bleach baths (½ cup of bleach in 40 gallons of water) twice weekly may be also considered to reduce *S. aureus* colonization. In one randomized trial the group who received the bleach baths plus intranasal mupirocin (5 days/mo) had significantly decreased severity of AD at 1 and 3 mo compared with placebo. Patients rinse off after the soaking. Further studies are needed to validate this technique.

Herpes simplex virus (HSV) can provoke recurrent dermatitis and may be misdiagnosed as *S. aureus* infection. The presence of punched-out erosions, vesicles, and infected skin lesions that fail to respond to oral antibiotics suggests HSV infection, which can be diagnosed by a Giemsa-stained Tzanck smear of cells scraped from the vesicle base or by viral polymerase chain reaction or culture. Topical corticosteroids should be temporarily discontinued if HSV infection is suspected. Reports of life-threatening dissemination of HSV infections in patients with AD who have widespread disease mandate antiviral treatment. Persons with AD are also susceptible to **eczema vaccinatum,** which is similar in appearance to eczema herpeticum and historically follows smallpox (vaccinia virus) vaccination. Cutaneous warts and molluscum contagiosum are additional viral infections affecting children with AD.

Dermatophyte infections also can contribute to exacerbation of AD. Patients with AD have been found to have a greater susceptibility to *Trichophyton rubrum* fungal infections than nonatopic control subjects. There has been particular interest in the role of *Malassezia furfur* (formerly known as *Pityrosporum ovale*) in AD because it is a lipophilic yeast commonly present in the seborrheic areas of the skin. IgE antibodies against *M. furfur* have been found in patients with head and neck dermatitis. A reduction of AD severity has been observed in those patients after treatment with antifungal agents.

COMPLICATIONS

Exfoliative dermatitis may develop in patients with extensive skin involvement. It is associated with generalized redness, scaling, weeping, crusting, systemic toxicity, lymphadenopathy, and fever, and is usually caused by superinfection (e.g., with toxin-producing *S. aureus* or HSV infection) or inappropriate therapy. In some cases, the withdrawal of systemic glucocorticoids used to control severe AD precipitates exfoliative erythroderma.

Eyelid dermatitis and chronic blepharitis may result in visual impairment from corneal scarring. **Atopic keratoconjunctivitis** is usually bilateral and can have disabling symptoms that include itching, burning, tearing, and copious mucoid discharge. Vernal conjunctivitis is associated with papillary hypertrophy or cobblestoning of the upper eyelid conjunctiva. It typically occurs in younger patients and has a marked seasonal incidence with spring exacerbations. **Keratoconus** is a conical deformity of the cornea believed to result from chronic rubbing of the eyes in patients with AD. Cataracts may be a primary manifestation of AD or from extensive use of systemic and topical glucocorticoids, particularly around the eyes.

PROGNOSIS

AD generally tends to be more severe and persistent in young children, particularly if they have null mutations in their filaggrin genes. Periods of remission occur more frequently as patients grow older. Spontaneous resolution of AD has been reported to occur after age 5 yr in 40-60% of patients affected during infancy, particularly for mild disease. Earlier studies suggested that approximately 84% of children outgrow their AD by adolescence; however, later studies reported that AD resolves in approximately 20% of children monitored from infancy until adolescence and becomes less severe in 65%. Of those adolescents treated for mild dermatitis, >50% may experience a relapse of disease as adults, which frequently manifests as hand dermatitis, especially if daily activities require repeated hand wetting. Predictive factors of a poor prognosis for AD include widespread AD in childhood, filaggrin gene null mutations, concomitant allergic rhinitis and asthma, family history of AD in parents or siblings, early age at onset of AD, being an only child, and very high serum IgE levels.

PREVENTION

Breastfeeding or a feeding with a hypoallergenic hydrolyzed formula may be beneficial. Probiotics and prebiotics may also reduce the incidence or severity of AD, but this approach is unproven. If an infant with AD is diagnosed with food allergy, the breast feeding mother may need to eliminate the implicated food allergen from her diet. Identification and elimination of triggering factors is the mainstay for prevention of flares as well as for the long-term treatment of AD.

Emollient therapy applied to the whole body for the first few months of life may enhance the cutaneous barrier and reduce the risk of eczema.

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Chapter 146

Insect Allergy

Julie Wang and Scott H. Sicherer

Allergic responses to stinging or, more rarely, biting insects vary from localized cutaneous reactions to systemic anaphylaxis. Allergic reactions that are caused by inhalation of airborne particles of insect origin result in acute and chronic respiratory symptoms of seasonal or perennial rhinitis, conjunctivitis, and/or asthma.

ETIOLOGY

Most reactions to stinging and biting insects, such as those induced by wasps, mosquitoes, flies, and fleas, are limited to a primary lesion isolated to the area of the sting or bite and do not represent an allergic response. Occasionally, insect stings or bites induce pronounced localized reactions or systemic reactions that may be based on immediate or delayed hypersensitivity reactions. Systemic allergic responses to insects are attributed most typically to immunoglobulin (Ig) E antibody–mediated responses, which are caused primarily by stings from venomous insects of the order Hymenoptera and more rarely from ticks, spiders, scorpions, and *Triatoma* (kissing bug). Members of the order Hymenoptera include apids (honeybee, bumblebee), vespids

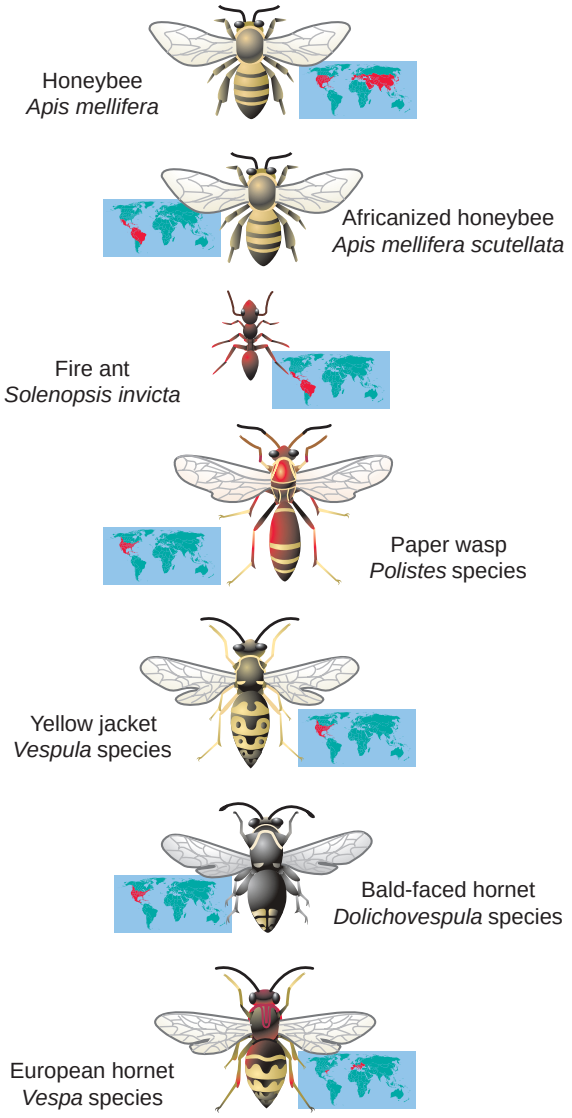


Figure 146-1 Species of Hymenoptera and their geographical distribution. *(From Freeman TM: Hypersensitivity to Hymenoptera stings,* N Engl J Med *351:1978–1984, 2004.)*

(yellow jacket, wasp, hornet), and formicids (fire and harvester ants) (Fig. 146-1). Among winged stinging insects, yellow jackets are the most notorious for stinging because they are aggressive and ground dwelling, and they linger near activities involving food. Hornets nest in trees, whereas wasps build honeycomb nests in dark areas such as under porches; both are aggressive if disturbed. Honeybees are less aggressive, nest in tree hollows, and, unlike the stings of other flying Hymenoptera, honeybee stings almost always leave a barbed stinger with venom sac.

In the United States, fire ants are found increasingly in the Southeast, living in large mounds of soil. When disturbed, the ants attack in large numbers, anchor themselves to the skin by their mandibles, and sting multiple times in a circular pattern. Sterile pseudopustules form at the sting sites. Systemic reactions to stinging insects occur in 0.4-0.8% of children and 3% of adults and account for approximately 40 deaths each year in the United States.

Although reactions to insect bites are common, IgE-mediated reactions are infrequently reported and anaphylaxis is rare. The *Triatoma* (kissing bug) bite causes an erythematous plaque that is painless. Mosquito bites generally result in local reactions that are pruritic. Large local reactions to mosquito bites can occur in some young children; this is known as Skeeter syndrome, and is often misdiagnosed as cellulitis. The tabanid species (horsefly, deerfly), commonly found in rural and suburban areas, are large flies that induce painful bites.

IgE antibody–mediated allergic responses to airborne particulate matter carrying insect emanations contribute to seasonal and perennial symptoms affecting the upper and lower airways. Seasonal allergy is attributed to exposures to a variety of insects, particularly aquatic insects such as the caddis fly and midge, or lake fly, at a time when larvae pupate and adult flies are airborne. Perennial allergy is attributed to sensitization to insects such as cockroaches and ladybugs, as well as house dust mite, which is phylogenetically related to spiders rather than insects and has 8 rather than 6 legs.

PATHOGENESIS

Hymenoptera venoms contain numerous components with toxic and pharmacologic activity and with allergenic potential. These constituents include vasoactive substances such as histamine, acetylcholine, and kinins; enzymes such as phospholipase and hyaluronidase; apamin; melittin; and formic acid. The majority of patients who experience systemic reactions after Hymenoptera stings have IgE-mediated sensitivity to antigenic substances in the venom. Some venom allergens are homologous among members of the Hymenoptera order; others are family specific. There is substantial cross-reactivity among vespid venoms, but these venom allergies are distinct from honeybee venom allergies.

Localized skin responses to biting insects are caused primarily by vasoactive or irritant materials derived from insect saliva, and rarely occur from IgE-associated responses. Systemic IgE-mediated allergic reactions to salivary proteins of biting insects such as mosquitoes are reported but uncommon.

A variety of proteins derived from insects can become airborne and induce IgE-mediated respiratory responses, causing inhalant allergies. The primary allergen from the caddis fly is a hemocyanin-like protein, and that from the midge fly is derived from hemoglobin. Allergens from the cockroach are the best studied and are derived from cockroach saliva, secretions, fecal material, and debris from skin casts.

CLINICAL MANIFESTATIONS

Clinical reactions to stinging venomous insects are categorized as local, large local, generalized cutaneous, systemic, toxic, and delayed/late. Simple **local reactions** involve limited swelling and pain, and generally last <24 hr. **Large local reactions** develop over hours and days, involve swelling of extensive areas (>10 cm) that are contiguous with the sting site, and may last for days. **Generalized cutaneous reactions** typically progress within minutes and include cutaneous symptoms of urticaria, angioedema, and pruritus beyond the site of the sting. **Systemic reactions** are identical to anaphylaxis from other triggers and may include symptoms of generalized urticaria, laryngeal edema, bronchospasm, and hypotension. Stings from a large number of insects at once may result in **toxic reactions** of fever, malaise, emesis, and nausea owing to the chemical properties of the venom in large doses. Serum sickness, nephrotic syndrome, vasculitis, neuritis, or encephalopathy may occur as **delayed/late reactions** to stinging insects.

Insect bites are usually urticarial but may be papular or vesicular. Papular urticaria affecting the lower extremities in children is usually caused by multiple bites. Occasionally, individuals have large local reactions. IgE antibody–associated immediate- and late-phase allergic responses to mosquito bites sometimes mimic cellulitis.

Inhalant allergy caused by insects results in clinical disease similar to that induced by other inhalant allergens such as pollens. Depending on individual sensitivity and exposure, reactions may result in seasonal or perennial rhinitis, conjunctivitis, and/or asthma.

DIAGNOSIS

The diagnosis of allergy from stinging and biting insects is generally evident from the history of exposure, typical symptoms, and physical findings. The diagnosis of Hymenoptera allergy rests in part on the identification of venom-specific IgE by prick skin testing or in vitro testing. The primary reasons to pursue testing are to confirm reactivity when venom immunotherapy (VIT) is being considered or when it is clinically necessary to confirm venom hypersensitivity as a cause of a reaction. Venoms of 5 Hymenoptera (honeybee, yellow jacket, yellow

hornet, white-faced hornet, and wasp), as well as the jack jumper ant in Australia and whole-body extract of fire ant, are available for skin testing. Although skin tests are considered to be the most sensitive modality for detection of venom-specific IgE, additional evaluation with an in vitro serum assay for venom-specific IgE is recommended if skin test results are negative in the presence of a convincing history of a severe systemic reaction. With in vitro tests, there is a 20% incidence of both false-positive and false-negative results, so it is not appropriate to exclude venom hypersensitivity based on this test alone. If initial skin prick and in vitro test results are negative in the context of a convincing history of a severe reaction, repeat testing is recommended before concluding that allergy is unlikely. Skin tests are usually accurate within 1 wk of a sting reaction, but occasionally a refractory period is observed that warrants retesting after 4-6 wk if the initial results are negative. If repeat skin prick and in vitro results are still negative despite a convincing history, occult mast cell disorders should be considered and a baseline serum tryptase should be measured. As many as 40% of skin test–positive subjects may not experience anaphylaxis on sting challenge, so testing without an appropriate clinical history is potentially misleading.

The diagnosis of inhalant insect allergy may be evident from a history of typical symptoms. A chronic respiratory symptom during long-term exposure, as may occur with cockroach allergy, is less amenable to identification by history alone. Skin prick or in vitro immunoassay tests for specific IgE to the insect are used to confirm inhalant insect allergy. Allergy tests may be particularly warranted for potential cockroach allergy in patients with persistent asthma and known cockroach exposure.

TREATMENT

For local cutaneous reactions caused by insect stings and bites, treatment with cold compresses, topical medications to relieve itching, and, occasionally, the use of a systemic antihistamine and oral analgesic are appropriate. Stingers should be removed promptly by scraping, with caution not to squeeze the venom sac because doing so could inject more venom. Sting sites rarely become infected, possibly owing to the antibacterial actions of venom constituents. Vesicles left by fire ant stings that are scratched open should be cleansed to prevent secondary infection.

Anaphylactic reactions after a Hymenoptera sting are treated exactly like anaphylaxis from any cause; epinephrine is the drug of choice. Adjunctive treatment includes antihistamines, corticosteroids, intravenous fluids, oxygen, and transport to the emergency room. (see Chapter 149). Referral to an allergist-immunologist should be considered for patients who have experienced a generalized cutaneous or systemic reaction to an insect sting, need education about avoidance and emergency treatment, may be candidates for VIT, or have a condition that may complicate management of anaphylaxis (e.g., use of β-blockers).

Venom Immunotherapy

Hymenoptera VIT is highly effective (95-97%) in decreasing the risk for severe anaphylaxis. The selection of patients for VIT depends on several factors (Table 146-1). Individuals with local reactions regardless of age are not at increased risk for severe systemic reactions on a subsequent sting and are not candidates for VIT. The risk of a systemic reaction for those who experienced a large local reaction is no more than 5-10%; testing or VIT is usually not recommended, and prescription of self- injectable epinephrine is considered optional but usually not necessary. There is growing evidence that VIT can reduce the size and duration of large, local reactions, and therefore VIT may be considered for those with frequent or unavoidable large, local reactions. *Those who experience severe systemic reactions, such as airway involvement or hypotension, and have specific IgE to venom allergens should receive immunotherapy.* Immunotherapy against winged Hymenoptera is not usually indicated for children ≤16 yr of age in whom stings have caused only generalized urticaria or angioedema, because their risk for a systemic reaction after a subsequent sting is approximately 10%. If a systemic reaction does occur, it is likely to be isolated skin reactions, with <5% risk of a more severe reaction and <1% risk of life-threatening anaphylaxis. The risk could be reduced to 1% after treatment with VIT, so it is an option to consider if multiple future stings are anticipated. *Immunotherapy against Hymenoptera is indicated in those ≥17 yr of age who have specific IgE to venom allergens and a history of generalized urticaria or a systemic reaction,* because their risk for future systemic reactions is 30-60%. VIT is usually not indicated if there is no evidence of IgE to venom.

The incidence of adverse effects in the course of treatment is not trivial in adults, as 50% experience large local reactions and about 10% experience systemic reactions. The incidence of both local and systemic reactions is much lower in children. Patients treated with honeybee venom are at higher risk for systemic reactions to VIT than those receiving treatment with vespid venom. Individuals with mast cell disorders are at increased risk for severe anaphylaxis and more frequent systemic reactions with VIT.

It is uncertain how long immunotherapy with Hymenoptera venom should continue. In general, a 3-5 year treatment duration is recommended because >80% of adults who have received 5 yr of therapy tolerate challenge stings without systemic reactions for 5-10 yr after completion of treatment. Long-term responses to treatment are even better for children. Follow-up over a mean of 18 yr of children with moderate to severe insect sting reactions who received VIT for a mean treatment period of 3-5 yr and were stung again showed a reaction rate of only 5%; untreated children experienced a reaction rate of 32%. Whereas duration of therapy with VIT may be individualized, it is clear that a significant number of untreated children retain their allergy. Lifelong treatment may be considered for those who have had severe life-threatening anaphylaxis with insect stings, those with honeybee allergy, and those with occupational exposures to Hymenoptera. Lifelong VIT should also be considered for those with mast cell disorders as these individuals have a higher rate of failure of VIT and relapse when VIT is discontinued.

Less is known about the natural history of fire ant hypersensitivity and efficacy of immunotherapy for this allergy. The criteria for starting immunotherapy are similar to those for hypersensitivities to other Hymenoptera, but there is stronger consideration to treat children ≤16 yr of age with VIT if they have experienced only generalized

Table 146-1 Indications for Venom Immunotherapy Against Winged Hymenoptera

SYMPTOMS	AGE	SKIN TEST/IN VITRO TEST	RISK OF SYSTEMIC REACTION IF UNTREATED*	VIT RECOMMENDED
Large local reaction	Any	Usually not indicated	5-10%	Usually not indicated
Generalized cutaneous reaction	≤16 yr	Usually not indicated	10%	Usually not indicated
	≥17 yr	Positive result	20%	Yes
		Negative result	—	No
Systemic reaction	Any	Positive result	Child: 40% Adult: 30-60%	Yes
		Negative result	—	Usually no

*Risks generally decrease after 10 yr.

urticaria. Only whole-body fire ant extract is commercially available for diagnostic skin testing and immunotherapy.

Inhalant Allergy

The symptoms of inhalant allergy caused by insects are managed as for other causes of seasonal or perennial rhinitis (see Chapter 143), conjunctivitis (see Chapter 147), and asthma (see Chapter 144).

PREVENTION

Avoidance of stings and bites is essential. To reduce the risk of stings, sensitized individuals should avoid attractants such as perfumes and bright-colored clothing outdoors, wear gloves when gardening, and wear long pants and shoes with socks when walking in the grass or through fields. Typical insect repellents do not guard against Hymenoptera. Nests of these insects should be removed if they are close to the home.

Individuals who have had generalized cutaneous or systemic reactions to Hymenoptera stings should have immediate access to **self-injectable epinephrine.** Adults responsible for allergic children, and older patients who can self-treat, must be carefully taught the indications for and technique of administration of this medication. Particular attention is necessary for children in out-of-home daycare centers, at school, or attending camps, to ensure that an emergency action plan is in place. The individual at risk for anaphylaxis from an insect sting should also wear an identification bracelet indicating the allergy.

Avoidance of the insect is the preferred management of inhalant allergy. This can prove difficult, particularly, for instance, for those living in multiple-dwelling apartments, where eradication of cockroaches is problematic. Immunotherapy for dust mites is effective and should be considered in conjunction with avoidance measures. In contrast, there is limited data regarding the efficacy of cockroach immunotherapy.

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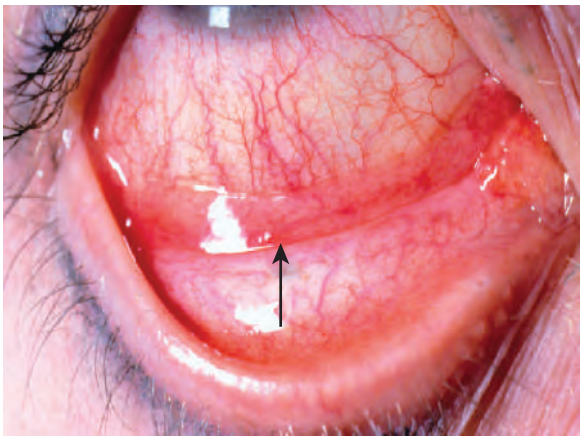


Figure 147-1 Allergic conjunctivitis. Arrow indicates area of chemosis in the conjunctivitis. *(From Adkinson NF Jr, Bochner BS, Busse WW, et al, editors:* Middleton's allergy principles and practice, *ed 7, vol 2, Philadelphia, Elsevier, 2009, p. 1121.)*

Chapter 147

Ocular Allergies

Mark Boguniewicz, Christine B. Cho, and Scott H. Sicherer

The eye is a common target of allergic disorders because of its marked vascularity and direct contact with allergens in the environment. The conjunctiva is the most immunologically active tissue of the external eye. Ocular allergies can occur as isolated target organ disease or more commonly in conjunction with nasal allergies. Ocular symptoms can significantly affect quality of life.

CLINICAL MANIFESTATIONS

There are a few distinct entities that constitute allergic eye disease, all of which have bilateral involvement. Sensitization is necessary for all of these except for giant papillary conjunctivitis. Vernal keratoconjunctivitis and atopic keratoconjunctivitis are potentially sight-threatening.

Allergic Conjunctivitis

Allergic conjunctivitis is the most common hypersensitivity response of the eye, affecting approximately 25% of the general population and 30% of children with atopy. It is caused by direct exposure of the mucosal surfaces of the eye to environmental allergens. Patients complain of variable ocular itching, rather than pain, with increased tearing. Clinical signs include bilateral injected conjunctivae with vascular congestion that may progress to chemosis, or conjunctival swelling, and a watery discharge (Fig. 147-1). Allergic conjunctivitis occurs in a seasonal or, less commonly, perennial form. **Seasonal allergic conjunctivitis** is typically associated with allergic rhinitis (see Chapter 143) and is most commonly triggered by pollens. Major pollen groups in the temperate zones include trees (late winter to early spring), grasses (late spring to early summer), and weeds (late summer to early fall), but seasons can vary significantly in different parts of the country. Mold spores can also cause seasonal allergy symptoms, principally in the summer and fall. Seasonal allergy symptoms may be aggravated by coincident exposure to perennial allergens. **Perennial allergic conjunctivitis** is triggered by allergens such as animal danders or dust mites that are present throughout the year. Symptoms are usually less severe than with seasonal allergic conjunctivitis. Because pollens and soil molds may be present intermittently by season, and exposure to allergens such as furred animals may be perennial, classification as intermittent (symptoms present <4 days/wk or for <4 wk) and persistent (symptoms present >4 days/wk and for >4 wk) has been proposed.

Vernal Keratoconjunctivitis

Vernal keratoconjunctivitis is a severe bilateral chronic inflammatory process of the upper tarsal conjunctival surface that occurs in a limbal or palpebral form. It may threaten eyesight if there is corneal involvement. Although vernal keratoconjunctivitis is not immunoglobulin E mediated, it occurs most frequently in children with seasonal allergies, asthma, or atopic dermatitis. Vernal keratoconjunctivitis affects boys twice as often as girls and is more common in persons of Asian and African descent. It affects primarily children in temperate areas, with exacerbations in the spring and summer. Symptoms include severe ocular itching exacerbated by exposure to irritants, light, or perspiration. In addition, patients may complain of severe photophobia, foreign-body sensation, and lacrimation. Giant papillae occur predominantly on the upper tarsal plate and are typically described as **cobblestoning** (Fig. 147-2). Other signs include a stringy or thick, ropey discharge, cobblestone papillae, transient yellow-white points in the limbus (Trantas dots) and conjunctiva (Horner points), corneal "shield" ulcers, and Dennie lines (Dennie-Morgan folds), which are prominent symmetric skinfolds that extend in an arc from the inner canthus beneath and parallel to the lower lid margin. Children with vernal keratoconjunctivitis have measurably longer eyelashes, which may represent a reaction to ocular inflammation.

Atopic Keratoconjunctivitis

Atopic keratoconjunctivitis is a **chronic** inflammatory ocular disorder most commonly involving the lower tarsal conjunctiva. It may threaten eyesight if there is corneal involvement. Almost all patients have **atopic dermatitis,** and a significant number have asthma. Atopic

keratoconjunctivitis rarely presents before late adolescence. Symptoms include severe bilateral ocular itching, burning, photophobia, and tearing with a mucoid discharge that are much more severe than in allergic conjunctivitis and persist throughout the year. The bulbar conjunctiva is injected and chemotic; cataracts may occur. Trantas dots or giant papillae may also be present. Eyelid eczema can extend to the periorbital skin and cheeks with erythema and thick, dry scaling. Secondary staphylococcal blepharitis is common because of eyelid induration and maceration.

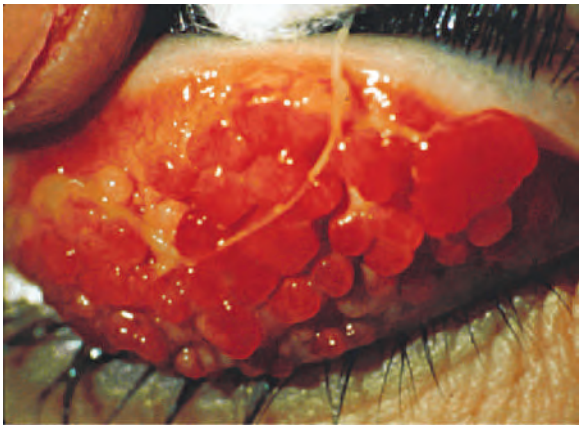


Figure 147-2 Vernal keratoconjunctivitis. Cobblestone papillae and ropey discharge are seen on the underside (tarsal conjunctiva) of the upper eyelid. *(From Adkinson NF Jr, Bochner BS, Busse WW, et al, editors:* Middleton's allergy principles and practice, *ed 7, vol 2, Philadelphia, Mosby/Elsevier, 2009, p. 1124.)*

Giant Papillary Conjunctivitis

Giant papillary conjunctivitis has been linked to chronic exposure to foreign bodies, such as contact lenses, both hard and soft, ocular prostheses, and sutures. Symptoms and signs include mild bilateral ocular itching, tearing, a foreign-body sensation, and excessive ocular discomfort with mild mucoid discharge with white or clear exudate on awakening, which may become thick and stringy. Trantas dots, limbal infiltration, bulbar conjunctival hyperemia, and edema may develop.

Contact Allergy

Contact allergy typically involves the eyelids but can also involve the conjunctivae. It is being recognized more frequently in association with increased exposure to topical medications, contact lens solutions, and preservatives.

DIAGNOSIS

Nonallergic conjunctivitis can be viral, bacterial, or chlamydial in origin. It is typically unilateral but can be bilateral with symptoms initially developing in 1 eye (see Chapter 626). Symptoms include stinging or burning rather than itching and often a foreign-body sensation. Ocular discharge can be watery, mucoid, or purulent. Masqueraders of ocular allergy also include nasolacrimal duct obstruction, foreign body, blepharoconjunctivitis, dry eye, uveitis, and trauma.

TREATMENT

Primary treatment of ocular allergies includes avoidance of allergens, cold compresses, and lubrication. Secondary treatment regimens include the use of oral or topical antihistamines and, if necessary, topical decongestants, mast cell stabilizers, and antiinflammatory agents (Table 147-1). Drugs with dual antihistamine and mast cell blocking activities provide the most advantageous approach in treating allergic conjunctivitis, with both fast-acting symptomatic relief and

Table 147-1 Topical Ophthalmic Medications for Allergic Conjunctivitis

DRUG AND TRADE NAMES	MECHANISM OF ACTION AND DOSING	CAUTIONS AND ADVERSE EVENTS
Azelastine hydrochloride 0.05% Optivar	Antihistamine Children ≥3 yr: 1 gtt bid	Not for treatment of contact lens–related irritation; the preservative may be absorbed by soft contact lenses. Wait at least 10 min after administration before inserting soft contact lenses.
Emedastine difumarate 0.05% Emadine	Antihistamine Children ≥3 yr: 1 gtt qid	Soft contact lenses should not be worn if the eye is red. Wait at least 10 min after administration before inserting soft contact lenses.
Levocabastine hydrochloride 0.05% Livostin	Antihistamine Children ≥12 yr: 1 gtt bid-qid up to 2 wk	Not for use in patients wearing soft contact lenses during treatment.
Pheniramine maleate	Antihistamine/vasoconstrictor	Avoid prolonged use (>3-4 days) to avoid rebound symptoms. Not for use with contact lenses.
0.3%/Naphazoline hydrochloride 0.025% Naphcon-A, Opcon-A	Children >6 yr: 1-2 gtt qid	
Cromolyn sodium 4% Crolom, Opticrom	Mast cell stabilizer Children >4 yr 1-2 gtt q4-6h	Can be used to treat giant papillary conjunctivitis and vernal keratitis. Not for use with contact lenses.
Lodoxamide tromethamine 0.1% Alomide	Mast cell stabilizer Children ≥2 yr: 1-2 gtt qid up to 3 mo	Can be used to treat vernal keratoconjunctivitis. Not for use in patients wearing soft contact lenses during treatment.
Nedocromil sodium 2% Alocril	Mast cell stabilizer Children ≥3 yr 1-2 gtt bid	Avoid wearing contact lenses while exhibiting the signs and symptoms of allergic conjunctivitis.
Pemirolast potassium 0.1% Alamast	Mast cell stabilizer Children >3 yr: 1-2 gtt qid	Not for treatment of contact lens–related irritation; the preservative may be absorbed by soft contact lenses. Wait at least 10 min after administration before inserting soft contact lenses.
Epinastine hydrochloride 0.05% Elestat	Antihistamine/mast cell stabilizer Children ≥3 yr 1 gtt bid	Contact lenses should be removed prior to use. Wait at least 15 min after administration before inserting soft contact lenses. Not for the treatment of contact lens irritation.

Continued

Table 147-1 Topical Ophthalmic Medications for Allergic Conjunctivitis—cont'd

DRUG AND TRADE NAMES	MECHANISM OF ACTION AND DOSING	CAUTIONS AND ADVERSE EVENTS
Ketotifen fumarate 0.025% Zaditor	Antihistamine/mast cell stabilizer Children ≥3 yr 1 gtt bid q8-12h	Not for treatment of contact lens–related irritation; the preservative may be absorbed by soft contact lenses. Wait at least 10 min after administration before inserting soft contact lenses.
Olopatadine hydrochloride 0.1%, 0.2% Patanol Pataday	Antihistamine/mast cell stabilizer Children ≥3 yr: 1 gtt bid (8 hr apart) 1 gtt q day	Not for treatment of contact lens–related irritation; the preservative may be absorbed by soft contact lenses. Wait at least 10 min after administration before inserting soft contact lenses.
Alcaftadine, 0.25% Lastacaft	Antihistamine/mast cell stabilizer Children > 2 yr: 1 gtt bid q8-12 hr	Contact lenses should be removed prior to application, may be inserted after 10 minutes. Not for the treatment of contact lens irritation.
Bepotastine besilate 1.5% Bepreve	Antihistamine/mast cell stabilizer Children >2 yr: 1 gtt bid q8-12 hr	Contact lenses should be removed prior to application, may be inserted after 10 minutes. Not for the treatment of contact lens irritation.
Ketorolac tromethamine 0.5% Acular	NSAID Children ≥3 yr: 1 gtt qid	Avoid with aspirin or NSAID sensitivity. Use ocular product with caution in patients with complicated ocular surgeries, corneal denervation or epithelial defects, ocular surface diseases (e.g., dry eye syndrome), repeated ocular surgeries within a short period of time, diabetes mellitus, or rheumatoid arthritis; these patients may be at risk for corneal adverse events that may be sight-threatening. Do not use while wearing contact lenses.
Fluorometholone 0.1%, 0.25% suspension (0.1%, 0.25%) and ointment (0.1%) FML, FML Forte, Flarex	Fluorinated corticosteroid Children ≥2 yr, 1 gtt into conjunctival sac of affected eye(s) bid-qid. During initial 24–48 hr, dosage may be increased to 1 gtt q 4 hr. Ointment (approximately 1.3 cm in length) into the conjunctival sac of affected eye(s) 1–3 times daily. May be applied q 4 hr during initial 24–48 hr of therapy	If improvement does not occur after 2 days, patient should be reevaluated. Patient should remove soft contact lenses prior to administering (contains benzalkonium chloride) and delay reinsertion of lenses for ≥15 minutes after administration. Close monitoring for development of glaucoma and cataracts.

NSAID, nonsteroidal antiinflammatory drug.

disease-modifying action. Children often complain of stinging or burning with use of topical ophthalmic preparations and usually prefer oral antihistamines for allergic conjunctivitis. It is important not to contaminate topical ocular medications by allowing the applicator tip to contact the eye or eyelid. Using refrigerated medications may decrease some of the discomfort associated with their use. Topical decongestants act as vasoconstrictors, reducing erythema, vascular congestion, and eyelid edema, but do not diminish the allergic response. Adverse effects of topical vasoconstrictors include burning or stinging and rebound hyperemia or conjunctivitis medicamentosa with chronic use. Combined use of an antihistamine and a vasoconstrictive agent is more effective than use of either agent alone. Use of topical nasal corticosteroids for allergic rhinoconjunctivitis decreases ocular symptoms, presumably through a naso-ocular reflex.

Tertiary treatment of ocular allergy includes topical or, rarely, oral corticosteroids and should be conducted in conjunction with an ophthalmologist. Local administration of topical corticosteroids may be associated with increased intraocular pressure, viral infections, and cataract formation. Other immunomodulatory medications, such as topical tacrolimus or topical cyclosporine are used as steroid-sparing agents by ophthalmologists. Allergen immunotherapy can be very effective in seasonal and perennial allergic conjunctivitis, especially when associated with rhinitis, and can decrease the need for oral or topical medications to control allergy symptoms.

Because vernal conjunctivitis and atopic keratoconjunctivitis can be associated with visual morbidity, if these diagnoses are suspected, the patient should be referred to an ophthalmologist.

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Chapter 148

Urticaria (Hives) and Angioedema

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Urticaria and angioedema affect 20% of individuals at some point in their lives. Episodes of hives that last for <6 wk are considered acute, whereas those that occur on most days of the week for >6 wks are designated chronic. The distinction is important, because the causes and mechanisms of urticaria formation and the therapeutic approaches are different in each instance.

ETIOLOGY AND PATHOGENESIS

Acute urticaria and angioedema are often caused by an allergic immunoglobulin (Ig) E–mediated reaction (Table 148-1). This form of urticaria is a self-limited process that occurs when an allergen activates mast cells in the skin. Common causes of acute generalized urticaria include foods, drugs (particularly antibiotics), and stinging insect venoms. If an allergen (latex, animal dander) penetrates the skin locally, hives often can develop at the site of exposure. Acute urticaria can also result from non–IgE-mediated stimulation of mast cells,

Table 148-1 Etiology of Acute Urticaria

Foods	Egg, milk, wheat, peanuts, tree nuts, soy, shellfish, fish, strawberries (direct mast cell degranulation)
Medications	Suspect all medications, even nonprescription or homeopathic
Insect stings	Hymenoptera (honeybee, yellow jacket, hornets, wasp, fire ants), biting insects (papular urticaria)
Infections	Bacterial (streptococcal pharyngitis, *Mycoplasma*, sinusitis); viral (hepatitis, mononucleosis [Epstein-Barr virus], coxsackieviruses A and B); parasitic *(Ascaris, Ancylostoma, Echinococcus, Fasciola, Filaria, Schistosoma, Strongyloides, Toxocara, Trichinella);* fungal (dermatophytes, *Candida*)
Contact allergy	Latex, pollen, animal saliva, nettle plants, caterpillars
Transfusion reactions	Blood, blood products, or IV immunoglobulin administration

From Lasley MV, Kennedy MS, Altman LC: Urticaria and angioedema. In Altman LC, Becker JW, Williams PV, editors: Allergy in primary care, *Philadelphia, 2000, WB Saunders, p. 232.*

Table 148-2 Etiology of Chronic Urticaria

Idiopathic/autoimmune	Approximately 30% of chronic urticaria cases are physical urticaria and 60-70% are idiopathic. Of the idiopathic cases approximately 35-40% have anti-IgE or anti-FcεRI (high-affinity IgE receptor α chain) autoantibodies (autoimmune chronic urticaria)
Physical	Dermatographism Cholinergic urticaria Cold urticaria Delayed pressure urticaria Solar urticaria Vibratory urticaria Aquagenic urticaria
Autoimmune diseases	Systemic lupus erythematosus Juvenile idiopathic arthritis Thyroid (Graves, Hashimoto) Celiac disease Inflammatory bowel disease Leukocytoclastic vasculitis
Autoinflammatory/ periodic fever syndromes	NOMID (neonatal onset multisystem inflammatory disease) Muckle-Wells syndrome Familial cold autoinflammatory syndrome Cold urticarial, immunodeficiency, autoimmunity as a result of *PLCG2* deficiency
Neoplastic	Lymphoma Mastocytosis Leukemia
Angioedema	Hereditary angioedema (autosomal dominant inherited deficiency of C1-esterase inhibitor) Acquired angioedema Angiotensin-converting enzyme inhibitors

From Lasley MV, Kennedy MS, Altman LC: Urticaria and angioedema. In Altman LC, Becker JW, Williams PV, editors: Allergy in primary care, *Philadelphia, 2000, WB Saunders, p. 234.*

caused by radiocontrast agents, viral agents (including hepatitis B and Epstein-Barr virus), opiates, and nonsteroidal antiinflammatory agents. The diagnosis of chronic urticaria is established when lesions occur on most days of the week for >6 wk and are not physical urticaria or recurrent acute urticaria with repeated exposures to a specific agent (Table 148-2). In about half the cases, chronic urticaria is accompanied by angioedema. Rarely, angioedema occurs without urticaria. Angioedema without urticaria is often a result of allergy, but recurrent angioedema raises a question about other diagnoses.

A typical hive is an erythematous, pruritic raised wheal that blanches with pressure, is transient, and resolves without residual lesions, unless the area was intensely scratched. In contrast, urticaria associated with serum sickness reactions, systemic lupus erythematosus or other vasculitides, in which a skin biopsy reveals a small-vessel vasculitis, often have distinguishing clinical features. Lesions that burn more than itch, last >24 hr, do not blanch, blister, heal with scarring, or are associated with bleeding into the skin (purpura) suggest urticarial vasculitis. Atypical aspects of the gross appearance of the hives or associated symptoms should heighten concern that the urticaria or angioedema may be the manifestation of a systemic disease process.

PHYSICAL URTICARIA

Physically induced urticaria and angioedema share the common property of being induced by an environmental stimulus, such as a change in temperature or direct stimulation of the skin with pressure, stroking, vibration, or light (Table 148-3).

Cold-Dependent Disorders

Cold urticaria is characterized by the development of localized pruritus, erythema, and urticaria/angioedema after exposure to a cold stimulus. Total-body exposure as seen with swimming in cold water can cause massive release of vasoactive mediators, resulting in hypotension, loss of consciousness and even death if not promptly treated. The diagnosis is confirmed by challenge testing for an isomorphic cold reaction by holding an ice cube in place on the patient's skin for 4 min. In patients with cold urticaria, an urticarial lesion develops about 10 minutes after removal of the ice cube and upon rewarming of the chilled skin. Cold urticaria can be associated with the presence of **cryoproteins,** such as cold agglutinins, cryoglobulins, cryofibrinogen, and the Donath-Landsteiner antibody seen in secondary syphilis (paroxysmal cold hemoglobinuria). In patients with cryoglobulins, the isolated proteins appear to transfer cold sensitivity and activate the complement cascade upon in vitro incubation with normal plasma. The term **idiopathic cold urticaria** generally applies to patients without abnormal circulating plasma proteins such as cryoglobulins. Cold urticaria has also been reported after viral infections. Cold urticaria must be distinguished from the **familial cold autoinflammatory syndrome** (see "Diagnosis," later).

Cholinergic Urticaria

Cholinergic urticaria is characterized by the onset of small punctate pruritic wheals surrounded by a prominent erythematous flare associated with exercise, hot showers, and sweating. Once the patient cools down, the rash usually subsides in 30-60 min. Occasionally, symptoms of more generalized cholinergic stimulation, such as lacrimation, wheezing, salivation, and syncope, are observed. These symptoms are mediated by cholinergic nerve fibers that innervate the musculature via parasympathetic neurons and innervate the sweat glands by cholinergic fibers that travel with the sympathetic nerves. Elevated plasma histamine values parallel the onset of urticaria triggered by changes in body temperature.

Dermatographism

The ability to write on skin, termed dermatographism (also called dermographism or urticaria factitia), may occur as an isolated

Table 148-3 Diagnostic Testing for Urticaria and Angioedema

DIAGNOSIS	DIAGNOSTIC TESTING
Food and drug reactions	Elimination of offending agent, skin testing, and challenge with suspected foods
Autoimmune urticaria	Autologous serum skin test; antithyroid antibodies; antibodies against the high-affinity IgE receptor
Thyroiditis	Thyroid-stimulating hormone; antithyroid antibodies
Infections	Appropriate cultures or serology
Collagen vascular diseases and cutaneous vasculitis	Skin biopsy, CH_{50}, C1q, C4, C3, factor B, immunofluorescence of tissues, antinuclear antibodies, cryoglobulins
Malignancy with angioedema	CH_{50}, C1q, C4, C1-INH determinations
Cold urticaria	Ice cube test
Solar urticaria	Exposure to defined wavelengths of light, red blood cell protoporphyrin, fecal protoporphyrin, and coproporphyrin
Dermatographism	Stroking with narrow object (e.g., tongue blade, fingernail)
Pressure urticaria	Application of pressure for defined time and intensity
Vibratory urticaria	Vibration for 4 min
Aquagenic urticaria	Challenge with tap water at various temperatures
Urticaria pigmentosa	Skin biopsy, test for dermographism
Hereditary angioedema	C4, C2, CH_{50}, C1-INH testing by protein and function
Familial cold urticaria	Challenge by cold exposure, measurement of temperature, white blood cell count, erythrocyte sedimentation rate, and skin biopsy
C3b inactivator deficiency	C3, factor B, C3b inactivator determinations
Chronic idiopathic urticaria	Skin biopsy, immunofluorescence (negative result), autologous skin test

disorder or may accompany chronic urticaria or other physical urticaria, such as cholinergic and cold urticaria. It can be diagnosed by observing the skin after stroking it with a tongue depressor. In patients with dermatographism, a linear response occurs secondary to reflex vasoconstriction, followed by pruritus, erythema, and a linear flare caused by secondary dilation of the vessel and the extravasation of plasma.

Pressure-Induced Urticaria and Angioedema

Pressure-induced urticaria differs from most types of urticaria or angioedema in that symptoms typically occur 4-6 hr after pressure has been applied. The disorder is clinically heterogeneous. Some patients may complain of swelling secondary to pressure with normal-appearing skin (no urticaria), so the term *angioedema* is more appropriate. Other lesions are predominantly urticarial and may or may not be associated with significant swelling. When urticaria is present, an infiltrative skin lesion is seen, characterized by a perivascular mononuclear cell infiltrate and dermal edema similar to that seen in chronic idiopathic urticaria. Symptoms occur at sites of tight clothing; foot swelling is common after walking; and buttock swelling may be prominent after sitting for a few hours. This condition can coexist with chronic idiopathic urticaria or can occur separately. The diagnosis is confirmed by challenge testing in which pressure is applied perpendicular to the skin. This is often done with a sling attached to a 10 lb weight that is placed over the patient's arm for 20 min.

Solar Urticaria

Solar urticaria is a rare disorder in which urticaria develops within minutes of direct sun exposure. Typically, pruritus occurs first, in approximately 30 sec, followed by edema confined to the light-exposed area and surrounded by a prominent erythematous zone. The lesions usually disappear within 1-3 hr after cessation of sun exposure. When large areas of the body are exposed, systemic symptoms may occur, including hypotension and wheezing. Solar urticaria has been classified into 6 types, depending on (1) the wavelength of light that induces skin lesions and (2) the ability or inability to transfer the disorder passively with serum IgE. The rare inborn error of metabolism, **erythropoietic protoporphyria,** can be confused with solar urticaria because of the development of itching and burning of exposed skin immediately after sun exposure. In erythropoietic protoporphyria, fluorescence of ultraviolet-irradiated red blood cells can be demonstrated and protoporphyrins are found in the urine.

Aquagenic Urticaria

Patients with aquagenic urticaria demonstrate small wheals after contact with water, regardless of its temperature, and are thereby distinguishable from patients with cold urticaria or cholinergic urticaria. Direct application of a compress of water to the skin is used to test for the presence of aquagenic urticaria. In some of these patients, chlorine or other trace contaminants are responsible for the reaction.

CHRONIC IDIOPATHIC URTICARIA AND ANGIOEDEMA

A common disorder of unknown origin, chronic idiopathic urticaria and angioedema is often associated with normal routine laboratory values and no evidence of systemic disease. Chronic urticaria does not appear to result from an allergic reaction. It differs from allergen-induced skin reactions and from physically induced urticaria in that histologic studies reveal a cellular infiltrate predominantly around small venules. Skin examination reveals infiltrative hives with palpably elevated borders, sometimes varying greatly in size and/or shape but generally being rounded.

Biopsy of the typical lesion reveals non-necrotizing, perivascular, mononuclear cellular infiltration. Many types of histopathologic processes can occur in the skin and manifest as urticaria. Patients with **hypocomplementemia** and **cutaneous vasculitis** can have urticaria and/or angioedema. Biopsy of these lesions in patients with urticaria, arthralgias, myalgias, and an elevated erythrocyte sedimentation rate (ESR) as manifestations of necrotizing venulitis can reveal fibrinoid necrosis with a predominantly neutrophilic infiltrate. Yet the urticarial lesions may be clinically indistinguishable from those seen in the more typical, nonvasculitic cases.

There is an increased association of chronic urticaria with the presence of antithyroid antibodies. Affected patients generally have antibodies to thyroglobulin or a microsomally derived antigen (peroxidase) even if they are euthyroid. The incidence of elevated thyroid antibodies in patients with chronic urticaria is ≈12%, compared with 3-6% in the general population. Although some patients show clinical reduction of the urticaria with thyroid replacement therapy, others do not. The role of thyroid autoantibodies in chronic urticaria is uncertain. It has been proposed that their presence may reflect a tendency of the patient to develop autoantibodies, but that they may not play a direct role in chronic urticaria. Of patients with chronic urticaria, 35-40% have a positive **autologous serum skin test** result: If serum from these patients is intradermally injected into their skin, a significant wheal and flare reaction develops. Such patients frequently have a complement-activating IgG antibody directed against the α subunit of the IgE receptor that can crosslink the IgE receptor (α subunit) and degranulate mast cells and basophils. An additional 5-10% of patients

with chronic urticaria have anti-IgE antibodies rather than an anti–IgE receptor antibody. These patients, classified as having autoimmune urticaria, tend to have a more severe clinical course than patients without evidence of autoantibodies, but the difference is not dramatic.

DIAGNOSIS

The diagnosis of both acute and chronic urticaria is primarily clinical and requires that the physician be aware of the various forms of urticaria.

Urticaria is transient, pruritic, erythematous, raised wheals, with flat tops and edema that may become tense and painful. The lesions may coalesce and form polycyclic, serpiginous, or annular lesions (Figs. 148-1 and 148-2). Individual lesions usually last 20 min to 3 hr, and rarely more than 24 hr. The lesions often disappear only to reappear at another site. **Angioedema** involves the deeper subcutaneous tissues in locations such as the eyelids, lips, tongue, genitals, dorsum of the hands or feet, or wall of the gastrointestinal (GI) tract.

Drugs and foods are the most common causes of acute urticaria. Allergy skin testing for foods can be helpful in sorting out causes of acute urticaria, especially when supported by historical evidence. The role of an offending food can then be proven by elimination and careful challenge in a controlled setting. In the absence of information implicating an ingestant cause, skin testing for foods and implementation of elimination diets are generally not useful for either acute or chronic urticaria. Patients with delayed urticaria 3-6 hr after a meal consisting of mammalian meat should be evaluated for IgE to galactose-alpha-1,3-galactose ("alpha-gal"), a carbohydrate moiety. Alpha-gal has been identified as a trigger in this circumstance, with sensitization apparently linked to tick bites in specific geographic regions, such as the mid-Atlantic area of the United States. Skin testing for aeroallergens is not indicated unless there is a concern about contact urticaria (animal dander or grass pollen). Dermatographism is frequent in patients with urticaria and can complicate allergy skin testing by causing false-positive reactions, but this distinction is usually discernable.

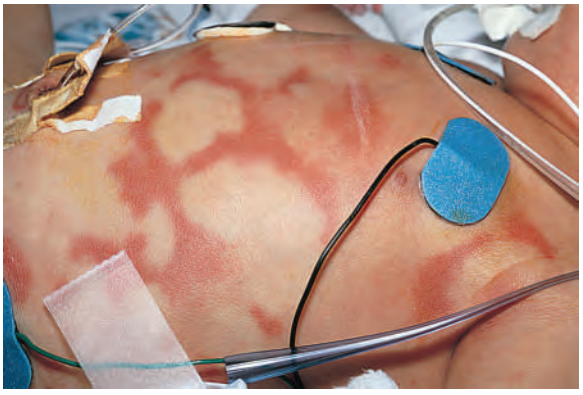


Figure 148-1 Polycyclic lesions of urticaria associated with prostaglandin E_2 infusion. *(From Eichenfield LF, Friedan IJ, Esterly NB:* Textbook of neonatal dermatology, *Philadelphia, 2001, WB Saunders, p. 300.)*



Figure 148-2 Annular urticaria of unknown etiology. *(From Eichenfield LF, Friedan IJ, Esterly NB:* Textbook of neonatal dermatology, *Philadelphia, 2001, WB Saunders, p. 301.)*

An exogenous cause of chronic urticaria is rarely identified, reflecting the wide variety of allergens with which we come in contact. Autoimmune diseases are rare causes of chronic urticarial or angioedema. An autologous serum skin test may be useful in establishing the diagnosis of autoimmune urticaria. In vitro testing for serum-derived activity that activates basophils involves detection of the expression of the surface marker CD63 or CD203c by donor basophils after incubation with patient serum. The clinical applicability and significance of these tests remains debated. The **differential diagnosis** of chronic urticaria includes cutaneous or systemic mastocytosis, complement-mediated mast cell degranulation as may occur with the presence of circulating immune complexes, malignancies, mixed connective tissue diseases, and cutaneous blistering disorders (e.g., bullous pemphigoid; see Table 148-2). In general, laboratory testing should be limited to a complete blood cell count with differential, ESR determination, urinalysis, thyroid autoantibody testing, and liver function tests. Further studies are warranted if the patient has fever, arthralgias, or elevated ESR (see Table 148-3). Testing for antibodies directed at the high affinity IgE receptor may be warranted in patients with intractable urticaria. Hereditary angioedema, a potentially life-threatening form of angioedema usually associated with deficient C1 inhibitor activity, is the most important familial form of angioedema (see Chapter 134.3), but is not associated with typical urticaria. In patients with eosinophilia, stools should be obtained for ova and parasite testing, because infection with helminthic parasites has been associated with urticaria. A syndrome of episodic angioedema/urticaria and fever with associated eosinophilia has been described in both adults and children. In contrast to other hypereosinophilic syndromes, this entity has a benign course.

Skin biopsy for diagnosis of possible **urticarial vasculitis** is recommended for urticarial lesions that persist at the same location for >24 hr, those with pigmented or purpuric components, and those that burn more than itch. Collagen vascular diseases such as systemic lupus may manifest urticarial vasculitis as a presenting feature. The skin biopsy in urticarial vasculitis typically shows endothelial cell swelling of postcapillary venules with necrosis of the vessel wall, perivenular neutrophil infiltrate, diapedesis of red blood cells, and fibrin deposition associated with deposition of immune complexes.

Mastocytosis is characterized by mast cell hyperplasia in the bone marrow, liver, spleen, lymph nodes, and skin. Clinical effects of mast cell activation are common, including pruritus, flushing, urtication, abdominal pain, nausea, and vomiting. The diagnosis is confirmed by a bone marrow biopsy showing increased numbers of spindle-shaped mast cells that express CD2 and CD25. **Urticaria pigmentosa** is the most common skin manifestation of mastocytosis and may occur as an isolated skin finding. It appears as small, yellow-tan to reddish brown macules or raised papules that urticate on scratching **(Darier sign).** This sign can be masked by antihistamines. The diagnosis is confirmed by a skin biopsy that shows increased numbers of dermal mast cells.

Physical urticaria should be considered in any patient with chronic urticaria and a suggestive history (see Table 148-3). Papular urticaria commonly occurs in small children, generally on the extremities. It manifests as grouped or linear, highly pruritic wheals or papules mainly on exposed skin at the sites of insect bites.

Exercise-induced anaphylaxis manifests as varying combinations of pruritus, urticaria, angioedema, wheezing, laryngeal obstruction, or hypotension after exercise (see Chapter 149). Cholinergic urticaria is differentiated by positive results of heat challenge tests and the rare occurrence of anaphylactic shock. The combination of ingestion of various food allergens (shrimp, celery, or wheat) and postprandial exercise has been associated with urticaria/angioedema and

anaphylaxis. In patients with this combination disorder, food or exercise alone does not produce the reaction.

Muckle-Wells syndrome and **familial cold autoinflammatory syndrome** are rare, dominantly inherited conditions associated with recurrent urticaria-like lesions. Muckle-Wells syndrome is characterized by arthritis and joint pain that usually appears in adolescence. It is associated with progressive nerve deafness, recurrent fever, elevated ESR, hypergammaglobulinemia, renal amyloidosis, and a poor prognosis. Familial cold autoinflammatory syndrome is characterized by a cold-induced rash that has urticarial features but is rarely pruritic. Cold exposure leads to additional symptoms such as conjunctivitis, sweating, headache, and nausea. Patient longevity is usually normal.

TREATMENT

Acute urticaria is a self-limited illness requiring little treatment other than antihistamines and avoidance of any identified trigger. Hydroxyzine and diphenhydramine are sedating but are effective and commonly used for treatment of urticaria. Loratadine, fexofenadine, and cetirizine are also effective and are preferable because of reduced frequency of drowsiness and longer duration of action (Table 148-4). Epinephrine 1:1,000, 0.01 mL/kg (maximum: 0.3 mL) intramuscularly usually provides rapid relief of acute, severe urticaria/angioedema but is seldom required. A short course of oral corticosteroids should be given only for very severe episodes of urticaria and angioedema that are unresponsive to antihistamines.

The best treatment of physical urticaria is avoidance of the stimulus. Antihistamines are also helpful. Cyproheptadine in divided doses is the drug of choice for cold-induced urticaria. Treatment of dermatographism consists of local skin care and antihistamines; for severe symptoms, high doses may be needed. The initial objective of therapy is to decrease pruritus so that the stimulation for scratching is diminished. A combination of antihistamines, sunscreens, and avoidance of sunlight is helpful for most patients.

Chronic urticaria only rarely responds favorably to dietary manipulation. Removal of recognized urticarial aggravators such as salicylates and β-blockers should be considered. The mainstay of therapy is the use of nonsedating or low-sedating H_1 antihistamines. In those patients not showing response to standard doses, pushing the H_1 blockade with higher than the usual recommended doses of these agents is a common next approach. The 3-drug combination of H_1 and H_2 antihistamine combined with a leukotriene receptor antagonist (montelukast) is helpful for many patients. If hives persist after maximal H_1- and/or H_2-receptor blockade has been achieved, a brief course of oral corticosteroids may be considered, but long-term steroid use is best avoided. Treatment with cyclosporine 4-6 mg/kg/day has been effective in some adults with chronic urticaria but its use is limited by hypertension and/or nephrotoxicity. Immunomodulatory agents such as omalizumab (anti-IgE antibody) that have been used with success in cases of chronic urticarial that are refractory to other therapies, but are not approved for the treatment of this condition by the FDA. These include omalizumab (anti-IgE), cyclosporine, hydroxychloroquine, sulfasalazine, colchicine, dapsone, mycophenolate, intravenous immunoglobulin, and plasmapheresis.

Table 148-4 Treatment of Urticaria and Angioedema

CLASS/DRUG	DOSE	FREQUENCY
ANTIHISTAMINES, TYPE H_1 (SECOND GENERATION)		
Fexofenadine	6-11 yr: 30 mg	bid
	>12 yr: 60 mg	
	Adult: 180 mg	Once daily
Loratadine	2-5 yr: 5 mg	Once daily
	>6 yr: 10 mg	
Desloratadine	6-11 mo: 1 mg	Once daily
	12 mo-5 yr: 1.25 mg	
	6-11 yr: 2.5 mg	
	>12 yr: 5 mg	
Cetirizine	6-23 mo: 2.5 mg	Once daily
	2-6 yr: 2.5-5mg	
	>6 yr: 5-10 mg	
Levocetirizine	6 mo-5 yr: 1.25 mg	Once daily
	6-11 yr: 2.5 mg	Once daily
	>12 yr: 5 mg	Once daily
ANTIHISTAMINES, TYPE H_2		
Cimetidine	Infants: 10-20 mg/kg/day	Divided q6-12h
	Children: 20-40 mg/kg/day	
Ranitidine	1 mo-16 yr: 5-10 mg/kg/day	Divided q12h
Famotidine	3-12 mo: 1 mg/kg/day	Divided q12h
	1-16 yr: 1-2 mg/kg/day	
LEUKOTRIENE PATHWAY MODIFIERS		
Montelukast	12 mo-5 yr: 4 mg	Once daily
	6-14 yr: 5 mg	
	>14 yr: 10 mg	
Zafirlukast	5-11 yr: 10 mg	bid
IMMUNOMODULATORY DRUGS		
Cyclosporine	4-6 mg/kg/day	Once daily*
Sulfasalazine	>6 yr: 30 mg/kg/day	Divided q6h†
Intravenous immunoglobulin (IVIG)	400 mg/kg/day	5 consecutive days

*Monitor blood pressure and serum creatinine, potassium, and magnesium levels monthly.

†Monitor complete blood count and liver function tests at baseline, every 2 wk for 3 mo, and then every 1-3 mo.

HEREDITARY ANGIOEDEMA

Hereditary angioedema (HAE) (types 1 and 2) is an inherited autosomal dominant disease caused by low functional levels of the plasma protein C1 inhibitor (C1-INH) (see Chapter 134). Patients typically report episodic attacks of angioedema or deep localized swelling, most commonly on a hand or foot, that begin during childhood and become much more severe during adolescence. Cutaneous nonpitting and nonpruritic edema not associated with urticaria is the most common symptom. The swelling usually becomes more severe over about 1.5 days and then resolves over about the same period. In some patients attacks are preceded by the development of a rash, that is erythema marginatum, that is erythematous, not raised, and not pruritic. The second major symptom complex noted by patients is attacks of severe abdominal pain caused by edema of the mucosa of any portion of the GI tract. The intensity of the pain can approximate that of an acute abdomen, often resulting in unnecessary surgery. Either constipation or diarrhea during these attacks can be noted. The GI edema generally follows the same time course to resolution as the cutaneous attacks, and often does not occur at the same time as the peripheral edema. Patients usually have a prodrome, a tightness or tingling in the area that will swell, lasting most frequently for several hours, followed by the development of angioedema.

Laryngeal edema, the most feared complication of HAE, can cause complete respiratory obstruction. Although life-threatening attacks are infrequent, more than half of patients with HAE experience laryngeal involvement at some time during their lives. Dental work with the injection of procaine HCL (Novocain) into the gums is a common precipitant, but laryngeal edema can be spontaneous. The clinical condition may deteriorate rapidly, progressing through mild discomfort to complete airway obstruction over a period of hours. Soft-tissue edema can be readily seen when the disease involves the throat and uvula. If this edema progresses to difficulty swallowing secretions or a change in the tone of the voice, the patient may require emergency intubation or even tracheostomy to ensure an adequate airway. Other presentations are less common. These patients typically do not respond well to treatment with epinephrine, antihistamines, or glucocorticoids.

In most cases the cause of the attack is unknown, but in some patients trauma or emotional stress clearly precipitates attacks. Drugs like angiotensin-converting enzyme inhibitors that inhibit the degradation of bradykinin make the disease strikingly worse, and estrogens also make attacks more severe. In some females menstruation also regularly induces attacks. The frequency of attacks varies greatly among

affected individuals and at different times in the same individual. Some individuals experience weekly episodes, whereas others may go years between attacks. Episodes can start at any age.

C1-INH is a member of the serpin family of proteases, similar to α-antitrypsin, antithrombin III, and angiotensinogen. These proteins stoichiometrically inactivate their target proteases by forming stable, 1:1 complexes with the protein to be inhibited. Synthesized primarily by hepatocytes, C1-INH is also synthesized by monocytes. The regulation of the protein production is not completely understood, but it is believed that androgens may stimulate C1-INH synthesis, because patients with the disorder respond clinically to androgen therapy with raised serum levels of C1-INH. C1-INH deficiency is an autosomal dominant disease, with as many as 25% of patients giving no family history. Because all C1-INH–deficient patients are heterozygous for this gene defect, it is believed that half the normal level of C1-INH is not sufficient to prevent attacks.

Although named for its action on the first component of complement (C1 esterase), C1-INH also inhibits components of the fibrinolytic, clotting, and kinin pathways. Specifically, C1-INH inactivates plasmin-activated Hageman factor (factor XII), activated factor XI, plasma thromboplastin antecedent, and kallikrein. Within the complement system, C1-INH blocks the activation of C1 and the rest of the classic complement pathway by binding to C1r and C1s. Without adequate C1-INH, unchecked activation of C1 causes cleavage of C4 and C2, the following proteins in the complement cascade. Levels of C3 are normal. The major factor responsible for the edema formation is now known to be bradykinin, an important nonapeptide mediator that can induce leakage of postcapillary venules. Bradykinin is derived from cleavage of the circulating protein high molecular weight kininogen by the plasma enzyme kallikrein.

Two genetic types of C1-INH deficiency are described that result in essentially the same phenotypic expression. The C1-INH gene is located on chromosome 11 in the p11-q13 region. The inheritance is autosomal dominant with incomplete penetrance. Persons inheriting the abnormal gene can have a clinical spectrum ranging from asymptomatic to severely affected. Type 1 HAE is the most common form, accounting for approximately 85% of cases. Synthesis of C1-INH is blocked at the site of the faulty allele or the protein is not secreted normally because of faulty protein processing, but secretion occurs at the normal allele. The result is secretion of the normal protein, yielding quantitative serum concentrations of C1-INH that are approximately 20-40% of normal. Type 2 HAE accounts for approximately 15% of cases. Mutations of one of the amino acids near the active site of the inhibitor lead to synthesis of nonfunctional C1-INH protein and again less than half of the normal functioning protein. Patients with type 2 HAE have either normal or increased concentrations of the protein and low values in assays of C1-INH function.

A clinical syndrome resembling HAE and termed type 3 HAE has been described that affects mostly women and has a tendency to cause fewer abdominal attacks and more upper airway attacks. In this condition, no abnormalities of complement or of C1-INH have been described. Approximately 20% of affected patients have been found to have a gain-of-function abnormality of clotting factor XII, but the fundamental cause is still unknown.

The FDA has approved purified C1-INH for prophylaxis to prevent attacks. Androgens like the gonadotropin inhibitor danazol were previously used to prevent attacks. Weak androgens have many side affects that preclude their use in some patients. Their use in children is problematic because of the possibility of premature closure of the epiphyses, and these agents are not used in pregnant women. The fibrinolysis inhibitor ε-aminocaproic acid is also effective in preventing attacks and has been used in children, but its use was attended by the development of severe fatigue and muscle weakness over time.

In 2008, the FDA approved, for adolescents and older, the use of purified C1-INH (Cinryze), prepared from human plasma given intravenously for prophylaxis of this disease following clinical trials. The half-life of this plasma protein is relatively short, on the order of 40 hr, and the approved regimen is 1,000 units given twice a week. In 2009, a similar purified C1-inhibitor product, Berinert, used as 20 units/kg intravenously, was approved for the treatment of acute attacks. A recombinant C1-INH product has been approved for treatment of acute attacks in Europe, but is not currently approved for treatment in the United States. In 2009, a kallikrein inhibitor, ecallantide, given subcutaneously, was approved by the FDA for acute treatment in patients age 16 yr and older. This 60 amino acid peptide causes anaphylaxis in the rare patient, and is approved to be given only by medical personnel. In 2010, a bradykinin type 2 receptor antagonist, icatibant was approved for acute treatment in patients age 18 yr and older. All treatments are most effective when given early in an attack, and begin to have noticeable effect after about 1-4 hr after treatment.

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Chapter 149

Anaphylaxis

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Anaphylaxis is defined as a serious allergic reaction that is rapid in onset and may cause death. Anaphylaxis in children, particularly infants, is underdiagnosed. Anaphylaxis occurs when there is a sudden release of potent biologically active mediators from mast cells and basophils, leading to cutaneous (urticaria, angioedema, flushing), respiratory (bronchospasm, laryngeal edema), cardiovascular (hypotension, dysrhythmias, myocardial ischemia), and gastrointestinal (nausea, colicky abdominal pain, vomiting, diarrhea) symptoms (Table 149-1).

ETIOLOGY

The most common causes of anaphylaxis in children are different for hospital and community settings. Anaphylaxis occurring in the hospital results primarily from allergic reactions to medications and latex. Food allergy is the most common cause of anaphylaxis occurring outside the hospital, accounting for about half of the anaphylactic reactions reported in pediatric surveys from the United States, Italy, and South Australia (Table 149-2). Peanut allergy is an important cause of food-induced anaphylaxis, accounting for the majority of fatal and near-fatal reactions. In the hospital, latex is a particular problem for children undergoing multiple operations, such as patients with spina bifida and urologic disorders, and has prompted many hospitals to switch to latex-free products. Patients with latex allergy may also experience food-allergic reactions from homologous proteins in foods such as bananas, kiwi, avocado, chestnut, and passion fruit. Anaphylaxis to galactose-α-1,3-galactose has been reported 3-6 hr after eating meat.

EPIDEMIOLOGY

The overall annual incidence of anaphylaxis in the United States is estimated at 50 cases/100,000 persons/yr, totaling >150,000 cases/yr, with the highest rate for the pediatric age group (0-19 yr) at 70/100,000 persons/yr. An Australian parental survey found that 0.59% of children 3-17 yr of age had experienced at least 1 anaphylactic event. Having asthma and the severity of asthma are important anaphylaxis risk factors (Table 149-3).

PATHOGENESIS

Principal pathologic features in fatal anaphylaxis include acute bronchial obstruction with pulmonary hyperinflation, pulmonary edema, intraalveolar hemorrhaging, visceral congestion, laryngeal edema, and urticaria and angioedema. Acute hypotension is attributed to vasomotor dilation and/or cardiac dysrhythmias.

Most cases of anaphylaxis are believed to be the result of activation of mast cells and basophils via cell-bound allergen-specific

Table 149-1 Symptoms and Signs of Anaphylaxis in Infants

ANAPHYLAXIS SYMPTOMS THAT INFANTS CANNOT DESCRIBE	ANAPHYLAXIS SIGNS THAT MAY BE DIFFICULT TO INTERPRET/UNHELPFUL IN INFANTS, AND WHY	ANAPHYLAXIS SIGNS IN INFANTS
GENERAL Feeling of warmth, weakness, anxiety, apprehension, impending doom	Nonspecific behavioral changes such as persistent crying, fussing, irritability, fright, suddenly becoming quiet	
SKIN/MUCUS MEMBRANES Itching of lips, tongue, palate, uvula, ears, throat, nose, eyes, etc.; mouth-tingling or metallic taste	Flushing (may also occur with fever, hyperthermia, or crying spells)	Rapid onset of hives (potentially difficult to discern in infants with acute atopic dermatitis; scratching and excoriations will be absent in young infants); angioedema (face, tongue, oropharynx)
RESPIRATORY Nasal congestion, throat tightness; chest tightness; shortness of breath	Hoarseness, dysphonia (common after a crying spell); drooling or increased secretions (common in infants)	Rapid onset of coughing, choking, stridor, wheezing, dyspnea, apnea, cyanosis
GASTROINTESTINAL Dysphagia, nausea, abdominal pain/cramping	Spitting up/regurgitation (common after feeds), loose stools (normal in infants, especially if breastfed); colicky abdominal pain	Sudden, profuse vomiting
CARDIOVASCULAR Feeling faint, presyncope, dizziness, confusion, blurred vision, difficulty in hearing	Hypotension (need appropriate-size blood pressure cuff; low systolic blood pressure for children is defined as <70 mm Hg from 1 mo to 1 yr, and less than (70 mm Hg + [2 × age in yr]) from 1-10 yr; tachycardia, defined as >140 beats/min from 3 mo to 2 yr, inclusive; loss of bowel and bladder control (ubiquitous in infants)	Weak pulse, arrhythmia, diaphoresis/sweating, collapse/unconsciousness
CENTRAL NERVOUS SYSTEM Headache	Drowsiness, somnolence (common in infants after feeds)	Rapid onset of unresponsiveness, lethargy, or hypotonia; seizures

Adapted from Simons FER. Anaphylaxis in infants: can recognition and management be improved? J Allergy Clin Immunol *120:537–540, 2007.*

Table 149-2 Anaphylaxis Triggers in the Community*

ALLERGEN TRIGGERS (IgE-DEPENDENT IMMUNOLOGIC MECHANISM)*
Foods (e.g., peanut, tree nuts, shellfish, fish, milk, egg, wheat, soy, sesame, meat [galactose-α-1,3-galactose])
Food additives (e.g., spices, colorants, vegetable gums, and contaminants)
Stinging insects: Hymenoptera species (e.g., bees, yellow jackets, wasps, hornets, and fire ants)
Medications (e.g., β-lactam antibiotics, ibuprofen)
Biologic agents (e.g., monoclonal antibodies [infliximab, omalizumab] and allergens [challenge tests, specific immunotherapy])
Natural rubber latex
Vaccines
Inhalants (rare) (e.g., horse or hamster dander, grass pollen)
Previously unrecognized allergens (foods, venoms, biting insect saliva, medications, biologic agents)
OTHER IMMUNE MECHANISMS (IGE INDEPENDENT)
IgG mediated (infliximab, high-molecular-weight dextrans)
Immune aggregates (IVIG)
Drugs (aspirin, NSAID, opiates, contrast material, ethylene oxide/dialysis tubing)
Complement activation
Physical factors (e.g., exercise†, cold, heat, sunlight/ultraviolet radiation)
Ethanol
Idiopathic*

*In the pediatric population, some anaphylaxis triggers, such as hormones (progesterone), seminal fluid, and occupational allergens, are uncommon, as is idiopathic anaphylaxis.

†Exercise with or without a cotrigger, such as a food or medication, cold air, or cold water.

IVIG, intravenous immunoglobulin; NSAID, nonsteroidal antiinflammatory drug.

Adapted from Leung DYM, Sampson HA, Geha RS, et al: Pediatric allergy principles and practice, *New York, 2010, Elsevier, p. 652.*

Table 149-3 Patient Risk Factors for Anaphylaxis

AGE-RELATED FACTORS
Infants: anaphylaxis can be hard to recognize, especially if the first episode; patients cannot describe symptoms
Adolescents and young adults: increased risk taking behaviors such as failure to avoid known triggers and to carry an epinephrine autoinjector consistently
Pregnancy: risk of iatrogenic anaphylaxis—for example, from β lactam antibiotics to prevent neonatal group B streptococcal infection, agents used perioperatively during caesarean sections, and natural rubber latex
Older people: increased risk of death because of concomitant disease and drugs
CONCOMITANT DISEASES
Asthma and other chronic respiratory diseases
Cardiovascular diseases
Mastocytosis
Allergic rhinitis and eczema*
Depression, cognitive dysfunction, substance misuse
DRUGS
β-Adrenergic blockers†
Angiotensin-converting enzyme (ACE) inhibitors†
Sedatives, antidepressants, narcotics, recreational drugs, and alcohol may decrease the patient's ability to recognize triggers and symptoms
COFACTORS THAT AMPLIFY ANAPHYLAXIS
Exercise: anaphylaxis associated with exercise may be food dependent or food independent; nonsteroidal antiinflammatory drugs and other listed cofactors may also be relevant
Acute infection such as an upper respiratory tract infection
Fever
Emotional stress
Disruption of routine—for example, travel and jet lag
Premenstrual status in women and girls

*Atopic diseases are a risk factor for anaphylaxis triggered by food, latex, and exercise, but not for anaphylaxis triggered by most drugs or by insect stings

†Patients taking β-adrenergic blockers or ACE inhibitors seem to be at increased risk for severe anaphylaxis. In addition, those taking β-adrenergic blockers may not respond optimally to epinephrine treatment and may need glucagon, a polypeptide with non–catecholamine-dependent inotropic and chronotropic cardiac effects, atropine for persistent bradycardia, or ipratropium for persistent bronchospasm.

Modified from Simons FER, Sheikh A: Anaphylaxis: the acute episode and beyond. BMJ *2013;346:f602 (Box 2, p. 32).*

Table 149-4 Diagnosis of Anaphylaxis

Anaphylaxis is highly likely when any *1* of the following 3 criteria is fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin and/or mucosal tissue (e.g., *generalized* hives, pruritus or flushing, swollen lips/tongue/uvula) *AND AT LEAST 1 OF THE FOLLOWING:*
   a. Respiratory compromise (e.g., dyspnea, wheeze/bronchospasm, stridor, reduced peak PEF, hypoxemia)
   b. Reduced BP 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/mucosal tissue (e.g., *generalized* hives, itch/flush, swollen lips/tongue/uvula)
   b. Respiratory compromise (e.g., dyspnea, wheeze/bronchospasm, stridor, reduced PEF, hypoxemia)
   c. Reduced BP or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence)
   d. *Persistent* gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)
3. Reduced BP following exposure to ***known** allergen for that patient* (minutes to several hours):
   a. Infants and children: low systolic BP (age-specific) or >30% drop in systolic BP
   b. Adults: systolic BP <90 mm Hg or >30% drop from patient's baseline

BP, blood pressure; PEF, peak expiratory flow.

Modified from Sampson HA, Muñoz-Furlong A, Campbell RL, et al: Second symposium on the definition and management of anaphylaxis: summary report. Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium, J Allergy Clin Immunol *117:391–397, 2006.*

immunoglobulin (Ig) E molecules. Patients initially must be exposed to the responsible allergen to generate allergen-specific antibodies. In many cases, the child and the parent are unaware of the initial exposure, which may be from passage of food proteins in maternal breast milk or skin exposures. When the child is reexposed to the sensitizing allergen, mast cells and basophils, and possibly other cells, such as macrophages, release a variety of mediators (histamine, tryptase) and cytokines that can produce allergic symptoms in any or all target organs. Clinical anaphylaxis may also be caused by mechanisms other than IgE-mediated reactions, including direct release of mediators from mast cells by medications and physical factors (morphine, exercise, cold), disturbances of leukotriene metabolism (aspirin and nonsteroidal antiinflammatory drugs), immune aggregates and complement activation (blood products), probable complement activation (radiocontrast dyes, dialysis membranes), and IgG-mediated reactions (high-molecular-weight dextran, chimeric or humanized monoclonal antibodies) (see Table 149-2).

CLINICAL MANIFESTATIONS AND DIAGNOSIS

The onset of symptoms may vary depending on the cause of the reaction. Reactions from ingested allergens (foods, medications) are delayed in onset (minutes to 2 hr) compared with those from injected allergens (insect sting, medications) and tend to have more gastrointestinal symptoms. Initial symptoms may include any of the following constellation of symptoms: pruritus about the mouth and face; a sensation of warmth, weakness, and apprehension (sense of doom); flushing, urticaria and angioedema, oral or cutaneous pruritus, tightness in the throat, dry staccato cough and hoarseness, periocular pruritus, nasal congestion, sneezing, dyspnea, deep cough and wheezing; nausea, abdominal cramping, and vomiting, especially with ingested allergens; uterine contractions (manifesting as lower back pain); and faintness and loss of consciousness in severe cases. Some degree of obstructive laryngeal edema is typically encountered with severe reactions. Cutaneous symptoms may be absent in up to 20% of cases, and the acute onset of severe bronchospasm in a previously well asthmatic person should suggest the diagnosis of anaphylaxis. Sudden collapse in the absence of cutaneous symptoms should also raise suspicion of vasovagal collapse, myocardial infarction, aspiration, pulmonary embolism, or seizure disorder. Laryngeal edema, especially with abdominal pain, may also be a result of hereditary angioedema (see Chapter 148). Symptoms in infants may not be easy to identify (see Table 149-1).

LABORATORY FINDINGS

Laboratory studies may indicate the presence of IgE antibodies to a suspected causative agent, but this result is not definitive. Plasma histamine is elevated for a brief period but is unstable and difficult to measure in a clinical setting. **Plasma tryptase** is more stable and remains elevated for several hours but often is not elevated, especially in food-induced anaphylactic reactions.

DIAGNOSIS

A National Institutes of Health–sponsored expert panel has recommended an approach to the diagnosis of anaphylaxis (Table 149-4). The differential diagnosis includes other forms of shock (hemorrhagic, cardiogenic, septic), vasopressor reactions including flush syndromes such as carcinoid syndrome, excess histamine syndromes (systemic mastocytosis), ingestion of monosodium glutamate, scombroidosis, and hereditary angioedema. In addition, panic attack, vocal cord dysfunction, pheochromocytoma, and red man syndrome (caused by vancomycin) should be considered.

TREATMENT

Anaphylaxis is a medical emergency requiring aggressive management with **intramuscular (first line)** *or intravenous* ***epinephrine,*** intramuscular or intravenous H_1 and H_2 antihistamine antagonists, oxygen, intravenous fluids, inhaled β-agonists, and corticosteroids (Table 149-5, Fig. 149-1). The initial assessment should ensure an adequate airway with effective respiration, circulation, and perfusion. Epinephrine is the most important medication, and there should be no delay in its administration. Epinephrine should be given by the intramuscular route to the lateral thigh (1:1000 dilution, 0.01 mg/kg; max 0.5 mg). For children ≥12 yr, many recommend the 0.5 mg intramuscular dose. The intramuscular dose can be repeated 2 or 3 times at intervals of 5-15 min if an intravenous continuous epinephrine infusion has not yet been started and symptoms persist. The 1:10,000 dilution of epinephrine should be used for intravenous administration. If IV access is not readily available, then epinephrine can be administered via the endotracheal or intraosseous routes. Anaphylaxis refractory to repeated doses of epinephrine has anecdotally been treated with glucagon or methylene blue. The patient should be placed in a supine position and lower extremities elevated when there is concern for hemodynamic compromise. Fluids are also important in patients with shock. Other drugs (antihistamines, glucocorticosteroids) have a secondary role in the management of anaphylaxis. Patients may experience **biphasic anaphylaxis,** which occurs when anaphylactic symptoms recur after apparent resolution. The mechanism of this phenomenon is unknown, but it appears to be more common when therapy is initiated late and symptoms at presentation are more severe. It does not appear to be affected by the administration of corticosteroids during the initial therapy. More than 90% of biphasic responses occur within 4 hr, so patients should be observed for at least 4 hr before being discharged from the emergency department. Referrals should be made to appropriate specialists for further evaluation and follow-up.

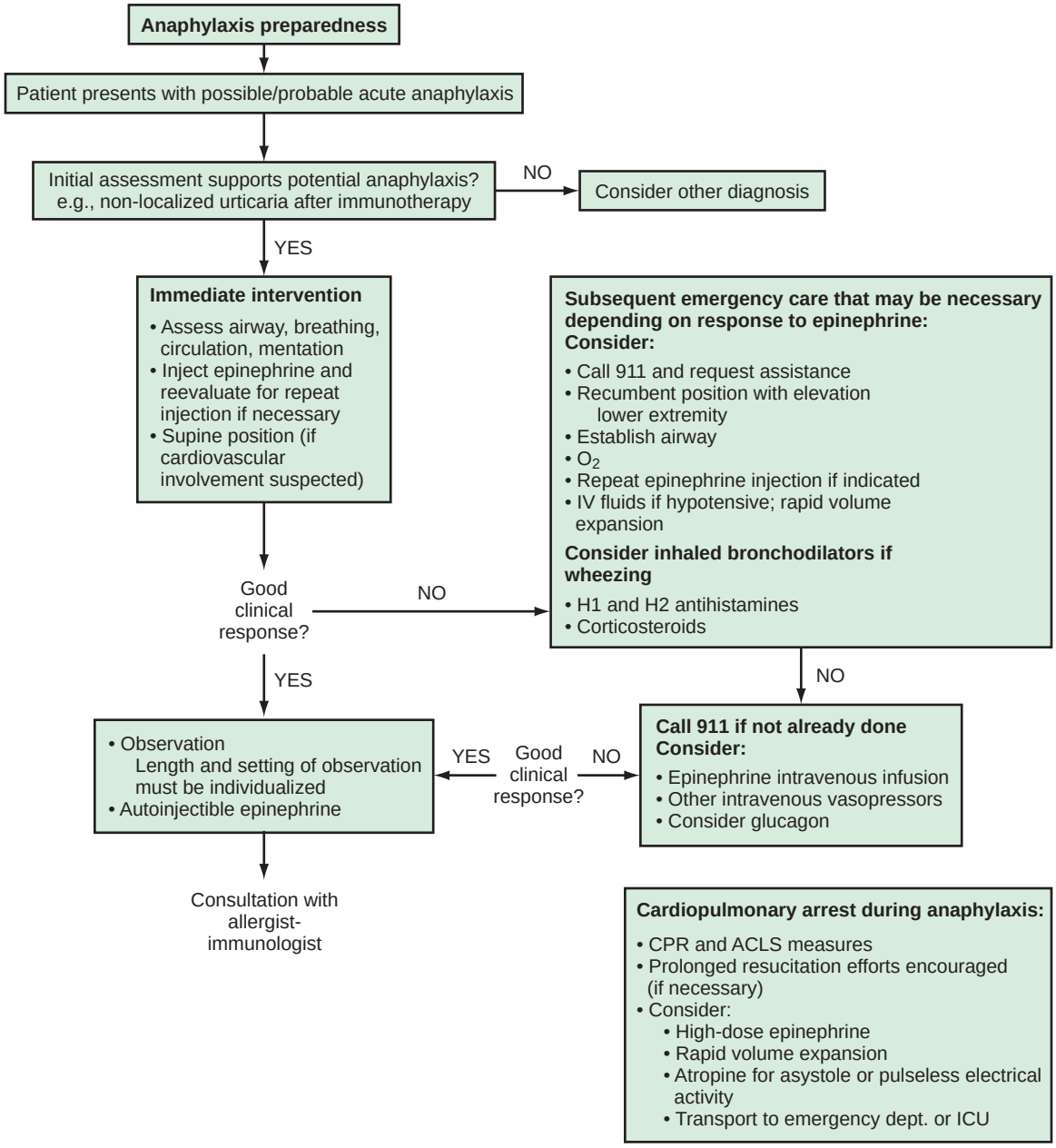


Figure 149-1 Algorithm for the treatment of anaphylactic event in the outpatient setting. IV, Intravenous. *(From Lieberman P, Nicklas RA, Oppenheimer J, et al: The diagnosis and management of anaphylaxis practice parameter: 2010 update,* J Allergy Clin Immunol *126:477–480 e471–442, 2010 [Fig. E2].)*

Table 149-5 Management of a Patient with Anaphylaxis

TREATMENT	MECHANISM(S) OF EFFECT	DOSAGE(S)	COMMENTS; ADVERSE REACTIONS
PATIENT EMERGENCY MANAGEMENT (DEPENDENT ON SEVERITY OF SYMPTOMS)			
Epinephrine (adrenaline)	α_1, β_1, β_2 adrenergic effects	0.01 mg/kg up to 0.5 mg IM in lateral thigh Weight 8-25 kg: Adrenaclick, Auvi-Q, EpiPen Jr (0.15 mg) IM Weight >25 kg: Adrenaclick, Auvi-Q, EpiPen (0.3 mg) IM	Tachycardia, hypertension, nervousness, headache, nausea, irritability, and tremor
Cetirizine (liquid)	Antihistamine (competitive of H_1 receptor)	Cetirizine liquid–5 mg/5 mL 0.25 mg/kg up to 10 mg PO	Hypotension, tachycardia, and somnolence
Alt: diphenhydramine	Antihistamine (competitive of H_1 receptor)	1.25 mg/kg up to 50 mg PO or IM	Hypotension, tachycardia, somnolence, and paradoxical excitement
Transport **to an Emergency Facility**			
EMERGENCY PERSONNEL MANAGEMENT (DEPENDENT ON SEVERITY OF SYMPTOMS)			
Epinephrine (adrenaline)	α_1, β_1, β_2 adrenergic effects	0.01 mg/kg up to 0.5 mg IM in lateral thigh Epinephrine autoinjector: 0.15 mg for 8-25kg, 0.3 mg for >25 kg 0.01 mL/kg/dose of 1:1,000 solution up to 0.5 mL IM May repeat every 10-15 min For severe hypotension: 0.01 mL/kg/dose of 1:10,000 slow IV push	Tachycardia, hypertension, nervousness, headache, nausea, irritability, and tremor
Supplemental oxygen and airway management			
Volume expanders			
Crystalloids (normal saline or Ringer lactate)		30 mL/kg in 1st hr	Rate titrated against blood pressure response If tolerated, place patient supine with legs raised
Colloids (hydroxyethyl starch)		10 mL/kg rapidly followed by slow infusion	Rate titrated against blood pressure response If tolerated, place patient supine with legs raised
Antihistamines			
Cetirizine (liquid)	Antihistamine (competitive of H_1 receptor)	Cetirizine liquid–5 mg/5 mL 0.25 mg/kg up to 10 mg PO	Hypotension, tachycardia, and somnolence
Alt: diphenhydramine	Antihistamine (competitive of H_1 receptor)	1.25 mg/kg up to 50 mg PO, IM, or IV	Hypotension, tachycardia, somnolence, and paradoxical excitement
Ranitidine	Antihistamine (competitive of H_2 receptor)	1 mg/kg up to 50 mg IV Should be administered slowly	Headache, mental confusion
Alt: cimetidine	Antihistamine (competitive of H_2 receptor	4 mg/kg up to 200 mg IV Should be administered slowly	Headache, mental confusion
Corticosteroids			
Methylprednisolone	Antiinflammatory	Solu-Medrol (IV) 1-2 mg/kg up to 125 mg IV Depo-Medrol (IM) 1 mg/kg up to 80 mg IM	Hypertension, edema, nervousness, and agitation
Prednisone	Antiinflammatory	1 mg/kg up to 75 mg PO	Hypertension, edema, nervousness, and agitation
Nebulized albuterol	β-Agonist	(0.83 mg/mL [3 mL]) via mask with O_2	Palpitations, nervousness, central nervous system stimulation, tachycardia; use to supplement epinephrine when bronchospasm appears unresponsive; may repeat
POSTEMERGENCY MANAGEMENT			
Antihistamine		Cetirizine (5-10 mg qd) or loratadine (5-10 mg qd) for 3 days	
Corticosteroids		*Optional:* Oral prednisone (1 mg/kg up to 75 mg) daily for 3 days	
Preventive treatment			
Prescription for epinephrine autoinjector and antihistamine			
Provide written plan outlining patient emergency management (may download form from http://www.foodallergy.org)			
Follow-up evaluation to determine/confirm etiology			
Immunotherapy for insect sting allergy			
Patient education			
Instruction on avoidance of causative agent			
Information on recognizing early signs of anaphylaxis			
Stress early treatment of allergic symptoms to avoid systemic anaphylaxis			
Encourage wearing medical identification jewelry			

IM, intramuscularly; IV, intravenously; PO, by mouth.

PREVENTION

For patients experiencing anaphylactic reactions, the triggering agent should be avoided and education regarding early recognition of anaphylactic symptoms and administration of emergency medications should be provided. Patients with food allergies must be educated in allergen avoidance, including active reading of food ingredient labels and knowledge of potential contamination and high-risk situations. Any child with food allergy and a history of asthma, peanut, tree nut, fish or shellfish allergy, or a previous anaphylactic reaction should be given an epinephrine autoinjector (Adrenaclick, Auvi-Q, EpiPen), liquid cetirizine (or alternatively, diphenhydramine), and a written emergency plan in case of accidental ingestion. A form can be downloaded from Food Allergy Research & Education at http://www.foodallergy.org.

In cases of food-associated exercise-induced anaphylaxis, children must not exercise within 2-3 hr of ingesting the triggering food and, like children with exercise-induced anaphylaxis, should exercise with a friend, learn to recognize the early signs of anaphylaxis (sensation of warmth and facial pruritus), stop exercising, and seek help immediately if symptoms develop. Children experiencing a systemic anaphylactic reaction including respiratory symptoms to an insect sting should be evaluated and treated with immunotherapy, which is more than 90% protective. Reactions to medications can be reduced and minimized by using oral medications in preference to injected forms and avoidance of cross-reacting medications. Low osmolarity radiocontrast dyes and pretreatment can be used in patients in whom previous reactions are suspected. The use of nonlatex gloves and materials should be used in children undergoing multiple operations. Any child who is at risk for anaphylaxis should receive emergency medications (including epinephrine autoinjector), education on identification of signs and symptoms of anaphylaxis and proper administration of medications, and a written emergency plan in case of accidental exposure, and encouraged to wear medical identification jewelry.

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Chapter 150

Serum Sickness

Anna Nowak-Węgrzyn and Scott H. Sicherer

Serum sickness is a systemic, immune complex–mediated hypersensitivity vasculitis classically attributed to the therapeutic administration of foreign serum proteins or other medications (Table 150-1).

ETIOLOGY

Immune complexes involving heterologous (animal) serum proteins and complement activation are important pathogenic mechanisms in serum sickness. Antibody therapies derived from the horse or sheep are available for treatment of envenomation by the black widow spider and a variety of snakes, for treatment of botulism, and for immunosuppression (antithymocyte globulin). The availability of alternative medical therapies, modified or bioengineered antibodies, and biologics of human origin have supplanted the use of nonhuman antisera, reducing the risk of serum sickness. A *serum sickness–like reaction* may be attributed to drug allergy, triggered by antibiotics (particularly cefaclor). In contrast to a true serum sickness, serum sickness–like reactions do not exhibit the immune complexes, hypocomplementemia, vasculitis, and renal lesions that are seen in serum sickness reactions.

PATHOGENESIS

Serum sickness is a classic example of a type III hypersensitivity reaction caused by antigen–antibody complexes. In the rabbit model using bovine serum albumin as the antigen, symptoms develop with the appearance of antibody against the injected antigen. As free antigen concentration falls and antibody production increases over days, antigen–antibody complexes of various sizes develop in a manner analogous to a precipitin curve. Whereas small complexes usually circulate harmlessly and large complexes are cleared by the reticuloendothelial system, intermediate-sized complexes that develop at the point of slight antigen excess may deposit in blood vessel walls and tissues. There the immune microprecipitates induce vascular (leukocytoclastic vasculitis with immune complex deposition) and tissue damage through activation of complement and granulocytes.

Complement activation (C3a, C5a) promotes chemotaxis and adherence of neutrophils to the site of immune complex deposition. The processes of immune complex deposition and of neutrophil accumulation may be facilitated by increased vascular permeability, owing to the release of vasoactive amines from tissue mast cells. Mast cells may be activated by binding of antigen to immunoglobulin (Ig) E or through contact with anaphylatoxins (C3a). Tissue injury results from the liberation of proteolytic enzymes and oxygen radicals from the neutrophils.

CLINICAL MANIFESTATIONS

The symptoms of serum sickness generally begin 7-12 days after injection of the foreign material, but may appear as late as 3 wk afterward. The onset of symptoms may be accelerated if there has been earlier exposure or previous allergic reaction to the same antigen. A few days before the onset of generalized symptoms, the site of injection may become edematous and erythematous. Symptoms usually include fever, malaise, and rashes. Urticaria and morbilliform rashes are the predominant types of skin eruptions. In a prospective study of serum sickness induced by administration of equine antithymocyte globulin, an initial rash was noted in most patients. It began as a thin serpiginous band of erythema along the sides of the hands, fingers, feet, and toes at the junction of the palmar or plantar skin with the skin of the dorsolateral surface. In most patients, the band of erythema was replaced

Table 150-1 Proteins and Medications that Cause Serum Sickness*

PROTEINS FROM OTHER SPECIES
Antithymocyte globulin
Antitetanus toxoid
Antivenin (Crotalidae) polyvalent (horse serum based)
Crotalidae polyvalent immune Fab (ovine serum based)
Antirabies globulin
Infliximab
Rituximab
Etanercept
Anti-HIV antibodies ([PE]HRG214)
Hymenoptera stings
Streptokinase
DRUGS
Antibiotics
Cefaclor
Penicillins
Trimethoprim sulfate
Minocycline
Meropenem
Neurologic
Bupropion
Carbamazepine
Phenytoin
Sulfonamides
Barbiturates

*Based on review of most current literature. Other medications that are not listed are also cited to cause serum sickness.

HIV, human immunodeficiency virus.

From Aceves SS, Serum Sickness IN Burg FD, Ingelfinger JR, Polin RA, Gershon AA, editors, Current Pediatric Therapy, *ed 18, Philadelphia, Elsevier, 2006, Chapter 20, Table 1, p. 1138.*

by petechiae or purpura, presumably because of low platelet counts or local damage to small blood vessels. Additional symptoms include edema, myalgia, lymphadenopathy, symmetric arthralgia or arthritis involving multiple joints, and gastrointestinal complaints, including pain, nausea, diarrhea, and melena. Symptoms typically resolve within 2 wk of removal of the offending agent, although in unusual cases, symptoms can persist for as long as 2-3 mo.

Carditis, glomerulonephritis, Guillain-Barré syndrome, and peripheral neuritis are rare complications. Serum sickness–like reactions from drugs are characterized by fever, pruritus, urticaria, and arthralgias that usually begin 1-3 wk after drug exposure. The urticarial skin eruption becomes increasingly erythematous as the reaction progresses and can evolve into dusky centers with round plaques.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of serum sickness and serum sickness-like reactions includes viral illnesses with exanthems, hypersensitivity vasculitis, Kawasaki disease, acute rheumatic fever, acute meningococcal or gonococcal infection, endocarditis, systemic onset juvenile idiopathic arthritis (Still disease), Lyme disease, hepatitis and other types of drug reactions (see Chapter 152).

DIAGNOSIS

In most cases, the diagnosis of serum sickness is made clinically based upon the characteristic pattern of acute or subacute onset of a rash, fever, and severe arthralgia and myalgia disproportionate to the degree of swelling, occurring after exposure to a potential culprit.

The patients who appear moderately or severely ill, or who are not taking a medication that can be readily identified as the culprit, should be evaluated with the following laboratory tests:

- Complete blood count and differential; thrombocytopenia is often present.
- Erythrocyte sedimentation rate and C-reactive protein; erythrocyte sedimentation rate is usually elevated.
- Urinalysis; mild proteinuria, hemoglobinuria, and microscopic hematuria may be seen.
- Serum chemistries, including blood urea nitrogen, creatinine, and liver function tests.
- Complement studies, including CH50, C3, and C4; serum complement levels (C3 and C4) are generally decreased and reach a nadir at about day 10. C3a anaphylatoxin may be increased.
- Testing for specific infectious diseases, if indicated by the history or physical examination.
- Appropriate viral or bacterial cultures if an infection is suspected.

Skin biopsies are not usually necessary for confirming the diagnosis, because the findings are variable and not specific for serum sickness. Direct immunofluorescence studies of skin lesions often reveal immune deposits of IgM, IgA, IgE, or C3.

TREATMENT

There are no evidence-based guidelines or controlled trials upon which to base therapy recommendations. Treatment is primarily supportive, consisting of discontinuation of the offending agent, antihistamines for pruritus, and nonsteroidal antiinflammatory agents and analgesics for low-grade fever and mild arthralgia. When the symptoms are especially severe, for example, fever >38.5°C (101.3°F), severe arthralgia or myalgia, or renal dysfunction, systemic corticosteroids can be used. Prednisone (1-2 mg/kg/day, max 60 mg/day) for 1-2 wk is usually sufficient. Once the offending agent is discontinued and depending on its half-life, symptoms resolve spontaneously in 1-4 wk. Symptoms lasting longer suggest another diagnosis.

PREVENTION

The primary mode of prevention of serum sickness is to seek alternative therapies. In some cases, non–animal-derived formulations may be available (human-derived botulinum immune globulin). Other alternatives are partially digested antibodies of animal origin and engineered (humanized) antibodies. The potential of these therapies to elicit serum sickness–like disease appears low. When only animal-derived antitoxin/antivenom is available, skin tests should be performed before administration of serum, but this procedure indicates the risk only of anaphylaxis, not of serum sickness. For patients who have evidence of anaphylactic sensitivity to horse serum, a risk-to-benefit assessment must be made to determine the need to proceed with treatment. If needed, the serum can usually be successfully administered by a process of rapid desensitization using protocols of gradual administration outlined by the manufacturers. Serum sickness is not prevented by desensitization or by pretreatment with corticosteroids.

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Chapter 151

Food Allergy and Adverse Reactions to Foods

Anna Nowak-Węgrzyn, Hugh A. Sampson, and Scott H. Sicherer

Adverse reactions to foods consist of any untoward reaction following the ingestion of a food or food additive and are classically divided into **food intolerances** (e.g., **lactose intolerance**), which are adverse physiologic responses, and **food allergies,** which are adverse immunologic responses and can be immunoglobulin (Ig) E-mediated or non–IgE-mediated (Tables 151-1 to 151-3). Like other atopic disorders, food allergies appear to have increased over the past 3 decades, primarily in countries with a Western lifestyle. Worldwide, estimates of food allergy prevalence range from 1-10%; in the United States, food allergies affect an estimated 3.5% of the U.S. population. Up to 6% of children experience food allergic reactions in the 1st 3 yr of life, including approximately 2.5% with cow's milk allergy, 1.5% with egg allergy, and 1% with peanut allergy. Peanut allergy prevalence tripled over the past decade. Most children "outgrow" milk and egg allergies, with approximately 50% doing so by school-age. In contrast, approximately 80-90% of children with peanut, nut, or seafood allergy retains their allergy for life.

PATHOGENESIS

Food intolerances are the result of a variety of mechanisms, whereas food allergy is predominantly caused by IgE-mediated and/or cell-mediated mechanisms. In susceptible individuals exposed to certain allergens, food-specific IgE antibodies are formed that bind to Fcε receptors on mast cells, basophils, macrophages, and dendritic cells. When food allergens penetrate mucosal barriers and reach cell-bound IgE antibodies, mediators are released that induce vasodilation, smooth muscle contraction, and mucus secretion, which result in symptoms of immediate hypersensitivity (allergy). Activated mast cells and macrophages may release several cytokines that attract and activate other cells, such as eosinophils and lymphocytes, leading to prolonged inflammation. Symptoms elicited during acute IgE-mediated reactions can affect the **skin** (urticaria, angioedema, flushing), **gastrointestinal tract** (oral pruritus, angioedema, nausea, abdominal pain, vomiting, diarrhea), **respiratory tract** (nasal congestion, rhinorrhea, nasal pruritus, sneezing, laryngeal edema, dyspnea, wheezing), and **cardiovascular system** (dysrhythmias, hypotension, loss of consciousness). In the other major form of food allergies, lymphocytes, primarily food allergen–specific T cells, secrete excessive amounts of various

Table 151-1 Adverse Food Reactions

FOOD INTOLERANCE (NON–IMMUNE SYSTEM-MEDIATED, NONTOXIC, NONINFECTIOUS)
Host factors
Enzyme deficiencies—lactase (primary or secondary), sucrase/isomaltase, hereditary fructose intolerance, galactosemia
Gastrointestinal disorders—inflammatory bowel disease, irritable bowel syndrome, pseudoobstruction, colic
Idiosyncratic reactions—caffeine in soft drinks ("hyperactivity")
Psychologic—food phobias, obsessive/compulsive disorder
Migraines (rare)
Food factors (toxic or infectious or pharmacologic)
Infectious organisms—*Escherichia coli, Staphylococcus aureus, Clostridium perfringens, Shigella,* botulism, *Salmonella, Yersinia, Campylobacter*
Toxins—histamine (scombroid poisoning), saxitoxin (shellfish)
Pharmacologic agents—caffeine, theobromine (chocolate, tea), tryptamine (tomatoes), tyramine (cheese), benzoic acid in citrus fruits (perioral flare)
Contaminants—heavy metals, pesticides, antibiotics

FOOD ALLERGY
IgE-mediated
Cutaneous—urticaria, angioedema, morbilliform rashes, flushing, contact urticarial
Gastrointestinal—oral allergy syndrome, gastrointestinal anaphylaxis
Respiratory—acute rhinoconjunctivitis, bronchospasm
Generalized—anaphylactic shock, exercise induced anaphylaxis
Mixed IgE- and non–IgE-mediated
Cutaneous—atopic dermatitis, contact dermatitis
Gastrointestinal—allergic eosinophilic esophagitis and gastroenteritis
Respiratory—asthma
Non–IgE-mediated
Cutaneous—contact dermatitis, dermatitis herpetiformis (celiac disease)
Gastrointestinal—food protein–induced enterocolitis, proctocolitis, and enteropathy syndromes, celiac disease, food protein induced enteropathy
Respiratory—food-induced pulmonary hemosiderosis (Heiner syndrome)
Unclassified

IgE, immunoglobulin E.

Table 151-2 Differential Diagnosis of Adverse Food Reactions

GASTROINTESTINAL DISORDERS (WITH VOMITING AND/OR DIARRHEA)
Structural abnormalities (pyloric stenosis, Hirschsprung disease, reflux)
Enzyme deficiencies (primary or secondary):
Disaccharidase deficiency—lactase, fructase, sucrase-isomaltase
Galactosemia
Malignancy with obstruction
Other: pancreatic insufficiency (cystic fibrosis), peptic disease

CONTAMINANTS AND ADDITIVES
Flavorings and preservatives—rarely cause symptoms:
Sodium metabisulfite, monosodium glutamate, nitrites
Dyes and colorings—very rarely cause symptoms (urticaria, eczema):
Tartrazine
Toxins:
Bacterial, fungal (aflatoxin), fish-related (scombroid, ciguatera)
Infectious organisms:
Bacteria (*Salmonella, Escherichia coli, Shigella*)
Virus (rotavirus, enterovirus)
Parasites (*Giardia, Akis simplex* [in fish])
Accidental contaminants:
Heavy metals, pesticides
Pharmacologic agents:
Caffeine, glycosidal alkaloid solanine (potato spuds), histamine (fish), serotonin (banana, tomato), tryptamine (tomato), tyramine (cheese)

PSYCHOLOGIC REACTIONS
Food phobias

Table 151-3 Natural History of Food Allergy and Cross-Reactivity Between Common Food Allergies

FOOD	USUAL AGE AT ONSET OF ALLERGY	CROSS REACTIVITY	USUAL AGE AT RESOLUTION
Hen's egg white	0-1 yr	Other avian eggs	7 yr (75% of cases resolve)*
Cow's milk	0-1 yr	Goat's milk, sheep's milk, buffalo milk	5 yr (76% of cases resolve)*
Peanuts	1-2 yr	Other legumes, peas, lentils; coreactivity with tree nuts	Persistent (20% of cases resolve)
Tree nuts	1-2 yr; in adults, onset occurs after cross reactivity to birch pollen	Other tree nuts; coreactivity with peanuts	Persistent (9% of cases resolve)
Fish	Late childhood and adulthood	Other fish (low cross-reactivity with tuna and swordfish)	Persistent†
Shellfish	Adulthood (in 60% of patients with this allergy)	Other shellfish	Persistent
Wheat*	6-24 mo	Other grains containing gluten (rye, barley)	5 yr (80% of cases resolve)
Soybeans*	6-24 mo	Other legumes	2 yr (67% of cases resolve)
Kiwi	Any age	Banana, avocado, latex	Unknown
Apples, carrots, and peaches§	Late childhood and adulthood	Birch pollen, other fruits, nuts	Unknown

*Recent studies suggest that resolution may occur at a later age, especially in children with multiple food allergies and lifetime peak food-specific IgE >50 kU_A/L.
†Fish allergy that is acquired in childhood can resolve.
§Allergy to fresh apples, carrots, and peaches (**oral allergy syndrome**) is commonly caused by heat-labile proteins. Fresh fruit causes oral pruritus, but cooked fruit is tolerated. There is generally no risk of anaphylaxis, although in rare cases, allergies to cross-reactive lipid transfer protein can cause anaphylaxis after ingestion of fruits (e.g., peach) and vegetables.
Modified from Lack G: Food allergy, N Engl J Med *359:1252–1260, 2008, Table 1.*

cytokines that lead to a "delayed," more chronic inflammatory process affecting the **skin** (pruritus, erythematous rash), **gastrointestinal tract** (failure to thrive, early satiety, abdominal pain, vomiting, diarrhea), or **respiratory tract** (food-induced pulmonary hemosiderosis). Mixed IgE and cellular responses to food allergens can also lead to chronic disorders such as atopic dermatitis, asthma, and allergic eosinophilic esophagitis and gastroenteritis.

Children in whom IgE-mediated food allergies develop may be sensitized by food allergens penetrating the gastrointestinal barrier, referred to as **class 1 food allergens,** or by food allergens that are partially homologous to plant pollens penetrating the respiratory tract, referred to as **class 2 food allergens.** Any food may serve as a class 1 food allergen, but **egg, milk, peanuts, tree nuts, fish, soy, and wheat** account for 90% of food allergies during childhood. Many of the major allergenic proteins of these foods have been characterized. There is variable but significant cross-reactivity with other proteins within an individual food group. Exposure and sensitization to these proteins often occur very early in life. Virtually all milk allergies develop by 12 mo of age and all egg allergies by 18 mo of age, and the median age of first peanut allergic reactions is 14 mo, Because allergic reactions to these high-risk allergens occur in infancy, it was once thought that avoidance of these foods and delayed introduction to the diet would prevent allergy. Indeed, the opposite is probably true and delayed introduction of these foods actually increases the risk of allergy. Current recommendations are to introduce egg, peanut products, fish, wheat, and other allergenic foods after 4-6 mo of exclusive breast feeding (Table 151-4).

Class 2 food allergens are typically vegetable, fruit or nut proteins that are partially homologous with pollen proteins (see Table 151-3). With the development of seasonal allergic rhinitis from birch, grass, or ragweed pollens, subsequent ingestion of certain uncooked fruits or vegetables provokes the **oral allergy syndrome.** Intermittent ingestion of allergenic foods may lead to acute symptoms such as urticaria or anaphylaxis, whereas prolonged exposure may lead to chronic disorders such as atopic dermatitis and asthma. Cell-mediated sensitivity typically develops to class 1allergens.

CLINICAL MANIFESTATIONS

From a clinical and diagnostic standpoint, it is most useful to subdivide food hypersensitivity disorders according to the predominant target organ (Table 151-5) and immune mechanism (see Table 151-1).

Gastrointestinal Manifestations

Gastrointestinal food allergies are often the first form of allergy to affect infants and young children and typically manifest as irritability, vomiting or "spitting-up," diarrhea, and poor weight gain. Cell-mediated hypersensitivities without IgE involvement predominate, making standard allergy tests such as prick skin tests and in vitro tests for food-specific IgE antibodies of little diagnostic value.

Food protein–induced enterocolitis syndrome (FPIES) typically manifests in the first several months of life as irritability, intermittent vomiting and protracted diarrhea, and may result in dehydration (Table 151-6). Vomiting generally occurs 1-3 hr after feeding, and continued exposure may result in abdominal distention, bloody diarrhea, anemia, and failure to thrive. Symptoms are most commonly provoked by cow's milk or soy protein–based formulas. A similar enterocolitis syndrome occurs in older infants and children from rice, oat, wheat, egg, peanut, nut, chicken, turkey, or fish. Hypotension occurs in approximately 15% of cases after allergen ingestion and may initially be thought to be caused by sepsis. FPIES usually resolves by age 3 yr.

Food protein-induced proctocolitis presents in the first few mo of life as blood-streaked stools in otherwise healthy infants (see Table 151-6). Approximately 60% of cases occur among breastfed infants, with the remainder largely among infants fed cow's milk or soy

Table 151-4 Prevention of Food Allergy

Exclusive breast feeding for 4-6 mo
Introduce solid (complementary) foods after 4-6 mo of exclusive breast feeding
Introduce low-risk complementary foods 1 at a time
Introduce potentially highly allergenic foods (fish, eggs, peanut products, milk, wheat) soon after the lower-risk foods (no need to avoid or delay)
Don't avoid allergenic foods during pregnancy or nursing
Soy-based formulas do not prevent allergic disease

Table 151-5 Symptoms of Food-Induced Allergic Reactions

TARGET ORGAN	IMMEDIATE SYMPTOMS	DELAYED SYMPTOMS
Cutaneous	Erythema Pruritus Urticaria Morbilliform eruption Angioedema	Erythema Flushing Pruritus Morbilliform eruption Angioedema Eczematous rash
Ocular	Pruritus Conjunctival erythema Tearing Periorbital edema	Pruritus Conjunctival erythema Tearing Periorbital edema
Upper respiratory	Nasal congestion Pruritus Rhinorrhea Sneezing Laryngeal edema Hoarseness Dry staccato cough	
Lower respiratory	Cough Chest tightness Dyspnea Wheezing Intercostal retractions Accessory muscle use	Cough, dyspnea, and wheezing
GI (oral)	Angioedema of the lips, tongue, or palate Oral pruritus Tongue swelling	
GI (lower)	Nausea Colicky abdominal pain Reflux Vomiting Diarrhea	Nausea Abdominal pain Reflux Vomiting Diarrhea Hematochezia Irritability and food refusal with weight loss (young children)
Cardiovascular	Tachycardia (occasionally bradycardia in anaphylaxis) Hypotension Dizziness Fainting Loss of consciousness	
Miscellaneous	Uterine contractions Sense of "impending doom"	

Note: This table is presented as Table IV in the Guidelines.
GI, gastrointestinal.
From Boyce JA, Assa'ad A, Burks AW, et al: Guideline for the diagnosis and management of food allergy in the United States: report of the NIAID-sponsored expert panel, J Allergy Clin Immunol *126(6):S1–S58, 2010 (Table IV, p. S19).*

Table 151-6 Food Protein-Induced Gastrointestinal Syndromes

	FPIES	PROCTOCOLITIS	ENTEROPATHY	EOSINOPHILIC GASTROENTEROPATHIES*
Age at onset	1 day–1 year	1 day–6 months	Dependent of age of exposure to antigen, cow's milk and soy up to 2 yr	Infant to adolescent
Food proteins implicated				
Most common	Cow's milk, soy	Cow's milk, soy	Cow's milk, soy	Cow's milk, soy, egg white, wheat, peanut
Less common	Rice, chicken, turkey, fish, pea	Egg, corn, chocolate	Wheat, egg	Meats, corn, rice, fruits, vegetables, fish
Multiple food hypersensitivities	>50% both cow's milk and soy	40% both cow's milk and soy	Rare	Common
Feeding at the time of onset	Formula	>50% exclusive breast feeding	Formula	Formula
Atopic background				
Family history of atopy	40-70%	25%	Unknown	~50% (often history of eosinophilic esophagitis)
Personal history of atopy	30%	22%	22%	~50%
Symptoms				
Emesis	Prominent	No	Intermittent	Intermittent
Diarrhea	Severe	No	Moderate	Moderate
Bloody stools	Severe	Moderate	Rare	Moderate
Edema	Acute, severe	No	Moderate	Moderate
Shock	15%	No	No	No
Failure to thrive	Moderate	No	Moderate	Moderate
Laboratory findings				
Anemia	Moderate	Mild	Moderate	Mild-moderate
Hypoalbuminemia	Acute	Rare	Moderate	Mild-severe
Methemoglobinemia	May be present	No	No	No
Allergy evaluation				
Food prick skin test	Negative†	Negative	Negative	Positive in ~50%
Serum food allergen IgE	Negative†	Negative	Negative	Positive in ~50%
Total IgE	Normal	Negative	Normal	Normal to elevated
Peripheral blood eosinophilia	No	Occasional	No	Present in <50%
Biopsy findings				
Colitis	Prominent	Focal	No	May be present
Lymph nodular hyperplasia	No	Common	No	Yes
Eosinophils	Prominent	Prominent	Few	Prominent; also neutrophilic infiltrates, papillary elongation and basal zone hyperplasia
Food challenge	Vomiting in 2-4 hr; diarrhea in 5-8 hr	Rectal bleeding in 6-72 hr	Vomiting, diarrhea, or both in 40-72 hr	Vomiting and diarrhea in hours to days
Treatment	Protein elimination, 80% respond to casein hydrolysate and symptoms clear in 3-10 days; rechallenge in 1.5-2 yr	Protein elimination, symptoms clear in 3 days with casein hydrolysate, resume/ continue breastfeeding on maternal antigen-restricted diet	Protein elimination, symptoms clear in 1-3 wk, rechallenge and biopsy in 1-2 yr	Protein elimination, good response to casein hydrolysate, excellent response to elemental diet, symptoms clear within 2-3 wk, excellent acute response to steroids; rechallenge and biopsy in 1-2 yr
Natural history	Cow's milk: 60% resolved by 2 yr Soy: 25% resolved by 2 yr	Resolved by 9-12 months	Most cases resolve in 2-3 yr	Typically a prolonged, relapsing course
Reintroduction of the food	Inpatient food challenge	At home, gradually advancing from 1 oz to full feedings over 2 weeks	Home, gradually advancing	Home, gradually advancing

*Eosinophilic gastroenteropathies encompass esophagitis, gastritis, gastroenterocolitis.
†If positive, may be a risk factor for persistent disease.
FPIES, food protein-induced enterocolitis syndrome.
From Nowak-Wegrzyn A, Muraro A: Food protein-induced enterocolitis syndrome. Curr Opin Allergy Immunol *9:371-377, 2009 (Table 1, p. 372).*

protein–based formula. Blood loss is typically modest, but can occasionally produce anemia.

Food protein–induced enteropathy often manifests in the first several months of life as diarrhea, often with steatorrhea and poor weight gain (see Table 151-6). Symptoms include protracted diarrhea, vomiting in up to 65% of cases, failure to thrive, abdominal distention, early satiety, and malabsorption. Anemia, edema, and hypoproteinemia occur occasionally. **Cow's milk sensitivity** is the most common cause of this food protein–induced enteropathy in young infants, but it has also been associated with sensitivity to soy, egg, wheat, rice, chicken, and fish in older children. **Celiac disease,** the most severe form of protein-induced enteropathy, occurs in about 1 : 100 of the U.S. population, although it may be "silent" in many patients (see Chapter 338.2). The full-blown form is characterized by extensive loss of absorptive villi and hyperplasia of the crypts, leading to malabsorption, chronic diarrhea, steatorrhea, abdominal distention, flatulence, and weight loss or failure to thrive. Oral ulcers and other extraintestinal symptoms secondary to malabsorption may occur. Genetically susceptible individuals (HLA-DQ2 or HLA-DQ8) demonstrate a cell-mediated response to tissue transglutaminase deamidated gliadin (a fraction of gluten), which is found in wheat, rye, and barley.

Eosinophilic esophagitis (EoE) may appear from infancy through adolescence, more frequently in boys (see Chapter 324). In young children, it is primarily cell mediated and manifests as chronic gastroesophageal reflux, intermittent emesis, food refusal, abdominal pain, dysphagia, irritability, sleep disturbance, and failure to respond to conventional reflux medications. EoE is a clinicopathologic diagnosis. The diagnosis is confirmed when 15 eosinophils per high-power field are seen on esophageal biopsy during treatment with proton pump inhibitors. **Eosinophilic gastroenteritis** occurs at any age and causes symptoms similar to those of EoE as well as prominent weight loss or failure to thrive, both of which are the hallmarks of this disorder. More than 50% of patients with this disorder are atopic, however food-induced IgE-mediated reactions have been implicated only in a minority of patients. Generalized edema secondary to hypoalbuminemia may occur in some infants with marked protein-losing enteropathy.

Oral allergy syndrome (pollen-associated food allergy syndrome) is an IgE-mediated hypersensitivity that occurs in many older children with birch and ragweed pollen-induced allergic rhinitis. Symptoms are usually confined to the oropharynx and consist of the rapid onset of oral pruritus, tingling and angioedema of the lips, tongue, palate, and throat, and occasionally a sensation of pruritus in the ears and tightness in the throat. Symptoms are generally short lived and are caused by local mast cell activation following contact with fresh fruit and vegetable proteins that cross-react with birch pollen (apple, carrot, potato, celery, hazel nuts, kiwi, cherry, pear), grass pollen (potato, tomato, watermelon, kiwi), and ragweed pollen (banana, melons such as watermelon and cantaloupe).

Acute gastrointestinal allergy generally manifests as acute abdominal pain and vomiting that accompany IgE-mediated allergic symptoms in other target organs.

Skin Manifestations

Cutaneous food allergies are also common in infants and young children.

Atopic dermatitis is a form of eczema that generally begins in early infancy and is characterized by pruritus, a chronically relapsing course, and association with asthma and allergic rhinitis (see Chapter 145. Although not often apparent from history, at least 30% of children with moderate to severe atopic dermatitis have food allergies. The younger the child and the more severe the eczema, the more likely food allergy is playing a pathogenic role in the disorder.

Acute urticaria and angioedema are among the most common symptoms of food allergic reactions (see Chapter 148). The onset of symptoms may be very rapid, within minutes after ingestion of the responsible allergen. Symptoms result from activation of IgE-bearing mast cells by food allergens that are absorbed and circulated rapidly throughout the body. Foods most commonly incriminated in children include egg, milk, peanuts, and nuts, although reactions to various seeds (sesame, poppy) and fruits (kiwi) are becoming more common. Chronic urticaria and angioedema are rarely caused by food allergies.

Perioral dermatitis is often a contact dermatitis caused by substances in toothpaste, gums, lipstick, to medications. **Perioral flushing** is often noted in infants fed citrus fruits and may be caused by benzoic acid in the food. It may also occur during nursing. In both situations, it is benign. Flushing may also be caused by auriculotemporal nerve (Frey) syndrome (familial, forceps delivery), which resolves spontaneously.

Respiratory Manifestations

Respiratory food allergies are uncommon as isolated symptoms. Although many parents believe that nasal congestion in infants is often caused by milk allergy, studies show this not to be the case. **Food-induced rhinoconjunctivitis** symptoms typically accompany allergic symptoms in other target organs, such as skin, and consist of typical allergic rhinitis symptoms (periocular pruritus and tearing, nasal congestion and pruritus, sneezing, rhinorrhea). Wheezing occurs in approximately 25% of IgE-mediated food allergic reactions, but only approximately 10% of asthmatic patients have food-induced respiratory symptoms.

Anaphylaxis

Anaphylaxis is defined as a serious, multisystem allergic reaction that is rapid in onset and potentially fatal. Food allergic reactions are the single most common cause of anaphylaxis seen in hospital emergency departments in the United States. In addition to the rapid onset of cutaneous, respiratory, and gastrointestinal symptoms, patients may demonstrate cardiovascular symptoms, including hypotension, vascular collapse, and cardiac dysrhythmias, which are presumably caused by massive mast cell–mediator release. **Food-associated exercise-induced anaphylaxis** occurs more frequently among teenage athletes, especially females (see Chapter 149).

DIAGNOSIS

A thorough medical history is necessary to determine whether a patient's symptomatology represents an adverse reaction (see Table 151-2), whether the adverse food reaction is an intolerance or food allergic reaction, and if the latter, whether it is likely to be an IgE-mediated or a cell-mediated response (Fig. 151-1). The following facts should be established: (1) the food suspected of provoking the reaction and the quantity ingested, (2) the interval between ingestion and the development of symptoms, (3) the types of symptoms elicited by the ingestion, (4) whether ingesting the suspected food produced similar symptoms on other occasions, (5) whether other inciting factors, such as exercise, are necessary, and (6) the interval from the last reaction to the food.

Prick skin tests and in vitro laboratory tests are useful for demonstrating IgE sensitization, defined as presence of food-specific IgE antibodies. Many fruits and vegetables require prick-prick skin testing with fresh produce because labile proteins are destroyed during commercial preparation. A negative skin test result virtually excludes an IgE-mediated form of food allergy. Conversely, the majority of children with positive skin test responses to a food do not react when the food is ingested, so more definitive tests, such as quantitative IgE tests or food elimination and challenge, are often necessary to establish a diagnosis of food allergy. Serum food-specific IgE levels ≥15 kU_A/L for milk (≥5 kU_A/L for children ≤1 yr), ≥7 kU_A/L for egg (≥2 kU_A/L for children <2 yr), and ≥14 kU_A/L for peanut are associated with a >95% likelihood of clinical reactivity to these foods in children with suspected reactivity. In the absence of a clear history of reactivity to a food and evidence of food-specific IgE antibodies, definitive studies must be performed before recommendations are made for avoidance or the use of highly restrictive diets that may be nutritionally deficient, logistically impractical, disruptive to the family, expensive, and a potential source of future feeding disorders. IgE-mediated food allergic reactions are generally very food specific, so the use of broad exclusionary diets, such as avoidance of all legumes, cereal grains, or animal products, is not warranted (Tables 151-3 and 151-7).

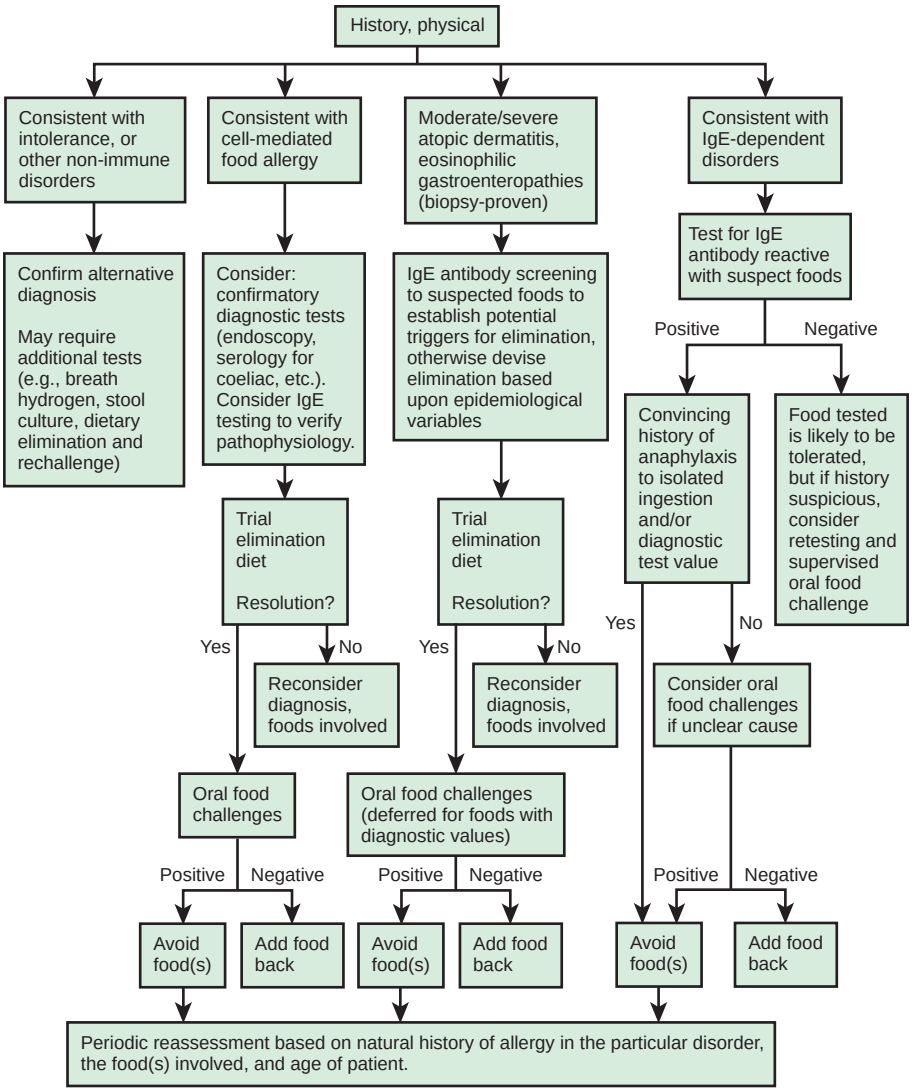


Figure 151-1 General scheme for diagnosis of food allergy. *(From Sicherer SH: Food allergy,* Lancet *360:701–710, 2002.)*

Table 151-7 Clinical Implications of Cross-Reactive Proteins in IgE-Mediated Allergy

FOOD FAMILY	RISK OF ALLERGY TO ≥1 MEMBER (%; APPROXIMATE)	FEATURE(S)
Legumes	5	Main causes of reactions are peanut, soybean, lentil, lupine, and garbanzo (chickpea)
Tree nuts (e.g., almond, cashew, hazelnut, walnut, brazil)	35	Reactions are often severe
Fish	50	Reactions can be severe
Shellfish	75	Reactions can be severe
Grains	20	
Mammalian milks	90	Cow's milk is highly cross reactive with goat's or sheep's milk (92%) but not with mare's milk (4%)
Rosaceae (pitted fruits)	55	Risk of reactions to more than three related foods is very low (<10%), symptoms are usually mild (oral allergy syndrome)
Latex-food	35	For individuals allergic to latex, banana, kiwi, fig, chestnut, and avocado are the main causes of reactions
Food-latex	11	Individuals allergic to banana, kiwi, fig, chestnut, and avocado may be at an increased risk of reactions to latex

Modified from Sicherer SH: Food allergy, Lancet *360:701–710, 2002.*

Table 151-8 ACIP and AAP Red Book Recommendations for Administering Vaccines to Patients with Egg Allergy

VACCINE	ACIP	AAP RED BOOK
MMR/MMRV	May be used	May be used
Influenza	Receive with some precautions*	Receive with some precautions*
Rabies	Use caution	No specific recommendation
Yellow fever	Contraindicated, but desensitization protocols may be followed to administer vaccine if necessary (citing PI)	Contraindicated, but desensitization protocols may be followed to administer vaccine if necessary (citing PI)

AAP, American Academy of Pediatrics; ACIP, Advisory Committee on Immunization Practices.

From Boyce JA, Assa'ad A, Burks AW, et al: Guideline for the diagnosis and management of food allergy in the United States: report of the NIAID-sponsored expert panel, J Allergy Clin Immunol *126(6):S1–S58, 2010 (Table V, p S31).*

*In 2012, recommendations changed to suggest those with mild egg allergy receive the inactivated influenza vaccine in the primary care setting with a 30 minute observation and preparedness to treat anaphylaxis. Those with severe egg allergy are referred to an allergist.

There are no laboratory studies to help identify foods responsible for cell-mediated reactions. Consequently, **elimination diets followed by food challenges** are the only way to establish the diagnosis. Allergists experienced in dealing with food allergic reactions and able to treat anaphylaxis should perform food challenges. Before a food challenge is initiated, the suspected food should be eliminated from the diet for 10-14 days for IgE-mediated food allergy and up to 8 wk for some cell-mediated disorders, such as EoE. Some children with cell-mediated reactions to cow's milk do not tolerate hydrolysate formulas and must receive amino acid–derived formulas. If symptoms remain unchanged despite appropriate elimination diets, it is unlikely that food allergy is responsible for the child's disorder.

TREATMENT

Appropriate identification and elimination of foods responsible for food hypersensitivity reactions are the only validated treatments for food allergies. Complete elimination of common foods (milk, egg, soy, wheat, rice, chicken, fish, peanut, nuts) is very difficult because of their widespread use in a variety of processed foods. The lay organization Food Allergy Research and Education (FARE, www.foodallergy.org) provides excellent information to help parents deal with both the practical and emotional issues surrounding these diets. Validated educational materials are also available through the Consortium of Food Allergy Research (www.cofargroup.org). Children with asthma and IgE-mediated food allergy, peanut or nut allergy, or a history of a previous severe reaction should be given self-injectable epinephrine and a written emergency plan in case of accidental ingestion (see Chapter 149). Because many food allergies are outgrown, children should be reevaluated periodically by an allergist to determine whether they have lost their clinical reactivity. A number of clinical trials are beginning to evaluate the efficacy of oral, sublingual, and epicutaneous (patch) immunotherapy for the treatment of IgE-mediated food allergies (milk, egg, peanut). Combining oral immunotherapy with anti-IgE treatment (omalizumab) may be even more effective than oral immunotherapy alone. Furthermore, extensively heated milk or egg in baked products are tolerated by the majority of milk and egg allergic children. Regular ingestion of baked products with milk and egg appears to accelerate resolution of milk and egg allergy. Management of egg-allergic children who require immunizations is noted in Table 151-8.

PREVENTION

There is no consensus as to whether food allergies can be prevented. At present there is insufficient evidence to support the practice of restricting the maternal diet during pregnancy or breastfeeding or of delaying introduction of various allergenic foods to infants from atopic families (see Table 151-4). Exclusive breastfeeding for the first 4-6 mo of life may reduce allergic disorders in the first few years of life in infants at high risk for development of allergic disease. Potentially allergenic foods (eggs, milk, wheat, soy, peanut and tree nut products, fish) should be introduced after this period of exclusive breastfeeding and may prevent the development of allergies later in life. Use of partially hydrolyzed whey formulas may be beneficial if breast feeding cannot be continued for 4-6 mo or after weaning, especially to prevent eczema in high risk families, but his approach remains controversial. Probiotic supplements may also reduce the incidence and severity of eczema. Because some *skin preparations* contain peanut oil, which may sensitize young infants, especially those with cutaneous inflammation, such preparations should be avoided.

Bibliography is available at Expert Consult.

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Chapter 152

Adverse Reactions to Drugs

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Adverse drug reactions can be divided into predictable (type A) and unpredictable reactions (type B). **Predictable drug reactions,** including drug toxicity, drug interactions, and adverse effects, are dose dependent, can be related to known pharmacologic actions of the drug, and occur in patients without any unique susceptibility. **Unpredictable drug reactions** are dose independent, often are not related to the pharmacologic actions of the drug, and occur in patients who are genetically predisposed. These include idiosyncratic reactions, allergic (hypersensitivity) reactions, and pseudoallergic reactions. Allergic reactions require prior sensitization, manifest as signs or symptoms characteristic of an underlying allergic mechanism such as anaphylaxis or urticaria, and occur in genetically susceptible individuals. They can occur at doses significantly below the therapeutic range. **Pseudoallergic reactions** resemble allergic reactions but are caused by non–immunoglobulin (Ig) E-mediated release of mediators from mast cells and basophils. Drug-independent cross-reactive antigens can induce sensitization manifesting as drug allergy. Patients with cetuximab-induced anaphylaxis have IgE antibodies in pretreatment samples specific for galactose-α-1,3-galactose. Galactose-α-1,3-galactose is present on the antigen-binding portion of the cetuximab heavy chain and is similar to structures in the ABO blood group.

Table 152-1 Heterogeneity of Drug-Induced Allergic Reactions

ORGAN-SPECIFIC REACTIONS	CLINICAL FEATURES	EXAMPLES OF CAUSATIVE AGENTS
CUTANEOUS		
Exanthems	Diffuse fine macules and papules evolve over days after drug initiation Delayed-type hypersensitivity	Allopurinol, aminopenicillins, cephalosporins, antiepileptic agents, and antibacterial sulfonamides
Urticaria, angioedema	Onset within minutes of drug initiation Potential for anaphylaxis Often IgE mediated	IgE mediated: β-lactam antibiotics Bradykinin mediated: ACEI
Fixed drug eruption	Hyperpigmented plaques Recur at same skin or mucosal site	Tetracycline, NSAIDs, and carbamazepine
Pustules	Acneiform Acute generalized eczematous pustulosis (AGEP)	Acneiform: corticosteroids, sirolimus AGEP: antibiotics, calcium-channel blockers
Bullous	Tense blisters Flaccid blisters	Furosemide, vancomycin Captopril, penicillamine
SJS	Fever, erosive stomatitis, ocular involvement, purpuric macules on face and trunk with <10% epidermal detachment	Antibacterial sulfonamides, anticonvulsants, oxicam NSAIDs, and allopurinol
TEN	Similar features as SJS but >30% epidermal detachment Mortality as high as 50%	Same as SJS
Cutaneous lupus	Erythematous/scaly plaques in photodistribution	Hydrochlorothiazide, calcium-channel blockers, ACEIs
Hematologic	Hemolytic anemia, thrombocytopenia, granulocytopenia	Penicillin, quinine, sulfonamides
Hepatic	Hepatitis, cholestatic jaundice	Para-aminosalicylic acid, sulfonamides, phenothiazines
Pulmonary	Pneumonitis, fibrosis	Nitrofurantoin, bleomycin, methotrexate
Renal	Interstitial nephritis, membranous glomerulonephritis	Penicillin, sulfonamides, gold, penicillamine, allopurinol
MULTIORGAN REACTIONS		
Anaphylaxis	Urticaria/angioedema, bronchospasm, gastrointestinal symptoms, hypotension IgE- and non–IgE-dependent reactions	β-Lactam antibiotics, monoclonal antibodies
DRESS	Cutaneous eruption, fever, eosinophilia, hepatic dysfunction, lymphadenopathy	Anticonvulsants, sulfonamides, minocycline, allopurinol
Serum sickness	Urticaria, arthralgias, fever	Heterologous antibodies, infliximab
Systemic lupus erythematosus	Arthralgias, myalgias, fever, malaise	Hydralazine, procainamide, isoniazid
Vasculitis	Cutaneous or visceral vasculitis	Hydralazine, penicillamine, propylthiouracil

ACEI, angiotensin-converting enzyme inhibitor; DRESS, drug rash with eosinophilia and systemic symptoms; NSAID, nonsteroidal antiinflammatory drug (NSAID); SJS, Stevens-Johnson syndrome.
From Khan DA, Solensky R: Drug allergy, J Allergy Clin Immunol *125:S126–S137, 2010 (Table 1, p. S127).*

EPIDEMIOLOGY

The incidence of adverse drug reactions in the general as well as pediatric populations remains unknown, although data from hospitalized patients show it to be 6.7%, with a 0.32% incidence of fatal adverse drug reactions. Databases such as the FDA MedWatch program (http://www.fda.gov/medwatch/index.html) likely suffer from underreporting. Cutaneous reactions are the most common form of adverse drug reactions, with ampicillin, amoxicillin, penicillin, and trimethoprim-sulfamethoxazole being the most commonly implicated drugs (Tables 152-1 and 152-2). Although the majority of adverse drug reactions do not appear to be allergic in nature, 6-10% can be attributed to an allergic or immunologic mechanism. Importantly, given the high probability of recurrence of allergic reactions, these reactions should be preventable, and information technology–based interventions may be especially useful to reduce risk of reexposure.

PATHOGENESIS AND CLINICAL MANIFESTATIONS

Immunologically mediated adverse drug reactions have been classified according to the **Gell and Coombs classification:** immediate hypersensitivity reactions (type I), cytotoxic antibody reactions (type II), immune complex reactions (type III), and delayed-type hypersensitivity reactions (type IV). Immediate hypersensitivity reactions occur when a drug or drug metabolite interacts with preformed drug-specific IgE antibodies that are bound to the surfaces of tissue mast cells and/or circulating basophils. The cross-linking of adjacent receptor-bound IgE by antigen causes the release of preformed and newly synthesized mediators, such as histamine and leukotrienes, that contribute to the clinical development of urticaria, bronchospasm, or anaphylaxis. Cytotoxic reactions involve IgG or IgM antibodies that recognize drug antigen on the cell membrane. In the presence of serum complement, the antibody-coated cell is either cleared by the monocyte–macrophage system or is destroyed. Examples are drug-induced hemolytic anemia and thrombocytopenia. Immune complex reactions are caused by soluble complexes of drug or metabolite in slight antigen excess with IgG or IgM antibodies. The immune complex is deposited in blood vessel walls and causes injury by activating the complement cascade, as seen in serum sickness. Clinical manifestations include fever, urticaria, rash, lymphadenopathy, and arthralgias. Symptoms typically appear 1-3 wk after the last dose of an offending drug and subside when the drug and/or its metabolite is cleared from the body. Delayed-type hypersensitivity reactions are mediated by drug-specific T lymphocytes. Sensitization usually occurs via the topical route of administration, resulting in allergic contact dermatitis. Commonly implicated drugs include neomycin and local anesthetics in topical formulations.

Certain adverse drug reactions, including drug fever and the morbilliform rash seen with use of ampicillin or amoxicillin in the setting of Epstein-Barr virus infection, are not easily classified. Studies point to the role of T cells and eosinophils in delayed maculopapular reactions to a number of antibiotics. The mechanisms of T-cell–mediated drug hypersensitivity are not well understood. A novel hypothesis, the p-i concept, suggests pharmacologic interactions of drugs with immune receptors as another class of drug hypersensitivity. In T-cell–mediated

Table 152-2 Serious Non–IgE-Mediated Drug Eruptions

DIAGNOSIS	MUCOSAL LESIONS	TYPICAL SKIN LESIONS	PRODROMAL SIGNS AND SYMPTOMS	DRUG ASSOCIATED (%)	DRUGS MOST OFTEN IMPLICATED	TYPICAL TIME TO ONSET (wk)	ALTERNATIVE CAUSES NOT RELATED TO DRUGS
Drug hypersensitivity syndrome (DHS) or drug rash with eosinophilia and systemic symptoms (DRESS) syndrome	Infrequent	Severe exanthematous rash (could become edematous, pustular, purpuric), exfoliative dermatitis	30-50% involve fever, lymphadenopathy, hepatitis, nephritis, carditis, eosinophilia, atypical lymphocytes	≥90	Phenytoin, carbamazepine, phenobarbital, sulfonamides, allopurinol, minocycline, nitrofurantoin, terbinafine, vancomycin, dapsone, abacavir, nevirapine, nonsteroidal antiinflammatory drugs (NSAIDs)	1-6	Cutaneous lymphoma
Stevens-Johnson syndrome (SJS)	Erosions at ≥2 sites	Crops of lesions on skin, conjunctivae, mouth, and genitalia; detachment of ≤10% of body surface area	High fever, sore throat, rhinorrhea, cough	48-64	Sulfonamides, phenytoin, carbamazepine, barbiturates, allopurinol, aminopenicillins, NSAIDs	1-3	
Toxic epidermal necrolysis (TEN)	Erosions at ≥2 sites	Lesions similar to those with SJS; confluent epidermis separates readily with lateral pressure; detachment of ≥30% of body surface area	Fever, headache, sore throat; nearly all cases involve fever, "acute skin failure," leukopenia, lesions of the respiratory and/or gastrointestinal tracts	43-65	Sulfonamides, phenytoin, carbamazepine, barbiturates, allopurinol, aminopenicillins, NSAIDs	1-3	Exanthematous stage of Kawasaki disease; staphylococcal scalded-skin syndrome

Revised from Segal AR, Doherty KM, Leggott J, et al: Cutaneous reactions to drugs in children, Pediatrics *120:e1082–e1096, 2007.*

allergic drug reactions, the specificity of the T-cell receptor that is stimulated by the drug may be directed to a cross-reactive major histocompatibility complex–peptide compound. This information suggests that even poorly reactive native drugs are capable of transmitting a stimulatory signal via the T-cell receptor, which activates T cells and results in proliferation, cytokine production, and cytotoxicity. Previous contact with the causative drug is not obligatory, and an immune mechanism should be considered as the cause of hypersensitivity, even in reactions that occur with first exposure. Such reactions have been described for radiocontrast media and neuromuscular blocking agents.

Drug Metabolism and Adverse Reactions

Most drugs and their metabolites are not immunologically detectable until they have become covalently attached to a macromolecule. This multivalent hapten–protein complex forms a new immunogenic epitope that can elicit T- and B-lymphocyte responses. The penicillins and related β-lactam antibiotics are highly reactive with proteins and can directly haptenate protein carriers, possibly accounting for the frequency of immune-mediated hypersensitivity reactions with this class of antibiotics.

Incomplete or delayed metabolism of some drugs can give rise to toxic metabolites. Hydroxylamine, a reactive metabolite produced by cytochrome P450 oxidative metabolism, may mediate adverse reactions to sulfonamides. Patients who are slow acetylators appear to be at increased risk (see Chapter 59). In addition, cutaneous reactions in patients with AIDS treated with trimethoprim-sulfamethoxazole, rifampin, or other drugs may be a result of glutathione deficiency resulting in toxic metabolites. Serum sickness–like reactions in which immune complexes have not been documented, which occur most commonly with cefaclor, may result from an inherited propensity for hepatic biotransformation of drugs into toxic or immunogenic metabolites.

Risk Factors for Hypersensitivity Reactions

Risk factors for adverse drug reactions include prior exposure, previous reactions, age (20-49 yr), route of administration (parenteral or topical), dose (high), and dosing schedule (intermittent), as well as genetic predisposition (slow acetylators). Atopy does not appear to predispose patients to allergic reactions to low-molecular-weight compounds, but atopic patients in whom an allergic reaction develops have a significantly increased risk of serious reaction. Atopic patients also appear to be at greater risk for pseudoallergic reactions induced by radiocontrast media. Pharmacogenomics has an important role in identifying individuals at risk for certain drug reactions (see Chapter 59).

DIAGNOSIS

An accurate medical history is an important first step in evaluating a patient with a possible adverse drug reaction. Suspected drugs need to be identified along with dosages, route of administration, previous exposures, and dates of administration. In addition, underlying hepatic or renal disease may influence drug metabolism. A detailed description of past reactions may yield clues to the nature of the adverse drug reaction. The propensity for a particular drug to cause the suspected reaction can be checked with information in *Physicians' Desk Reference, Drug Eruption Reference Manual,* or directly from the drug manufacturer. It is important to remember, however, that the history may be unreliable, and many patients are inappropriately labeled as being drug allergic. This label can result in inappropriate withholding of a needed drug or class of drugs. In addition, relying solely on the history can lead to overuse of drugs reserved for special indications, such as vancomycin in patients in whom penicillin allergy is suspected. Approximately 90% of patients with a clinical history of penicillin allergy do not have evidence of penicillin-specific IgE antibodies on testing.

Skin testing is the most rapid and sensitive method of demonstrating the presence of *IgE antibodies* to a specific allergen. It can be performed with high-molecular-weight compounds, such as foreign antisera, hormones, enzymes, and toxoids. Reliable skin testing can also be performed with penicillin, but not with most other antibiotics. Most immunologically mediated adverse drug reactions are caused by metabolites rather than by parent compounds, and the metabolites for most drugs other than penicillin have not been defined. In addition, many metabolites are unstable or must combine with larger proteins to be useful for diagnosis. Testing with nonstandardized reagents requires caution in interpretation of both positive and negative results, because some drugs can induce nonspecific irritant reactions. Whereas a wheal-and-flare reaction is suggestive of drug-specific IgE antibodies, a negative skin test result does not exclude the presence of such antibodies because the relevant immunogen may not have been used as the testing reagent.

A positive skin test response to the major or minor determinants of penicillin has a 60% positive predictive value for an immediate hypersensitivity reaction to penicillin. In patients in whom skin test responses to the major and minor determinants of penicillin are negative, 97-99% (depending on the reagents used) tolerate the drug without an immediate reaction. At present, the major determinant of penicillin testing reagent PrePen (benzylpenicilloyl-polylysine) in the United States is available, but the minor determinant mixture has not been approved by the FDA as a testing reagent. Limited studies utilizing serum tests for IgE to β-lactams suggest high specificity (97-100%) but low sensitivity (29-68%). The positive and negative predictive values of skin testing for antibiotics other than penicillin are not well established. Nevertheless, positive immediate hypersensitivity skin test responses to nonirritant concentrations of nonpenicillin antibiotics may be interpreted as a presumptive risk of an immediate reaction to such agents.

Results of direct and indirect Coombs tests are often positive in drug-induced hemolytic anemia. Assays for specific IgG and IgM have been shown to correlate with a drug reaction in immune cytopenia, but, in most other reactions, such assays are not diagnostic. In general, many more patients express humoral or T-cell immune responses to drug determinants than express clinical disease. Serum tryptase is elevated with systemic mast cell degranulation and can be seen with drug-associated mast cell activation, although it is not pathognomonic for drug hypersensitivity, and nonelevated tryptase values can be seen in well-defined anaphylaxis.

TREATMENT

Specific **desensitization,** *which involves the progressive administration of an allergen to render effector cells less reactive, is reserved for patients with IgE antibodies to a particular drug for whom an alternative drug is not available or appropriate.* Specific protocols for many different drugs have been developed. Desensitization should be performed in a hospital setting, usually in consultation with an allergist and with resuscitation equipment available at all times. Although mild complications, such as pruritus and rash, are fairly common and often respond to adjustments in the drug dose or dosing intervals and medications to relieve symptoms, more severe systemic reactions can occur. Oral desensitization may be less likely to induce anaphylaxis than parenteral administration. Pretreatment with antihistamines or corticosteroids is not usually recommended. It is important to recognize that desensitization to a drug is effective only while the drug continues to be administered and that after a period of interruption or discontinuation, hypersensitivity can recur.

Graded challenges based on the administration of a drug in an incremental fashion until a therapeutic dose is achieved can be attempted with drugs causing non–IgE-mediated reactions, including trimethoprim-sulfamethoxazole. Graded challenges in aspirin- or nonsteroidal antiinflammatory drug (NSAID)–intolerant patients, particularly those with respiratory reactions, can also be performed. Patients with severe non–IgE-mediated hypersensitivity reactions should not receive the predisposing agents even in the small amounts used for skin testing (see Table 152-2).

β-Lactam Hypersensitivity

Penicillin is a frequent cause of anaphylaxis and is responsible for the majority of all drug-mediated anaphylactic deaths in the United States.

Although IgE-mediated reactions may occur after administration of penicillin by any route, parenteral administration is more likely to cause anaphylaxis. If a patient requires penicillin and has a previous history suggestive of penicillin allergy, it is necessary to perform skin tests on the patient for the presence of penicillin-specific IgE, ideally with both the major and minor determinants of penicillin. Skin tests for minor determinants of penicillin are important because approximately 20% of patients with documented anaphylaxis do not demonstrate skin reactivity to the major determinant. The major determinant is commercially available (Pre-Pen). The minor determinant mixture is currently not licensed and is synthesized as a nonstandardized testing reagent at select academic centers. Penicillin G is often used as a substitute for the minor determinant mixture, and may have negative predictive value similar to testing with major and minor determinants. Patients should be referred to an allergist capable of performing appropriate testing. If the skin test response is positive to either major or minor determinants of penicillin, the patient should receive an alternative non–cross-reacting antibiotic. If administration of penicillin is deemed necessary, desensitization can be performed by an allergist in an appropriate medical setting. Skin testing for penicillin-specific IgE is not predictive for delayed-onset cutaneous, bullous, or immune complex reactions. In addition, penicillin skin testing does not appear to resensitize the patient.

Other β-lactam antibiotics, including semisynthetic penicillins, cephalosporins, carbacephems, and carbapenems, share the β-lactam ring structure. Patients with late-onset morbilliform rashes with amoxicillin are not considered to be at risk for IgE-mediated reactions to penicillin and do not require skin testing before penicillin administration. Many patients with Epstein-Barr virus infections treated with ampicillin or amoxicillin can experience a nonpruritic rash. Similar reactions occur in patients who receive allopurinol as treatment for elevated uric acid or have chronic lymphocytic leukemia. If the rash to ampicillin or amoxicillin is urticarial or systemic or the history is unclear, the patient should undergo penicillin skin testing if a penicillin is needed. There have been reports of antibodies specific for semisynthetic penicillin side chains in the absence of β-lactam ring–specific antibodies, although the clinical significance of such side chain–specific antibodies is unclear.

Varying degrees of in vitro cross-reactivity have been documented between cephalosporins and penicillins. Although the risk of allergic reactions to cephalosporins in patients with positive skin test responses to penicillin appears to be low (<2%), anaphylactic reactions have occurred after administration of cephalosporins in patients with a history of penicillin anaphylaxis. If a patient has a history of penicillin allergy and requires a cephalosporin, skin testing for major and minor determinants of penicillin should preferably be performed to determine whether the patient has penicillin-specific IgE antibodies. If skin test results are negative, the patient can receive a cephalosporin with no greater risk than found in the general population. If skin test results are positive for penicillin, recommendations may include: administration of an alternative antibiotic; cautious graded challenge with appropriate monitoring, with the recognition that there is a 2% chance of inducing an anaphylactic reaction; and desensitization to the required cephalosporin. Cross-reactivity is most likely when the cephalosporin shares the same side chain as the penicillin (Table 152-3).

Conversely, patients who require penicillin and have a history of an IgE-mediated reaction to a cephalosporin should also undergo penicillin skin testing. Patients with a negative result can receive penicillin. Patients with a positive result should either receive an alternative medication or undergo desensitization to penicillin. In patients with a history of allergic reaction to one cephalosporin who require another cephalosporin, skin testing with the required cephalosporin can be performed, with the recognition that the negative predictive value of such testing is unknown. If the skin test response to the cephalosporin is positive, the significance of the test should be checked further in control subjects to determine whether the positive response is IgE mediated or an irritant response. The drug can then be administered by graded challenge or desensitization.

Carbapenems (imipenem, meropenem) represent another class of β-lactam antibiotics with a bicyclic nucleus that demonstrate a high degree of cross-reactivity with penicillins, although prospective studies suggest incidence of cross-reactivity on skin testing of approximately 1%. In contrast to β-lactam antibiotics, monobactams (aztreonam) have a monocyclic ring structure. Aztreonam-specific antibodies have been shown to be predominantly side chain–specific; data suggest that aztreonam can be safely administered to most penicillin-allergic subjects. On the other hand, administration of aztreonam to a patient with ceftazidime allergy may be associated with increased risk of allergic reaction owing to similarity of side chains.

Sulfonamides

The most common type of reaction to sulfonamides is a maculopapular eruption often associated with fever that occurs after 7-12 days of therapy. Immediate reactions, including anaphylaxis, as well as other immunologic reactions, have also been suggested. Hypersensitivity reactions to sulfonamides occur with much greater frequency in HIV-infected individuals. For patients in whom maculopapular rashes develop after sulfonamide administration, both graded challenge and desensitization protocols have been shown to be effective. These regimens should not be used in individuals with a history of Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN). Hypersensitivity reactions to sulfasalazine used for treatment of inflammatory bowel disease appear to result from the sulfapyridine moiety. Slow desensitization over ≈1 mo permits tolerance of the drug in many patients. In addition, oral and enema forms of 5-aminosalicylic acid, thought to be the pharmacologically active agent in sulfasalazine, are effective alternative therapies.

Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis

Blistering mucocutaneous disorders induced by drugs encompass a spectrum of reactions, including SJS and TEN (see Chapters 654.2 and 654.3). Epidermal detachment of <10% is suggestive of SJS, 30% detachment suggests TEN, and 10-30% detachment suggests overlap of the 2 syndromes. The features of SJS include confluent purpuric macules on face and trunk and severe, explosive mucosal erosions, usually at more than 1 mucosal surface, accompanied by fever and constitutional symptoms. Ocular involvement may be particularly severe, and the liver, kidneys, and lungs may also be involved. TEN, which appears to be related to keratinocyte apoptosis, manifests as

Table 152-3 Groups of β-Lactam Antibiotics That Share Identical R1-Group Side Chains*

Amoxicillin	Ampicillin	Ceftriaxone	Cefoxitin	Cefamandole	Ceftazidime
Cefadroxil	Cefaclor	Cefotaxime	Cephaloridine	Cefonicid	Aztreonam
Cefprozil	Cephalexin	Cefpodoxime	Cephalothin		
Cefatrizine	Cephradine Cephaloglycin Loracarbef	Cefditoren Ceftizoxime Cefmenoxime			

*Each column represents a group with identical R1 side chains.

From Solensky R, Khan DA: Drug allergy: an updated practice parameter. Ann Allergy Asthma Immunol *105:273e1–273e78, 2010 (Table 16, p. 273e49).*

widespread areas of confluent erythema followed by epidermal necrosis and detachment with severe mucosal involvement. The risk of infection and mortality are high. Skin biopsy differentiates subepidermal cleavage characteristic of TEN from intraepidermal cleavage characteristic of the scalded-skin syndrome induced by staphylococcal toxins. TEN must be treated in a burn unit. Corticosteroids are contraindicated because they can significantly increase the risk of infection. High intravenous doses of immunoglobulin have been shown to be beneficial in patients with TEN, likely because of inhibition of Fas-mediated keratinocyte cell death by naturally occurring Fas-blocking antibodies in the intravenous immunoglobulin preparation.

Hypersensitivity to Antiretroviral Agents

A growing number of adverse drug reactions have been observed with antiretroviral agents, including reverse transcriptase inhibitors, protease inhibitors, and fusion inhibitors. Hypersensitivity to abacavir is a well-recognized, multiorgan, potentially life-threatening reaction that occurs in HIV-infected children. The reaction is independent of dose, with onset generally within 9-11 days of initiation of drug therapy. Rechallenge can be accompanied by significant hypotension and potential mortality (rate of 0.03%), and thus hypersensitivity to abacavir is an absolute contraindication for any subsequent use. Prophylaxis with prednisolone does not appear to prevent hypersensitivity reactions to abacavir. Importantly, genetic susceptibility appears to be conferred by the HLA-B*5701 allele, with a positive predictive value of >70% and a negative predictive value of 95-98%. Genetic screening would be cost-effective in white populations but not in populations of African or Asian descent, in which HLA-B*5701 allele frequency is <1%.

Chemotherapeutic Agents

Hypersensitivity reactions to chemotherapeutic drugs have been described, including to monoclonal antibodies. Rapid desensitization to a variety of unrelated agents, including carboplatin, paclitaxel, and rituximab, can be safely achieved in a 12-step protocol. Of note, this approach appears to be successful in both IgE-mediated and non–IgE-mediated reactions.

Biologics

An increasing number of biologic agents have become available for the treatment of autoimmune, allergic, cardiovascular, infectious, and neoplastic diseases. Their use may be associated with a variety of adverse reactions, including hypersensitivity reactions. Given the occurrence of anaphylaxis, including cases with delayed onset and protracted progression in spontaneous postmarketing adverse event reports, the FDA issued a boxed warning regarding risk of anaphylaxis and need for patient monitoring with use of omalizumab (see Chapter 144).

Vaccines

Measles-mumps-rubella vaccine has been shown to be safe in egg-allergic patients (although rare reactions to gelatin or neomycin can occur). The ovalbumin content in influenza vaccine is generally low and the majority of egg-allergic patients tolerate the vaccine. Skin testing with the influenza vaccine is not recommended for egg-allergic patients, but may be helpful if allergy to the vaccine itself is suspected. Egg-allergic patients should be given the injectable, not the live intranasal vaccine and be observed for 30 min after vaccination, in a setting prepared to treat anaphylaxis. For those with egg-allergic reactions resulting in more than urticaria, administration by an allergist is recommended.

Perioperative Agents

Anaphylactoid (non–IgE-mediated anaphylaxis) reactions occurring during general anesthesia may be caused by induction agents (thiopental) or muscle-relaxing agents (succinylcholine, pancuronium). Quaternary ammonium muscle relaxants (succinylcholine) can act as bivalent antigens in IgE-mediated reactions. Negative skin test results do not necessarily predict that a drug will be tolerated. Latex allergy should always be considered in the differential diagnosis of a perioperative reaction.

Local Anesthetics

Adverse drug reactions associated with local anesthetic agents are primarily toxic reactions resulting from rapid drug absorption, inadvertent intravenous injection, or overdose. Local anesthetics are classified as esters of benzoic acid (group I) or amides (group II). Group I includes benzocaine and procaine; group II includes lidocaine, bupivacaine, and mepivacaine. In suspected local anesthetic allergy, skin testing followed by a graded challenge can be performed or an anesthetic agent from a different group can be used.

Insulin

Insulin use has been associated with a spectrum of adverse drug reactions, including local and systemic IgE-mediated reactions, hemolytic anemia, serum sickness reactions, and delayed-type hypersensitivity. In general, human insulin is less allergenic than porcine insulin, which is less allergenic than bovine insulin, but for individual patients, porcine or bovine insulin may be the least allergenic. Patients treated with nonhuman insulin have had systemic reactions to recombinant human insulin even on the first exposure. More than 50% of patients who receive insulin develop antibodies against the insulin preparation, although there may not be any clinical manifestations. Local cutaneous reactions usually do not require treatment and resolve with continued insulin administration, possibly owing to IgG-blocking antibodies. More severe local reactions can be treated with antihistamines or by splitting the insulin dose between separate administration sites. Local reactions to the protamine component of neutral protamine Hagedorn insulin may be avoided by switching to Lente insulin. Immediate-type reactions to insulin, including urticaria and anaphylactic shock, are unusual and almost always occur after reinstitution of insulin therapy in sensitized patients. Insulin therapy should not be interrupted if a systemic reaction to insulin occurs and continued insulin therapy is essential. Skin testing may identify a less-antigenic insulin preparation. The dose following a systemic reaction is usually reduced to one-third, and successive doses are increased in 2-5 unit increments until the dose resulting in glucose control is attained. Insulin skin testing and desensitization are required if insulin treatment is subsequently interrupted for more than 24-48 hr. Immunologic resistance usually occurs when high titers of predominantly IgG antibodies to insulin develop. A rare form of insulin resistance caused by circulating antibodies to tissue insulin receptors is associated with acanthosis nigricans and lipodystrophy. Coexisting insulin allergy may be present in up to a third of patients with insulin resistance. Approximately half of affected patients benefit from substitution with a less-reactive insulin preparation, based on skin testing.

Drug-Induced Hypersensitivity Syndrome

Drug-induced hypersensitivity syndrome, also referred to as DRESS (drug rash with eosinophilia and systemic symptoms) syndrome, is a potentially life-threatening syndrome that has been described primarily with anticonvulsants, although many other medications have been implicated (see Tables 152-1 and 152-2). It is characterized by fever, maculopapular rash, facial edema, eosinophilia, generalized lymphadenopathy, and potentially life-threatening damage of 1 or more organs, usually renal or hepatic. Onset is delayed, usually weeks after initiation of the medication. It has been associated with reactivation of human herpesvirus 6. *Treatment is withdrawal of the medication, systemic steroids, and supportive care, but symptoms can worsen or persist for weeks to months after the drug has been discontinued.*

Red Man Syndrome

Red man syndrome is caused by nonspecific histamine release and is most commonly described with administration of intravenous vancomycin. It can be prevented by slowing the vancomycin infusion rate or by preadministration of H_1-blockers.

Radiocontrast Media

Anaphylactoid reactions to radiocontrast media or dye can occur after intravascular administration and during myelograms or retrograde pyelograms. No single pathogenic mechanism has been defined, but it

is likely that mast cell activation accounts for the majority of these reactions. Complement activation has also been described. There is no evidence that sensitivity to seafood or iodine predisposes to radiocontrast media reactions. Predictive tests are not available. Patients who have atopic profiles, who are using β-blockers, and who have had prior anaphylactoid reactions are at increased risk. Other diagnostic alternatives should be considered, or patients can be given low-osmolality radiocontrast media with a pretreatment regimen including oral prednisone, diphenhydramine, and albuterol, with or without cimetidine or ranitidine.

Narcotic Analgesics

Opiates such as morphine and related narcotics can induce direct mast cell degranulation. Patients may experience generalized pruritus, urticaria, and occasionally, wheezing. If there is a suggestive history and analgesia is required, a nonnarcotic medication should be considered. If this intervention does not control pain, graded challenge with an alternative opiate is an option.

Aspirin and Nonsteroidal Antiinflammatory Drugs

Aspirin and NSAIDs can cause anaphylactoid reactions or urticaria and/or angioedema in children, and, rarely, asthma with or without rhinoconjunctivitis in adolescents. There is no skin or in vitro test to identify patients who may react to aspirin or other NSAIDs. Once aspirin or NSAID intolerance has been established, options include avoidance and pharmacologic desensitization and subsequent continued treatment with aspirin or NSAIDs, if indicated. A number of studies suggest that cyclooxygenase-2 inhibitors are tolerated by the majority of patients with NSAID-induced adverse reactions.

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