Immunology

PART XII

Section 1

Evaluation of the Immune System

Chapter 164

Orientation to the Consideration of Inborn Errors of Immunity

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Primary immune deficiency diseases (PIDDs) comprise more than 450 disorders that impair the development or function of the immune system. Most these disorders result from a single gene pathogenic variant, although more complex inheritance patterns can also occur.

The initial diagnosis and subsequent treatment of PIDDs are often delayed due to a low index of suspicion, a rare individual disease incidence, protein manifestations including infection, autoimmunity, cutaneous lesions, and failure to thrive all in the background of a higher frequency of more common childhood illnesses (nonspecific viral illness, allergy). This diagnostic delay can lead to irreversible end-organ damage or death.

Newborn screening for severe combined immune deficiency (SCID) has helped the early detection of SCID and other immune deficiencies associated with very low T cells. However, the vast majority of immune deficiencies will not be detected by this method. Physicians must be aware of concerning manifestations or events that suggest an underlying PIDD. The varied presentations and complex phenotypes, some of which have minimal or no infectious manifestations, make the initial diagnosis of PIDDs difficult (Table 164.1). Manifestations of PIDD include recurrent and/or sentinel infections, fever without a focus, periodontitis, poor formation of pus at a site of infection, and unusual inflammatory (including autoimmune) diseases. PIDDs may involve defects in one or more host defense mechanism, or they may be an independent isolated disorder or part of a recognizable syndrome (Table 164.2).

The immune system is primarily responsible for protecting the body against invading infectious pathogens. Recurrent (often in multiple sites), severe, or unusual infections are typical presentations of PIDDs. Viral, bacterial, fungal, and mycobacterial infections each require distinct arms of the immune system for eradication; identification of the microbe causing an infection is helpful in directing the evaluation of a patient with suspected PIDD (see Table 164.1; Table 164.3). Children who exceed the normal *frequency* of infections or who have very *prolonged* symptoms suggesting failure of pathogen clearance may also warrant evaluation. The typical preschool child can have 6-10 viral respiratory infections per year, making this assessment less than straightforward. Patients with PIDD are significantly more likely to have severe infections requiring hospitalization and prolonged or unsuccessful treatment with IV antibiotics. Infections with unusual pathogens (opportunistic organisms) or infections resulting from live attenuated virus vaccines (rotavirus, varicella, MMR) are important warning signs. Neutropenia or lymphocytopenia may be present.

In addition to pathogen defense, the immune system must demonstrate tolerance to the host and prevent excessive inflammation that can result in tissue damage. In addition to infections, patients can present with autoimmune disease and/or autoinflammatory conditions. The presence of a family history of PIDD or consanguinity should increase suspicion for these conditions.

The patient's clinical presentation can help guide the initial laboratory evaluation (Fig. 164.1).

INFECTION RED FLAGS

Infections are one of the more common reasons to initiate an immunologic evaluation. The pattern and etiology of the infections dictate the appropriate diagnostic evaluation. A high burden of infections in a child is the most common reason for referral to an immunology

Table 164.1 Patterns of Infections and Other Conditions in Primary Immunodeficiency

	ILLNESSES	
DISORDER	**TYPE OF INFECTION**	**OTHER CONDITIONS**
Antibody defects	Sinopulmonary infections (*Streptococcus pneumoniae, Haemophilus influenzae,* or *Mycoplasma sp.*) Gastrointestinal (enteroviruses, *Salmonella, Campylobacter, Giardia,* norovirus)	Autoimmune disease (thrombocytopenia, hemolytic anemia, neutropenia) Inflammatory bowel disease Lymphadenopathy, splenomegaly Otitis, mastoiditis
Cell-mediated immunity defects	Pneumonia *(Pneumocystis jirovecii), Mycobacterium avium-intracellulare* Severe Epstein-Barr infection Gastrointestinal disease (viruses, cytomegalovirus) Fungi of the skin, nails, mucous membranes	Failure to thrive Splenomegaly, lymphadenopathy
Defects of phagocytosis	Skin, liver, lymph nodes, abscesses (*Staphylococcus,* gram-negative bacteria, fungi)	Inflammatory bowel disease Granulomatous infiltrations
Defects of complement	Sepsis and other blood-borne encapsulated bacteria; meningitis, *(Streptococcus, Pneumococcus, Neisseria)*	Autoimmune disease (systemic lupus erythematosus, ANA+, glomerulonephritis)

ANA, Antinuclear antibodies.
From Leung DYM, Akdis CA, Bacharier LB, et al., eds. *Pediatric Allergy Principles and Practice.* 4th ed. Philadelphia: Elsevier; 2021. Table 4.1, p. 32.

Table 164.2 Types of Primary Immune Defects

IMMUNODEFICIENCIES AFFECTING CELLULAR AND HUMORAL IMMUNITY	
$T^-B^+NK^-$ SCID	Common gamma chain (IL2RG, X-linked), JAK3
$T^-B^+NK^+$ SCID	IL7-α, T-cell receptor defects, CD45, PNP deficiency
T^-B^- SCID	RAG1, RAG2 defects, adenosine deaminase deficiency
COMBINED IMMUNODEFICIENCIES, GENERALLY LESS SEVERE	
MHC class I and II defects; T-cell receptor defects; DOCK8, IL21, and IL21R, and others	
COMBINED IMMUNODEFICIENCIES WITH SYNDROMIC OR OTHER FEATURES	
With thrombocytopenia	Wiskott-Aldrich syndrome
DNA repair defects	Ataxia telangiectasia, Nijmegen breakage syndrome; Bloom syndrome, dyskeratosis congenital, LIG-4
Hyper-IgE syndromes	STAT3 loss of function, and others
Immuno-osseous dysplasias	Cartilage hair hypoplasia Schimke immuno-osseous dysplasia
Ectodermal dysplasia	IKBKG deficiency (NEMO)
THYMIC DEFECTS WITH ADDITIONAL CONGENITAL ANOMALIES	
DiGeorge, velocardiofacial syndrome CHARGE syndrome	
ANTIBODY DEFECTS	
Agammaglobulinemias	X-linked and autosomal forms of agammaglobulinemia
Hyper-IgM syndromes	X-linked and autosomal forms
IgG or IgA deficiency	IgG subclass and IgA deficiency
IgG, and IgA and or IgM deficiency	Common variable immunodeficiency
DISEASES OF IMMUNE DYSREGULATION	
Familial hemophagocytic lymphohistiocytosis	Perforin deficiency; UNC13D.
With hypopigmentation	Chédiak-Higashi, Griscelli, Hermansky-Pudlak syndromes
With autoimmunity	Autoimmune polyendocrinopathy with candidiasis and ectodermal dystrophy, autoimmune lymphoproliferative syndrome
With defects of regulatory T cells	X-linked immune dysregulation, polyendocrinopathy enteropathy (IPEX), defects of CTLA4, STAT3
Leading to severe Epstein-Barr virus	X-linked autoimmune lymphoproliferative syndrome, XIAP deficiency, magnesium transporter 1 (MAGT1)
With colitis	IL-10 defects
CONGENITAL DEFECTS OF PHAGOCYTE NUMBER OR FUNCTION	
Neutropenia	Elastase deficiency, HAX1 deficiency, and others
Defects of motility	Leukocyte adhesion deficiency
Defects of respiratory burst	Chronic granulomatous disease
Other nonlymphoid defects	GATA2 deficiency
DEFECTS IN INTRINSIC AND INNATE IMMUNITY	
Mycobacterial disease	IL-12, IL-23, INF-γ, STAT1 defects, and others
Warts	Epidermodysplasia verruciformis (EVER), hypogammaglobulinemia, infections, myelokathexis syndrome (WHIM)
Viral infections	STAT1, STAT2, IRF7, and others
Herpes simplex encephalitis	TLR3, UNC93B1
Fungal diseases	CARD9, IL17 defects, STAT1
Bacterial susceptibility	IRAK4, MYD88, IRAK1, and others
COMPLEMENT DEFICIENCY	
Classical pathway	C1q-C9 defects
Alternative pathway	Factors B, D, I, H, properdin, and others
Regulatory and membrane controls	Co-factor proteins

CHARGE defect, Disorder with coloboma, heart defects, atresia choanae (also known as choanal atresia), growth retardation, genital abnormalities, and ear abnormalities; Ig, immunoglobulin; MHC, major histocompatibility complex; NK, natural killer; PNP, purine nucleoside phosphorylase; SCID, severe combined immunodeficiency.
From Leung DYM, Akdis CA, Bacharier LB, et al., eds. *Pediatric Allergy Principles and Practice.* 4th ed. Philadelphia: Elsevier; 2021. Table 4.2, p. 33-34.

center; there are certain patterns that can collectively be thought of as **red flags**, mandating an immunologic evaluation.

Recurrent Sinopulmonary Infections

Recurrent bacterial sinopulmonary infections (ear, sinus, pneumonia) with encapsulated organisms are a common presentation for PIDDs. It can be challenging to define a number of infections that represent a threshold to begin an immunologic evaluation. Typically, most patients with a PIDD will have a diversity of sites impacted by infection; the frequency will be higher or the severity more severe than the clinician would expect. Recurrent sinopulmonary infections are highly suggestive of patients with antibody deficiencies, such as common variable immunodeficiency (CVID; see Chapter 165) or X-linked agammaglobulinemia (XLA; see Chapter 166). Patients often require *longer courses*

Table 164.3 Sentinel Infections and Related Genes

INFECTIONS	RECOGNIZED GENE DEFECTS AND WELL-CHARACTERIZED SYNDROMES
VIRUSES	
Herpes simplex encephalitis	*TBK1, TLR3, TRAF3, TRIF, UNC93B*
Cutaneous herpes simplex	Severe T-cell defects, *DOCK8, GATA2, WAS*
EBV—chronic	*CD21, CD27, CORO1A, ITK, MAGT1, PRKCD, CXCR4*
EBV—HLH	*AP3B1, LYST1, PRF1, RAB27A, SH2D1A, STX11, UNC13D, XIAP*
CMV	Severe T-cell defects, Good syndrome, *DOCK8, GATA2, STIM1, WAS*
Papilloma virus	Idiopathic CD4 lymphopenia, *ATM, CD40L, EVER1, EVER2, DOCK8, GATA2, IKBKG, MST1, RORH, STK4, CXCR4*
FUNGI	
Candida	*AIRE, CARD9, IL17F, IL17RA, STAT1*
Aspergillus	Idiopathic CD4 lymphopenia, *CYBA, CYBB, DOCK8, GATA2, ITGB2, NCF1, NCF2, NCF4, STAT3*
BACTERIA	
Pseudomonas	Congenital neutropenia, *IRAK4, ITGB2, MYD88, BTK* (neutropenia), *CD40LG* (neutropenia)
Salmonella	*CYBB, IFNGR1, IFNGR2, IL12B, IL12RB1*
Serratia	*CYBA, CYBB, NCF1, NCF2, NCF4*
Neisseria	*C5, C6, C7, C8A, C8B, C8G, C9, CFD, CFH, CFI, CFP*
Streptococcus pneumoniae	*C1QA, C1QB, C1QC, C4A + C4B, C2, C3, IRAK4, MYD88*
MYCOBACTERIA	
Mycobacteria	*CYBA, CYBB, GATA2, IFNGR1, IFNGR2, IKBKG, IL12, IL12RB1, IRF8, NCF1, NCF2, NCF4, STAT1, TYK2*

CMV, Cytomegalovirus; EBV, Epstein-Barr virus; HLH, hemophagocytic lymphohistiocytosis. From Sullivan KE, Stiehm ER, eds. *Stiehm's Immune Deficiencies.* 2nd ed. London: Elsevier; 2020. Table 1.2.

of antibiotics to clear infections and may not have improvement with standard interventions such as bilateral myringotomy tubes or sinus surgery.

Recurrent Invasive Pneumococcal Infections

Invasive pneumococcal infections (sepsis, septic arthritis, meningitis) may occur in patients with antibody deficiency (Table 164.4). A single episode need not imply a PIDD. Recurrent invasive pneumococcal infections should elicit an evaluation. Pneumococcus has a polysaccharide capsule that permits it to evade the immune system. Antibodies bind to these bacteria (opsonization), which facilitates phagocytosis and bacterial killing. The early complement fragment C3b also opsonizes bacteria, labeling it for destruction. Patients with **early classical complement component deficiencies** (see Chapter 173) have an increased risk of invasive infections with encapsulated bacteria such as pneumococcus. The spleen plays a key role in the phagocytosis and clearance of nonopsonized bacteria. Thus **primary or secondary asplenia** is associated with an increased risk of disseminated infections with pneumococcus (and meningococcus) requiring patients to take antibiotic prophylaxis. Patients with **toll-like receptor (TLR) defects** (IRAK4, MyD88, and NEMO deficiency) develop invasive pneumococcal and *Staphylococcus aureus* infections. These patients uniquely fail to (or minimally) manifest signs of inflammation (fevers, elevated CRP, ESR) despite having invasive infections; this is the result of a block in the pathway that produces inflammatory cytokines such as interleukin (IL)-6 and tumor necrosis factor (TNF)-α, critical for recruitment of neutrophils and fever generation.

Severe Papillomavirus

A number of PIDDs are characterized by recurrent, severe human papillomavirus (HPV) infections (see Table 164.3). Warts are common in the general population but high numbers should suggest a PIDD. Patients with WHIM syndrome (warts, hypogammaglobulinemia, immunodeficiency, myelokathexis) have a unique susceptibility to HPV-induced warts in addition to bacterial sinopulmonary infections and cutaneous abscesses (immunity to other viral infections is intact) (see Fig. 708.6). One of the hallmarks of **DOCK8 deficiency** is severe cutaneous viral infections with HPV, molluscum contagiosum, herpes simplex, and varicella zoster. Patients with **epidermodysplasia verruciformis** have markedly increased susceptibility to cutaneous HPV infections. Patients with **GATA2 deficiency** can suffer from severe disseminated HPV, including genital locations, and molluscum contagiosum infections. Treatment is distinct for each condition, but knowing

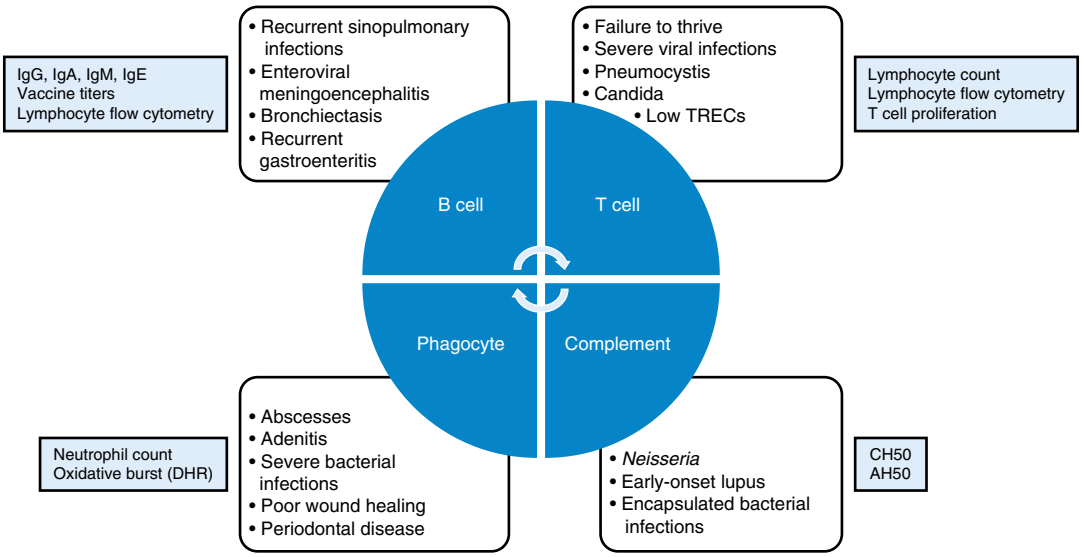

Fig. 164.1 When infections are the major manifestation of the inborn error of immunity, several types of laboratory tests can yield a diagnosis. The specific type of infection suggests the effector arm of the immune system that may be dysfunctional, and the testing can be applied in a targeted fashion. Laboratory evaluation is noted in the light blue boxes. DHR, dihydrorhodamine, Ig, immunoglobulin; TRECs, T cell receptor excision circles.

Table 164.4 Recurrent Invasive Pneumococcal Infections

CONDITION	GENE/CONDITION SUBSET	INHERITANCE	OTHER FEATURES
Asplenia	*ATRX*	XL	Developmental delay, low-set ears, single palmar crease
Asplenia	*HMOX1*	AR	Hemolysis, nephritis
Asplenia	*NKX2-5*	AD	
Asplenia	*RPSA*	AD	
Asplenia	*ZEB2*	AD	Mowat-Wilson syndrome, microcephaly, Hirschsprung disease, defects in corpus callosum
Asplenia	Gene unknown/syndromic		Can occur in heterotaxy syndromes
Antibody deficiency	*BTK*	XL	
Antibody deficiency	Hypogammaglobulinemia	Various	
Antibody deficiency	Specific antibody deficiency	Various	
Antibody deficiency	IgG subclass deficiency	Various	
Antibody deficiency	CVID	Various	
Innate immune deficiency	*MYD88*	AR	Poor fever formation
Innate immune deficiency	*IRAK4*	AR	Poor fever formation
Innate immune deficiency	*IKBKG*	XL	Peg teeth, ectodermal dysplasia
Complement deficiency	C2	AR	Can have lupus
Complement deficiency	C1	AR	Can have lupus
Complement deficiency	C4	AR	Can have lupus
Complement deficiency	C3	AR	Glomerulonephritis

AD, Autosomal dominant; AR, autosomal recessive; CVID, common variable immunodeficiency; XL, X-linked.

the immune etiology is critical because of the substantial morbidity associated with continually spreading warts.

Herpes Simplex Virus Encephalitis

Several innate PIDDs uniquely present with recurrent herpes simplex virus (HSV) encephalitis (without mucosal HSV infections) due to disruption of the signaling pathways regulating antiviral cytokines interferon (IFN)-α and -β, which are critical for control of HSV infections (see Table 164.3). Examples of these PIDDs include TLR3 deficiency, UNC93b deficiency, and interferon regulatory factor 3 (IRF3) deficiency. The importance of recognition relates to the likelihood of recurrence, with the attendant central nervous system (CNS) dysfunction that can result.

Epstein-Barr Virus

Severe life-threatening infections with fulminant Epstein-Barr virus (EBV) are a hallmark of certain PIDDs, whereas typical outpatient infectious mononucleosis infections are not concerning (see Chapter 301) (see Table 164.3). Patients with **familial hemophagocytic lymphohistiocytosis** (HLH) have a block in the cytotoxic lymphocyte (NK and CD8 T cell) pathway necessary to control EBV infections (see Chapter 556). Patients develop uncontrolled immune hyperactivation (cytokine storm) from unchecked EBV infections resulting in life-threatening HLH. Clinical symptoms include fever, hepatosplenomegaly, pancytopenia, and multi-system organ failure. There may be evidence of hemophagocytosis activated by macrophages in a bone marrow biopsy. Patients with **X-linked lymphoproliferative syndrome (XLP)** are predisposed to fatal fulminant EBV with or without HLH, as well as lymphoma. Patients with XLP who survive acute EBV infections will often go on to develop hypogammaglobulinemia. Multiple PIDD disorders have an increased risk of HLH (Table 164.5). These conditions are more likely to require hematopoietic cell transplantation (see Chapter 176) than HLH occurring in the non-PIDD community.

Severe *Candida*

Severe oral thrush from *Candida albicans* (as well as other opportunistic infections such a *Pneumocystis jiroveci*) can be seen in patients with SCID who have very low CD3 T cells (classically <300) and poor T-cell function; this mirrors the clinical phenotype of infants with HIV who also have low T cells (see Table 164.3). Intact T-cell IL-17 immunity is essential for control of *Candida* infections and overall decrements in the entire T-cell population or selective defects in the Th17 population are strongly associated with *Candida*. Patients with specific gene pathogenic variants in IL-17 signaling (IL-17RA, IL-17RC, IL-17F, and ACT1) present with **chronic mucocutaneous candidiasis** (CMCC; *Candida* infections of the skin, nails, mucosa). ***STAT1*** gain-of-function pathogenic variants result in decreased IL-17 production that also predisposes patients to skin and mucosal *Candida* infections. Autoimmune polyendocrinopathy candidiasis ectodermal dystrophy (APECED) is an autosomal recessive disease caused by mutations in the autoimmune regulator (AIRE) gene. Patients develop CMCC and autoimmune endocrine disorders such as hypoparathyroidism and adrenal insufficiency.

Aspergillus

Neutrophils are responsible for engulfing and killing fungal organisms. *Aspergillus* species are a major cause of infections in chronic granulomatous disease (CGD), a PIDD characterized by defective neutrophil function (see Table 164.3). CGD patients most commonly develop *Aspergillus* pneumonia or osteomyelitis, although all sites are susceptible to fungal infection. *Aspergillus nidulans* infections occur almost exclusively in CGD and result in a much higher rate of osteomyelitis and mortality than *A. fumigatus*. Exposure to *Aspergillus* through handling of mulch with gardening or exposure to hay can cause fulminant pneumonitis in CGD patients. Patients with **GATA2 deficiency** and ***STAT1*** gain-of-function pathogenic variants can develop fungal infections such as aspergillus and histoplasmosis as well as atypical mycobacteria. Patients with autosomal dominant **hyper-IgE syndrome**

Table 164.5 Primary Immune Deficiency Disease and Risk of Hemophagocytic Lymphohistiocytosis*

CONDITION	GENE/CONDITION SUBSET	INHERITANCE	RISK OF HLH	OTHER FEATURES
CD48 deficiency	*CD48*	AD	High	
Chédiak-Higashi syndrome	*LYST*	AR	High	Pigmentary dilution
NLRC4	*NLRC4*		High	IBD
Perforin deficiency (FHL2)	*PRF1*	AR	High	
Griscelli syndrome, type 2	*RAB27A*	AR	High	Pigmentary dilution
X-linked lymphoproliferative disease 1	*SH2D1A*	XL	High	
Syntaxin 11 deficiency (FHL4)	*STX11*	AR	High	
STXBP2/Munc18-2 deficiency (FHL5)	*STXBP2*	AR or AD	High	Hypogammaglobulinemia, IBD
UNC13D/Munc13-4 deficiency (FHL3)	*UNC13D*	AR	High	
X-linked lymphoproliferative disease 2	*XIAP*	XL	High	
CD27 deficiency	CD27	AR	Medium	Unable to control EBV
Chronic granulomatous disease	*All genetic types*	XL, AR	Low	Infections, granulomas
Hermansky-Pudlak syndrome, type 2	*AP3B1*	AR	Low	Pigmentary dilution
Hermansky-Pudlak syndrome, type 10	*AP3D1*	AR	Low	Pigmentary dilution
Lysinuric protein intolerance SLC7A7 deficiency	*SLC7A7*	AR	Low	Lung disease, feeding intolerance

*Other primary immune deficiency diseases, including most T-cell deficiencies have been associated with HLH in rare patients.
AD, Autosomal dominant; AR, autosomal recessive; HLH, Hemophagocytic lymphohistiocytosis; IBD, inflammatory bowel disease.

(STAT3 deficiency) commonly develop lung pneumatoceles (cavities), which can then become superinfected with *Aspergillus*.

Sentinel Bacterial Infections

Certain bacterial infections are considered *sentinel infections* because the pathogen is highly associated with specific PIDDs. The following bacteria are considered highly suspicious for CGD: *Burkholderia cepacia*, *Nocardia*, *Serratia marcescens*, *Chromobacterium violaceum*, and *Granulibacter bethesdensis*. Unlike patients with cystic fibrosis, *B. cepacia* in CGD can cause pneumonia but also rapidly fatal sepsis. Terminal complement (C5-C9) and alternative complement defects (properdin or factor D deficiency) have increased susceptibility to recurrent invasive *Neisseria* species (recurrent meningococcal and disseminated gonococcal infections). Complement deficiencies are also found more frequently in patients with meningitis due to unusual serotypes of *Neisseria*.

Mycobacterial Infections

Intact IL-12 and IFN-γ signaling is required to activate phagocytes such as macrophages to clear intracellular pathogens such as mycobacteria (see Table 164.3). Patients who have defects along this pathway such as IL-12 p40, IL-12 receptor, and **IFN-γ receptor deficiency** present with atypical mycobacterial infections; these infections can spread to bones and visceral organs (rather than isolated uncomplicated cervical lymphadenitis, which does not suggest a PIDD). STAT1 deficiency is associated with mycobacterial infections because STAT1 is required for IFN-γ signaling. Patients with NEMO deficiency due to pathogenic variants in *IKBKG* develop mycobacterial disease due to impaired IL-12 production in response to infection and impaired TLR signaling. Atypical mycobacteria also cause pulmonary disease in patients with CGD. Patients with the PIDDs mentioned previously born outside of the United States who receive the bacilli Calmette-Guérin (BCG) attenuated vaccine can present with disseminated BCG strain mycobacterial infection often complicating subsequent hematopoietic cell transplantation.

Severe Cryptosporidia

Cryptosporidium is a protozoan parasite that causes diarrheal disease in humans. Exposure occurs from contaminated drinking water sources as well as fresh water and public swimming pools. Patients with PIDD can develop infections outside of the GI tract such as the lungs, biliary tract, and pancreas. Intact T-cell immunity appears to play a critical role in resolution of *Cryptosporidium* infection as evidenced by the high incidence of this infection in patients with HIV. PIDDs with impaired T-cell immunity are characterized by increased risk for developing *Cryptosporidium*. In X-linked hyper-IgM syndrome, major histocompatibility complex (MHC) class II deficiency, DOCK8 deficiency, IL-21 receptor deficiency, sclerosing cholangitis, and cirrhosis from chronic *Cryptosporidium* infection can occur. The presence of liver disease from *Cryptosporidium* appears to increase the risk of mortality from curative hematopoietic cell transplantation.

SCHEMA FOR DIAGNOSIS

Clues to the diagnosis of a PIDD may be obtained by the past and current history and the physical exam (Tables 164.6 and 164.7)

Laboratory studies typically used in the diagnosis of PIDD are rudimentary. Typical laboratory studies measure the amount of antibody or count the numbers of a given cell type (T cells as an example). There is a relatively limited ability to test function. Figures 164.1 and 164.2 outline a strategy to approach the diagnostic testing for PIDDs.

NONINFECTIOUS PRESENTATIONS SUGGESTING PIDD

Autoimmunity and inflammation can be indicators of a possible PIDD. Infections may be falsely attributed to the medications used to control the autoimmunity or inflammation. Often the usual immunologic testing is normal. Many of the autoimmune or autoinflammatory disorders associated with PIDD may need to be identified through genetic sequencing.

Autoimmunity

Autoimmunity can be the presenting manifestation of a PIDD. Rather than having the more familiar infectious phenotype, these patients have defects in tolerance or lymphocyte function that compromise their homeostasis. HLH is a profound form of immune dysregulation (see Chapter 556.2). These conditions are important to recognize because *targeted* therapies can be beneficial and because they can evolve to complex phenotypes with severe morbidity. The typical laboratory

Table 164.6 Clinical Aids to the Diagnosis of Immunodeficiency

SUGGESTIVE OF B-CELL DEFECT (HUMORAL IMMUNODEFICIENCY)
Recurrent bacterial infections of the upper and lower respiratory tracts
Recurrent skin infections, meningitis, osteomyelitis secondary to encapsulated bacteria *(Streptococcus pneumoniae, Haemophilus influenzae, Staphylococcus aureus, Neisseria meningitidis)*
Severe *Giardia lamblia* infections
Paralysis after vaccination with live attenuated poliovirus
Reduced levels of immunoglobulins
SUGGESTIVE OF T-CELL DEFECT (COMBINED IMMUNODEFICIENCY)
Systemic illness after vaccination with any live virus or BCG
Unusual life-threatening complication after infection with benign viruses (giant cell pneumonia with measles; varicella pneumonia)
Chronic oral candidiasis after 6 mo of age
Chronic mucocutaneous candidiasis
Graft versus host disease after blood transfusion
Reduced lymphocyte counts for age
Low level of immunoglobulins
Absence of lymph nodes and tonsils
Small thymus
Chronic diarrhea
Failure to thrive
Recurrent infections with opportunistic organisms
Generalized, recurrent, recalcitrant warts
SUGGESTIVE OF MACROPHAGE DYSFUNCTION
Disseminated atypical mycobacterial infection, recurrent *Salmonella* infection
Fatal infection after BCG vaccination
CONGENITAL SYNDROMES WITH IMMUNODEFICIENCY
Ataxia-telangiectasia: ataxia, telangiectasia
Autoimmune polyglandular syndrome: hypofunction of one or more endocrine organs, chronic mucocutaneous candidiasis
Cartilage-hair hypoplasia: short-limbed dwarfism, sparse hair, neutropenia
Wiskott-Aldrich syndrome: thrombocytopenia, male gender, eczema
Chédiak-Higashi syndrome: oculocutaneous albinism, nystagmus, recurrent bacterial infections, peripheral neuropathies
DiGeorge syndrome (22q deletion syndrome): unusual facies, heart defect, hypocalcemia
CHARGE syndrome: coloboma, heart defects, atresia choanae, retarded growth, genital hypoplasia, ear anomalies/deafness
Short-limb skeletal dysplasia with combined immune deficiency: metaphyseal dysplasia, ADA deficiency, or Omenn syndrome
X-linked agammaglobulinemia with growth hormone deficiency: hypogammaglobulinemia, growth hormone deficiency
Kabuki syndrome: long palpebral fissures, prominent eyelashes, congenital heart disease
Timothy syndrome: prolonged QT, congenital heart disease, developmental delay
PTEN tumor hamartoma syndrome: multiple hamartomas, cancer
SUGGESTIVE OF ASPLENIA
Heterotaxia, complex congenital heart disease, Howell-Jolly bodies on blood smear, sickle cell anemia

ADA, Adenosine deaminase; BCG, bacille Calmette-Guérin.
From Verbsky JW, Routes JM. Recurrent fever, immune deficiency, and autoinflammatory disorders. In: Kliegman RM, Toth H, Bordini BJ, Basel D, eds. *Nelson Pediatric Symptom-Based Diagnosis.* 2nd ed. Philadelphia: Elsevier; 2023.Table 54.7, p. 1028.

evaluations used in the diagnosis of the PIDD are often unrevealing or minimally abnormal, leading to delay in diagnosis and implementation of appropriate therapy. The prognosis may be poor; hematopoietic cell transplantation is recommended.

Early-Onset Systemic Lupus Erythematosus

Prepubertal systemic lupus erythematosus (SLE) is uncommon and onset of SLE before 5 years of age is exceptionally unusual (Table 164.8); onset before 5 years of age suggests a monogenic condition such as early complement component deficiencies (see Chapter 173). Complement deficiencies also have an infection phenotype. SLE is the dominant phenotype for C1 and C4 deficiencies. The mechanism by which these complement deficiencies lead to susceptibility to SLE is through impaired clearance of apoptotic material and compromised tolerance. SLE may present in infancy in C1 and C4 deficiencies and it is typically severe. C2 deficiency, in contrast, is associated with a milder susceptibility to SLE and proportionally higher susceptibility to infection. Other gene defects associated with early-onset SLE include lymphocyte defects such as *PRKCD*, *FAS*, and *FASL*. Manifestations of the **interferonopathies** such as Aicardi Goutières can resemble SLE and may have a high rate of antinuclear antibodies (ANA). CNS involvement and a cutaneous vasculopathy are hallmarks of interferonopathies (see Chapter 205).

Early-Onset Enteropathy

Small bowel enteropathy in these conditions is defined as non–gluten sensitive and associated with villous blunting or atrophy (Table 164.9). A key component of the differential diagnosis is the congenital diarrheas associated with either solute carrier defects or altered epithelial function (see Chapter 385). However, many of the solute carrier defects do not have villous blunting or atrophy. The early-onset enteropathy conditions are most often related to T-cell defects in intolerance and are classically associated with dysfunctional regulatory T cells such as in **IPEX** (immune dysregulation enteropathy X-linked). Identical but milder enteropathy is also seen in patients with **STAT5B deficiency** and **IL2RA deficiency**. Both of these molecules are required for critical signal transduction in regulatory T cells. Although enteropathy is often the presenting manifestation in these regulatory T-cell deficiency states, many of these patients will develop additional autoimmune features. The progression of autoimmune involvement of different organ systems can only be altered through hematopoietic cell transplantation. Enteropathy can also be seen in older individuals with one of the immune dysregulation conditions associated with **CVID**. In these conditions, the enteropathy may appear in early childhood or as late as middle age. The key to suspecting a monogenic immune dysregulation condition is the finding of villous atrophy that is not gluten-restriction responsive. Expanded populations of intraepithelial lymphocytes are also common.

Pleomorphic Autoimmunity

Autoimmunity in children usually does not imply an inherited monogenic condition (Table 164.10). In a setting where there is a strong family history and a suspected autosomal dominant condition, the first onset of autoimmunity may prompt a genetic evaluation; a single organ autoimmune disease does not strongly suggest that there is a monogenic condition underlying that autoimmune disease.

Pleomorphic autoimmunity refers to autoimmune disease affecting multiple organs in a pattern that is not typical for either age of onset or evolution. SLE can affect a number of organs as can mixed connective tissue disease, but it would be unusual for those conditions to also be associated with diabetes mellitus or autoimmune hepatitis. When autoimmunity does not fall cleanly into a particular diagnosis, it is suggestive of pleomorphic autoimmunity.

There is a broad range of defects in T- and B-cell tolerance and conditions associated with impaired regulation of T-cell behavior that can lead to an array of autoimmune conditions. The organs affected by autoimmunity typically accrue over time and in a pattern that is not standard for the known sporadic systemic autoimmune conditions. In some cases, these conditions may also have peculiar pathologic features that represent a clue that the underlying diagnosis is something other than a standard autoimmune disease of childhood. Table 164.10 attempts to categorize conditions according to the pathway implicated. There is wide heterogeneity in the timing of the autoimmune disease, the penetrance of the disease, and the end organs affected. This combination makes this particular subset of PIDD extraordinarily difficult to conceptualize. Only a high index of suspicion and the use of genetic evaluations can identify these patients who will often benefit from targeted therapeutics.

Table 164.7 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 versus host disease, Comèl-Netherton syndrome
Recurrent abscesses with pulmonary pneumatoceles	Hyper-IgE syndromes
Recurrent organ granulomas or abscesses, lung, liver, and rectum especially	CGD
Recurrent abscesses or cellulitis	CGD, hyper-IgE syndrome, leukocyte adhesion defect
Cutaneous granulomas	Ataxia telangiectasia, SCID, CVID, RAG deficiency
Oral ulcers	CGD, SCID, 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, IL-17, and IL-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 nails	Chronic lung disease caused by 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, CGD
Immune thrombocytopenia	B-cell immune defects, ALPS
SKELETAL	
Short-limb dwarfism	Short-limb dwarfism with T-cell and/or B-cell immune defects
Bony dysplasia	ADA deficiency, cartilage-hair hypoplasia

ADA, Adenosine deaminase; ALPS, autoimmune lymphoproliferative syndrome; CGD, chronic granulomatous disease; CVID, common variable immunodeficiency; IPEX, X-linked immune dysfunction enteropathy polyendocrinopathy; SCID, severe combined immunodeficiency.
From Goldman L, Ausiello D, ed. *Cecil Textbook of Medicine.* 22nd ed. Philadelphia: Saunders; 2004. p 1599.

Inflammatory Diseases

Many of the recognized inflammatory diseases are the periodic fever (autoinflammatory) syndromes (see Chapter 204). Distinguishing fevers related to infection and those fevers that are driven by endogenous immune dysfunction is often initially difficult. The first contact with the healthcare system may be by a subspecialist who may only recognize the initial presenting manifestation. The inflammatory diseases are typically managed according to the pathway that is defective; therefore the distinction between these conditions and the autoimmune conditions is critically important.

Very Early Onset Inflammatory Bowel Disease

A key setting where a monogenic inflammatory condition should be considered is infantile-onset inflammatory bowel disease or early-onset inflammatory bowel disease with additional autoimmune features (see Chapter 382.1). Overall, approximately 20% of children who develop inflammatory bowel disease prior to 6 years of age will have a monogenic immune-based condition. The frequency increases with infantile onset or with panenteric disease. The diagnosis is most often established through genetic sequencing because the implicated genes are numerous and diverse (see Chapters 174 and 382.3). These conditions are managed with targeted biologic or small molecule agents with a few select patient subsets requiring hematopoietic cell transplantation.

Fever Syndromes

The central feature of the inherited fever syndromes is fever arising in the absence of infectious trigger (see Chapter 204). Infants and toddlers may have infections with a frequency of one per month and take as long as 2 weeks to recover. Nevertheless, the parents will often remark that the fevers "came out of the blue" or no one else in the household was ill at the time and express surprise at the frequency with which their child has been diagnosed with a viral infection with no viral symptoms. Some of the fever syndromes have fever that is typically isolated with no additional end-organ effects, whereas others have fever as a component of a much larger systemic inflammatory picture.

The most familiar inherited fever syndromes are those associated with inflammasome activation and typically treated with IL-1 inhibitors. A key consideration in the differential diagnosis for these conditions is the nongenetic condition called periodic fever aphthous stomatitis pharyngitis adenitis (PFAPA; see Chapter 204).

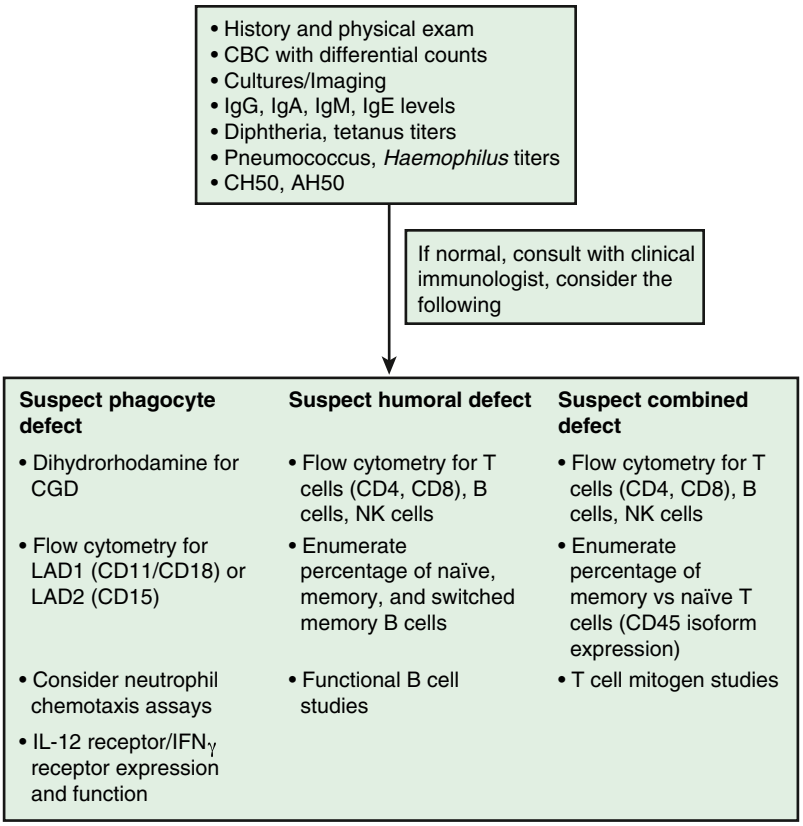

Fig. 164.2 Initial work-up and follow-up studies of patients with suspected immune deficiency. Consultation with a clinical immunologist is recommended to guide advanced testing and interpret results. CGD, Chronic granulomatous disease; Ig, immunoglobulin; LAD, leukocyte adhesion defect; NK, natural killer; IL, interleukin; IFN, interferon. *(From Verbsky JW, Routes JM. Recurrent fever, immune deficiency, and autoinflammatory disorders. In Kliegman RM, Toth H, Bordini BJ, Basel D, eds. Nelson Pediatric Symptom-Based Diagnosis. 2nd ed. Philadelphia: Elsevier; 2023. Fig. 54.9, p. 1029.)*

Table 164.8 Early-Onset Monogenic Systemic Lupus Erythematosus

PATHWAY	GENE	INHERITANCE	SLE FREQUENCY	OTHER FEATURES
Complement	*C1QA*	AR	High	Infections
Complement	*C1QB*	AR	High	Infections
Complement	*C1QC*	AR	High	Infections
Complement	*C1R*	AR	High	Infections
Complement	*C1S*	AR	High	Infections
Complement	*C2*	AR	Low	Infections
Complement	*C3*	AR	Low	Infections, GN
Complement	*C4*	AR	High	Infections
Type I Interferon-AGS	*ADAR*	AR or AD (DN)	Low	AGS, CNS
Type I Interferon-AGS	*IFIH1*	AD (GOF)	Low	AGS, arthropathy, CNS
Type I Interferon-AGS	*RNASEH2A/B/C*	AR	Low	AGS
Type I Interferon-AGS	*SAMHD1*	AR	Low	AGS, FCL, CNS
Type I Interferon-AGS	*TREX1*	AR or AD (DN)	Low	AGS, FCL
Type I Interferon	*ACP5*	AR	High	Bone, CNS
Type I Interferon	*DNASE1*	AR	High	
Type I Interferon	*DNASE2*	AR	High	GN
Type I Interferon	*DNASE1L3*	AR	High	HUVS
Type I Interferon	*OTUD1*	AD	Medium	Arthritis, IBD
Type I Interferon	*STING*	AD (GOF)	Medium	Vasculopathy, arthritis, ILD

Continued

Table 164.8 Early-Onset Monogenic Systemic Lupus Erythematosus—cont'd

PATHWAY	GENE	INHERITANCE	SLE FREQUENCY	OTHER FEATURES
RAS/MAPK	*KRAS*	AD	Low	Short stature
RAS/MAPK	*PTPN1*	AD	Low	Short stature
RAS/MAPK	*SHOC2*	AD	Low	Noonan-like syndrome
Proteasome	*PSMA3*	AD	Low	Dermatosis, lipodystrophy
Proteasome	*PSMB4*	AD	Low	Dermatosis, lipodystrophy
Proteasome	*PSMB8*	AD	Low	Dermatosis, lipodystrophy
Proteasome	*PSMB9*	AD	Low	Dermatosis, lipodystrophy
Apoptosis	*FASLG*	AD	Medium	ALPS
Apoptosis	*TNFRSF6*	AD	Medium	ALPS
Tolerance	*PRKCD*	AR	High	Infections
Tolerance	*RAG1/2*	AR	Medium	Infections, granulomas
Oxidase	*CYBB*	XL	Low	Males, CGD; females, discoid SLE
AKT	*PTEN*	AD	Medium	Malignancy risk
Collagen	*PEPD*	AR	Low	Leg ulcers
Amino acids	*SLC7A7*	AR	Low	Lysinuric protein intolerance
Carbohydrate	*MAN2B1*	AR	Low	Mannosidase
NFKappaB	*TNFAIP3*	AD	Medium	Vasculitis, ALPS
Adenosine	*ADA2*	AR	Low	Vasculitis, CNS, ALPS
Transcription factor	IKZF1	AD	Low	Leukemia, infections

AD, Autosomal dominant; AGS, Aicardi Goutières syndrome; ALPS, autoimmune lymphoproliferative syndrome; AR, autosomal recessive; CNS, central nervous system; DN, dominant negative; FCL, familial chilblains lupus; GOF, gain of function; GN, glomerulonephritis; HUVS, hypocomplementemic urticarial vasculitis; IBD, inflammatory bowel disease; ILD: interstitial lung disease; SLE, systemic lupus erythematosus; XL, X-linked.

Table 164.9 Early-Onset Enteropathy (Not Gluten Sensitive)

CONDITION	GENE	INHERITANCE	ENTEROPATHY FREQUENCY	OTHER FEATURES
Microvillous inclusion disease	*MYO5B*	AR	Always	Neonatal onset
Microvillous inclusion disease	*STX3*	AR	Always	Neonatal onset
Tufting enteropathy	*EPCAM*	AR	Always	Neonatal onset
Tufting enteropathy	*SPINT2*	AR	Always	Keratitis, anal/choanal atresia
Trichohepatoenteric syndrome	*SKIV2L*	AR	Always	Trichorrhexis nodosa, IUGR
Trichohepatoenteric syndrome	*TTC37*	AR	Always	Trichorrhexis nodosa, IUGR
Multiple intestinal atresia	*TTC7A*	AR	High	Lymphopenia, IA
Immune dysregulation	*CARD11*	AD	Low	CVID, alopecia, atopy
Immune dysregulation	*CTLA4*	AD	Medium (broad age of onset)	LP, CVID, infections
Immune dysregulation	*DEF6*	AR	Medium	Cardiomyopathy, infections
Immune dysregulation	*FOXP3*	XL	Always	Diabetes
Immune dysregulation	*ICOS*	AR	Medium (broad age of onset)	LP, CVID, infections
Immune dysregulation	*IL2RA*	AR	Low	Lymphopenia, infections, LP
Immune dysregulation	*LRBA*	AR	Medium (broad age of onset)	LP, CVID, infections
Immune dysregulation	*MALT1*	AR	High	Infections, LP, eczema
Immune dysregulation	*RLTPR*	AR	Medium	Infections, EBV
Immune dysregulation	*STAT1*	AD (GOF)	High	*Candida,* diabetes
Immune dysregulation	*STAT3*	AD (GOF)	High	Short, LP
Immune dysregulation	*XIAP*	XL	High	EBV, HLH
MHC class II deficiency	*RFXANK*	AR	Low	Infection, cytopenias
MHC class II deficiency	*CIITA*	AR	Low	Infection, cytopenias
MHC class II deficiency	*RFX5*	AR	Low	Infection, cytopenias
MHC class II deficiency	*RFXAP*	AR	Low	Infection, cytopenias

AD, Autosomal dominant; AR, autosomal recessive; CVID, Common variable immune deficiency; EBV, Epstein-Barr virus; GOF, gain of function; HLH, hemophagocytic lymphohistiocytosis; IA, intestinal atresia and fibrosis; IUGR, intrauterine growth retardation; LP, lymphocytic infiltrates in multiple organs; MHC, major histocompatibility complex; XL, X-linked.

Table 164.10 Pleomorphic Autoimmunity (Autoimmunity Not Limited to a Single Organ)

PATHWAY	GENE	INHERITANCE	MAIN ORGANS INVOLVED	NONIMMUNE FEATURES	INFECTIONS
B-cell tolerance	*AID*	AR	Lymphoid hyperplasia, cytopenias, GI		High IgM, frequent infections
T-cell tolerance	*AIRE*	AR/AD	Endocrine organs, lung, skin	Nail dystrophy	*Candida*
T-cell tolerance	*ARPC1B*	AR	Cytopenias, GI	Thrombocytopenia	Frequent infections
T-cell tolerance	*CTLA4*	AD	GI, lung, CNS		Frequent infections
T-cell tolerance	*COPA*	AD	Lung, joint, renal		
T-cell tolerance	*FOXP3*	XL	GI, endocrine, skin		
T-cell tolerance	*HAVCR2*	AR	HLH, panniculitis, SLE-like, joint	Lymphoma	
T-cell tolerance	*IL2RA*	AR	Skin, GI, endocrine		Viral
T-cell tolerance	*IL2RB*	AR	GI, skin		Viral
T-cell tolerance	*ITCH*	AR	Joints, lung, enteropathy	Developmental delay	
T-cell tolerance	*JAK1*	AD (GOF)	Skin, renal, GI		
T-cell tolerance	*LRBA*	AR	GI, lung, CNS		
T-cell tolerance	*ORAI1*	AR	Cytopenias, vasculitis	Myopathy, poor dental enamel	Frequent infections
T-cell tolerance	*PRKCD*	AR	SLE-like		Frequent infections
T-cell tolerance	*PTEN*	AD	Cytopenias, GI, endocrine	Malignancy, macrocephaly, developmental delay	
T-cell tolerance	*STAT1*	AD (GOF)	GI, endocrine		*Candida*
T-cell tolerance	*STAT3*	AD (GOF)	GI, lung, endocrine	Short stature	
T-cell tolerance	*STIM1*	AR	Cytopenias, Sjögren syndrome	Myopathy, poor dental enamel	Frequent infections
T-cell tolerance	*TPP2*	AR	Hematopoietic	CNS	Viral
T-cell tolerance	*WAS*	XL	Cytopenias, GI	Thrombocytopenia	Frequent infections
T-cell tolerance	*WIP*	AR	Cytopenias, GI	Thrombocytopenia	Frequent infections
Inflammatory pathway	*RBCK1*	AR	Joints, skin, GI	Amylopectin deposits in muscle	Frequent infections
Inflammatory pathway	*RIPK1*	AD	GI, joint	HSM episodic	Fevers
Inflammatory pathway	*RNF31*	AR	Joints, skin	Amylopectin deposits in muscle	Frequent infections, CVID-like
Inflammatory pathway	*TNFAIP3*	AD	Mucosal ulcers, GI, arthritis, skin		Fevers
Lysinuric protein intolerance	*SLC7A7*	AR	HLH, SLE, PAP	HSM, poor growth, osteoporosis, renal	Infections trigger metabolic decompensation

AD, Autosomal dominant; AR, autosomal recessive; CNS, central nervous system; CVID, common variable immune deficiency; GI, gastrointestinal, GOF, gain of function; HLH, hemophagocytic lymphohistiocytosis; HSM, hepatosplenomegaly; PAP, pulmonary alveolar proteinosis; SLE, systemic lupus erythematosus; XL, X-linked.

Although genetic fever syndromes may have a cutaneous component, abdominal pain, or nausea, fever is by far the dominant manifestation. There may be a family history or there may be an ethnic background that suggests the diagnosis (e.g., familial Mediterranean fever).

Other fever syndromes are related to proteasome dysfunction. These often have a very strong cutaneous component that can be a neutrophilic dermatosis or more of a vasculopathic picture with chilblains affecting the ears, fingers, and toes. Over time, these conditions may develop lipodystrophy. Fever is often seen in these conditions before 5 years of age. Treatment often includes a Jak inhibitor.

In their most severe form, interferonopathies present with the infantile-onset leukoencephalopathy called **Aicardi Goutières syndrome**. There are milder variants leading to interferon production that can be associated with later onset and a picture more typical for SLE. The earlier the onset the more likely there is to be significant brain involvement. These conditions are treated with Jak inhibitors.

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Section 2

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

Chapter 165

T-Cell and Combined Deficiencies

Ramsay L. Fuleihan

T-CELL AND COMBINED DEFICIENCIES

T lymphocytes (T cells) play a central role in the orchestration and regulation of the adaptive immune response. CD4 T cells help B cells synthesize specific IgG, IgA, and IgE antibodies and develop into memory B cells, help macrophages kill intracellular pathogens, and regulate the immune response. CD8 T cells kill virus-infected or malignant cells. Immune deficiency diseases that disrupt T-cell development or function are usually severe, affecting multiple aspects of adaptive immunity, and are thus *combined immune deficiency diseases*. A hallmark of the adaptive immune response is specific recognition of pathogen proteins via antigen receptors, the T-cell receptor (TCR) in T cells and immunoglobulin in B cells. Antigen receptors have a variable region that is formed by random rearrangement of two to three gene segments, V(D)J, allowing a large variety of antigen recognition. TCRs recognize a fragment of a protein that is presented by the major histocompatibility complex (MHC) molecules; therefore the randomly generated variable region of the TCR needs to be able to interact with the individual's MHC molecules. During T-cell development in the thymus, only thymocytes with TCRs that recognize the individual's MHC molecules are selected to survive (positive selection) and all other thymocytes die (by neglect). Among the thymocytes that survive, those with self-reactive TCRs are eliminated (negative selection) or develop into regulatory T cells to prevent autoimmune disease (Fig. 165.1). There is a symbiotic relationship between the thymus and developing thymocytes, where the absence of a thymus affects T-cell development and the absence of thymocytes leads to disruption of the thymic architecture. Pathogenic gene variants affecting any of the signaling pathways, DNA recombination, and repair enzymes as well as the thymic environment can lead to T-cell and combined immune deficiency diseases.

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165.1 Severe Combined Immunodeficiencies

Ramsay L. Fuleihan

Severe combined immunodeficiency (SCID) is caused by diverse pathogenic gene variants that lead to absence of T- and B-cell function. Patients with this group of disorders have the most severe immunodeficiency.

GENETICS AND PATHOGENESIS

SCID is caused by pathogenic variants in genes crucial for lymphoid cell development or function (Table 165.1 and Fig. 165.2). All patients with SCID have very small thymuses that contain no thymocytes and lack corticomedullary distinction and lack Hassall's corpuscles. The thymic epithelium appears histologically normal. Both the follicular and the paracortical areas of the spleen are depleted of lymphocytes. Lymph nodes, tonsils, adenoids, and Peyer patches are absent or extremely underdeveloped.

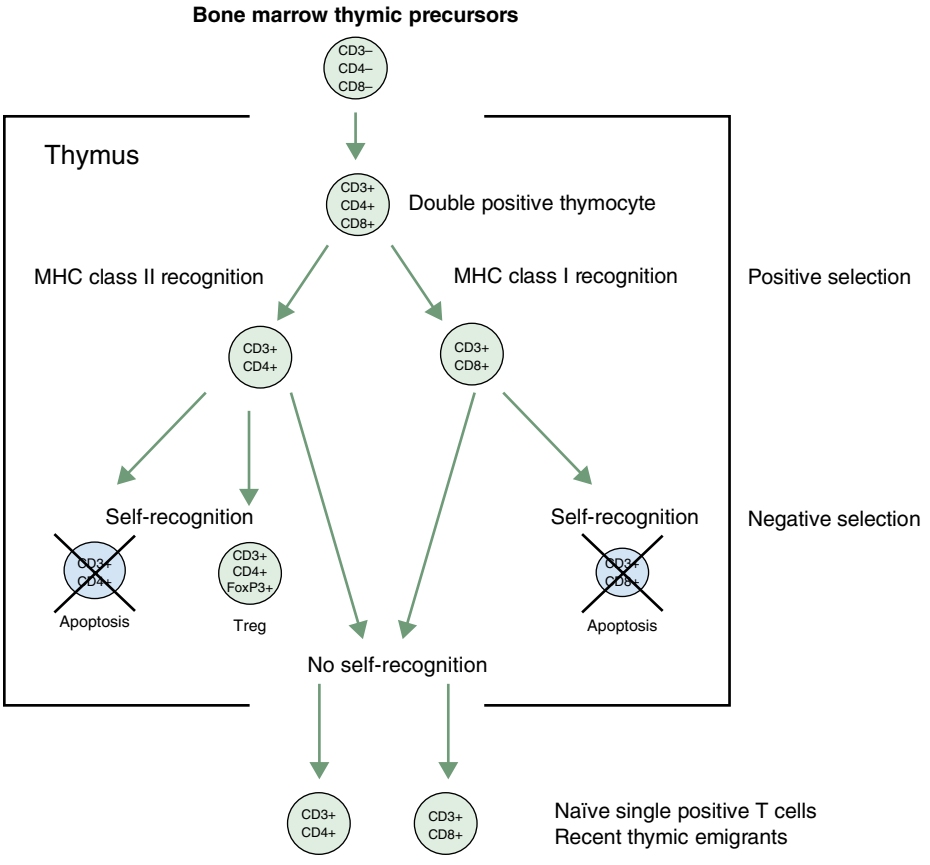

Fig. 165.1 Schematic representation of T-cell development in the thymus. Thymocyte precursors leave the bone marrow and enter the thymus with no expression of CD3, CD4, or CD8 (double negative T cells). Later the thymocytes express CD3 and both CD4 and CD8. If the newly formed T-cell receptor (TCR) recognizes major histocompatibility complex (MHC) class I or class II molecules, the thymocytes receive a positive selection signal and develop into CD8 or CD4 single positive thymocytes, respectively. Single positive thymocytes with TCR that recognize self-proteins will be killed by apoptosis or develop into regulatory T cells (Treg) to prevent autoimmune disease. Single positive thymocytes that are non–self-reactive leave the thymus as naïve single positive T cells ready to engage in the immune response when needed.

Table 165.1 Genetic Basis of Severe Combined Immunodeficiency and SCID Variants

DISEASE	INHERITANCE	PATHOGENESIS	ADDITIONAL FEATURES	TREATMENT
T^-B^- SCID				
Reticular dysgenesis	AR	Impaired mitochondrial energy metabolism and leukocyte differentiation	Severe neutropenia, deafness Pathogenic variants in adenylate kinase 2	GCSF, HSCT
Reticular dysgenesis	AD	Impaired hematopoiesis	Severe neutropenia but no deafness, gain-of-function variant in RAC2	HSCT
Adenosine deaminase deficiency	AR	Accumulation of toxic purine nucleosides	Neurologic, hepatic, renal, lung, skeletal, bone marrow abnormalities	HSCT, PEG-ADA, gene therapy
RAG1 and RAG2 deficiency	AR	Defective V(D)J recombination	None	HSCT
Artemis deficiency	AR	Defective V(D)J recombination, radiation sensitivity	*DCLERE1C* pathogenic gene variants	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, birdlike facies, bone defects	HSCT
T^-B^+ SCID				
γ_c (CD132) deficiency	XL	Abnormal signaling via γ_c-ILRs (IL-2, 4, 7, 9, 15, 21)	None	HSCT, gene therapy
Jak3 deficiency	AR	Abnormal signaling downstream of γ_c	None	HSCT
IL-7Rα deficiency	AR	Abnormal IL-7R signaling	Thymus absent	HSCT
CD45 deficiency	AR		None	HSCT
CD3δ deficiency	AR	Arrest of thymocytes differentiation at $CD4^-CD8^-$ stage	Thymus size may be normal	HSCT
CD3ε deficiency	AR	Arrest of thymocytes differentiation at $CD4^-CD8^-$ stage	γ/δ T cells absent	HSCT
CD3ζ deficiency	AR	Abnormal signaling	None	HSCT
Coronin-1A deficiency	AR	Abnormal T-cell egress from thymus and lymph nodes	Normal thymus size Attention deficit disorder	HSCT
LAT deficiency	AR	Defective T-cell development in the thymus	Autoimmune disease	HSCT
SLP76	AR	Abnormal signaling	Neutrophil defect, skin abscesses, rash, autoimmunity	HSCT attempted

γ_c, Common gamma chain; AD, Autosomal dominant; 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; R, receptor; RAG1, RAG2, recombinase-activating genes 1 and 2; SCID, severe combined immune deficiency; V(D)J, variable, diversity, joining domains; XL, X-linked.

Adapted from Roifman CM, Grunebaum E. Primary T-cell immunodeficiencies. In: Rich RR, Fleisher TA, Shearer WT, et al., eds. *Clinical Immunology*. 4th ed. Philadelphia: Saunders; 2013. pp. 440-441.

The 4 most common types of SCID are the X-linked forms caused by pathogenic variants in *CD132*, autosomal recessive *RAG1* and *RAG2* deficiencies, and adenosine deaminase (ADA) deficiency. Additional forms are listed in Table 165.1. For X-linked SCID and *ADA* deficiency, gene therapy exists, but genetic counseling is the most compelling reason for genetic sequencing to identify the pathogenic gene variant. Several specific pathogenic gene variants are associated with increased sensitivity to radiation and chemotherapy, and their early identification can lead to a better transplant experience by avoiding or reducing dosages of conditioning agents.

CLINICAL MANIFESTATIONS

SCID is included in the newborn screening program in all states in the United States and in several countries around the world. Thus infants can be identified and treated prior to development of symptoms, which has dramatically improved the survival of infants with SCID. A few genetic types of SCID are not detected by newborn screening, and there are many countries where newborn screening for SCID is not yet performed. Therefore an awareness of the clinical presentation of SCID remains important in the early diagnosis and treatment of patients.

When infants with SCID are not detected through newborn screening, they most often present with **infection** during infancy. Diarrhea, pneumonia, otitis media, sepsis, and cutaneous infections are common presentations. Infections with a variety of opportunistic organisms, either through direct exposure or immunization, can lead to death. Potential infectious threats include *Candida albicans, Pneumocystis jiroveci* (PJP), parainfluenza 3 virus, adenovirus, respiratory syncytial virus (RSV), cytomegalovirus (CMV), Epstein-Barr virus (EBV), varicella-zoster virus, measles virus, and attenuated organisms from the MMRV (measles, mumps, rubella, varicella), rotavirus, oral polio, nasal influenza, yellow fever, or bacille Calmette-Guérin (BCG) vaccines. Disseminated BCG infection may be the presenting feature of SCID in countries where the vaccine is given at birth. Infants with SCID 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 maternal immunocompetent T cells

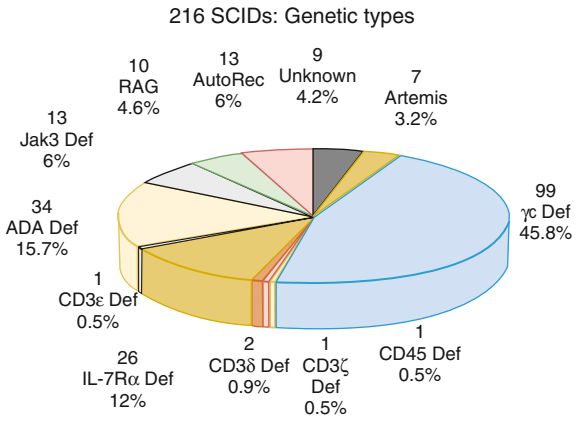

Fig. 165.2 Relative frequencies of the different genetic types of severe combined immunodeficiency (SCID) among 216 patients seen consecutively. *(From Buckley RH, Orange JS. Primary immunodeficiency diseases. In: Burks AW, Holgate ST, O'Hehir RE, et al., eds. Middleton's Allergy: Principles and Practice. 9th ed. Philadelphia: Elsevier; 2020. Fig. 69.2, p. 1126.)*

Fig. 165.3 Typical clinical features in an infant with Omenn syndrome. Note generalized erythroderma with scaly skin, alopecia, and edema. *(From Notarangelo LD. T cell immunodeficiencies. In: Leung DYM, Akdis CA, Bacharier LB, et al., eds. Pediatric Allergy Principles and Practice. 4th ed. Philadelphia: Elsevier; 2021. Fig 6.1.)*

that crossed the placenta during pregnancy. The latter is usually not fatal but can be severe. This devastating presentation is characterized by expansion of the allogeneic cells, rash, hepatosplenomegaly, and diarrhea. A third presentation is often called **Omenn syndrome**, caused by hypomorphic pathogenic variants in SCID-causing genes, which allow few T cells to be generated in the infant that then expand, unregulated, and cause a clinical picture similar to GVHD (Fig. 165.3) with a severe dermatitis, lymphadenopathy, and diarrhea. The difference in this case is that the cells are the infant's own cells. Dermatitis, especially if it is difficult to treat, failure to thrive, and infection in the first 6 months of life, particularly severe infections from commonly mild pathogens or opportunistic organisms, should raise the suspicion of SCID.

All genetic types of SCID are associated with profound immunodeficiency. A small number have other associated features or atypical features that are important to recognize. ADA deficiency can be associated with pulmonary alveolar proteinosis and chondroosseous dysplasia. Adenylate kinase 2 (AK2) deficiency causes a picture referred to as **reticular dysgenesis** where neutrophils, myeloid cells, and lymphocytes are all low. This condition is also often associated with deafness.

DIAGNOSIS

A high index of suspicion is very important in the diagnosis of SCID. A key feature of SCID is that almost all patients will have a low lymphocyte count. Some patients may have a normal lymphocyte count from proliferation of B cells and/or natural killer (NK) cells. A combination of infection and a persistently low lymphocyte count is an indication to test for SCID. The diagnostic strategy both for symptomatic infants and those detected by newborn screening or with a family history of SCID is to perform flow cytometry to quantitate the T, B, and NK cells in the infant (Fig. 165.4). The CD45RA (naïve T-cell) and CD45RO (memory T-cell) markers can be helpful to identify patients with maternal engraftment or Omenn syndrome with predominantly memory T cells. Identification of a limited TCR repertoire is also helpful in the diagnosis of Omenn syndrome. T-cell function is often assessed by measuring proliferative responses to stimulation with mitogens.

Gene sequencing is often done by requesting a SCID gene panel or a more extensive primary immunodeficiency (PID) gene panel. There are certain laboratory features that predict specific gene defects. When both T and B cells are low with normal numbers of NK cells, often a gene encoding a protein involved in V(D)J recombination is the cause such as *RAG1* and *2*. Similarly, certain cytokine receptor defects are associated with specific SCID lymphocyte phenotypes, such as absent T cells and NK cells, but normal or elevated numbers of B cells in X-SCID caused by pathogenic variants in the common gamma chain (CD132) of cytokine receptors. Pathogenic variants in Janus kinase *(JAK)3*, which signal downstream of CD132, cause an autosomal recessive form of SCID affecting both females and males, with an identical lymphocyte phenotype as X-SCID.

The diagnosis of SCID can be established by the presence of a known pathogenic gene variant, low T-cell counts with proliferative response to the mitogen phytohemagglutinin (PHA) less than 10% of a normal control, or the identification of maternal T cells in the child. In male infants, this can be determined by fluorescence in situ hybridization (FISH) for the X and Y chromosomes.

Newborn Screening

Newborn screening for SCID has allowed the early diagnosis and treatment of SCID, improving the outcome of therapy and changing the natural history of the disease. Newborn screening is based on quantitative polymerase chain reaction (PCR) of T-cell receptor excision circles (TRECs), which are formed during V(D)J rearrangement of the variable region of the TCR chains. These TRECs do not replicate during cell division; they are thus present in most or all recent thymic emigrants but get diluted out as T cells divide in the periphery. The TREC assay identifies low numbers of recent thymic emigrants, which is not diagnostic of SCID, but raises suspicion to proceed with an evaluation of lymphocyte subsets and function followed by confirmation with genetic testing. Other diseases with low T-cell counts may also be identified by newborn screening and include 22Q11.2 deletion syndrome, Rac2 deficiency, trisomy 21, and idiopathic lymphopenia, which was not well appreciated until newborn screening was implemented. In many countries, kappa excision circles (KRECs), generated during B-cell development, are assayed simultaneously with TRECs allowing a larger number of types of SCID to be identified as well as allowing identification of infants with agammaglobulinemia.

TREATMENT

SCID is a true pediatric immunologic emergency. Unless immunologic reconstitution is achieved through hematopoietic stem cell transplantation (HSCT) or gene therapy, death usually occurs during the first year of life and almost invariably before 2 years of age. HSCT in the first 100 days of life or in an infant prior to infection is associated with a 95% survival rate. In 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, although T-cell reconstitution is improved with pretransplant conditioning including reduced-intensity protocols.

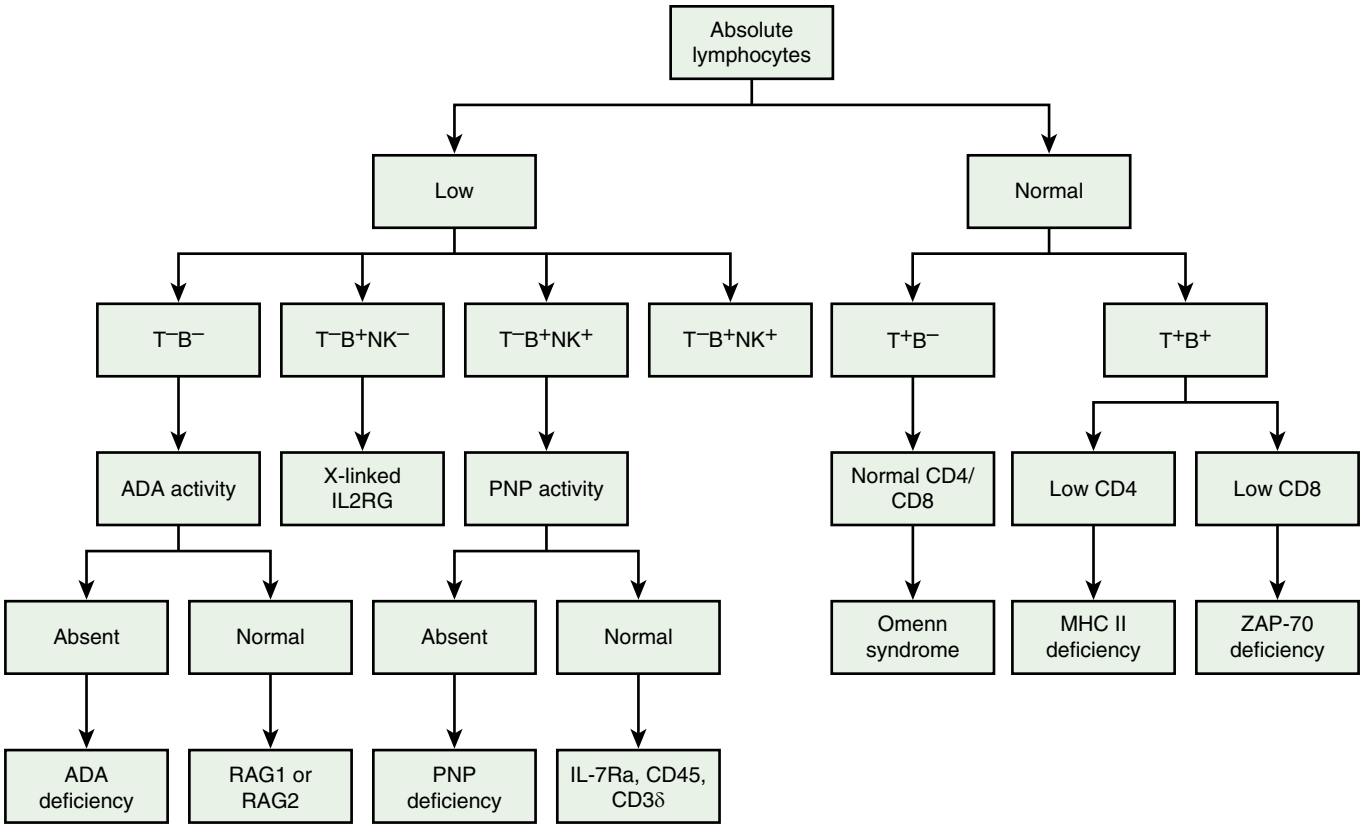

Fig. 165.4 Using the absolute lymphocytes count as a starting place to suggest the type of severe combined immunodeficiency (SCID) that may be present. ADA, Adenosine deaminase; MHC, major histocompatibility complex; PNP, purine nucleoside phosphorylase. *(From Cunningham-Rundles C. Approach to the child with recurrent infections and molecular diagnosis. In: Leung DYM, Akdis CA, Bacharier LB, et al., eds. Pediatric Allergy Principles and Practice. 4th ed. Philadelphia: Elsevier; 2021. Fig. 4.2.)*

Bone marrow transplantation remains the most important and effective therapy for SCID. In ADA-deficient and X-linked SCID, there has been success in correcting the immune defects with ex vivo gene transfer to autologous hematopoietic stem cells. Initial protocols of gene therapy for X-linked SCID resulted in **insertional mutagenesis** with the development of leukemic-like clonal T cells or lymphoma in some patients. Modification of the gene therapy protocol has greatly reduced the risk of insertional mutagenesis. ADA-deficient SCID can also be treated with enzyme replacement by repeated injections of polyethylene glycol-ADA (PEG-ADA), although the immune reconstitution achieved is not as effective as with HSCT or gene therapy. Until definitive therapy can be achieved, SCID patients should be treated with supportive care for prevention and treatment of infections with immunoglobulin replacement and microbial prophylaxis starting at 4-6 weeks of age including PJP prophylaxis as well as viral and fungal prophylaxis. Breastfeeding should be avoided if the mother is CMV or EBV positive as infection can be transmitted via breast milk.

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165.2 Combined Immunodeficiencies

Ramsay L. Fuleihan

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

Studies of cellular immune function may show lymphopenia, deficiencies of T cells, specific T-cell subsets, or switched memory B cells, and extremely low but not absent lymphocyte proliferative responses to mitogens, antigens, or allogeneic cells in vitro. Peripheral lymphoid tissues may demonstrate paracortical lymphocyte depletion. The thymus is usually small, with a paucity of thymocytes and usually no Hassall's corpuscles.

There is a large number and variety of CIDs caused by pathogenic variants in many different genes. A list of known causes of CID with some of their characteristic features can be found in Tables 165.2 to 165.7.

COMBINED IMMUNODEFICIENCIES THAT ARE GENERALLY LESS PROFOUND THAN SCID

Several types of CID are characterized by a severe immunodeficiency but affected patients tend to survive longer than patients with SCID (see Table 165.2). These patients are susceptible to severe viral, opportunistic, and/or fungal infections. Their laboratory features are variable from normal lymphocyte subsets to a severe deficiency of CD4, CD8, or both cell types. Invariably, T-cell function is decreased but proliferative responses to mitogens and, in some cases, to antigens may be normal, making it difficult to have unifying laboratory characteristics for this group of diseases. The severity of clinical infection and/or the presence of a family history of CID should raise suspicion and initiate a laboratory evaluation for these diseases.

COMBINED IMMUNODEFICIENCY FROM DEFICIENCY IN CD4 T-CELL HELPER FUNCTION

CD4 T cells play an important role in orchestrating the immune response. Helper function from CD4 T cells is critical for immunoglobulin isotype switching, somatic hypermutation, and B-cell memory

Table 165.2 Combined Immunodeficiencies Generally Less Profound Than SCID

DISEASE (DEFICIENCY)	INHERITANCE	PATHOGENESIS	ADDITIONAL FEATURES	TREATMENT
CD40 Ligand (CD154)	XL	Defective CD40 ligand:CD40 signaling	Opportunistic infections, neutropenia, biliary tract and liver disease/cancer, neuroectodermal cancer	HSCT
CD40	AR	Defective CD40 ligand:CD40 signaling	Opportunistic infections, neutropenia, biliary tract and liver disease	HSCT
ICOS	AR		Autoimmunity, gastroenteritis, granulomas	
ICOS Ligand	AR	Decreased T and B cells	Neutropenia	
CD3γ	AR	Low TCR expression	Autoimmunity of variable severity	
CD8	AR	Absent CD8 T cells	May be asymptomatic	
ZAP-70 LOF	AR	Low CD8 T cells, poor CD4 T-cell function	May have immune dysregulation, autoimmunity	HSCT
ZAP-70 LOF/GOF	AR	Low CD8 T cells	Severe autoimmunity, bullous pemphigoid, inflammatory colitis	HSCT
MHC class I (TAP1, TAP2, TAPBP, β_2-microglobulin)	AR	Low CD8 T cells, absent MHC I on lymphocytes and thymic epithelium	Vasculitis, pyoderma gangrenosum	
MHC class II (CIITA, RFX5, RFXANK, RFXAP)	AR	Low CD4 T cells absent MHC II on lymphocytes and thymic epithelium	Failure to thrive, liver biliary tract disease	HSCT
IKAROS	AD	No memory T cells or B cells	Opportunistic infections, early CID onset	
DOCK2	AR	Low T cells and poor NK cell function	Invasive herpesvirus infections, poor interferon responses	
Polymerase and (POLD1, POLD2)	AR	Low CD4 T cells	Skin infections, warts and molluscum, short stature, intellectual disability	
RHOH	AR	Restricted TCR repertoire	HPV infection, lung granulomas, molluscum, lymphoma	
STK4	AR	Low CD4 T cells	Intermittent neutropenia, viral and *Candida* infection, lymphoproliferation, autoimmune cytopenias, lymphoma, congenital heart disease	
TCRα	AR	Absent TCRαβ	Immune dysregulation, autoimmunity, diarrhea	
LCK	AR	Poor TCR signaling, low CD4 T cells and low regulatory T cells, restricted TCR repertoire	Immune dysregulation, autoimmunity	
ITK	AR	Decreased T-cell activation, progressive decline in CD4 T cells	EBV-associated B-cell lymphoproliferation, immune dysregulation	
MALT1	AR	Poor T-cell proliferation		
CARD11 LOF	AR	Poor T-cell proliferation	Opportunistic infections	
BCL10	AR	Poor T-cell antigen or anti-CD3 proliferation, few memory T cells and Tregs	Candidiasis, gastroenteritis	
IL-21	AR	Low T-cell function, low memory/switched B cells	Opportunistic infections, liver disease	
IL-21R	AR	Low cytokine production, low T-cell antigen proliferation		
OX40	AR	Low Ag-specific memory CD4 T cells	Impaired immunity to HHV8, Kaposi's sarcoma	
IKBKB	AR	Impaired TCR activation, absent Treg and γ/δ T cells	Opportunistic infections	HSCT
NIK	AR	Poor T-cell antigen proliferation, low switched memory B cells	*Cryptosporidium* infection	
RelB	AR	Reduced TCR diversity with poor proliferation to mitogens and absent to antigens		

Continued

Table 165.2 Combined Immunodeficiencies Generally Less Profound Than SCID—cont'd

DISEASE (DEFICIENCY)	INHERITANCE	PATHOGENESIS	ADDITIONAL FEATURES	TREATMENT
RelA haploinsufficiency	AD	Impaired NFκB activation with decreased inflammatory cytokines	Chronic mucocutaneous ulceration	
Moesin	XL	Defective T-cell migration and proliferation	Varicella infections, neutropenia	
TFRC	AR	Poor T-cell proliferation, low memory B cells	Neutropenia, thrombocytopenia	
c-Rel	AR	Poor T- and B-cell proliferation, low memory CD4 and low memory B cells	*Mycobacteria* and *Salmonella* infections, opportunistic infections, defective innate immunity	
FCHO1	AR	Poor T-cell proliferation	Mycobacterial infections, lymphoproliferation, failure to thrive	

Ag, antigen; AD, Autosomal dominant; AR, autosomal recessive; CID, combined immune deficiency; EBV, Epstein-Barr virus; HHV8, human herpesvirus-8; HPV, human papillomavirus; HSCT, hematopoietic stem cell transplantation; IL, interleukin; GOF, gain of function; LOF, loss of function; MHC, major histocompatibility complex; NK, natural killer; R, receptor; TCR, T-cell receptor; Treg, regulatory T cell; XL, X-linked.
Adapted from Tangye SG, Al-Herz W, Bousfiha A, et al. Human inborn errors of immunity: 2022 update on the classification from the International Union of Immunological Societies Expert Committee. *J Clin Immunol* 2022;42:1473–1507.

Table 165.3 DNA Repair Defects Other Than Causing SCID

DISEASE	GENE	INHERITANCE	PATHOGENESIS	ADDITIONAL FEATURES	TREATMENT
Ataxia-telangiectasia	*ATM*	AR	Progressive decrease in T cells, poor T-cell proliferation	Ataxia, telangiectasia, elevated IgM, lymphoreticular malignancy, increased radiosensitivity, chromosomal instability and translocations	Ig replacement, supportive care, avoid ionizing radiation
Nijmegen breakage syndrome	*NBS1*	AR	Progressive decrease in T cells	Microcephaly, dysmorphic features, lymphomas and solid tumors, hyper-IgM	Ig replacement, supportive care, avoid ionizing radiation
Bloom syndrome	*BLM*	AR	Marrow failure, low Ig	Short stature, dysmorphic facies, sun-sensitive erythema, leukemia, lymphoma, chromosomal instability	Ig replacement, supportive care, avoid ionizing radiation
Immunodeficiency with centromeric instability and facial anomalies (ICF types 1, 2, 3, 4)	*DNMT3B* *ZBTB24* *CDCA7* *HELLS*	AR	Decreased T cells, decreased response to PHA, hypogammaglobulinemia with variable antibody deficiency	Facial dysmorphism, developmental delay, macroglossia, opportunistic infections, malabsorption, cytopenias, malignancies, multiradial configurations of chromosomes 1, 9, 16	Ig replacement, supportive care, avoid ionizing radiation
PMS2 deficiency	*PMS2*	AR	Low B cells, abnormal antibody responses	Café-au-lait spots, hyper-IgM, lymphoma, colorectal carcinoma, brain tumors	Ig replacement, supportive care, avoid ionizing radiation
Radiosensitivity, immune deficiency, dysmorphic features, learning difficulties (RIDDLE) syndrome	*RNF168*	AR	Low IgG or IgA	Short stature, mild defects of motor control to ataxia, may have learning difficulties	Ig replacement, supportive care, avoid ionizing radiation
MCM4 deficiency	*MCM4*	AR	Low number and function of NK cells	Short stature, B-cell lymphoma, adrenal failure	Supportive care, avoid ionizing radiation
Polymerase ε subunit 1 deficiency (FILS syndrome)	*POLE1*	AR	Decreased T-cell proliferation	Short stature, facial dysmorphism, livedo	Ig replacement, supportive care, avoid ionizing radiation

Continued

Table 165.3 DNA Repair Defects Other Than Causing SCID—cont'd

DISEASE	GENE	INHERITANCE	PATHOGENESIS	ADDITIONAL FEATURES	TREATMENT
Polymerase ε subunit 2 deficiency	*POLE2*	AR	Lymphopenia, absent T-cell proliferation to Ags, hypogammaglobulinemia	Disseminated BCG, autoimmunity (type 1 diabetes), hypothyroidism, facial dysmorphism	Ig replacement, supportive care, avoid ionizing radiation
Ligase 1 deficiency	*LIG1*	AR	Lymphopenia, increased γ/δ T cells, decreased T-cell proliferation, hypogammaglobulinemia antibody deficiency	Growth restriction, sun sensitivity, radiation sensitivity, macrocytic RBC	Ig replacement, supportive care, avoid ionizing radiation
NSMCE3 deficiency	*NSMCE3*	AR	Decreased T cells and T-cell response to mitogens and antigens	Thymic hypoplasia, severe lung disease, chromosomal breakage, radiation sensitivity	Ig replacement, supportive care, avoid ionizing radiation
ERCC6L2 deficiency	*ERCC6L2*	AR	Lymphopenia	Facial dysmorphism, microcephaly, bone marrow failure	Supportive care, avoid ionizing radiation
GINS1 deficiency	*GINS1*	AR	Low NK cells, high IgA with low IgM and IgG	Neutropenia, IUGR	Supportive care, avoid ionizing radiation

Ag, Antigen; AR, Autosomal recessive; BCG, bacilli Calmette-Guérin; FILS, facial dysmorphism, immunodeficiency, livedo, and short stature; ICF, instability, centromeric, facial anomalies; Ig, immunoglobulin; IUGR, intrauterine growth retardation; NK, natural killer; PHA, phytohemagglutinin; RBC, red blood cell.
Adapted from Tangye SG, Al-Herz W, Bousfiha A, et al. Human inborn errors of immunity: 2022 update on the classification from the International Union of Immunological Societies Expert Committee. *J Clin Immunol* 2022;42:1473–1507.

Table 165.4 Immunoosseous Dysplasias

DISEASE	GENE	INHERITANCE	PATHOGENESIS	ADDITIONAL FEATURES	TREATMENT
Cartilage hair hypoplasia	*RMRP*	AR	Normal to severely decreased T-cell counts Decreased T-cell proliferation	Short-limbed dwarfism with metaphyseal dysostosis, sparse hair, bone marrow failure, autoimmunity, susceptibility to lymphoma and other cancers, impaired spermatogenesis, neuronal dysplasia of the intestine	HSCT for the immunodeficiency
Schimke immuno-osseous dysplasia	*SMARCAL1*	AR	Decreased T cells	Short stature, spondyloepiphyseal dysplasia, intrauterine growth restriction; nephropathy; bacterial, viral, fungal infections; may present as SCID; bone marrow failure	HSCT for the immunodeficiency
MYSM1 deficiency	*MYSM1*	AR	Decreased T cells, naïve T cells, and NK cells B-cell deficiency with hypogammaglobulinemia	Short stature; recurrent infections; congenital bone marrow failure, myelodysplasia; immunodeficiency affecting B cells and granulocytes; skeletal anomalies; cataracts; developmental delay	HSCT for the immunodeficiency
MOPD1 deficiency (Roifman syndrome)	*RNU4ATAC*	AR	Decreased NK cell function Decreased total and memory B cells Hypogammaglobulinemia, variably decreased specific antibodies	Recurrent bacterial infections; lymphadenopathy; spondyloepiphyseal dysplasia, extreme intrauterine growth restriction; retinal dystrophy; facial dysmorphism; may present with microcephaly; short stature	HSCT for the immunodeficiency
Immunoskeletal dysplasia with neurodevelopmental abnormalities (*EXTL3* deficiency)	*EXTL3*	AR	Decreased T cells, decreased to normal Ig levels	Short stature; cervical spinal stenosis, neurodevelopmental impairment; eosinophilia; may have early infant mortality	HSCT for the immunodeficiency

AR, Autosomal recessive; HSCT, hematopoietic stem cell transplantation; Ig, immunoglobulin; NK, natural killer; SCID, severe combined immune deficiency.
Adapted from Tangye SG, Al-Herz W, Bousfiha A, et al. Human inborn errors of immunity: 2022 update on the classification from the International Union of Immunological Societies Expert Committee. *J Clin Immunol* 2022;42:1473–1507.

Table 165.5 Other Combined Immunodeficiencies

DISEASE	GENE	INHERITANCE	PATHOGENESIS	ADDITIONAL FEATURES	TREATMENT
PNP deficiency	*PNP*	AR	Progressive decrease in T cells	Autoimmune hemolytic anemia, neurologic impairment	HSCT
Immunodeficiency with multiple intestinal atresias	*TTC7A*	AR	Variable T-cell counts but may be as low as SCID with low TRECs at NBS	Multiple intestinal atresias, intrauterine polyhydramnios, early demise, bacterial (sepsis), viral and fungal infections	HSCT for severe T-cell deficiency
Trichohepatoenteric syndrome (THES)	*TTC37* *SKIV2L*	AR	Impaired IFNγ production, variably low switched memory B cells, hypogammaglobulinemia, may have low antibody responses	Respiratory infections; IUGR; facial dysmorphic features, wooly hair; early-onset intractable diarrhea, liver cirrhosis; platelet abnormalities	
Hepatic venoocclusive disease with immunodeficiency (VODI)	*SP110*	AR	Decreased memory T and B cells; low IgG, IgA, and IgM; absent germinal centers and tissue plasma cells	Hepatic venoocclusive disease Susceptibility to opportunistic infections: PJP, CMV, *Candida* Thrombocytopenia, hepatosplenomegaly, cerebrospinal leukodystrophy	
BCL11B deficiency	*BCL11B*	AD	Decreased T-cell counts with poor proliferation	Congenital abnormalities, neonatal teeth, dysmorphic facies; absent corpus callosum, neurocognitive deficits	
EPG5 deficiency (Vici syndrome)	*EPG5*	AR	Very low CD4 T cells, decreased Ig levels especially IgG2, defective B cells	Chronic mucocutaneous candidiasis, recurrent infections, agenesis of the corpus callosum, microcephaly, cataracts; cardiomyopathy, skin hypopigmentation, intellectual disability	
HOIL1 deficiency	*RBCK1*	AR	Decreased memory B cells with poor antibody response to polysaccharide antigens	Bacterial infections, autoinflammation, amylopectinosis	
HOIP deficiency	*RNF31*	AR	Decreased memory B cells with decreased Ig levels	Bacterial infections, autoinflammation, amylopectinosis, lymphangiectasia	
Hennekam lymphangiectasia-lymphedema syndrome	*CCBE1 FAT4*	AR	Variably decreased T- and B-cell counts, decreased Ig levels	Facial anomalies and other dysmorphic features, lymphangiectasia and lymphedema	
Activating de novo mutations in nuclear factor, erythroid 2-like (NFE2L2)	*NFE2L2*	AD	Decreased switched memory B cells, hypogammaglobulinemia and decreased antibody responses	Recurrent respiratory and skin infections; growth restriction, developmental delay; white matter cerebral lesions; increased level of homocysteine; increased expression of stress response genes	
STAT5b deficiency	*STAT5B*	AR	Slightly decreased T cells, decreased Treg number and function, hypogammaglobulinemia with elevated IgE	Growth-hormone insensitive dwarfism, dysmorphic features, eczema, lymphocytic interstitial pneumonitis, autoimmunity	
STAT5b deficiency	*STAT5B*	AD (dominant negative variants)	Increased IgE	Growth failure, eczema, lack immune defects of AR STAT5b deficiency	
Kabuki syndrome (type 1 and 2)	*KMT2D* *KDM6A*	AD XL (females may be affected)	Low IgA, occasionally low IgG	Typical facial abnormalities, cleft or high arched palate, skeletal abnormalities, short stature; intellectual disability; congenital heart defects; recurrent infections (otitis media, pneumonia); autoimmunity	

Continued

Table 165.5 Other Combined Immunodeficiencies—cont'd

DISEASE	GENE	INHERITANCE	PATHOGENESIS	ADDITIONAL FEATURES	TREATMENT
KMT2A deficiency (Wiedemann-Steiner syndrome)	*KMT2A*	AD	Decreased memory B cells, hypogammaglobulinemia with decreased antibody responses	Respiratory infections; short stature; hypertelorism; hairy elbows; developmental delay, intellectual disability	

AD, Autosomal dominant; AR, Autosomal recessive; CMV, cytomegalovirus; HSCT, hematopoietic stem cell transplantation; IFN, interferon; Ig, immunoglobulin; IUGR, intrauterine growth retardation; NBS, newborn screening; PJP, *Pneumocystis jiroveci*; PNP, purine nucleoside phosphorylase; SCID, severe combined immune deficiency; TREC, T-cell receptor excision circle; Treg, regulatory T cells; XL, X-linked.
Adapted from Tangye SG, Al-Herz W, Bousfiha A, et al. Human inborn errors of immunity: 2022 update on the classification from the International Union of Immunological Societies Expert Committee. *J Clin Immunol* 2022;42:1473–1507.

Table 165.6 Thymic Disorders

DISEASE	GENE	INHERITANCE	PATHOGENESIS	ADDITIONAL FEATURES	TREATMENT
DiGeorge/Velocardio-facial syndrome/ chromosome 22Q11.2 deletion syndrome *TBX1* deficiency	22Q11.2del including *TBX1, TBX1* Unknown	AD (Unknown defects are sporadic)	Variable T-cell counts, may have low TRECs at NBS, may have hypogammaglobulinemia	Conotruncal cardiac defects, hypoparathyroidism, abnormal facies, velopalatal insufficiency, intellectual disability, autoimmunity	Thymic transplant for severe T-cell deficiency
CHARGE syndrome	*CHD7* *SEMA3E* Unknown	AD AD	Variable T-cell counts, may have low TRECs at NBS, may have hypogammaglobulinemia	Coloboma of eye; heart anomaly; choanal atresia; intellectual disability; genital and ear anomalies (CHARGE), CNS malformation	Thymic transplant for severe T-cell deficiency
Winged helix nude *FOXN1* deficiency	*FOXN1*	AR	Very low T cells, decreased Ig levels	Severe infections, abnormal thymic epithelium, congenital alopecia, nail dystrophy, neural tube defect	Thymic transplant attempted
FOXN1 haploinsufficiency	*FOXN1*	AD	Severe T-cell lymphopenia at birth, normal by adulthood	Recurrent, viral and bacterial respiratory tract infections; (eczema, dermatitis), nail dystrophy	
Chromosome 10p13-p14 deletion syndrome (10p13-p14DS)	10p13-p14del	AD	T-cell lymphopenia rarely with decreased proliferation to mitogens and antigens, may have hypoplastic thymus	Hypoparathyroidism, renal disease, deafness, growth retardation, facial dysmorphism, cardiac defects may be present, may have recurrent infections	
Chromosome 11q deletion syndrome (Jacobsen syndrome)	11q23del	AD	T-, B-, and NK cell lymphopenia, low switched memory B cells, variable Ig levels and antibody responses	Recurrent respiratory infections; multiple warts; facial dysmorphism, growth retardation	Ig replacement for antibody deficiency
PAX1	*PAX1*	AR	Absent thymus	Omenn-like syndrome	HSCT attempted, thymic transplantation attempted

AD, Autosomal dominant; AR, Autosomal recessive; del, deletion; CNS, central nervous system; HSCT, hematopoietic stem cell transplantation; TREC, T-cell receptor excision circle; NBS, newborn screening; Ig, immunoglobulin.
Adapted from Tangye SG, Al-Herz W, Bousfiha A, et al. Human inborn errors of immunity: 2022 update on the classification from the International Union of Immunological Societies Expert Committee. *J Clin Immunol* 2022;42:1473–1507.

Table 165.7 Hyper IgE Syndromes

DISEASE	GENE	INHERITANCE	PATHOGENESIS	ADDITIONAL FEATURES	TREATMENT
HIE (Job syndrome)	*STAT3*	AD (DN LOF)	Decreased response to *STAT3*-activating cytokines; decreased Th17, T follicular helper, MAIT, NKT cells, reduced memory B cells, elevated IgE	Coarse facial features, broad nasal bridge; staphylococcal abscesses, eczema, pneumatoceles, pulmonary *Aspergillus,* PJP, mucocutaneous candidiasis; hyperextensible joints, osteoporosis and bone fractures, scoliosis, retained primary teeth; coronary and cerebral aneurysms	Bacterial and fungal prophylaxis
DOCK8 deficiency	*DOCK8*	AR	T-cell lymphopenia with poor proliferation, few Tregs with poor function, reduced MAIT and NKT cells, very high IgE	Low NK cells with poor function Eosinophilia, recurrent infections, cutaneous viral, fungal and staphylococcal infections, severe atopy/allergic disease, cancer diathesis	HSCT
IL-6 receptor deficiency	*IL6R*	AR	Decreased switched memory B cells, very high IgE	Recurrent pyogenic infections, cold abscesses, elevated IL-6 levels	Bacterial prophylaxis
IL-6 signal transducer (IL6ST) deficiency	*IL6ST*	AR	Decreased Th17 cells, reduced memory B cells, high IgE, variable antibody responses	Bacterial infections, abscesses, eczema, pulmonary abscesses, pneumatoceles; bone fractures; scoliosis; retention of primary teeth; craniosynostosis	Bacterial prophylaxis
IL6ST	*IL6ST*	AD (DN)	Increased Th2, naïve T cells, low memory T and B cells, low to normal NK cell counts, elevated IgE with normal or low IgG	Similar to AD HIE syndrome: dermatitis/eczema, eosinophilia, recurrent skin infections, pneumonia, bronchiectasis, pneumatoceles, pulmonary aspergillosis, connective tissue defects (scoliosis, face, joints, fractures, palate, tooth retention)	Bacterial and fungal prophylaxis
IL6ST	*IL6ST*	AR (LOF)	Death in utero or in neonatal period	Fatal Stuve-Wiedemann-like syndrome; skeletal dysplasia, lung dysfunction, renal abnormalities, thrombocytopenia, dermatitis, eczema, defective acute phase response, complete unresponsiveness to IL-6 family cytokines	None
ZNF341 deficiency	*ZNF341*	AR	Decreased Th17 and NK cells, reduced memory B cells, decreased response to *STAT3*-activating cytokines	Similar to AD-HIE: mild facial dysmorphism; early-onset eczema, mucocutaneous candidiasis, bacterial skin infections, *Staphylococcus aureus* abscesses, recurrent bacterial respiratory infections, pneumatoceles; hyperextensible joints; bone fractures and retention of primary teeth	Bacterial and fungal prophylaxis
ERBIN deficiency	*ERBB2IP*	AD	Increased Treg, moderate increased IgE	Susceptibility to *S. aureus,* eczema, recurrent respiratory infections, hyperextensible joints, scoliosis, arterial dilatation in some patients	Bacterial prophylaxis
Loeys-Dietz syndrome	*TGFBR1, TGFBR2*	AD	Elevated IgE	Recurrent respiratory infections; eczema, food allergies; hyperextensible joints, scoliosis, retention of primary teeth; aortic aneurysms	Bacterial prophylaxis
Comèl-Netherton syndrome	*SPINK5*	AR	Low memory B cells, elevated IgE and IgA, variable antibody responses	Congenital ichthyosis, bamboo hair, atopic diathesis, bacterial infections, failure to thrive	Bacterial prophylaxis; Ig replacement for antibody deficiency
PGM3 deficiency	*PGM3*	AR	May have low T cells, B cells, memory B cells, normal or elevated IgG, IgA, and high IgE, eosinophilia	Severe atopy; autoimmunity; bacterial and viral infections; short stature, brachydactyly, dysmorphic facial features; intellectual disability and cognitive impairment, delayed CNS myelination in some patients	
CARD11 deficiency	*CARD11 DN LOF*	AD	Defective T-cell activation and proliferation, high IgE, Th2 skewing, poor specific antibody production, impaired activation of the NF-κB and mTORC1 pathways	Variable atopy, eczema, food allergy, eosinophilia; cutaneous viral infections, recurrent respiratory infections; lymphoma; CID	Ig replacement for antibody deficiency

AD, Autosomal dominant; AR, Autosomal recessive; CID, combined immunodeficiency; CNS, central nervous system; DN, dominant negative; HIE, hyper-IgE; Ig, immunoglobulin; IL, interleukin; IL6ST, gp130 common signal transducer of the IL-6 cytokine family; LOF, loss of function; MAIT, mucosal-associated invariant T cells; NKT, natural killer T cells; PJP, *Pneumocystis jiroveci*; Th, T helper; Treg, regulatory T cells.

Adapted from Tangye SG, Al-Herz W, Bousfiha A, et al. Human inborn errors of immunity: 2022 update on the classification from the International Union of Immunological Societies Expert Committee. *J Clin Immunol* 2022;42:1473–1507.

formation as well as helping macrophages kill intracellular pathogens. In addition, patients with poor or absent CD4 T-cell helper function are susceptible to opportunistic infection. The consequences of defects in CD40 ligand and CD40 highlight the role CD4 T-cell–dependent helper function plays in immunity.

CD40 LIGAND AND CD40 DEFICIENCY

CD40 ligand (CD154) deficiency (X-linked) and similarly, CD40 deficiency (autosomal recessive), cause a severe form of **hyper-IgM syndrome** that is a CID.

Genetics and Pathogenesis

Pathogenic variants in the CD40 ligand or CD40 genes, disrupt the interaction between CD4 T cells and antigen-presenting cells (APCs): dendritic cells, monocytes/macrophages, and B cells. CD40 ligand is expressed on activated CD4 T cells and delivers signals to APC via CD40 to stimulate expression of co-stimulatory molecules that help T-cell activation and differentiation, immunoglobulin isotype switching and somatic hypermutation in B cells as well as memory B-cell development, and signals to macrophages to kill intracellular pathogens. Therefore disruption of the CD40 signaling pathway affects several key elements of the adaptive immune response leading to a CID disease characterized by failure of immunoglobulin isotype switching, a process important for synthesis of IgG, IgA, and IgE antibodies; failure of somatic hypermutation, a process by which B cells generate antibodies of higher affinity; and absent B-cell memory, susceptibility to opportunistic infections including PJP, and *Cryptosporidium* and enhanced susceptibility to some cancers especially of the liver or of neuroectodermal origin.

Clinical Manifestations

Recurrent and opportunistic infections usually develop in the first year of life. About half the patients present with PJP pneumonia. Recurrent bacterial sinopulmonary infections are also common as well as *Cryptosporidium* infection and sclerosing cholangitis. Chronic or recurrent neutropenia is also a feature of this disease, although the pathogenesis of neutropenia is not well known. Patients have a higher susceptibility to cancer of the liver or biliary tree as well as primitive neuroectodermal carcinoma, which usually develop after the first 10 years of life. Few patients survive beyond 30 years of age. Some patients with milder genetic variations present in adolescence with parvovirus-induced aplastic anemia.

Diagnosis

Serum immunoglobulin levels show very low or absent IgG, IgA, and IgE, with normal or elevated IgM. Some patients have normal serum IgA levels, likely the result of a non–CD40-dependent isotype switching mechanism. The term hyper-IgM is a misnomer because most patients are identified before they have elevation of serum IgM levels. Lymphocyte subsets as well as lymphocyte proliferation to mitogens are usually normal. Characteristically, there is an absence or paucity of switched memory B cells. Patients may or may not have neutropenia, which can be severe. Flow cytometry for expression of CD40 on resting B cells or CD40 ligand on activated T cells can identify patients with these defects. Staining for CD40 ligand expression with soluble CD40 will identify all CD40 ligand variants that prevent binding to CD40. Gene sequencing of CD40 and CD40 ligand can be done separately or within a larger PID gene panel with known pathogenic variants confirming the disease.

Treatment

Patients should be treated with immunoglobulin replacement therapy and PJP prophylaxis as soon as the diagnosis is suspected. Attention to hygiene and clean drinking water as well as avoiding swimming in lakes will help prevent exposure to opportunistic organisms such as *Cryptosporidium*. HSCT can be curative and is recommended if the patient has a matched related or unrelated donor. Outcomes after stem cell transplantation have a trend toward improved survival and a reduced risk for cancer and improved quality of life.

MHC CLASS II DEFICIENCY AND OTHER CAUSES OF CD4 T-CELL DEFICIENCY

MHC class I and II molecules play an important role in T-cell development and function by presenting a peptide fragment from a pathogen-derived protein to the TCR of CD8 or CD4 T cells, respectively. MHC class II molecules are required for processing and presentation of peptides derived from exogenous antigens to CD4 T cells and for positive selection of CD4 T cells in the thymus. Therefore MHC class II deficiency is a severe form of **bare lymphocyte syndrome** resulting in decreased CD4 T cells and impairment in their function.

Clinical Manifestations

Patients with low, or occasionally normal, CD4 T-cell numbers from MHC class II deficiency are susceptible to bacterial, viral, fungal, and opportunistic infections. Patients usually present in the first year of life with respiratory infections, chronic diarrhea, and failure to thrive. *Cryptosporidium* infections may be associated with sclerosing cholangitis and liver failure.

Genetics and Pathogenesis

MHC class II deficiency results from defects in genes encoding for transcription factors necessary for expression of MHC class II molecules from the HLA-DR, HLA-DP, and HLA-DQ loci including CIITA, RFXANK, RFX5, and RFXAP, which explains the concomitant loss of expression from all three loci.

Diagnosis

Immunodeficiencies with MHC class II deficiency can be identified by absent or low CD4 T cells on lymphocyte phenotyping by flow cytometry and absent MHC class II molecules. In some cases, CD8 T-cell numbers are also decreased. Lymphocyte proliferation to mitogens is normal but absent in response to antigens.

Treatment

The prognosis for MHC class II deficiency is poor with most patients dying in the first decade of life. HSCT has been performed and improves CD4 T-cell proliferation but not numbers because it does not correct the expression of MHC class II molecules on thymic epithelial cells. The outcome of HSCT in MHC class II deficiency is not as good as in SCID and other severe immunodeficiency diseases.

MHC CLASS I DEFICIENCY AND OTHER CAUSES OF CD8 T-CELL DEFICIENCY

MHC class I molecules play an important role in T-cell development and function by presenting a peptide fragment from an intracellular pathogen, such as viruses, or cancer-derived proteins to the TCR of CD8 T cells. In the thymus, MHC class I molecules provide the positive selection signal for thymocytes to develop into CD8 T cells. Therefore the absence of MHC class I molecules in the thymus (and on all nucleated cells) is associated with very low or absent CD8 T cells. There are several other pathogenic gene variants that cause a deficiency in CD8 T cells.

Genetics and Pathogenesis

MHC class I deficiency results from pathogenic variants in the transporter associated with antigen processing (TAP) 1 or 2, TAP binding protein, or β_2-microglobulin genes. The TAP proteins play an important role in allowing the expression of MHC class I molecules on the surface of all nucleated cells and β_2-microglobulin associates with MHC class I molecules on the surface of cells.

Clinical Manifestations

Patients with low CD8 T cells from MHC class I deficiency may be asymptomatic in some cases but may present with chronic respiratory infections including bronchiectasis and granulomatous skin ulcers.

Diagnosis

Immunodeficiency patients with MHC class I deficiency can be identified by absent or low CD8 T cells on lymphocyte phenotyping by flow

cytometry and absent MHC class I molecules. Lymphocyte proliferation is normal.

Treatment
MHC class I deficiency is treated with supportive therapy and avoidance of immunosuppression if possible.

OTHER FORMS OF CD8 DEFICIENCY
CD8 α Gene Defects
CD8 deficiency also results from pathogenic variants in the CD8 α gene. Patients are susceptible to bacterial and viral respiratory infections. CD8 T-cell numbers are low and there is an increase in CD4-CD8- T cells. Lymphocyte proliferation is normal. CD8 α deficiency is also treated with supportive therapy and avoidance of immunosuppression if possible.

Defects in the Zeta-Associated Protein 70
The zeta-associated protein (ZAP-70) is a severe immunodeficiency similar to SCID with absent or very low numbers of CD8 T cells. Although CD4 T cells develop in adequate numbers, they are defective in proliferation and function. Patients with ZAP-70 deficiency are susceptible to all types of infection including opportunistic infections, disseminated varicella, and mucocutaneous candidiasis with failure to thrive and diarrhea. The diagnosis of ZAP-70 deficiency can be made by low CD8 T-cell counts and deficient T-cell proliferation to mitogens that can be rescued by bypassing ZAP-70 signaling with phorbol ester and ionomycin, helping confirm that the defect is in the proximal signaling pathway in T cells. The diagnosis is confirmed by identification of a homozygous or combined heterozygous pathogenic variant in the ZAP-70 gene. Treatment of ZAP-70 deficiency requires HSCT. Immunoglobulin replacement and microbial prophylaxis should be initiated until immune reconstitution after HSCT is achieved.

COMBINED IMMUNODEFICIENCIES WITH CONGENITAL THROMBOCYTOPENIA
Wiskott-Aldrich Syndrome
Wiskott-Aldrich syndrome (WAS) is an X-linked recessive disorder characterized by atopic dermatitis, thrombocytopenic purpura with normal-appearing megakaryocytes but small defective platelets, and susceptibility to infection.

Genetics and Pathogenesis
The Wiskott-Aldrich syndrome protein (WASP) controls the assembly of actin filaments required for cell migration and cell-cell interactions. Specific pathogenic variants in the WASP gene cause X-linked thrombocytopenia (XLT) without immunodeficiency and gain-of-function variants cause X-linked severe congenital neutropenia. A similar phenotype to WAS occurs with pathogenic variants in the WASP interactive Protein (WIP) that is an autosomal recessive disease affecting both females and males.

Clinical Manifestations
Patients often have prolonged bleeding from the circumcision site or bloody diarrhea during infancy. The thrombocytopenia is not caused initially by antiplatelet antibodies, although autoimmunity may develop later in life. **Atopic dermatitis** and **recurrent infections** usually develop during the first year 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. Infections, bleeding, and EBV-associated malignancies are major causes of death.

Diagnosis
The predominant immunoglobulin pattern is a low serum level of IgM, elevated IgA and IgE, and a normal or slightly low IgG. Percentages of T cells are moderately reduced, and lymphocyte responses to mitogens are variably depressed. The presence of low numbers of platelets that are small in size is typical. Immunologically, patients with this defect uniformly have an impaired humoral immune response to polysaccharide antigens, as evidenced by absent or greatly diminished isohemagglutinins, and poor or absent antibody responses after immunization with polysaccharide vaccines. In addition, antibody responses to protein and conjugate vaccines may also be diminished.

Treatment
Good supportive care includes appropriate nutrition, immunoglobulin replacement, use of killed vaccines, and aggressive management of eczema and associated cutaneous infections. Because of their profound antibody deficiency, these patients should be given immunoglobulin replacement regardless of their serum levels of the different immunoglobulin isotypes. HSCT is the treatment of choice when a high-quality matched donor is available and is usually curative. Gene therapy has resulted in sustained benefits in several patients. As in X-SCID, early trials of gene therapy were associated with the development of malignancy.

In addition to WAS and WIP deficiency, there is a third cause of immunodeficiency with thrombocytopenia from pathogenic variants in the *ARPC1B* gene affecting Arp2/3-mediated filament branching presenting with mild thrombocytopenia but normal-sized platelets and recurrent infections. Patients have high IgA and IgE as in WAS.

DNA REPAIR DEFECTS OTHER THAN THOSE CAUSING SCID
DNA repair plays an important role during lymphocyte development and differentiation including V(D)J recombination and immunoglobulin isotype switching. Therefore defects in DNA repair enzyme are frequently associated with CID and many have other characteristic features to identify them (see Table 165.3).

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

Genetics and Pathogenesis
The ataxia-telangiectasia pathogenic variant *(ATM)* gene encodes a protein critical for responses to DNA damage. 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 T cells and elevated numbers of γ/δ T cells. The thymus is very hypoplastic, exhibits poor organization, and lacks Hassall's 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 age 10-12 years. The telangiectasias begin to develop at 3-6 years of age, contributing to a delay in diagnosis. Recurrent sinopulmonary infections occur in approximately 80% of 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. Carriers of pathogenic variants have an increased incidence of malignancy.

Diagnosis
Patients have elevated serum α-fetoprotein levels. The most frequent humoral immunologic abnormality is the selective absence of IgA, which occurs in 50–80% of these patients. IgG2 or total IgG levels may be decreased, and specific antibody levels may be decreased or normal. Some patients have an elevated serum IgM level. Identification of homozygous or compound heterozygous pathogenic variants in the *ATM* gene confirms the diagnosis.

Treatment
Therapy in ataxia-telangiectasia is supportive but includes immunoglobulin replacement and avoidance of ionizing radiation unless absolutely necessary to establish a clinical diagnosis and initiate appropriate treatment.

Immunoosseous Dysplasias
Immunoosseous dysplasias are a group of combined immune deficiency diseases affecting bone development as well as T-cell development or function. They are characterized by skeletal abnormalities and recurrent infections (see Table 165.4).

CARTILAGE-HAIR HYPOPLASIA
Cartilage-hair hypoplasia (CHH) is an unusual form of **metaphyseal dysplasia** with frequent and severe infections. It occurs with a high frequency among the Amish and Finnish people (Chapter 741).

Genetics and Pathogenesis
CHH is an autosomal recessive condition. Numerous pathogenic variants that cosegregate with the CHH phenotype have been identified in the untranslated RNase MRP *(RMRP)* gene. The RMRP endoribonuclease consists of an RNA molecule bound to several proteins and has at least two functions: cleavage of RNA in mitochondrial DNA synthesis and nucleolar cleaving of pre-RNA. Defects 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. Infections range from mild to severe (Fig. 165.5). 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 metaphysis and flaring of the costochondral junctions of the ribs.

Diagnosis
The diagnosis of CHH is suspected by the clinical constellation of skeletal dysplasia and immune deficiency and supporting laboratory findings. Homozygous or compound heterozygous pathogenic variants in the *RMRP* gene confirms the diagnosis.

Treatment
Treatment of CHH is supportive. Some patients have been treated with HSCT, which will correct the T-cell immunodeficiency and erythrogenesis but will not affect other organ systems.

ANHIDROTIC ECTODERMAL DYSPLASIA WITH IMMUNODEFICIENCY
Anhidrotic ectodermal dysplasia with immunodeficiency (EDA-ID) is a CID characterized by susceptibility to infection, thin sparse hair, abnormal dentition (conical teeth), and absence of salivary gland (Chapter 690).

Genetics and Pathogenesis
X-linked EDA-ID results from hypomorphic gene variants in the *IKKγ* gene that encodes the NF-κB essential modulator **(NEMO)**. Complete loss-of-function (LOF) variants are deleterious early in embryogenesis. Carriers of LOF variants have features of incontinentia pigmenti. NEMO is a member of the IKK complex that phosphorylates the inhibitor of NF-κB (IκB), which then allows NF-κB to translocate to the nucleus and turn on gene expression. In lymphocytes, NF-κB is involved in signaling via the antigen receptors, the tumor necrosis factor (TNF) receptor family, and toll-like receptors as well as the interleukin (IL)-1 receptor. Defects in NEMO affect both the innate and adaptive immune systems and can be severe. Autosomal dominant gain-of-function variants in IκBα also result in a similar phenotype

Fig. 165.5 Metaphyseal dysplasia, McKusick type. Note the fine, sparse hair and short limbs. *(From Jones KL, Jones MC, Del Campo M. Smith's Recognizable Patterns of Human Malformation. 8th ed. Philadelphia: Elsevier; 2022. Fig.1, p. 529.)*

that affects both females and males as well as gain-of-function variants in IKBKB. The latter is also associated with recurrent bacterial, viral, and fungal infections, but the ectodermal defects are variable.

Clinical Manifestations
Patients with EDA-ID suffer from recurrent and severe infections from gram-positive and gram-negative bacteria, mycobacteria, viruses, and fungi. Patients have thin sparse hair and conical teeth and may have colitis. More severe variants may be associated with osteopetrosis and lymphedema; their disease is termed OL-EDA-ID (osteopetrosis, lymphedema, EDA-ID).

Diagnosis
The diagnosis can be suspected from the clinical features of anhidrosis, ectodermal dysplasia, and recurrent infections. Patients frequently present with hypogammaglobulinemia as in the hyper-IgM syndrome because CD40 signaling involves NF-κB, with elevated IgM in some patients. Most if not all patients have poor NK cell function. The diagnosis can be confirmed by identification of hypomorphic variants in the *IKKγ* gene or gain-of-function variants in the *IκBα* gene.

Treatment
Patients are usually treated with immunoglobulin replacement and close monitoring. The outcome is dependent on the severity of the phenotype. HSCT has been successful in some patients, but it may not correct the colitis or other features of the disease.

Calcium Channel Defects
Calcium signaling plays an important role in T-cell activation, where initially calcium is released from the endoplasmic reticulum into the cytoplasm, which is sensed by STIM1 that in turn activates calcium release activated channels (CRACs), which are made up of the pore-forming subunit ORAI-1, to bring in additional calcium from outside the cell. Intracellular calcium activates calcium-dependent enzymes including calcineurin, which activates the nuclear factor of activated T cells (NFAT), which

translocates to the nucleus and activates gene transcription including IL-2 and the CD40 ligand. Pathogenic variants in *ORAI-1* or *STIM1* result in a CID associated with hypotonia because calcium is also important for muscle function.

Clinical Manifestations

Patients with calcium channel defects have recurrent and severe infections with bacteria, viruses, and fungi. They typically have pneumonia but may present with a variety of infections including BCG lymphadenitis, chronic rotavirus diarrhea, and mucocutaneous candidiasis. They may also present with failure to thrive, ectodermal dysplasia defective dental enamel, and mydriasis. Patients also have a nonprogressive hypotonia.

Diagnosis

Patients have normal numbers of T cells, but the T cells have decreased or have absent proliferation to mitogens, antigens, or anti-CD3. Although serum immunoglobulins are normal or increased, specific antibody levels are diminished and NK cell function may also be decreased as B cells and NK cells also depend on calcium signaling for their activation. The clinical features and laboratory test results are similar for both *ORA-1* and *STIM1* deficiency. Therefore genetic testing is required to identify the specific pathogenic variants, which will aid in genetic counseling and prenatal diagnosis.

Treatment

HSCT is the optimal treatment for the immunodeficiency; however, it does not correct the hypotonia, which may contribute to recurrent pneumonia.

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165.3 Thymic Disorders

Ramsay L. Fuleihan

The thymus is the organ where T-cell development occurs and central T-cell tolerance to self-proteins develops by negative selection of self-reactive thymocytes or development of regulatory T cells. Defects in thymic development affect T-cell development causing a variable degree of T-cell immunodeficiency and are associated with higher risk for the development of autoimmunity.

DIGEORGE/VELOCARDIOFACIAL SYNDROME/ CHROMOSOME 22Q11.2 DELETION SYNDROME (22Q11.2DS)

Chromosome 22q11.2 deletion syndrome is the most common of the T-cell disorders, occurring in about 1 in 3,000 births in the United States. Chromosome 22q11.2 deletions disrupt development of the third and fourth 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 posteriorly rotated ears (see Chapter 99) (Fig. 165.6). With advanced fetal ultrasound and fetal echocardiography, the diagnosis is often identified prenatally. Other patients may be identified by low TREC counts on newborn screening for SCID or sometimes by the development of hypocalcemic seizures during the neonatal period.

Genetics and Pathogenesis

Chromosome 22q11.2 deletions occur with high frequency because complex repeat sequences that flank the region represent a challenge for DNA polymerase. This condition is inherited in an autosomal dominant fashion and occurs with comparable frequency in all populations. Within the deleted region, haplosufficiency for the TBX1 transcription factor appears to underlie the majority of the phenotype. The phenotype is highly variable; a subset of patients has a phenotype that has also been called **DiGeorge syndrome**, **velocardiofacial syndrome**, or **conotruncal anomaly face syndrome**.

Fig. 165.6 Typical facial appearance of a child with DiGeorge syndrome. Notice the microstomia, hypertelorism, upturned nose, and posteriorly rotated and small, low-set ears. *(From Chinn IK, Chinen J, Shearer WT. Primary immunodeficiency diseases. In: Cherry JD, Harrison GJ, Kaplan SL, et al., eds. Feigin and Cherry's Textbook of Pediatric Infectious Diseases. 8th ed. Philadelphia: Elsevier; 2019. Fig. 67.1, p. 641.)*

Variable hypoplasia of the thymus occurs in 75% of the patients with the deletion, which is more frequent than total aplasia; aplasia is present in <1% of patients with 22q11.2 deletion syndrome. Slightly less than half of patients with complete thymic aplasia are hemizygous at chromosome 22q11.2. Approximately 15% are born to diabetic mothers. Another 15% of infants have no identified risk factors. Approximately 30% 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). Pathogenic variants 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; some have pathogenic variants in *SEMA3E*.

Clinical Manifestations

Children with partial thymic *hypoplasia* may have little trouble with infections and grow normally. Patients with thymic *aplasia* (complete DiGeorge syndrome) resemble patients with SCID in their susceptibility to infections with low-grade or opportunistic pathogens, including fungi, viruses, and *P. jiroveci*, and to GVHD from nonirradiated blood transfusions. Patients with thymic aplasia 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 similar to patients with **Omenn syndrome** or maternal T-lymphocyte engraftment.

It is critical to ascertain in a timely manner whether an infant has thymic aplasia, because this disease is fatal without treatment. A T-cell count should be obtained on all infants born with primary hypoparathyroidism, CHARGE syndrome, and conotruncal cardiac anomalies with syndromic features. Some but not all infants are identified by newborn screening for SCID and when 22q11.2 deletion is suspected, a calcium level should be obtained at the time of T-cell evaluation. The three manifestations with the highest morbidity in early infancy are profound immunodeficiency, severe cardiac anomaly, and seizures from hypocalcemia. Thus an early focus on these concerns is warranted even before the diagnosis is confirmed. Affected patients may also develop autoimmune cytopenias, juvenile idiopathic arthritis, atopy, and malignancies (lymphomas).

Diagnosis

The clinical features of DiGeorge/CHARGE/22Q11.2DS will help in establishing the diagnosis, but there is a wide variety of clinical phenotypes. In most patients, 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. Lymphocyte responses to mitogen stimulation are absent, reduced, or normal, depending on the degree of thymic deficiency. Immunoglobulin levels are often normal, but there is an increased frequency of IgA deficiency, low IgM levels, and some patients develop progressive hypogammaglobulinemia. FISH for 22Q11.2 may identify patients with 22Q11.2DS as well as the more sensitive DNA microarray. Pathogenic variants in *TBX1* may be found in DiGeorge syndrome, and pathogenic variants in *CHD7* or *SEMA3E* in CHARGE syndrome.

Treatment

The immunodeficiency in thymic aplasia is correctable by cultured allogenic (donor derived) thymic tissue transplants. Following thymic tissue transplantation, a cytokine release syndrome may develop. Some infants with thymic aplasia have been given nonirradiated unfractionated bone marrow or peripheral blood transplants from a human leukocyte antigen–identical sibling, with subsequent improved immune function because of adoptively transferred T cells. Infants and children with low T-cell counts but not low enough to consider transplantation should be monitored for evolution of immunoglobulin defects as well as autoimmunity. Infections in these patients are multifactorial. Their anatomy may not favor drainage of secretions; they have a higher rate of atopy, which may complicate infections; and their host defense may allow persistence of infections. Interventions range from hand hygiene, probiotics, prophylactic antibiotics, and risk management to immunoglobulin replacement for those who have demonstrated defective humoral immunity. Live-viral vaccines should be avoided until adequate CD4 and CD8 T-cell counts are confirmed and normal response to antigens is documented with T-cell proliferation to antigens or a protective antibody response to a protein vaccine such as tetanus.

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165.4 Inborn Errors of Immunity with a Strong Atopic Diathesis

Ramsay L. Fuleihan

AUTOSOMAL DOMINANT HYPER-IgE SYNDROME *STAT3* DEFICIENCY (JOB SYNDROME)

This syndrome is associated with early-onset atopy and recurrent skin and lung infections.

Genetics and Pathogenesis

The autosomal dominant hyper-IgE syndrome is caused by heterozygous pathogenic variants in the gene encoding signal transducer and activator of transcription 3 *(STAT3)*. These pathogenic variants result in a dominant negative effect. The many clinical features are caused by compromised signaling downstream of the IL-6, type I interferon, IL-22, IL-10, and epidermal growth factor (EGF) receptors.

Clinical Manifestations

The characteristic clinical features 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. Patients often have a history 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 of atopic eczema and does not always persist. There can be a prominent forehead, deep-set wide-spaced eyes, a broad nasal bridge, a wide fleshy nasal tip, mild prognathism, facial asymmetry, and hemihypertrophy, although these are most evident in adulthood. In older children, delay in shedding primary teeth, recurrent fractures, and scoliosis occur.

These patients demonstrate an *exceptionally high serum IgE concentration*; usually normal concentrations of IgG, IgA, and IgM; pronounced blood and sputum eosinophilia; and poor antibody and cell-mediated responses to neoantigens. Although IgE levels >2,000 IU/mL are characteristic, IgE levels may fluctuate and even decrease in adulthood. 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 T-helper type 17 (Th17) 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's corpuscles and thymic architecture are normal.

Fig. 165.7 Mucocutaneous inflammation and infections in DOCK8-HIES. Severe eczema, molluscum contagiosum and fungal skin infections, and benign tumorous mucosa proliferations progressing from the inner eyelid and from oral mucosa are clinical signs of DOCK8-HIES. *(From Hagl B, Heinz V, Schlesinger A, et al. Key findings to expedite the diagnosis of hyper-IgE syndromes in infants and young children. Pediatr Allergy Immunol. 2016;27[2]:177-184. Fig. 1)*

Treatment

Therapy is generally directed at prevention of infection using antimicrobials including antibiotics and antifungals as well as immunoglobulin replacement.

DOCK8 DEFICIENCY

Deficiency of DOCK8 (dedicator of cytokinesis 8) is an autosomal recessive severe immunodeficiency that most often presents with impressively severe eczema in infancy and toddlerhood, food allergy, and eosinophilic esophagitis. Patients commonly have cutaneous viral infections with herpes simplex virus (HSV), varicella, or molluscum contagiosum; susceptibility to infection by CMV and EBV; recurrent pneumonia leading to bronchiectasis; and opportunistic infections with PJP. In some patients, cryptosporidia causes sclerosing cholangitis (Fig. 165.7). The infectious susceptibility tends to worsen over time, as do the laboratory features of immune dysfunction, most often low T-cell counts and poor proliferative function. Serum IgE levels tend to be elevated with eosinophilia, whereas other immunoglobulin levels may be decreased, especially IgM. Specific antibody levels are variably decreased. Patients are also susceptible to autoimmune disease as well as cancer. Although these patients can survive to adulthood without transplantation, they suffer many complications and their quality of life is often poor. For this reason, most patients are now transplanted early in life to avoid the later complications.

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Chapter 166

B-Cell and Antibody Deficiencies

Vivian P. Hernandez-Trujillo and Camile Ortega

Of the primary immunodeficiency diseases (PIDDs), those affecting antibody production are the most prevalent. Selective absence of IgA is the most common defect, with rates ranging from 1 in 333 to 1 in 18,000 persons among different races and ethnicities. 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. These conditions have a complex and likely polygenic inheritance, as do the common variable immunodeficiency (CVID) syndromes. The gene defects for many primary antibody deficiency disorders have been identified (Table 166.1). 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.

166.1 Agammaglobulinemia

Vivian P. Hernandez-Trujillo and Camile Ortega

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. These patients present with an increased susceptibility to infection (Fig. 166.1) and have increased risk of neutropenia and autoimmunity, particularly presenting as colitis.

Genetics and Pathogenesis

The variant 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. Some pre-B cells are found in the bone marrow, but 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.

Several autosomal recessive defects have also been shown to result in agammaglobulinemia with an absence of circulating B cells (see Table 166.1; Table 166.2), including pathogenic variants in the genes encoding the (1) μ heavy chain gene; (2) Igα and (3) Igβ signaling molecules; (4) B-cell linker adaptor protein (BLNK); (5) surrogate light chain, λ5/14.1; (6) leucine-rich repeat-containing 8 (LRRC8); (7) p85α subunit of phosphatidylinositol-3 kinase; (8) p110 δ subunit of phosphatidylinositol-3 kinase; (9) TCF3; (10) SLC39A7; and (11) TOP2B. These are rare but are clinically indistinguishable from the X-linked form (see Fig. 166.1).

Clinical Manifestations/Complications

Most males afflicted with XLA remain well during the first 6-9 months 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 (Fig. 166.2). Infections with *Mycoplasma* are also particularly problematic, specifically as they can affect the joints. Chronic fungal infections are seen; *Pneumocystis jirovecii* pneumonia rarely occurs. Viral infections are usually handled normally, with the exceptions of hepatitis viruses and enteroviruses. There are examples of paralysis when live polio vaccine was administered to these patients, and chronic, eventually fatal, central nervous system (CNS) infections with various echoviruses and coxsackieviruses have occurred in a significant number of patients. An enterovirus-associated myositis resembling dermatomyositis has also been observed. Enteroviral encephalitis can also be life-threatening in patients with XLA. **Neutropenia**, typically seen at diagnosis when infected, can be associated with *Pseudomonas* or staphylococcal infections. In addition, *Pseudomonas* can lead to severe and life-threatening invasive infections. *Giardia* can also lead to diarrhea and weight loss. A sudden decrease in serum IgG level should prompt an evaluation for *Giardia*.

Long-term complications include bronchiectasis and colitis, presenting like an inflammatory bowel disease. Gastrointestinal (GI) disease has been increasingly reported in patients with XLA. Although immune globulin replacement decreased severe infectious complications, the chronic lung disease persisted in a recent cohort study. In addition, in a separate cohort, infections were highest before initiation of antibody replacement; however, patients continued to have infections despite adequate IgG levels.

Diagnosis

The diagnosis of XLA should be suspected if lymphoid hypoplasia is found on physical examination (minimal or no tonsillar tissue and no 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; total immunoglobulins are usually <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 XLA, whereas they are typically normal in transient hypogammaglobulinemia of infancy. In infants below the age of 6 months, care should be taken when interpreting normal IgG, which can represent maternal IgG passed in utero. In this case, flow cytometry is essential in making the diagnosis of XLA. Flow cytometry is an important test to demonstrate the absence of circulating B cells, which will distinguish XLA from most types of **CVID**, the hyper-IgM syndrome, and transient **hypogammaglobulinemia** of infancy (Fig. 166.3). Genetic testing is also available to detect absence of Btk.

AUTOSOMAL RECESSIVE AGAMMAGLOBULINEMIA

Autosomal recessive agammaglobulinemia (ARA) is a clinically indistinguishable disorder from XLA presenting in males and females. The successful assembly and subsequent signaling capacity of the pre-B cell receptor complex (pre-BCR) in the bone marrow is central to the production of B cells and antibody-secreting plasma cells. A pathogenic variant in any of the components of the pre-BCR, or in the downstream signaling cascade, results in these rare forms of agammaglobulinemia (see Fig. 166.1).

Genetics and Pathogenesis

Hematopoietic stem cells develop into B cells in the bone marrow. The maturation into antibody-secreting plasma cells occurs in peripheral lymphoid tissues. B-cell development relies on a tightly regulated sequence of events from the pro-B cell stage to the formation of the pre-BCR and onward (see Fig. 166.1).

The pre-BCR is composed of the membrane form of the μ heavy chain, the surrogate light chain composed of VpreB and λ5/14.1 and the immunoglobulin-associated signal transducing chains, Igα and Igβ. An autosomal pattern of inheritance occurs in approximately 10% of agammaglobulinemic syndromes, and, in some affected families, there is known consanguinity. Approximately half of these pathogenic variants are in μ heavy (IGHM) and have a clinical picture that

Table 166.1 Genetic Basis of the Most Common Primary Antibody Deficiency Disorders

GENE	PHENOTYPE	DISORDER
BAFFR	CVID	Hypogammaglobulinemia
CD19	CVID	Hypogammaglobulinemia
CD20	CVID	Hypogammaglobulinemia
CD21	CVID	Hypogammaglobulinemia
CD81	CVID	Hypogammaglobulinemia
CTLA4	CVID	Hypogammaglobulinemia, pronounced lymphoproliferation and autoimmunity
ICOS	CVID	Hypogammaglobulinemia, autoimmunity, neoplasia
LRBA	CVID	Hypogammaglobulinemia, pronounced lymphoproliferation and autoimmunity
NFKB2	CVID	Hypogammaglobulinemia, autoimmunity
NFKB1	CVID	Hypogammaglobulinemia, autoimmunity
PIK3CD (AD)	CVID	Hypogammaglobulinemia, adenopathy
PI3KR1 (AD)	CVID	Hypogammaglobulinemia
TNFRSF13B	CVID	Hypogammaglobulinemia, low penetrance of disease
Unknown	CVID	Hypogammaglobulinemia, autoimmunity Majority of patients with CVID have no known gene variant
Unknown	IgG subclass deficiency	Variable association with infection
Unknown	Specific antibody deficiency	Normal immunoglobulin levels with poor vaccine responses
Unknown	Transient hypogammaglobulinemia of infancy	Vaccine responses are usually preserved, and most children outgrow this by age 3 yr
Unknown	Selective IgA deficiency	Low or absent IgA; low concentrations of all immunoglobulins and of switched memory B cells in CVID
BLNK	Agammaglobulinemia	Absence of antibody production, lack of B cells
BTK	Agammaglobulinemia	Absence of antibody production, lack of B cells, X-linked agammaglobulinemia
CD79A	Agammaglobulinemia	Loss of the Igα required for signal transduction, absence of antibody production, lack of B cells
CD79B	Agammaglobulinemia	Loss of the Igβ required for signal transduction, absence of antibody production, lack of B cells
IGHM	Agammaglobulinemia	Loss of the Ig heavy chain, absence of antibody production, lack of B cells
IGLL1	Agammaglobulinemia	Loss of the surrogate light chain, absence of antibody production, lack of B cells
PI3KR1 (AR)	Agammaglobulinemia	Loss of signal transduction through the B-cell receptor, absence of antibody production, lack of B cells
PIK3CD δ (AR)	Agammaglobulinemia	Severely impaired signal transduction through B-cell receptor, absence of antibody production, lack of B cells
SLC39A7	Agammaglobulinemia	Impaired signal transduction through the B-cell receptor, absence of antibody production, lack of B cells
TCF3	Agammaglobulinemia	Loss of a key transcription factor for B-cell development, absence of antibody production, lack of B cells
AID	Class switch defect	Failure to produce IgG, IgA, and IgE antibodies
CD40	Class switch defect	Failure to produce IgG, IgA, and IgE antibodies, *Pneumocystis* and *Cryptosporidium* susceptibility
CD154	Class switch defect	Failure to produce IgG, IgA, and IgE antibodies, *Pneumocystis* and *Cryptosporidium* susceptibility
INO80	Class switch defect	Failure to produce IgG, IgA, and IgE antibodies
MSH6	Class switch defect	Failure to produce IgG, IgA, and IgE antibodies, malignancy
UNG	Class switch defect	Failure to produce IgG, IgA, and IgE antibodies
CD27	EBV lymphoproliferation	Memory B-cell deficiency Hypogammaglobulinemia
NEMO	Anhidrotic ectodermal dysplasia with immunodeficiency	Phenotype highly variable but includes specific antibody deficiency and CVID

AD, autosomal dominant; AR, autosomal recessive; CVID, common variable immunodeficiency; EBV, Epstein-Barr virus.

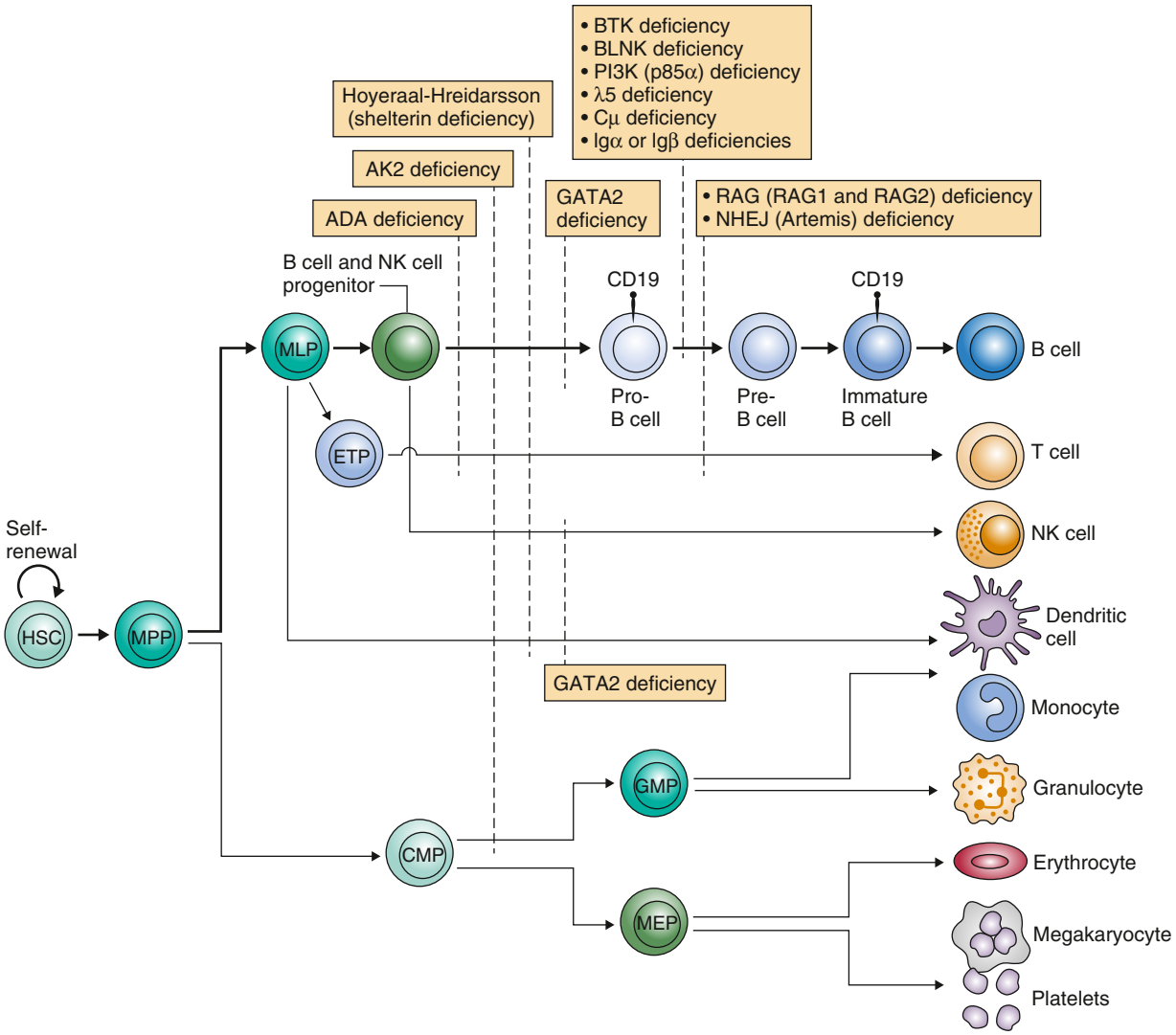

Fig. 166.1 B-cell development defects in primary antibody deficiencies (PADs) result from developmental defects that are either B-cell specific or affect several hematopoietic cell lineages. B-cell development occurs in the bone marrow, where hematopoietic stem cells (HSCs) undergo B-cell lineage specification. Some autosomal-recessive forms of severe combined immunodeficiency (SCID) are associated with an early defect in both B and T cells and are diagnosed in the first few months or years of life. For example, adenosine deaminase (ADA) deficiency leads to an accumulation of adenosines and thus the death of the lymphocytes. Moreover, adenylate kinase 2 (AK2) deficiency (also known as reticular dysgenesis) is a metabolic defect that mostly affects T cells, natural killer (NK) cells, neutrophils, and (in some cases) B cells. It is associated with very early onset hypogammaglobulinaemia or even agammaglobulinaemia. Dyskeratosis congenita is caused by mutations in genes encoding components of the telomerase or shelterin complexes; it is a rare inherited bone-marrow failure syndrome that leads to progressive B- and T-cell lymphopenia and hypogammaglobulinaemia. Finally, mutations in GATA2 (which encodes a transcription factor required for early differentiation of hematopoietic cells in the bone marrow) also lead to B-cell, dendritic cell, monocyte, and NK cell deficiencies. Successive B-cell differentiation stages are characterized by ordered gene expression and stochastic immunoglobulin gene rearrangements. The V(D)J recombination of the immunoglobulin locus is achieved by the lymphocyte-specific RAG molecules and the non–lymphocyte-specific nonhomologous end joining (NHEJ) complex and leads to the expression of the pre-B cell receptor (BCR). Defects in V(D)J recombination (as observed in RAG deficiency and NHEJ deficiency) typically result in the absence of mature B and T cells. The pre-BCR is affected in these cases, leading to PADs as V(D)J recombination is required for heavy chain expression. The dashed lines indicate a block of differentiation. BLNK, B-cell linker; Btk, Bruton tyrosine kinase; CMP, common myeloid progenitor; ETP, early T-cell precursor; GMP, granulocyte/macrophage progenitor; MEP, megakaryocyte/erythrocyte progenitor; MLP, multi-lymphoid progenitor; MPP, multipotent progenitor; PI3K, phosphoinositide 3-kinase. *(From Durandy A, Kracker S, Fischer A. Primary antibody deficiencies.* Nat Rev Immunol. *2013;13:519-533. Box 1, p. 520.)*

is similar to XLA. Variants in the genes encoding for Igα (CD79a), Igβ (CD79b), λ5 (IGLL1), BLNK, and p85α (PI3KR1) have been identified as other, more rare, causes for ARA in humans (see Fig. 166.1). Autosomal dominant forms of agammaglobulinemia have also been identified in patients with an unusual phenotype characterized by an increased expression of CD19, but with the absence of the BCR. Genetic studies demonstrated a de novo variant in the broadly expressed transcription factor E47, which functions as a quality control mechanism of enforcing a block to prevent cells that lack a pre-BCR from further development.

Clinical Manifestations

Absent peripheral B cells and severe hypogammaglobulinemia due to a developmental arrest at the pro-B stage to pre-B stage is characteristic of ARA. Although these patients generally have clinical findings that are indistinguishable from Btk mutations, patients with the pathogenic variants in any of the components of the BCR leading to ARA tend to have a more severe phenotype. ARA is diagnosed at a mean age of 11 months, rather than 35 months in patients with XLA. There is also a higher incidence of enteroviral infections and *Pseudomonas* sepsis with neutropenia. These differences suggest there is protective value in

Table 166.2 Patterns of Inheritance for Different Forms of Agammaglobulinemia

DISEASE	GENE/PROTEIN AFFECTED	PATTERN OF INHERITANCE
XLA	Btk	X-linked
IGHM	μ heavy chain	Autosomal recessive
Igα	CD79a	Autosomal recessive
Igβ	CD79b	Autosomal recessive
λ5	IGLL1	Autosomal recessive
BLNK	BLNK scaffolding protein	Autosomal recessive
PIK3R1	PIK3 regulatory subunit	Autosomal recessive
PIK3CD	PIK3 regulatory subunit	Autosomal recessive
SLC39A7	Zinc transporter protein ZIP7	Autosomal recessive
TCF3	Transcription factors E12 and E47	Autosomal recessive or autosomal dominant
LRRC8	LRRC8 deficiency	Autosomal dominant
Hoffman syndrome	TOP2B	Autosomal dominant

XLA, X-linked agammaglobulinemia.

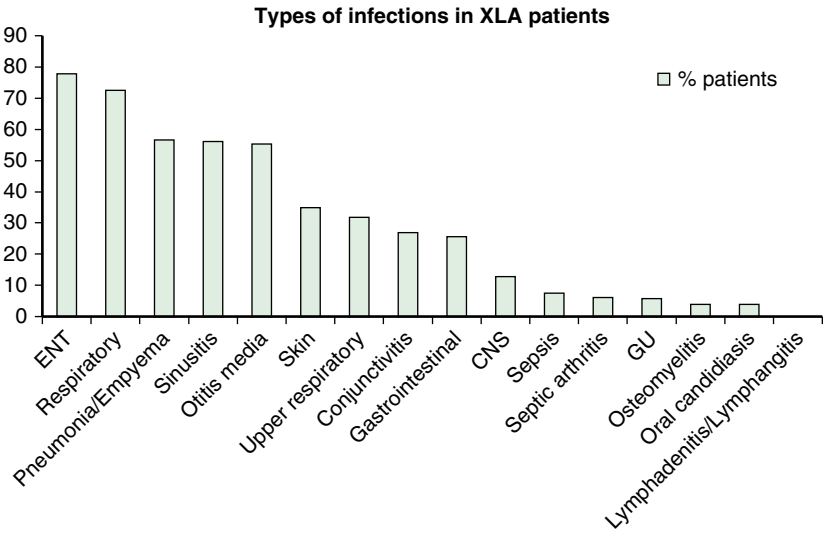

Fig. 166.2 Types of Infections in a cohort of X-linked agammaglobulinemia (XLA) patients. USIDNET Registry. Infections affect many body systems in XLA patients. CNS, Central nervous system: ENT, ear, nose, and throat; GU, genitourinary. *(Data from Groth D, Wright H, Marsh R, et al. X-linked agammaglobulinemia: Infection frequencies in 226 patients from the USIDNET Registry.* J Allergy Clin Immunol. *2020;145[2 Supplement]:AB80.)*

the small amount of immunoglobulins produced by patients with XLA. Treatment using immunoglobulin and aggressive use of antibiotics is identical to that for patients with XLA.

Diagnosis

Due to the early B-cell developmental arrest, ARA variants have been associated with the complete absence of $CD19^+$ B cells in the peripheral circulation and profound hypogammaglobulinemia. Identifying a genetic cause of ARA is challenging, and there is a need for a better understanding of susceptibility genes and modifying genetic factors. The goal of further areas of investigation should include the identification of variant genes in patients who do not appear to have defects in the genes already associated with immunodeficiency.

Whole genome sequencing will greatly facilitate the molecular diagnosis of abnormalities in additional genes that can cause ARA.

Inheritance Patterns

XLA affects males, as it is an X-linked disorder. The inheritance patterns include all female offspring as carriers, and none of the male offspring will be affected. Autosomal recessive forms of agammaglobulinemia result in both males and females affected, as each parent passes on the affected gene. Patients with agammaglobulinemia tend to have more severe disease, often presenting earlier in life compared with patients with hypogammaglobulinemia, specific antibody deficiency (SAD), or CVID.

Treatment with antibody replacement and prophylactic antibiotics for patients with any form of agammaglobulinemia is essential in preventing infections and will be further reviewed later.

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166.2 Hypogammaglobulinemia, Transient Hypogammaglobulinemia of Infancy, Specific Antibody Deficiency, and Common Variable Immunodeficiency

Vivian P. Hernandez-Trujillo and Camile Ortega

Patients with low IgG may present at different ages. Hypogammaglobulinemia results from low, but not absent, levels of serum immunoglobulins. If a patient is diagnosed with a specific pathologic genetic variant, this aids in making a specific diagnosis. Otherwise, in patients with a low IgG, the diagnosis may be arbitrary when considering the differential of hypogammaglobulinemia, SAD, and CVID (Tables 166.3 and 166.4).

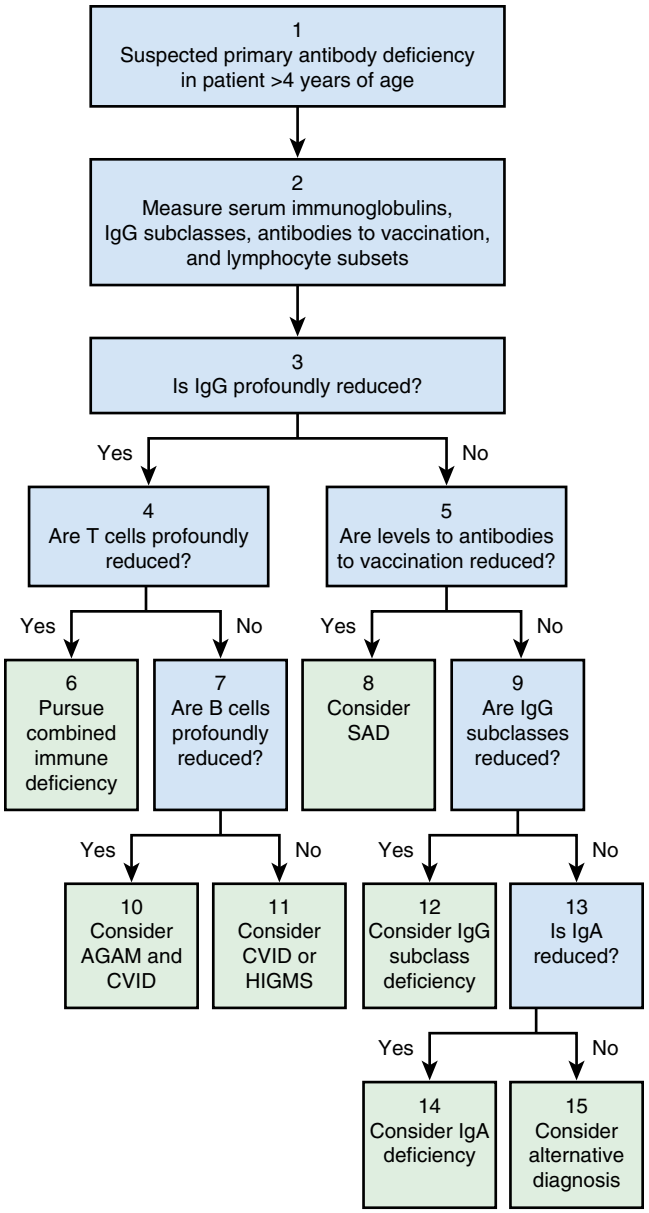

Fig. 166.3 Algorithm for evaluation of a patient with suspected primary antibody deficiency. AGAM, Congenital agammaglobulinemia; CVID, common variable immunodeficiency; HIGMS, hyperIgM syndrome; SAD, specific antibody deficiency. *(From Maglione PJ. Primary antibody deficiency. In: Leung DYM, Akdis CA, Bacharier LB, et al., eds.* Pediatric Allergy Principles and Practice. *4th ed. Philadelphia: Elsevier, 2021. Fig. 5.1.)*

HYPOGAMMAGLOBULINEMIA

The most common types of PIDD are antibody deficiencies characterized by hypogammaglobulinemia and recurrent infections and are usually present in childhood. Primary hypogammaglobulinemia represents a spectrum of disease, with more severe phenotypes characterized by profound hypogammaglobulinemia or agammaglobulinemic states, as was described in the previous section. SAD and CVID are presented in the following sections, and onset may occur later in childhood and adolescence. This is in contrast to transient hypogammaglobulinemia of infancy, which presents in the first few months of life.

The secondary forms are more common in adults and are a result of decreased production or increased loss. Decreased production can be drug induced (rituximab, glucocorticoids, and antiepileptics), from malignancy or premalignant disorders (chronic lymphocytic leukemia, lymphoma, multiple myeloma, or Waldenström macroglobulinemia), and from Good syndrome (thymoma with hypogammaglobulinemia). Increased loss can result from protein-losing enteropathies, intestinal lymphangiectasia, nephrotic syndrome, burns, and trauma.

Specific Antibody Deficiency

SAD is defined as patients, 2 years old and older, with recurrent infections and normal immunoglobulin isotypes who lack antibody response to purified *S. pneumoniae* capsular polysaccharide antigens, while responding normally to protein antigens.

Genetics and Pathogenesis

Infants demonstrate robust antibody responses to protein antigens through T-cell–dependent activation. Response to purified polysaccharide vaccines (PPVs) does not involve T-cell activation, and is only considered to be fully developed by 2 years of age. The response to protein antigens, including those contained in the protein conjugated vaccines (PCVs), typically remains intact in patients with SAD. In SAD, some patients' lack of response to PPV may represent physiologic immaturity of the immune system, and may resolve over time. In SAD patients with recurrent infections requiring antibiotics, there is likely an underlying immunologic abnormality. The cause for this delay in maturation remains unknown. Abnormalities in a specific pathogen-associated molecular pathway may be responsible for the variability in which individuals respond to specific protein or polysaccharide antigens despite normal total immunoglobulin levels. A number of cellular pathways produce antibodies against purified or conjugate polysaccharides and are likely to be altered by different defects. The response seen to PPV, which can occur in patients who lack a response to PCV, demonstrates how conjugate and purified polysaccharides induce antibodies through different activation pathways. The variation in phenotypes of SAD also supports the likelihood of different pathogenic mechanisms resulting in polysaccharide antibody deficiencies. The use of large-scale DNA studies, along with IgM memory and class-switched memory B cells as immunologic markers, is expected to provide useful information for the evaluation and management of patients with SAD in the future.

Clinical Manifestations

Patients with SAD present in a manner consistent with those with defects of humoral immunity. Frequent, severe, or prolonged sinopulmonary infections are most common. Rapid recurrence of infection on discontinuation of antibiotics, following initial improvement, is also common. Invasive and life-threatening infections are not frequent. Approximately half of children show resolution of SAD in 3 years and treatment may be temporary. A new diagnosis of SAD during adolescence or adulthood could indicate a previously missed diagnosis or progression of a mild phenotype. Pathogen susceptibility is not specific and not limited to *S. pneumoniae.* Other encapsulated bacteria, (*H. influenzae* and *Moraxella catarrhalis*), *Staphylococcus aureus* and respiratory viruses cause significant disease in SAD.

SAD patients with allergic disease are among the most challenging to identify due to increased risk of sinopulmonary infections resulting from persistent inflammation and anatomic dysfunction associated with asthma and rhinitis. It is important to consider underlying SAD in this population, as IgE-mediated sensitization is only present in some of these patients. Mucociliary or anatomic defects should also be considered in those who have developed high titers in response to natural infection, but maintain an abnormal pattern of infections.

Although lack of antibody response to polysaccharide antigens is found frequently in patients without any associated immune deficiency, selective antibody deficiencies are also common in patients with known PIDDs with normal total immunoglobulin levels such as ataxia telangiectasia, asplenia, hyper-IgE syndrome, selective IgA deficiency, IgG subclass deficiencies, Wiskott-Aldrich syndrome, and partial DiGeorge syndrome. A subset of adolescents and adults with SAD may progress to more severe forms of PIDD, including other forms of hypogammaglobulinemia and CVID.

Diagnosis

The gold standard for the diagnosis of SAD involves evaluating the response to the 23-valent pneumococcal polysaccharide vaccine (PPV23). In patients immunized with protein conjugated

Table 166.3 Main Phenotypes of Primary Antibody Deficiencies

PHENOTYPE	MAIN CLINICAL FEATURES	MAIN B-CELL FEATURES
Agammaglobulinemia	Bacterial infections (in respiratory tract) and enterovirus infections	Absence of CD19 B cells
Common variable immunodeficiency	Bacterial infections (in respiratory tract and gut), autoimmunity, cancer, and increased risk of granuloma	Highly variable; may see decreased memory B cells
Class switch defects	Bacterial and opportunistic infections	Decreased frequency of memory B cells
Selective IgA deficiency	Most often asymptomatic	Normal
IgG subclass deficiency	Frequent bacterial infections; diagnosis after age 2 yr	B-cell subsets normal
Selective polysaccharide antibody deficiency	Bacterial infections (after age 2 yr)	Normal IgG (including IgG2 and IgG4) levels, normal B-cell subsets

Table 166.4 Antibody Deficiency Disorders with Laboratory Evaluation

LABORATORY VALUES	XLA/AR AGAMMA	SELECTIVE IgA	SPECIFIC ANTIBODY DEFICIENCY	COMMON VARIABLE IMMUNODEFICIENCY	TRANSIENT HYPOGAMMA-GLOBULINEMIA
IgG	Decreased	Normal	Normal	Decreased to normal	Decreased
IgA	Decreased	Decreased	Normal	Decreased to normal	Normal
IgM	Decreased	Normal	Normal	Varies	Normal
LYMPHOCYTES					
B $CD19^+$	Decreased to absent	Normal	Normal	Decreased to normal memory B cells	Normal
T $CD4^+/CD3^+$	Normal to increased	Normal	Normal	Normal	Normal
$CD8^+/CD3^+$	Normal to increased	Normal	Normal	Normal	Normal
NK $16^+/56^+$	Normal to increased	Normal	Normal	Normal	Normal
SPECIFIC ANTIBODY TITERS					
Protein	Decreased	Normal	Normal	Decreased to normal	Normal
Polysaccharide	Decreased	Normal	Decreased	Decreased to normal	Normal

AR, Autosomal recessive; NK, natural killer; XLA, X-linked agammaglobulinemia.

pneumococcal vaccines (PCV-7, PCV-13, PCV-10, PCV-15, PCV-20), the evaluation must be based on the serotypes not present in conjugate vaccines. In unimmunized patients, a complete absence of protective titers to all serotypes is unusual, as most individuals would be expected to have developed some in response to natural infection by 2 years of age. The standard and reproducible method used for analysis is the third-generation World Health Organization enzyme-linked immunosorbent assay (ELISA) and the antigens are individual serotype specific capsular polysaccharides of pneumococci. Antibody titers are expressed as mg/mL and although titers as low as 0.35 mg/mL have been considered protective against invasive infections, a titer of 1.3 mg/mL is used as the threshold of response to PPV23 and generally considered protective against mucosal infections. **Four different phenotypes of SAD** have been described based on the response to the available pneumococcal vaccines: mild, moderate, severe, and memory. Although all phenotypes presume an abnormal pattern of infection, severity or susceptibility to infection may or may not correlate clinically. The severe phenotype is defined as nearly absent protective titers to ≤2 serotypes following PPV23. The moderate phenotype is based on age: for those less than 6 years old, less than 50% protective serotypes and those age 6 years old and greater, less than 70% protective serotypes. Many patients fall in the mild phenotype, which is less well defined as a failure of response to multiple phenotypes. The memory phenotype, also dependent on age, is defined as an adequate initial response and subsequent loss of protective titers within 6 months. The evaluation of specific antibodies against *S. pneumoniae* polysaccharides provides guidance in determining the need for additional immunization, antibiotic therapy, or IgG replacement therapy in SAD patients. Children and adults who have not been immunized and have not developed protective titers in response to natural infection should be immunized with PCV followed by PPV23, as they have been shown to respond both clinically and serologically. Patients who fail to respond to the initial challenge with PPV23 may respond to the conjugated vaccine, when given ≥1 year after PPV23. Most patients have an excellent prognosis with appropriate treatment.

COMMON VARIABLE IMMUNODEFICIENCY

CVID is a syndrome characterized by hypogammaglobulinemia after an initial period of apparent normal immune function. Serum IgG must be <2 standard deviations below the *age-adjusted* norms, with low IgA and/or IgM levels. CVID patients may appear similar clinically to those with XLA in the types of infections experienced and bacterial etiologic agents involved, except that enterovirus meningoencephalitis is rare in patients with CVID. In contrast to XLA, the sex distribution in CVID is almost equal, the age at onset is later, and infections may be less severe. CVID is the most common of the antibody defects.

Genetics and Pathogenesis

CVID is a phenotypic diagnosis with a polygenic inheritance in most cases. Genes known to produce the **CVID** phenotype when pathogenic variants occur include *ICOS* (inducible co-stimulator) 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 of receptors), *NFKB1* and *NFKB2*, *IKZF1*, *ATP6AP1*, *MOGS*, *TACI*, and *TRNT1* (Fig. 166.4). With rare exceptions, management of CVID does not depend on a genetic diagnosis. In the setting of atypical infections or autoimmunity, pursuing a genetic diagnosis can be useful because some genetic etiologies can have a poor prognosis and transplantation should be considered. Targeted treatment options may also be available to treat some forms of CVID related to *LRBA* or *CTLA4* pathogenic variants.

Despite normal numbers of circulating B cells in many patients and the presence of lymphoid cortical follicles, blood B cells from CVID patients do not differentiate normally into immunoglobulin-producing cells. They may have a deficiency of switched memory B cells.

Clinical Manifestations

The serum immunoglobulin and antibody deficiencies in CVID are associated with recurrent sinopulmonary infections (sinusitis, otitis, pneumonia). Most patients present before age 20. Close monitoring for the development of chronic lung disease is needed. Repeated pulmonary infections may produce bronchiectasis; interstitial lung disease is common (Fig. 166.5). Sepsis and meningitis with encapsulated bacteria occur more frequently than in the general population. Patients with recurrent infections as their only manifestation typically have a normal life expectancy and do well with immunoglobulin replacement. The presence of autoimmune disease or lymphoproliferation confers a poor prognosis, as antibody replacement does not improve these conditions. Patients with CVID often have autoantibody formation and normal-sized or enlarged tonsils and lymph nodes; about 25% of patients have splenomegaly. CVID has also been associated with a spruelike enteropathy with or without nodular lymphoid hyperplasia of the intestine. Other autoimmune diseases include alopecia areata, hemolytic anemia, thrombocytopenia, gastric atrophy, achlorhydria, and pernicious anemia. Lymphoid interstitial pneumonia, intestinal lung disease, pseudolymphoma, B-cell lymphomas, amyloidosis, and noncaseating sarcoid-like granulomas of the lungs (**granulomatous and lymphocytic interstitial lung disease [GLILD]**), spleen, skin, and liver also occur. Patients should be monitored closely over time for symptoms involving multiple tissues.

166.3 Class Switch Defects

Vivian P. Hernandez-Trujillo and Camile Ortega

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 pathogenic variants have been identified in the CD40 ligand gene on the X chromosome and three genes on autosomal chromosomes: the activation-induced cytidine deaminase (AID) gene, the uracil DNA glycosylase gene (UNG), and the CD40 gene on chromosome 20. Distinctive clinical features permit presumptive recognition of the type of pathogenic variants 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 CD40 LIGAND GENE

X-linked hyper-IgM is caused by pathogenic variants in the gene that encodes the CD40 ligand (CD154, CD40L), which is expressed on activated T-helper (Th) cells. Males 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. This disease, unlike the autosomal recessive forms of hyper-IgM, affects both B and T cells.

Genetics and Pathogenesis

The B cells are normal in this condition; the defect is in the T cells. CD40L is the ligand for CD40, which is present on B cells and monocytes. CD40L is upregulated on activated T cells. Mutations 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

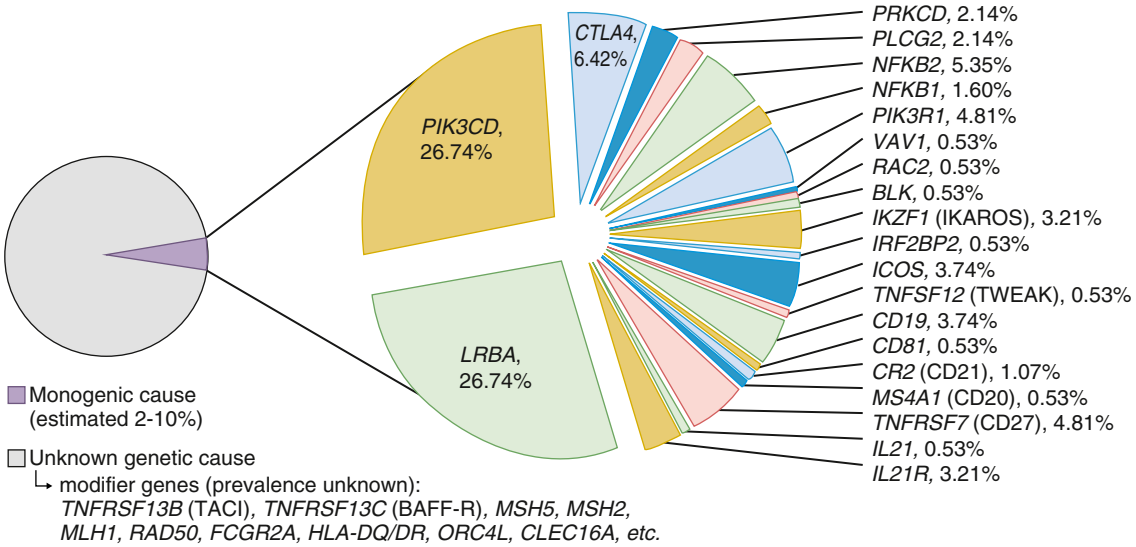

Fig. 166.4 Known genetic etiology of common variable immunodeficiency (CVID). **The majority of cases of CVID do not have a defined genetic cause.** Many of these are likely to be multifactorial, and the genomic duplication and deletion burden in CVID suggests this to be the case; 115 of the mutations have been identified. The colored pie chart represents their breakdown and relative frequency. *(From Bogaert DJ, Dullaers M, Lambrecht BN, et al. Genes associated with common variable immunodeficiency: One diagnosis to rule them all?* J Med Genet. *2016;53[9]:575-590. Fig 1.)*

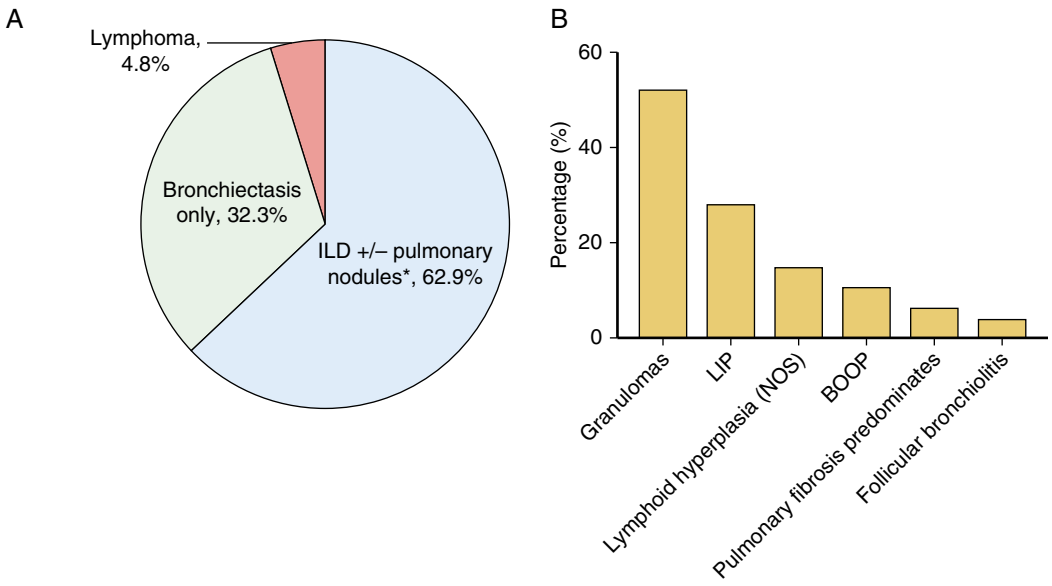

Fig. 166.5 Chronic lung disease in common variable immunodeficiency. **A**, Lung disease types by radiographs and/or pathology reports (n = 124). **B**, Interstitial lung disease pathologies (n = 46). *Thirteen of 65 subjects with ILD had concurrent bronchiectasis. BOOP, bronchiolitis obliterans organizing pneumonia; ILD, interstitial lung disease; LIP, lymphoid interstitial pneumonia. *(From Ho HE, Cunningham-Rundles C. Non-infectious complications of common variable immunodeficiency: Updated clinical spectrum, sequelae, and insights to pathogenesis.* Front Immunol. *2020;11:149. Fig. 1)*

interact with CD28/CTLA4 on T cells, resulting in failure of "crosstalk" between immune system cells.

Clinical Manifestations

Males with the CD40 ligand defect become symptomatic during the first or second year of life with recurrent pyogenic infections, including otitis media, sinusitis, pneumonia, and tonsillitis. They have marked susceptibility to *P. jirovecii* pneumonia and can be 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 numbers and in vitro responses to mitogens are normal, but there is decreased antigen-specific T-cell function. In addition to opportunistic infections such as *P. jirovecii* pneumonia, there is an increased incidence of extensive verruca vulgaris lesions, *Cryptosporidium* enteritis, subsequent liver disease, and an increased risk of malignancy.

Treatment

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 lifelong infusions of immune globulin. In patients with severe neutropenia, the use of granulocyte colony-stimulating factor has been beneficial.

AUTOSOMAL RECESSIVE HYPER-IgM

Genetics and Pathogenesis

In contrast to patients with the CD40L defect, B cells from these patients are not able to switch from IgM-secreting to IgG-, IgA-, or IgE-secreting cells, even when co-cultured with normal T cells. The defects are all B-cell intrinsic. The most common autosomal recessive defect is in a gene that encodes AID. AID deaminates cytosine into uracil in targeted DNA, which is followed by uracil removal by UNG. Severely impaired CSR was found in three 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. Histologic examination of the enlarged lymph nodes reveals the presence of giant germinal centers (5-10 times > normal) filled with highly proliferating B cells. Autosomal recessive hyper-IgM can be caused by defects in CD40. Clinical manifestations included recurrent sinopulmonary infections, *P. jirovecii* pneumonia, and *Cryptosporidium parvum* infections, very similar to the manifestations seen in X-linked hyper-IgM syndrome. Patients with *INO80* deficiency may present with severe bacterial infections; whereas in *MSH6* deficiency patients may have increased IgM, family or personal history of cancer, and low switch memory B cells.

Clinical Manifestations

Concentrations of serum IgG, IgA, and IgE are very low in AID, UNG, and CD40 deficiencies. 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 AID and UNG mutations have lymphoid hyperplasia, are generally older at age at onset, do not have susceptibility to *P. jirovecii* pneumonia, often do have isohemagglutinins, and are much less likely to have neutropenia unless it occurs on an autoimmune basis. The lymphoid hyperplasia distinguishes these patients from many others with antibody deficiency, particularly agammaglobulinemia, which leads to a paucity of lymphoid tissue. 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.

Treatment and Prognosis

With early diagnosis and antibody replacement, as well as good management of infections with antibiotics, patients with AID and UNG mutations generally have a more benign course than do those with the CD40L or CD40 defects. CD40 deficiency is rare but appears to mimic the manifestations of CD40L quite closely.

Treatment of Antibody Deficiency

Except for the CD40 ligand defect, for which stem cell transplantation is recommended, judicious use of antibiotics to treat documented infections and regular administration of immunoglobulin are the only effective treatments for primary B-cell disorders. The most common forms of replacement therapy are either intravenous or subcutaneous immune globulin (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 advancement 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 this has been resolved by the additional treatment step. There has been no documented transmission of HIV by any of these preparations. IVIG or SCIg at a dose of 400-600 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. Neutropenia associated with B-cell defects has responded to granulocyte colony-stimulating factor. Treatment of inflammatory bowel disease is essential in maintaining adequate IgG levels.

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166.4 Isotype Defects

Vivian P. Hernandez-Trujillo and Camile Ortega

SELECTIVE IgA DEFICIENCY

An isolated absence or near absence (<5 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. Patients may be asymptomatic or may develop sinopulmonary or gastrointestinal (GI) infections (especially *Giardia*). IgA deficiency is also associated with celiac disease and other autoimmune disorders. The diagnosis cannot be made until about 4 years of age, when IgA levels should be matured to adult levels.

The basic defect resulting in IgA deficiency is unknown. Phenotypically normal blood B cells are present. In these patients, normal levels of other isotypes and normal specific antibody levels are seen. This defect also often occurs in pedigrees containing individuals with CVID. Indeed, IgA deficiency may evolve into CVID over time. 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, GI, and urogenital tracts. Bacterial agents responsible are the same as in other antibody deficiency syndromes. Intestinal giardiasis is common. Serum concentrations of other immunoglobulins are usually normal in patients with selective IgA deficiency, although IgG2 (and other) subclass deficiency has been reported.

Serum antibodies to IgA are reported in as many as 44% of patients with selective IgA deficiency. These antibodies can cause nonhemolytic transfusion reactions. Washed 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 immune globulin preparations contain sufficient IgA to cause reactions. It is important to note that administration of immune globulin, which is >99% IgG, is not indicated because most IgA-deficient patients make IgG antibodies normally.

IgG Subclass Deficiencies

Some patients have deficiencies of one or more of the four subclasses of IgG despite normal or elevated total IgG serum concentration. Most patients may be asymptomatic. Some patients with absent or very low concentrations of IgG2 also have IgA deficiency. They may present with bacterial infections. 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. IgG subclass measurement is not cost-effective in evaluating immune function in the child with recurrent infections. 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 IgG2. For this reason, immune globulin 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 IgG1, IgG2, IgG4, and/or IgA1 as a result of gene deletions. These patients illustrate the importance of assessing specific antibody formation before deciding to initiate immune globulin therapy in IgG subclass–deficient patients. Low or undetectable levels of IgG subclasses alone is, therefore, not an indication for antibody replacement.

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166.5 Transient Hypogammaglobulinemia of Infancy

Vivian P. Hernandez-Trujillo and Camile Ortega

A common laboratory finding in infants, transient hypogammaglobulinemia represents developmental delay in the production of immunoglobulin. It is thought to occur in as many as 1:1,000 children. Most infants begin to produce IgG in the first 3 months of life, and the quantity produced increases throughout infancy. For reasons incompletely understood, a small number of infants either begin late or do not increase their production as expected. This condition will resolve with no intervention, but represents a source of diagnostic confusion. A key distinction is that responses to vaccines are usually preserved in this condition, whereas in the others, including SAD, antibody responses will be low to absent.

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Chapter 167

Natural Killer Cells

Jessica M. Palmieri, Vibha A. Szafron*, and Lisa Forbes Satter*

Natural killer (NK) cells are lymphocytes that have a critical role in the innate immune response to pathogenic challenge and cellular stress. NK cells are capable of rapid target cell killing and can quickly secrete large amounts of preformed granzymes and perforins in response to viral infections, especially those of the herpesvirus family. They are also crucial in tumor surveillance. NK cells are found in the circulating blood as approximately 3–15% of lymphocytes and are also found in both primary and secondary lymphoid tissues where they are in a constant state of surveillance for cellular abnormalities. NK cells use a detection system composed of a wide range of germline-encoded cell surface receptors that contribute to simultaneous NK activating and inhibitory signals. NK cells are constantly receiving both activating and inhibitory signals with the balance of signals tilted toward inactivation until NK cell recognition of a target cell occurs. With target cell recognition, the balance between inhibitory and activating signals leans in favor of activation and NK cell killing is initiated.

NK cells are defined as *innate immune lymphocytes* because unlike B and T lymphocytes, they do utilize recombination-activating gene (RAG) proteins required for DNA rearrangement and assemblage of diverse antigen-specific receptors in response to antigen exposure. However, they can develop long-lived and highly antigen-specific immunologic memory responses to different antigens through *RAG-independent adaptive immunity,* which provides lifelong immune memory responses. This means that despite a lack of receptor diversity accrued via DNA rearrangement like B cells and T cells, NK cells do have characteristics associated with the adaptive immune system; distinguishing healthy from diseased cells, producing robust antiviral responses, and maintaining a collection of long-lived cells that expand during cellular stress responses.

NK CELL MARKERS, SUBSETS, AND MATURATION

Mature NK cells are traditionally defined as non-T, non-B lymphocytes that can rapidly produce interferon gamma (IFN-γ) and can mediate cellular cytotoxicity. Like all lymphocytes, they express cluster of differentiation (CD) markers that identify their cell type and stage of development that are also upregulated or downregulated for cell homing purposes. However, there are no surface markers that are unique and specific for NK cells. NK cells have been traditionally identified by using flow cytometry to exclude the cellular surface presence of leukocyte expressing markers specific to other leukocytes, such as CD3 and CD5 (T cells), CD19 and CD20 (B cells), and CD13 and CD14 (myelomonocytic cells). Further identification of NK cells follows via their expression of CD56 (neural cell adhesion molecule-1) and/or CD16, their low-affinity Fc gamma receptor that mediates **antibody-dependent cellular cytotoxicity** (ADCC). Neither CD56 nor CD16 is specific or unique to the NK cell lineage; however, these CD markers are functionally important and thus used to characterize major subsets of NK cells.

NK cells develop from CD34 hematopoietic stem cells (HSCs) in the bone marrow and then undergo maturation in secondary lymphoid tissues. NK cell development occurs through a series of six functionally distinct developmental stages distinguishable by cellular expression of cell surface markers including CD34, CD117, CD94/NKG2A (surface inhibitory receptor), NKp80 (surface activating receptor), CD16, and CD57. Once mature, NK cells then circulate through the peripheral blood (PB) or are found in organ tissues such as the secondary lymphoid tissues, liver, lungs, uterus, kidneys, or gut. For example, stage 1 cells found in the bone marrow are marked by the presence of only CD34, and subsequent stages occur through the upregulation and downregulation of previously mentioned cell surface markers; whereas, stage 6 mature NK cells in the PB express Nkp80, CD16, and CD57 (Fig. 167.1).

NK cells express CD56 at different levels of development. $CD56^{bright}$ NK cells that express high levels of CD56, without expressing much CD16, are considered stage 4b and are approximately 3–10% of circulating PB NK cells. Most PB NK cells express CD16 and low levels of CD56 and are referred to as $CD56^{dim}$ NK cells. Distinguishing cells as $CD56^{bright}$ and $CD56^{dim}$ refers to the increased fluorescent intensity for $CD56^{+}$ cells seen in comparison to cells negative for CD56. $CD56^{bright}$ and $CD56^{dim}$ cells are functionally different. $CD56^{bright}$ NK cells are considered to be developmentally immature and produce higher levels of cytokines such as IFN-γ with less cytotoxic capacity. They can rapidly produce large amounts of cytokines and chemokines; however, they contain low levels of perforin and granzymes and have low or absent CD16, making them poor mediators of direct cytotoxicity and ADCC. In contrast, $CD56^{dim}$ cells are developmentally more mature, contain high levels of perforin, are cytotoxic, and recognize antibody-coated cells through CD16. $CD56^{dim}$ cells are able to produce large amounts of cytokines but not to the degree of $CD56^{bright}$ cells.

The cell surface marker expression for NK cells in the PB and tissues are phenotypically distinct due to the influence of each tissue's unique microenvironment. Similarly, the ratio of $CD56^{bright}$ and $CD56^{dim}$ NK subsets in the tissues is not the same as the ratios found in the PB. In the bone marrow, lung, spleen, subcutaneous adipose tissue, and breast tissue, $CD56^{dim}$ NK cells predominate, whereas $CD56^{bright}$ NK cells predominate in the mucosa-associated lymphoid tissues (MALTs; e.g., gastric and intestinal mucosa), liver, uterus, visceral adipose tissue, adrenal gland, and kidney.

NK Cell Functions

NK cells have a critical role in the control of tumor growth and metastasis and are vital for the innate immune response against infections, particularly certain viruses. Additionally, there is increasing recognition of the importance of NK cells in immunoregulation, coordination of immunity, and modulation of autoreactivity.

NK cell activity is a balance between inhibitory and activating signals. NK cell surfaces contain a wide range of receptors that affect NK cell expression. Healthy host cells express high amounts of major histocompatibility complex class I (MHC I) molecules that ligate NK cell inhibitory receptors and prevent unwanted killing of healthy cells. Infected or malignant host cells downregulate their MHC I expression and express ligands for NK cell activating receptors, which triggers NK cell killing of the diseased cell. The balance of signals for NK cell inhibition by MHC I expression in healthy cells and NK cell activation by MHC I downregulation during cellular stress allows NK cells to defend against viruses and tumors and have protective roles in fungal, extracellular bacterial, intracellular bacterial, and parasitic infections. Many viruses have evolved to specifically downregulate MHC I in cells they infect to prevent the host cell from presenting antigenic peptides to virus-specific cytotoxic T lymphocytes (CTLs). Although this strategy does allow virus-infected cell evasion from CTLs, it makes the infected cell more susceptible to recognition by NK cells.

The three main functions of NK cells include cytokine/chemokine production, contact-dependent co-stimulation, and cytotoxicity. Additionally, NK cells are capable of interfacing with the adaptive immune system through their IgG Fc receptor, CD16, which allows them to engage in antibody-dependent killing.

Cytokine/Chemokine Production

Activated NK cells secrete a wide variety of cytokines and chemokines in response to stimulation by interleukin (IL)-12, IL-15, and IL-18. IFN-γ is one of the most potent cytokines released by

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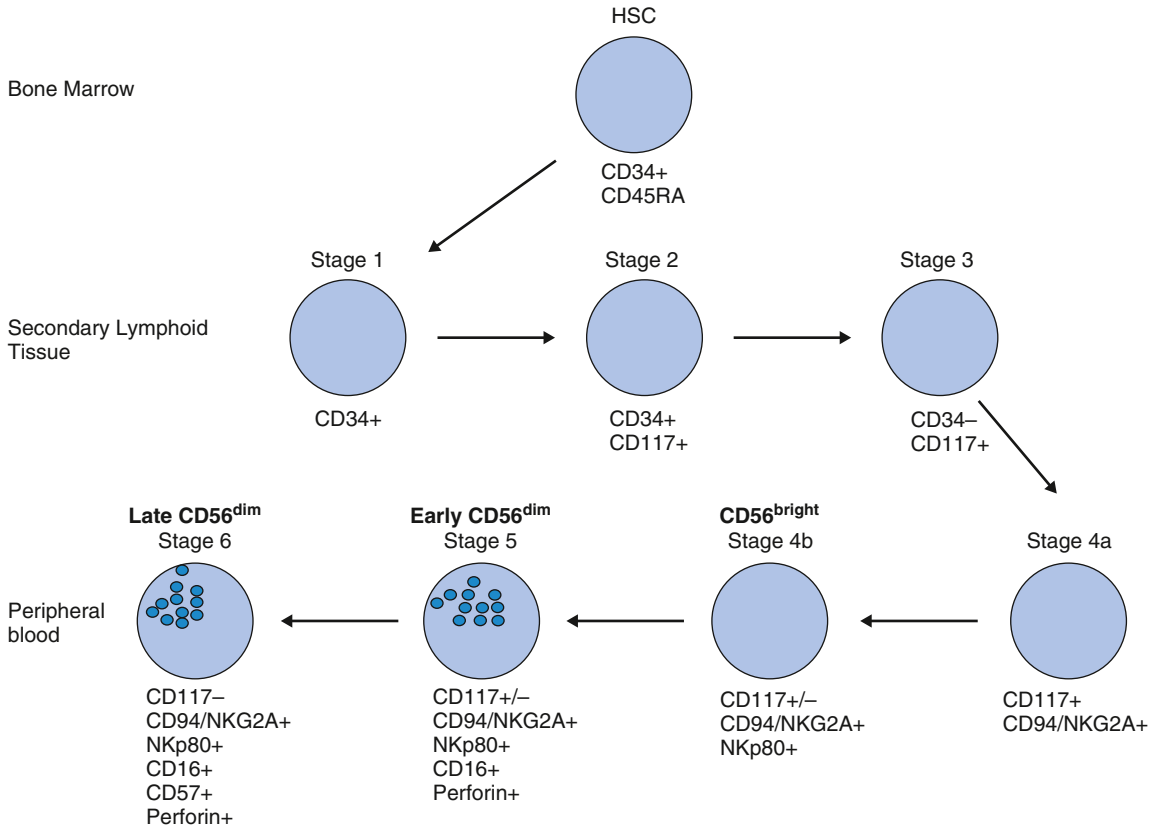

Fig. 167.1 Stages of NK cell development. HSC, Hematopoietic stem cell.

NK cells. It is crucial for the antiviral, antibacterial, and antitumor activity of NK cells through modulating death ligand expression of caspase, FasL, and TRAIL. NK cells are thus able to target cells for death through expression of these death ligands. Death ligand killing is not as rapid as lytic granule killing. Additional NK cell–released cytokines include TNF-α, IL-10, IL-5, and IL-13. NK cells also produce chemokines (chemotactic agents) such as MIP-1α, MIP-1β, IL-8, and RANTES. It is important to note that cytokines and chemokines in NK cells are compartmentalized separately from the lytic granules allowing them to be accessed separately from their cytotoxicity function.

Contact-Dependent Co-Stimulation

NK cells can promote and regulate immunity through direct receptor-ligand interactions with other cells, or contact-dependent co-stimulation. NK cells express or can be induced to express a variety of co-stimulatory and inhibitory ligands including the CD40 ligand, CD28, and PD-1, which can then interact with other types of immune cells to alter immune responses.

NK CELL SPONTANEOUS CYTOTOXICITY

Similar to cytotoxic T cells, NK cells secrete specialized lysosome-related organelles known as **lytic granules**. However, unlike CTLs, the lytic granules inside NK cells are preformed and abundant while the cell is at rest, which allows for their rapid killing response on recognition of cellular distress/disease. Lytic granule contents include **perforin** (pore-forming molecule) and pro-apoptotic enzymes such as **granzymes**. Once an NK cell recognizes an activation signal from a distressed cell, the NK cell will polarize its lytic granules toward the portion of the NK cell membrane in contact with the target cell where the lytic granules will then dock. This is followed by fusion of the secretory lysosome with the plasma membrane of the target cells. The site of NK cell connection with the target cell is called the **lytic immunologic synapse.**

Once a stable connection is formed at the lytic immunologic synapse, cellular killing by the lytic granules will be completed in less than 2 hours. Perforin will insert into the target cell membrane, which will allow for pro-apoptotic granzymes to travel to the target cell and initiate cellular killing.

NK CELL ANTIBODY-DEPENDENT KILLING

NK cells are also able to kill target cells via ADCC. NK cells have an IgG Fc receptor, CD16, expressed on their cell surfaces that allows them to recognize IgG-opsonized targets to promote killing without priming via lysing of the target cell. ADCC also causes NK cell secretion of cytokines like INF-γ for recruitment of adaptive immune cells.

Etiologies of NK Cell Deficiency

NK cells are lymphocytes that are critical for the immune response to viral infections. Patients with recurrent severe and refractory cutaneous viral and herpes viral infections should be evaluated for **NK cell deficiency (NKD)** with both enumeration and functional studies. However, ultimate evaluation should be completed with immunogenetic analysis as patients with diagnosed NKD may benefit from antiviral prophylaxis and eventual HSC transplant.

NKD accounts for a small subset of primary immunodeficiencies (PIDs) that often present as clinical and diagnostic challenges. In general, NKD is suspected in patients who appear to have increased susceptibility to herpesvirus infections as well as select other viral pathogens such a human papillomavirus (HPV).

NK cells can be decreased in number or function for many reasons. More commonly, severe illness and emotional stress can cause decreases of these cells. In addition, immunosuppressive medications such as corticosteroids, mycophenolate, cyclosporine, azathioprine, and 6-mercaptopurine can depress NK cells. Given many factors are known to affect the stability of NK cells, repetition of the test is required to document true deficiency. If a patient is found to have abnormal NK cell studies 3 times, drawn at least 1 month

apart, inborn errors in immunity should be also considered, as described next.

More than 50 PIDs include abnormalities in NK cells as part of their immunophenotypes. This occurs secondary to disruption in maturation, proliferation, or survival of NK cells. Forms of **severe combined immune deficiency (SCID)** including *IL2RG, JAK3,* and *AK2* deficiency are known to present with low or absent NK cell numbers. In addition, given the importance of lytic granule secretion to NK cytotoxicity, conditions with abnormal granule secretion, such as primary **hemophagocytic lymphohistiocytosis**, or abnormal cytoskeletal function, such as **Wiskott-Aldrich syndrome**, also can lead to NK cell aberrations.

NKDs are classified as classical or functional. In **classical NKD**, there is a significantly decreased or absent number of $CD3^{-}CD56^{+}$ cells, making up less than 1% of the total peripheral lymphocytes. Alternatively, although the number of NK cells can be normal in **functional NKD**, these cells are functionally impaired.

Classical NK Cell Deficiency

Classical NKDs include pathogenic variants in *MCM4*, *MCM10*, *GINS1*, *GATA2, RTEL1,* and *IRF8.*

MCM4 and *MCM10*

MCM (mini-chromosome maintenance complex member) 4 and 10 are a part of the MCM replisome progression complex important for DNA replication. *MCM4* is part of the *Cdc45-MCM2-7-GINS1* (CMG) helicase complex and *MCM10* is a replication factor associated with this complex. In times of cellular stress, variant complexes have resulted in abnormal DNA breakage (Fig. 167.2). These patients have a decreased number of NK cells, specifically $CD56^{dim}$ NK cells. $CD56^{dim}$ NK cells are mature NK cells that express CD16 (Fc receptor) and are important for ADCC. It is possible that $CD56^{dim}$ NK cells are particularly reliant on the MCM complex for survival. Alternatively, the pathogenic variant may cause an interruption along development before mature NK cell expansion. Patients with biallelic pathogenic variants in *MCM4* have Epstein-Barr virus (EBV)-driven lymphoproliferation and viral pneumonitis. As *MCM4* is widely expressed in many cells, these patients can also have adrenal insufficiency, short stature, and development delay.

MCM10-deficient patients have a similar immunologic phenotype related to their NK cell abnormalities and the patients reported were found to have severe cytomegalovirus (CMV) infection.

GINS1

Go-Ichi-Ni-San complex subunit 1 (GINS1) is a protein involved in the CMG helicase complex that is important for DNA replication. Biallelic pathogenic variants in *GINS* have been seen to cause growth retardation, neutropenia, and NKD. It is important to note that both $CD56^{dim}$ and $CD56^{bright}$ cells are affected in this disorder. *MCM4, MCM10,* and *GINS1* defects causing classical NKD suggests that chromosomal maintenance is critical to NK cell development and function.

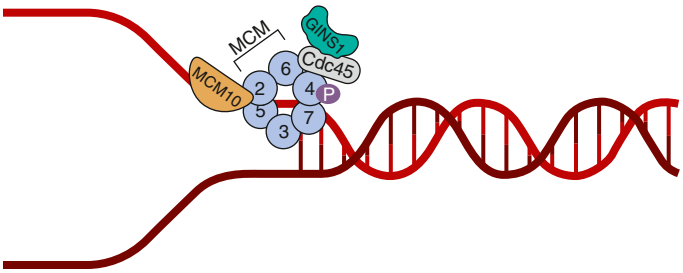

Fig. 167.2 Cell division cycle complex pathogenic variants associated with NK cell deficiency: *MCM4, MCM10, and GINS1*. Schematic illustration of the cell division cycle complex including the CMG (Cdc45, mini-chromosome maintenance [MCM 2-7], GINS1) helicase complex and *MCM10.*

GATA2

Pathogenic variants in *GATA2* (GATA-binding protein-2), inherited in an autosomal dominant manner, can cause immune aberrations affecting many different cell lines. The pathogenic variant prevents appropriate NK cell development with specific deficiency of immature $CD56^{bright}$ NK cells causing an absence of the $CD56^{bright}$ population, leaving a functionally impaired $CD56^{dim}$ population. These patients are known to have refractory HPV infections, among other cutaneous viral infections, myelodysplasias, cytopenias, and a risk of acute and chronic myeloid leukemias.

RTEL1

Biallelic pathogenic variants in regulator of telomerase elongation (*RTEL1)*, a DNA helicase, cause a form of **dyskeratosis congenita**, bone marrow failure, and immunodeficiency known as **Hoyeraal-Hreidarsson syndrome**. One patient reported with a history of disseminated varicella infection was found to have abnormal NK cells in number and function.

IRF8

Interferon regulatory factor 8 *(IRF8)* is a transcription factor involved in B-cell, dendritic cell, granulocyte, monocyte, and NK cell production. *IRF8* is vital for the NK cell response to viral infections and patients have been found to have severe EBV infections. Terminal NK cell maturation is disrupted and $CD56^{dim}$ cells are decreased in patients with biallelic *IRF8* pathogenic variants.

FUNCTIONAL NK CELL DEFICIENCY (FNKCD)

CD16 Deficiency

Patients with CD16 deficiency have severe infections with herpes viral pathogens such as varicella-zoster virus (VZV), herpes simplex virus (HSV) and EBV. One patient was reported to have EBV-driven Castleman disease. The deficiency is caused by a homozygous pathogenic variant in the *FCGR3A* gene, which encodes CD16. CD16 is the Fc receptor on NK cells required for ADCC. As CD16 deficiency is an FNKCD, patients have normal levels of NK cells, but abnormal function. Although CD16's main function is to facilitate ADCC, patients with CD16 deficiency have been found to have abnormal spontaneous cytotoxicity with normal antibody-dependent cytotoxicity (Fig. 167.3). Further analysis helped uncover a new function of the CD16 protein related to spontaneous cytotoxicity, which clarifies this unexpected finding. The variant sequence in CD16 deficiency encodes for the distal B73.1 domain of the CD16 molecule. Studies from patients with this pathogenic variant revealed that this region is needed for co-activation of the NK cell CD2 stimulatory receptor, which is required for spontaneous cytotoxicity. Alternatively, immunoglobulin binding, which is integral to ADCC, occurs at the proximal 3G8 domain of CD16, which is not affected by the variant. For diagnostic purposes, two anti-CD16 monoclonal antibodies are utilized against the distal B73.1 and proximal 3G8 domains. Therefore patients with CD16 deficiency will have absent B73.1 expression and normal 3G8 expression. These diagnostic tests can help identify patients with CD16 deficiency in addition to genetic analysis of *FCGR3A*.

ELF4

E74-like ETS transcription factor 4 (ELF4) is a protein involved in transactivation of gene promoters through DNA binding. Perforin expression, an important component of NK cell activity, has been shown to be dependent on ELF4-regulated promoters. Pathogenic variants in ELF4 can result in poor terminal NK cell maturation

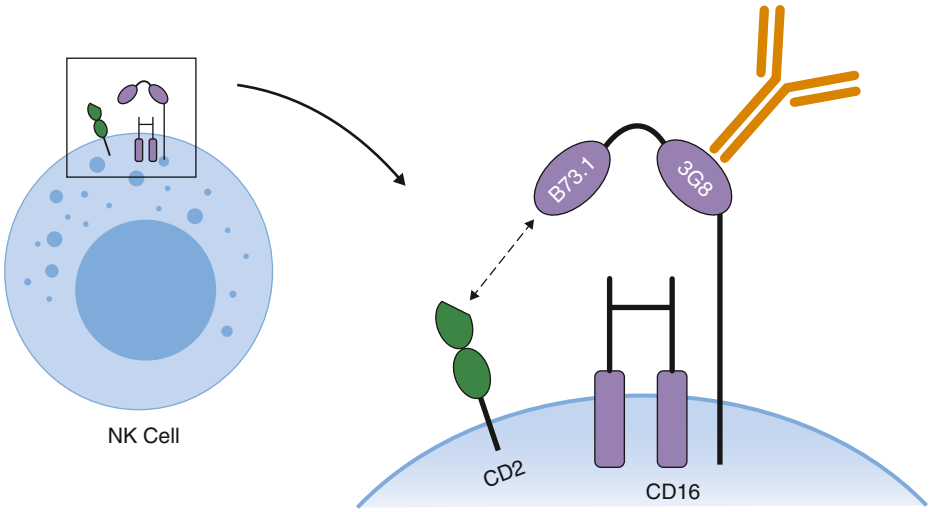

Fig. 167.3 Functional natural killer (NK) cell deficiency secondary to CD16 pathologic variants. Schematic of the CD16 (Fc) NK cell receptor. The proximal domain of the CD16 receptor, 3G8, binds the Fc portion of immunoglobulin, which is important for antibody-depending cytotoxicity. The distal domain of the CD16 receptor, B73.1, co-localizes with the CD2 stimulatory receptor facilitating spontaneous cytotoxicity. In *CD16* deficiency, the B73.1 domain of the CD16 receptor is not adequately expressed causing impaired spontaneous cytotoxicity.

from CD56^{bright} to CD56dim (cytotoxic) NK cells. A rare, hemizygous variant in ELF4, located on the X chromosome, has been described as a novel cause of NK cell deficiency. Patients with this variant can present with recurrent sinopulmonary and varicella zoster infections, as well as lymphoproliferative and malignant disease. Laboratory analysis has shown decreased number and function of NK cells, specifically with an abnormal immature NK cell CD56^{bright} to mature CD56dim NK cell ratio. Because these patients also can present with decreased B cells and hypogammaglobinemia, further work is needed to elucidate the role of ELF4 in B cell development and function.

NK Cell Diagnostic Tests

When evaluating for possible NK cell defects, it is important to examine the total NK cell count and percentage, the distribution of NK cell subsets, and NK cell function.

NK Cell Count and Percentage

The absolute NK cell count and NK cell percentage of total lymphocytes is often calculated using a lymphocyte subset analysis or enumeration assay. This test is performed using flow cytometry and will identify the CD16 and CD56 markers of NK cells. The majority of lymphocyte enumeration assays use a combined CD56/16 antibody and cannot distinguish between CD56^{bright} and CD56^{dim} NK cells. Further delineation of NK cell subsets (CD56^{dim}, CD56^{bright}, etc.) can be obtained with further flow cytometry for additional NK cell markers. Evaluation of NK cell phenotypes and ratios such as the CD56 bright to dim ratio becomes important in evaluating for NK cell defects such as *GATA2* deficiency.

FUNCTIONAL ASSAYS AVAILABLE FOR CLINICAL EVALUATION

NK Cell Cytotoxicity Assay

NK cytotoxic killing ability can be evaluated using a flow cytometry–based assay to quantify NK cell cytotoxic activity or a chromium release (^{51}CR) cytotoxicity assay. The ^{51}CR is technician dependent and requires the use of radioactive material. Many laboratories are doing the flow cytometry-based assay.

Individual clinical laboratories have normal ranges that are particular to their specific assay; however, the values for this assay are dependent on the percentage of NK cells present in the sample. A peripheral blood mononuclear cell (PBMC) sample with lower numbers of NK cells may not identify as much NK cell cytotoxicity as a sample with higher levels of NK cells, thus it is essential to take the percentage of NK cells into account when interpreting these assays.

CD107a Degranulation

Lysosomal-associated membrane protein-1 (LAMP-1) or CD107a is contained in NK cell lytic granules. CD107a is significantly upregulated on the surface of NK cells following lytic granule fusion with the NK cell membrane after activation by MHC I downregulated target cells. CD107a is thus often used as a way to evaluate activation-induced NK cell degranulation. In this test, NK cells are stimulated and the upregulation of CD107a is measured using flow cytometry.

CD107a degranulation has advantages and disadvantages when compared to the NK cell cytotoxicity assay. The main advantage is that CD107a degranulation can be measured in individual cells and is therefore independent of the NK cells percentage. The disadvantage is that it does not directly measure NK cell killing ability. NK cell killing can be impaired despite appropriate degranulation for reasons such as abnormal lytic effector molecules. Ten to 30% of resting NK cells can be induced to degranulate when measured by flow cytometry, and in normal individuals CD107a degranulation reasonably correlates with killing ability.

NK CELL DEFICIENCY TREATMENT

Primarily, treatment of NKD targets the infectious complications that occur in these patients. Specifically, HSV infections should be treated with antiviral therapy such as acyclovir. Long-term prophylaxis should be considered after completion of treatment. HPV infections can be significant and recurrent, and patients should be referred to dermatology for medical and surgical management.

Additional therapies such as immunoglobulin replacement and antimycobacterial prophylaxis can be utilized depending on the genetic cause of NKD. The only curative therapy for classical NKDs at this time is HSC transplantation.

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Section 3

The Phagocytic System

Chapter 168

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.

Neutrophils provide the rapid effector arm of the innate immune system. They circulate in the bloodstream for only about 6 hours (Table 168.1), but on encountering specific chemotactic signals, they adhere to the vascular endothelium and transmigrate into tissues. There 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 viewed 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. 168.1). Common lymphoid progenitor cells give rise to T- and B-cell precursors and their mature progeny. 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 495). 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.

Table 168.1 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, eds. *Cecil Textbook of Medicine*. 20th ed. Philadelphia: Saunders; 1996.

The proliferation, differentiation, and survival of immature hematopoietic progenitor cells are governed by hematopoietic growth factors, a family of glycoproteins (see Chapter 495). Along with 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 nondividing, 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 and macrophage colony-stimulating factors. 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 (G-CSF) and granulocyte-macrophage colony-stimulating factor (GM-CSF) 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 GATA1, 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 rise to initiate terminal differentiation.

Granulocytes survive for only 6-12 hours in the circulation; 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 168.1). 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 five mitotic divisions, takes place only during the first three 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 the sequential production of characteristic granule populations. A **myeloblast** is a relatively undifferentiated cell with a large oval nucleus, a sizable 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.

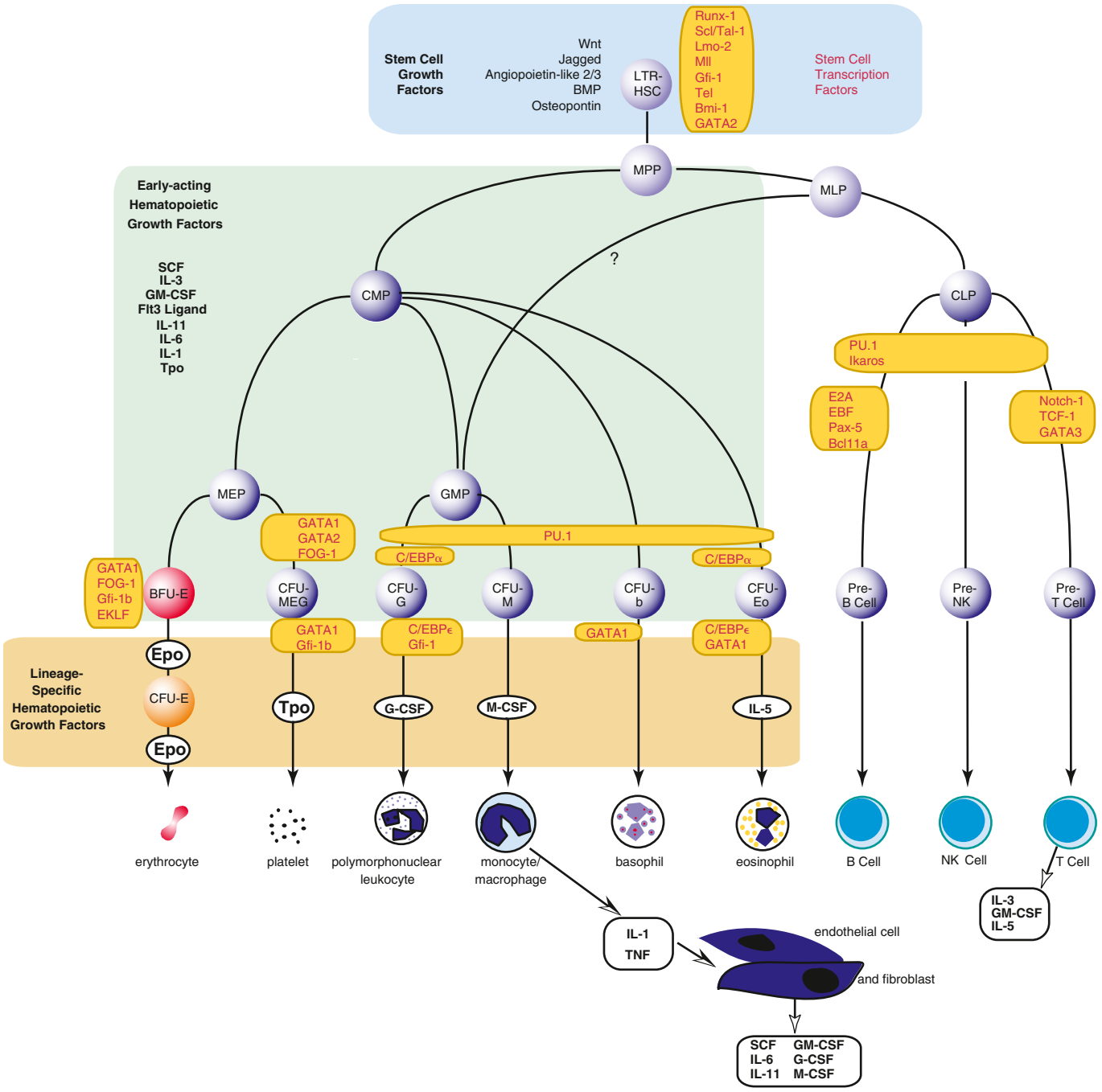

Fig. 168.1 Major cytokine sources and actions and transcription factor requirements for hematopoietic cells. Cells of the bone marrow microenvironment, such as macrophages, endothelial cells, and reticular fibroblastoid cells, produce macrophage, granulocyte-macrophage, and granulocyte colony-stimulating factors (M-CSF, GM-CSF, G-CSF), interleukin-6 (IL-6), and probably stem cell factor (SCF) (cellular sources not precisely determined) 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-acting and late-acting factors. Transcription factors important for survival or self-renewal of stem cells are shown in *red* at the *top*, whereas stages of hematopoiesis blocked after the depletion of indicated transcription factors are shown in *red* for multipotent and committed progenitors. *(From Sieff CA, Daley GQ, Zon LI. Anatomy and physiology of hematopoiesis. In: Orkin SH, Fisher DE, Ginsburg D, et al., eds. Nathan and Oski's Hematology and Oncology of Infancy and Childhood. 8th ed. Philadelphia: Elsevier; 2015. Fig 1.7.)*

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. 168.2). 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

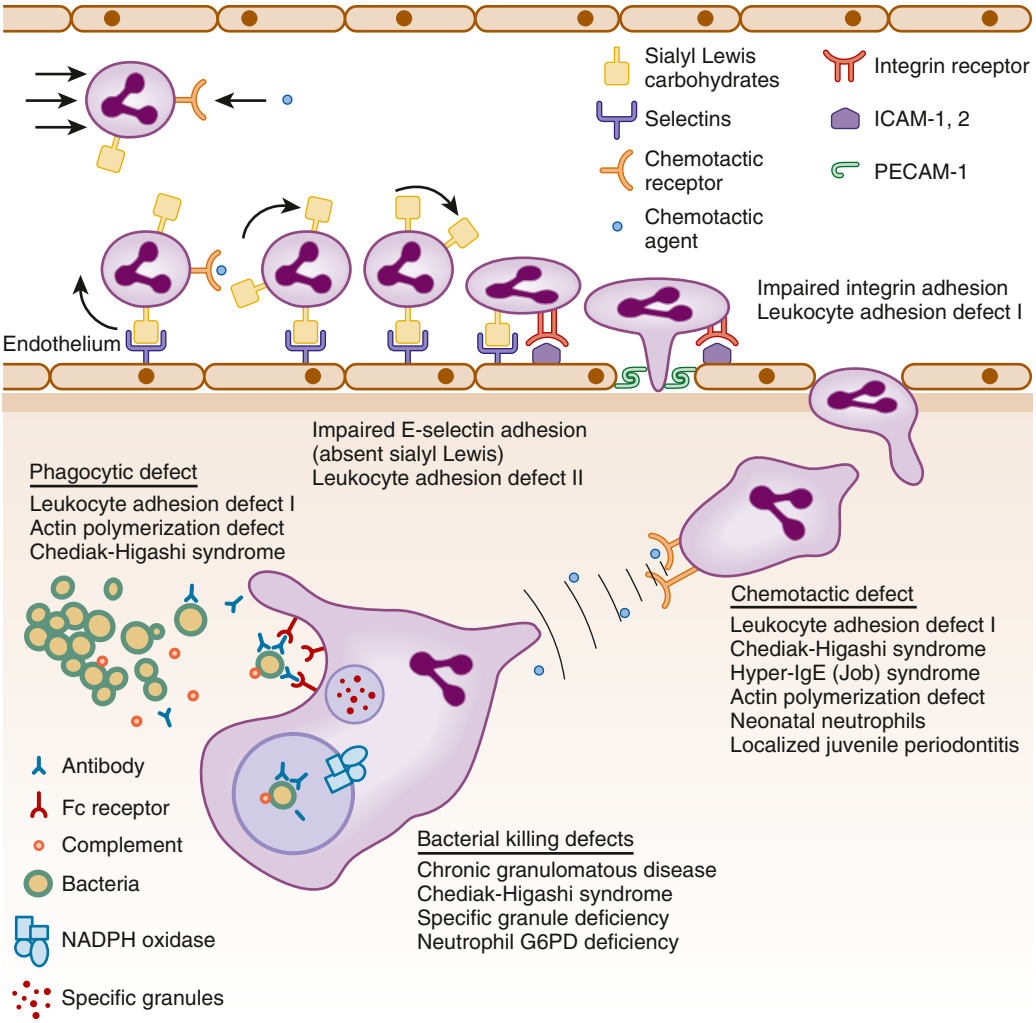

Fig. 168.2 The neutrophil-mediated inflammatory response and associated neutrophil dysfunction syndromes. Circulating neutrophils loosely attach to endothelium via selectins and roll along the vessel wall until they arrive at the site of infection. Inflammatory monokines, interleukin-1 (IL-1), and tumor 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 intracellular adhesion molecule (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. NADPH, Nicotinamide-adenine dinucleotide phosphate; PECAM, platelet endothelial cell adhesion molecule. *(Modified from Kyono W, Coates TD. A practical approach to neutrophil disorders. Pediatr Clin North Am. 2002;49:929.)*

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 (see Fig. 168.2). Exposure of neutrophils to these same activating factors induces 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-second 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, then 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. 168.3), where two 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 occur at the phagosome membrane as well (see Fig. 168.3), generating large amounts of superoxide (O_2^-) from molecular oxygen, which in turn decomposes to produce hydrogen peroxide (H_2O_2) and singlet oxygen. **Myeloperoxidase,** a major azurophil granule component, catalyzes the reaction

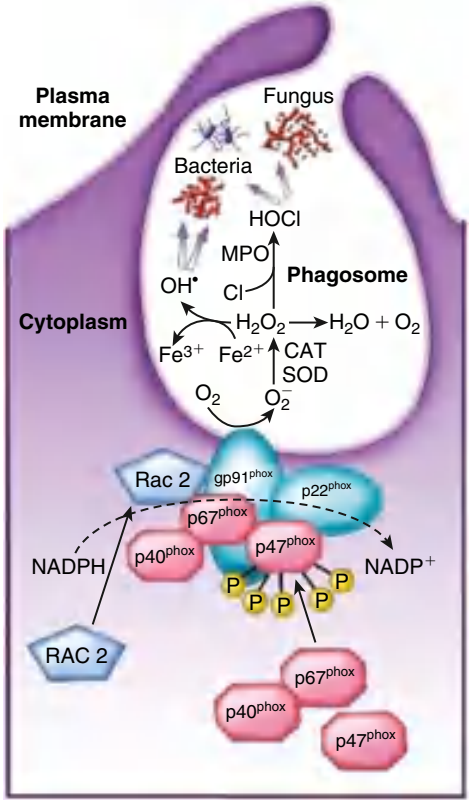

Fig. 168.3 Nicotinamide adenine dinucleotide phosphate (NADPH) oxidase components and activation. On activation of phagocytic cells, the 3 cytosolic components *(red)* of the NADPH oxidase (p67^{phox}, p47^{phox}, and p40^{phox}), plus the small guanosine triphosphatase (GTPase) protein Rac2, are translocated 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 catalyzes 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). H_2O_2 can follow different metabolic pathways into more potent reactive oxidants, such as OH• or HOCl) or degradation to $H_2O + O_2$. *(Adapted from Stiehm ER, Ochs HD, Winkelstein JA. Immunologic Disorders in Infants and Children, 5th ed. Philadelphia: Saunders; 2004, p. 622.)*

of H_2O_2 with ubiquitously present chloride ions to create hypochlorous acid (HOCl) in the phagosome. 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. In addition to the role of neutrophils in tissue damage, they are now known to play a significant role in regulation of inflammation and promoting tissue repair. Turning off inflammation and removing tissue debris is an important role and, like seeking and destroying bacteria, this process is highly regulated as well.

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Chapter 169

Eosinophils

Benjamin L. Wright and Brian P. Vickery

Eosinophils are nondividing, fully differentiated cells with a diameter of approximately 8 μm and a bilobed nucleus that are distinguished from other leukocytes by their morphology, constituent products, and association with specific diseases. Their characteristic membrane-bound specific granules stain bright pink with eosin and 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 185). Eosinophil granule proteins including major basic protein, eosinophil cationic protein, eosinophil-derived neurotoxin, and eosinophil peroxidase are thought to inflict epithelial cell damage, although recent studies indicate their role may be more nuanced and not purely destructive. Eosinophil granule contents activate other proinflammatory cells, including mast cells, basophils, neutrophils, and platelets and have the capacity to generate large amounts of the lipid mediators, which can cause vasoconstriction, smooth muscle contraction, and mucus hypersecretion (Fig. 169.1). Eosinophils are a source of several proinflammatory cytokines and have also been shown to influence T-cell recruitment and immune polarization in inflammatory settings. Thus eosinophils have considerable potential to initiate and sustain the 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 (e.g., VLA-4) to their ligands or counterstructures (VCAM-1) on the postcapillary endothelium. Eosinophils are recruited to tissues in inflammatory states by a group of chemokines known as **eotaxins** (eotaxin 1, 2, and 3). 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 (GI), and lower genitourinary tracts. The life span of eosinophils may extend for weeks within tissues.

Interleukin (IL)-5 selectively enhances eosinophil production, adhesion to endothelial cells, and function. Considerable evidence shows that IL-5 has a pivotal role in promoting eosinophilopoiesis. It is the predominant cytokine in allergen-induced pulmonary late-phase reaction, and antibodies against IL-5 (mepolizumab, reslizumab, benralizumab) decrease sputum eosinophils and reduce exacerbations in a subset of patients with asthma. Eosinophils also bear unique receptors for several chemokines, including RANTES (regulated on 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 peripheral blood eosinophilia. Calculated as the white blood cell (WBC) count/μL × percentage 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 169.1). These disorders may range from mild and transient to chronic and life-threatening. Importantly, blood eosinophil numbers do not always reflect the extent of eosinophil involvement in tissues and degranulation products may more accurately reflect disease activity. Because prolonged eosinophilia is associated with end-organ

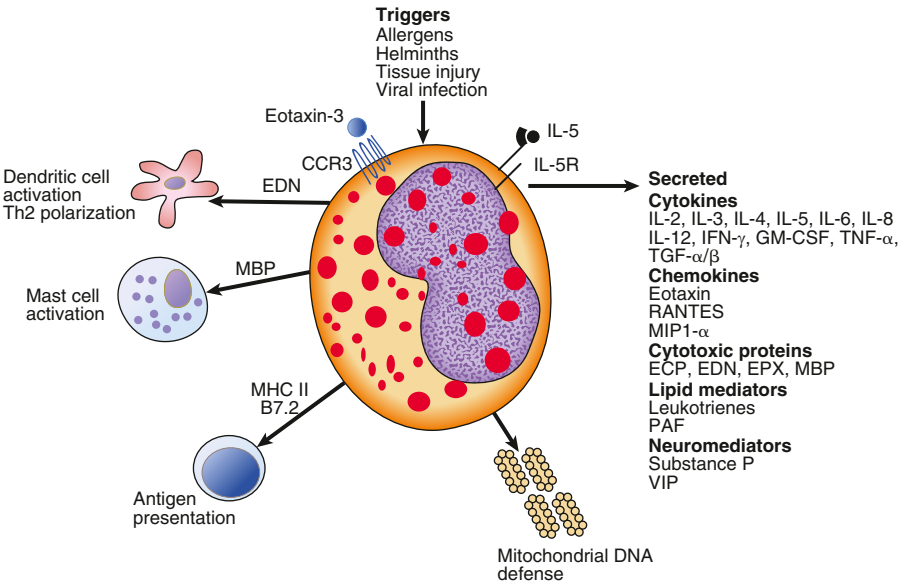

Fig. 169.1 Schematic diagram of an eosinophil and its diverse properties. Eosinophils are bilobed granulocytes that respond to diverse stimuli, including allergens, helminths, viral infections, allografts, and nonspecific tissue injury. Eosinophils express the receptor for interleukin (IL)-5, a critical eosinophil growth and differentiation factor, as well as the receptor for eotaxin and related chemokines (CCR3). The secondary granules contain four primary cationic proteins designated eosinophil peroxidase (EPX), major basic protein (MBP), eosinophil cationic protein (ECP), and eosinophil-derived neurotoxin (EDN). All four proteins are cytotoxic molecules; also, ECP and EDN are ribonucleases. In addition to releasing their preformed cationic proteins, eosinophils can release a variety of cytokines, chemokines, and neuromediators and generate large amounts of leukotriene C4 (LTC4). Last, eosinophils can be induced to express major histocompatibility complex (MHC) class II and co-stimulatory molecules and may be involved in propagating immune responses by presenting antigen to T cells. PAF, platelet activating factor; VIP, vasoactive intestinal peptide. *(From Leung YM, Szefler SJ, Bomilla FA, Akdis CA, Sampson HA. Pediatric Allergy: Principles and practice. 3rd ed. Philadelphia: Elsevier; 2016. p. 42.)*

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 typically 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 193). 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.

Eosinophilic gastrointestinal diseases (EGIDs) are important emerging allergic causes of eosinophilia in tissue and, in some cases, peripheral blood (see Chapter 383). In these conditions, eosinophils are recruited to the esophagus, stomach, and/or intestine, where they may cause tissue inflammation and clinical symptoms such as dysphagia, food aversion, abdominal pain, vomiting, or diarrhea. Eosinophilic esophagitis is the most common EGID. Treatment options include proton pump inhibitors, allergen elimination diets, topical corticosteroids, and biologics (e.g. dupilumab). Patients with nonesophageal EGIDs often require treatment with systemic steroids.

Infectious Diseases

Eosinophilia is often associated with invasive infection with multicellular helminthic parasites, which are the most common cause in developing countries. Table 169.1 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 344). Eosinophilia often *does not* occur in established parasitic infections that are well contained within tissues or are solely intraluminal in the GI 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 three 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 344). Most young children are asymptomatic, but some develop fever, pneumonitis, hepatomegaly, and hypergammaglobulinemia accompanied by severe eosinophilia. Isohemagglutinins are frequently elevated, and serology can establish the diagnosis.

Two fungal diseases may be associated with eosinophilia: aspergillosis in the form of **allergic bronchopulmonary aspergillosis** (see Chapter 283) and **coccidioidomycosis** (see Chapter 286) following primary infection, especially in conjunction with erythema nodosum. HIV infection 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 three diagnostic criteria for this disorder are (1) AEC >1,500 cells/μL persisting for 6 months or longer or at least on two 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, GI) involvement. Organ-specific signs and symptoms direct the diagnostic evaluation, but common initial tests used to evaluate hypereosinophilia and potential end-organ complications include a comprehensive metabolic panel, inflammatory markers, troponin level, urinalysis, antineutrophil cytoplasmic antibodies, immunoglobulin levels, vitamin B_{12} level, tryptase level, stool examination for ova and parasites, parasite serologies, HIV testing, and a chest x-ray. Eosinophilic endomyocardial disease, one of the most serious and life-threatening complications, can cause heart failure from endomyocardial thrombosis and fibrosis. Screening for cardiac involvement should also include an electrocardiogram, an echocardiogram, and in some cases a cardiac MRI. Evaluation of the hypereosinophilic syndrome requires morphologic review of the blood and marrow, cytogenetics, fluorescence in situ hybridization, immunophenotyping by flow cytometry, and T-cell clonality assessment to detect histopathologic or clonal evidence for hematolymphoid neoplasm. Eosinophilic leukemia, a clonal myeloproliferative variant, may be distinguished from idiopathic hypereosinophilic syndrome

Table 169.1 Causes of Eosinophilia

ALLERGIC DISORDERS
Allergic rhinitis
Asthma
Acute and chronic urticaria
Atopic dermatitis
Angioedema
Hypersensitivity drug reactions (drug rash with eosinophilia and systemic symptoms [DRESS])
Eosinophilic gastrointestinal disorders
Interstitial nephritis
Mastocytosis

INFECTIOUS DISEASES
Tissue-Invasive Helminth Infections and Other Infections
Trichinosis
Toxocariasis
Strongyloidiasis
Ascariasis
Filariasis
Schistosomiasis
Echinococcosis
Amebiasis
Malaria
Scabies
Toxoplasmosis
Pneumocystis jirovecii
Scarlet fever
Allergic bronchopulmonary aspergillosis (ABPA)
Coccidioidomycosis
Human immunodeficiency virus (HIV)

MALIGNANT DISORDERS
Hodgkin disease and T-cell lymphoma
Acute myelogenous leukemia
Myeloproliferative disorders
Eosinophilic leukemia
Brain tumors

GASTROINTESTINAL DISORDERS
Inflammatory bowel disease
Peritoneal dialysis
Chronic active hepatitis
Eosinophilic Gastrointestinal Disorders
Eosinophilic esophagitis
Eosinophilic gastritis
Eosinophilic enteritis
Eosinophilic colitis

RHEUMATOLOGIC DISEASE
Rheumatoid arthritis
Eosinophilic fasciitis
Scleroderma
Dermatomyositis
Systemic lupus erythematosus
IgG4-related disease
Eosinophilic granulomatosis with polyangiitis (Churg-Strauss vasculitis)

IMMUNODEFICIENCY/IMMUNE DYSREGULATION DISEASE
Hyperimmunoglobulin E syndromes
Wiskott-Aldrich syndrome
Graft-versus-host disease
Omenn syndrome
Severe congenital neutropenia
Autoimmune lymphoproliferative syndromes (ALPS)
Immune dysregulation, polyendocrinopathy, X-linked (IPEX) and IPEX-like syndrome
Transplant rejection (solid organ)

MISCELLANEOUS
Thrombocytopenia with absent radii
Hypersensitivity pneumonitis
Adrenal insufficiency
Postirradiation of abdomen
Histiocytosis with cutaneous involvement
Hypereosinophilic syndromes
Cytokine infusion
Pemphigoid

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, a tyrosine kinase inhibitor, which helps target the fusion oncoprotein (Fig. 169.2).

Therapy is aimed at suppressing eosinophilia and is initiated with corticosteroids. Patients with possible exposure to *Strongyloides* should receive concomitant empiric treatment with ivermectin to prevent corticosteroid-associated hyperinfection syndrome. Imatinib mesylate may be effective in FIP1L1-PDGFRA–negative patients. Hydroxyurea or interferon-alfa 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 about 75% after 3 years.

Miscellaneous Diseases

Eosinophilia is observed in many patients with primary immunodeficiency syndromes, especially hyper-IgE syndrome, Wiskott-Aldrich syndrome, and Omenn syndrome (see Chapter 165). Eosinophilia is also frequently present in the syndrome of thrombocytopenia with absent radii and in familial reticuloendotheliosis with eosinophilia. Eosinophilia can be found in patients with Hodgkin disease, as well as in acute lymphoid and myeloid leukemia. Other considerations include GI disorders such as ulcerative colitis, Crohn disease during symptomatic phases, chronic hepatitis, eosinophilic granulomatosis with polyangiitis (Churg-Strauss vasculitis), mastocytosis, and adrenal insufficiency.

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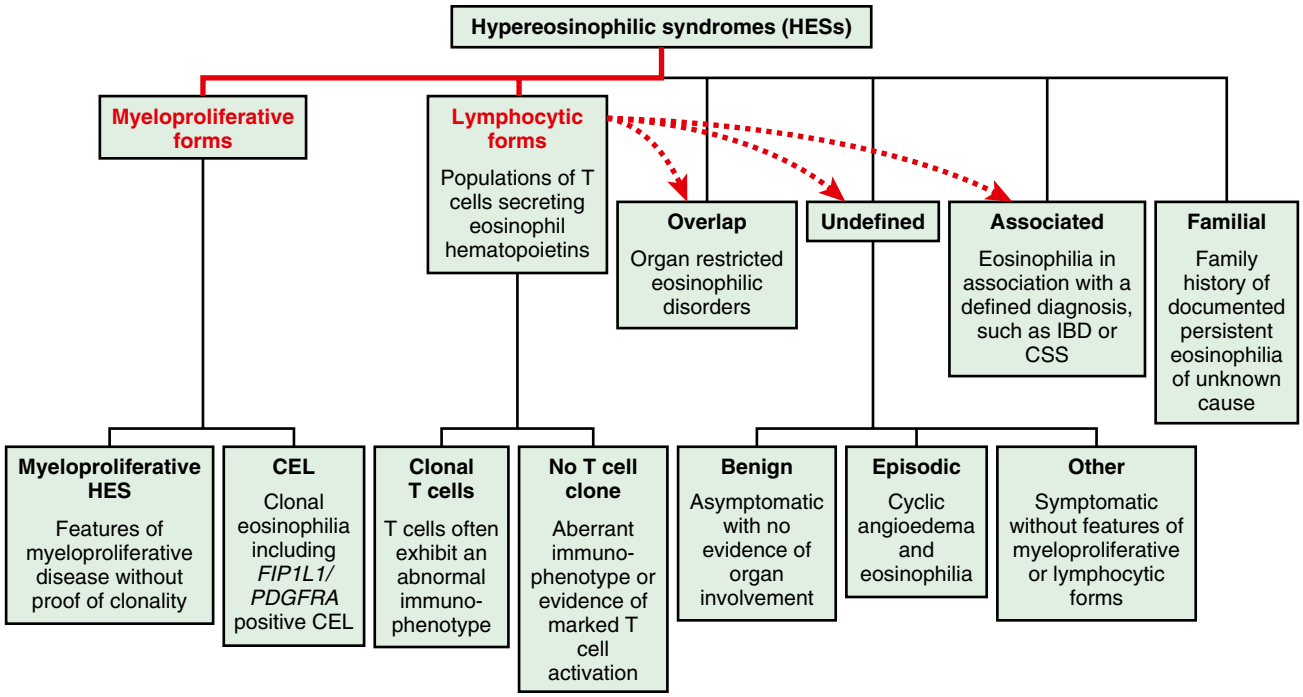

Fig. 169.2 Revised classification of hypereosinophilic syndromes. Changes from the previous classification are indicated in *red*. *Dashed arrows* identify hypereosinophilic syndrome (HES) forms for which at least some patients have T-cell–driven disease. Classification of myeloproliferative forms has 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. CEL, Chronic eosinophilic leukemia; CSS, Churg-Strauss syndrome; IBD, inflammatory bowel disease. *(From Simon HU, Rothenberg ME, Bochner BS, et al. Refining the definition of hypereosinophilic syndrome.* J Allergy Clin Immunol. *2010;126:45-49.)*

Chapter 170

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 hours after microbial invasion to contain the infection and prevent hematogenous dissemination. 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 168.2. Children with phagocytic dysfunction present at a young age with recurrent infections that often involve unusual organisms and are poorly responsive to treatment.

Primary defects of phagocytic function comprise <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, cutaneous lesions, or osteomyelitis rather than bloodstream infections (Tables 170.1 and 170.2; Fig. 170.1). In the past, diagnosis of these disorders relied on very specialized biologic assays. Because the genes for most of these disorders have been identified, the first step in diagnosis for all of these disorders is to obtain DNA analysis through commercially available genetic panels for immunodeficiency.

Chemotaxis, the direct migration of cells into sites of infection, involves a complex series of events (see Chapter 168). 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. One family with recessively inherited neutrophil actin dysfunction demonstrated that a pure severe chemotactic defect can result in fatal recurrent infection. Defective in vitro chemotaxis of neutrophils can be detected in children with 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. 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. Tender cutaneous nodular lesions may also be present and characteristically do not contain neutrophils. In fact, the 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 hands. The assays must be done on freshly obtained blood and are affected by many factors related to the blood sampling. It is best to assay other features of the suspected disorder, such as surface marker expression, to establish a specific diagnosis.

Table 170.1 Infections and White Blood Cell 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**	**MICRO-ORGANISM**	**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, hyper-IgE syndrome; LAD, leukocyte adhesion deficiency; MPO, myeloperoxidase; MSMD, mendelian susceptibility to mycobacterial disease; SCID, severe combined immunodeficiency.
From Leung DYM. *Pediatric Allergy: Principles and Practice*. 2nd ed. Philadelphia: Saunders; 2010. p. 134.

Table 170.2 Clinical Disorders of Neutrophil Function

DISORDER	ETIOLOGY	IMPAIRED FUNCTION	CLINICAL CONSEQUENCE
DEGRANULATION ABNORMALITIES			
Chédiak-Higashi syndrome (CHS)	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 hemophagocytic syndrome
Specific granule deficiency	Autosomal recessive; functional loss of myeloid transcription factor arising from a pathogenic variant or arising from reduced expression of *Gfi-1* or *C/EBPε*, 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 (LAD-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 iC3b to neutrophils and impaired adhesion to ICAM-1 and ICAM-2	Neutrophilia; recurrent bacterial infection associated with a lack of pus formation
Leukocyte adhesion deficiency 2 (LAD-2)	Autosomal recessive; loss of fucosylation of ligands for selectins and other glycol conjugates arising from pathogenic variants of 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 pathogenic variants 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 170.2 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, possibly the result of excessive IL-1β production	Recurrent fever, peritonitis, pleuritis, arthritis, 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, CHS, 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 one 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 (CGD)	X-linked and AR; 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	<5% of normal activity of G6PD	Failure to activate NADPH-dependent oxidase; hemolytic anemia	Infections with catalase-positive microorganisms
Myeloperoxidase deficiency	Autosomal recessive; failure to process modified precursor protein arising from missense variant	H_2O_2-dependent antimicrobial activity not potentiated by myeloperoxidase	None
Rac2 deficiency	Autosomal dominant; dominant negative inhibition by variant 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; ELAM, endothelial-leukocyte adhesion molecule; FMF, familial Mediterranean fever; G6PD, glucose-6-phosphate dehydrogenase; GDP, guanosine diphosphate; ICAM, intracellular adhesion molecule; IL-1, interleukin-1; NADPH, nicotinamide adenine dinucleotide phosphate; NK, natural killer.

Adapted from Curnutte JT, Boxer LA. Clinically significant phagocytic cell defects. In: Remington JS, Swartz MN, eds. *Current Clinical Topics in Infectious Disease*. 6th ed. New York: McGraw-Hill; 1985. p. 144.

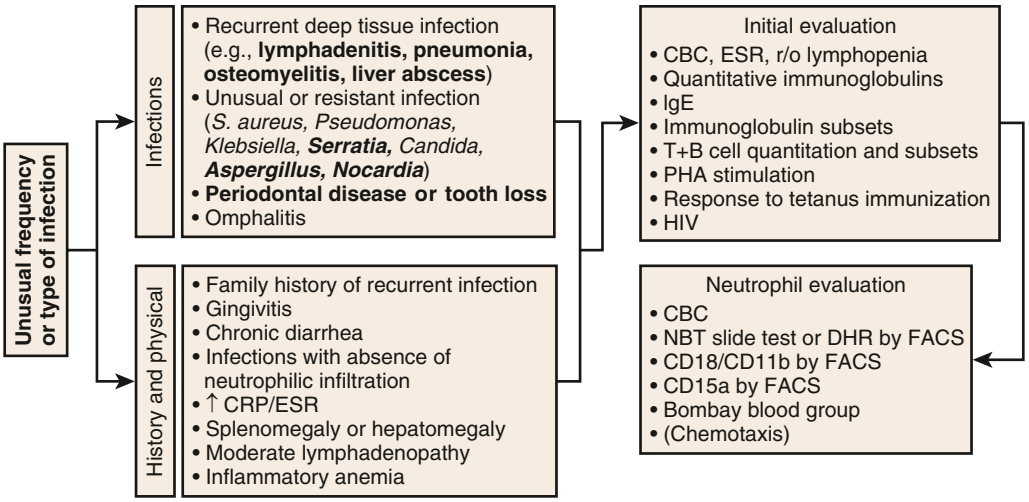

Fig. 170.1 Algorithm for clinical evaluation of patients with recurrent infections. Shown are the evaluations that can be done in a routine clinical laboratory. The complete blood count (CBC) can detect marked leukocytosis in leukocyte adhesion deficiency (LAD) and giant granules of Chédiak-Higashi syndrome may be seen on the smear. Chemotaxis and all other neutrophil function assays require highly specialized research laboratories. CD, Cluster of differentiation; CRP, C-reactive protein; DHR, dihydrorhodamine; ESR, erythrocyte sedimentation rate; FACS, fluorescence-activated cell sorter; HIV, human immunodeficiency virus; IgE, immunoglobulin E; NBT, nitroblue tetrazolium; PHA, phytohemagglutinin. *(Adapted from Dinauer, MC, Coates TD: Disorders of neutrophil function. In: Hoffman R, Benz EJ, Silberstein LE, et al., eds.* Hematology: Basic Principles and Practice. *6th ed. Philadelphia: Saunders; 2012.)*

LEUKOCYTE ADHESION DEFICIENCY

Leukocyte adhesion deficiency types 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 recurrent bacterial and fungal infections and depressed inflammatory responses despite striking blood neutrophilia (Table 170.3).

Genetics and Pathogenesis

LAD-1 results from pathogenic variants of the gene on chromosome 21q22.3 encoding CD18, the 95-kDa β_2-leukocyte transmembrane integrin subunit. Normal neutrophils express four heterodimeric adhesion molecules: LFA-1 (CD11a/CD18), Mac-1 (CD11b/CD18, also known as CR3 or iC3b receptor), p150,95 (CD11c/CD18), and $\alpha_{1\beta2}$ (CD11d/CD18). These four transmembrane adhesion molecules are composed of unique extracellular α_1 encoded on chromosome 16, and they 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 pathogenic variants 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 168), 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. Therefore other neutrophil functions such as degranulation and oxidative metabolism normally triggered by iC3b binding are also greatly 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 (CDG-IIc)** derives from pathogenic variants in the gene encoding a specific guanosine diphosphate (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 those seen in LAD-1, and failure of leukocytes to undergo β_2- and β_1-integrin–mediated adhesion and migration. Pathogenic variants 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 who can have cord separation at age 3 weeks or later. Skin infection may progress to large chronic ulcers with polymicrobial infection, including anaerobic organisms (Fig. 170.2). 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. 170.3). Infected areas characteristically have very little neutrophilic infiltration (absent pus).

The pathogens infecting patients with LAD-1 are similar to those affecting patients with severe neutropenia (see Chapter 171) and

Table 170.3 Leukocyte Adhesion Deficiency Syndromes

LEUKOCYTE ADHESION DEFICIENCY (LAD)	TYPE 1 (LAD-1)	TYPE 2 (LAD-2 OR CDG-IIc)	TYPE 3 (LAD-3)	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)	β_2-Integrin 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

CDG-IIc, Congenital disorder of glycosylation IIc, OMIM, Online Mendelian Inheritance in Man.
From Leung DYM. *Pediatric Allergy: Principles and Practice.* 2nd ed. Philadelphia: Saunders; 2010. p. 139.

Fig. 170.2 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 Practice. *4th ed. Philadelphia: Saunders; 2013, p. 273.)*

Fig. 170.3 Oral pathology in a patient with leukocyte adhesion deficiency type 1 (LAD-1). Gingivitis and severe periodontitis are hallmarks of LAD-1. *(From Rich RR.* Clinical Immunology: Principles and Practice. *4th ed. Philadelphia: Saunders; 2013, p. 273.)*

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 have significantly reduced severity and frequency of infections compared with 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, although 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). One patient was successfully treated with ustekinumab, an inhibitor of interleukins 12 and 23. Other treatment is largely supportive. Patients can be maintained on prophylactic trimethoprim/sulfamethoxazole (TMP/SMX) 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.

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 556.2). 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 as abnormalities in natural killer (NK) function, again related to granule dysfunction.

Genetics and Pathogenesis

LYST (for lysosomal traffic regulator), the gene variant 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. While HSCT can cure the neutrophil defect and hemophagocytic lymphohistiocytosis, it does nothing for neurologic complications.

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 (CGD) to be falsely positive. Unlike CGD, eosinophils in severe MPO deficiency will still reduce DHR and yield a normal reaction.

Treatment

There is no specific therapy for MPO deficiency. 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, affecting 4-5 per 1 million individuals; it is caused by four genes: one X-linked and three autosomal recessive inheritance (Table 170.4).

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. 168.3). Oxidase activation initiates with phosphorylation of a cationic cytoplasmic protein, $p47^{phox}$ (47-kDa phagocyte oxidase protein). Phosphorylated $p47^{phox}$, together with two 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. The flavocytochrome is a heterodimer composed of $p22^{phox}$ and highly glycosylated $gp91^{phox}$. The

Table 170.4 Classification of Chronic Granulomatous Disease

COMPONENT AFFECTED	INHERITANCE	SUBTYPE*	FLAVOCYTOCHROME b SPECTRUM	NBT SCORE (% POSITIVE)	INCIDENCE (% OF CASES)
gp91^{phox}	X	X91^{0}	0	0	60
		X91^{-}	Low	80-100 (weak)	5
		X91^{-}	Low	5-10	<1
		X91^{+}	0	0	1
p22^{phox}	A	A220	0	0	4
		A22^{+}	N	0	<1
p47^{phox}	A	A470	N	0†	25
p67^{phox}	A	A670	N	0	5
		A67^{+}	N	0	<1
p40^{phox}	A	A40^{-}	N	100	<1

*In this nomenclature, the first letter represents the mode of inheritance (X-linked [X] or autosomal recessive [A]), whereas the number indicates the *phox* component that is genetically affected. The superscript symbols indicate whether the level of protein of the affected component is undetectable (^{0}), diminished ($^{-}$), or normal ($^{+}$), as measured by immunoblot analysis.

†Can be weakly positive.

NBT, Nitroblue tetrazolium.

From Dinauer MC, Newburger PE, Borregaard N. Phagocyte system and disorders of granulopoiesis and granulocyte function. In: Orkin SH, Fisher DE, Ginsburg D, et al., eds. *Nathan and Oski's Hematology and Oncology of Infancy and Childhood.* 8th ed. Philadelphia: Elsevier; 2015. Table 22.12, p. 833.

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 pathogenic variants in *CYBB*, an X-chromosome gene encoding gp91^{phox}. Approximately 35% of patients inherit CGD in an autosomal recessive fashion resulting from pathogenic variants in the *NCF1* gene on chromosome 7, encoding p47^{phox}. Defects in the genes 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. 170.4). Hematoxylin-eosin–stained sections from patients' tissues show multiple granulomas that give CGD its descriptive name.

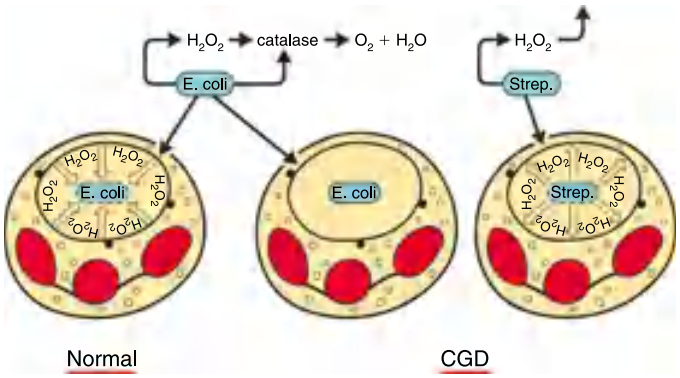

Fig. 170.4 Pathogenesis of chronic granulomatous disease (CGD). The manner in which the metabolic deficiency of the CGD neutrophil predisposes the host to infection is shown schematically. Normal neutrophils stimulate hydrogen peroxide (H_2O_2) in the phagosome containing ingested *Escherichia coli*. Myeloperoxidase is delivered to the phagosome by degranulation, as indicated by the *closed circles*. In this setting, H_2O_2 acts as a substrate for myeloperoxidase to oxidize halide to hypochlorous acid and chloramines that kill the microbes. The quantity of H_2O_2 produced by the normal neutrophil is sufficient to exceed the capacity of catalase, an H_2O_2-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 H_2O_2 because the neutrophils do not produce it, and the H_2O_2 generated by microorganisms themselves is destroyed by their own catalase. When CGD neutrophils ingest streptococci, which lack catalase, the organisms generate enough H_2O_2 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. *(Adapted from Boxer LA. Quantitative abnormalities of granulocytes. In: Beutler E, Lichtman MA, Coller BS, et al., eds.* Williams Hematology. *6th ed. New York: McGraw-Hill; 2001. p. 845.)*

Clinical Manifestations

Although the clinical presentation is variable, several features suggest the diagnosis of CGD. These include any patient with *recurrent* pneumonia, lymphadenitis, hepatic, subcutaneous, or other abscesses, osteomyelitis at multiple sites, family history of recurrent infections, or any infection with an unusual catalase-positive organism requires evaluation (Fig. 170.5). Other clinical features include chronic colitis or enteritis, gastric outlet or ureteral obstruction from granulomas, or bloodstream infection caused by *Salmonella*, *Burkholderia cepacia,* or *Candida*.

The onset of clinical signs and symptoms usually occurs in early infancy, although a few patients with very rare CGD subtypes have presented later in life. The attack rate and severity of infections are exceedingly variable; however, the infection incidence decreases in the second decade, coincident with maturation of the lymphocyte and humoral immunity. The most common pathogen is *S. aureus,* but 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 mycobacteria, including the bacille 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. Patients may have 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 CGD.

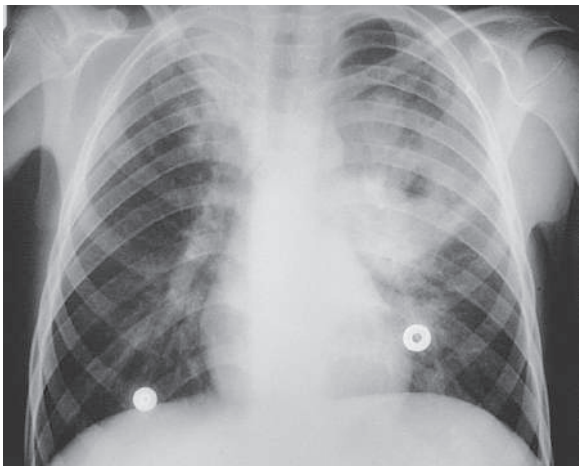

Fig. 170.5 Chest radiograph of a 10-year-old boy with chronic granulomatous disease shows a left-sided pulmonary infiltrate and cavitary lung lesion. Biopsy revealed an *Aspergillus fumigatus* infection. *(From Chinn IK, Chinen J, Shearer WT. Primary immunodeficiency diseases. In Cherry JD, Harrison GJ, Kaplan SL, et al., eds.* Feigin and Cherry's Textbook of Pediatric Infectious Diseases. *8th ed. Philadelphia: Elsevier; 2019. Fig. 67.6, p. 652.)*

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 corticosteroids and discontinuation of interferon-γ treatment.

Laboratory Findings

The diagnosis is most often made by performing flow cytometry using DHR to measure oxidant production through its increased fluorescence when oxidized by hydrogen peroxide (H_2O_2). The nitroblue tetrazolium dye test is frequently cited in the literature but is only rarely used clinically. The X-linked carrier state is usually easily diagnosed in the mother by DHR fluorescence through 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. HSCT transplant for all patients with CGD is strongly recommended 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 physicians. Curative therapy at an early age is strongly recommended by many experts.

Patients with CGD should be given daily oral TMP/SMX because it reduces the number of bacterial infections. A placebo-controlled study found that interferon-γ 50 μg/m^2 three times per week 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 <50 kg and ≤5 years old) 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 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. If it does not, however, a search for deep tissues is warranted, as is consideration of empirical 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 many 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 weeks or more of parenteral antibiotics. Infections should be treated for at least 1 week past normalization of ESR to prevent recurrence. Severe pneumonias can be cleared completely but may require many months of parenteral antibiotics. Especially because cultures are often not helpful, many support an "antibiotic sensitivity by sedimentation rate response" approach to treatment. The ESRs are often 40-80 mm/hr or more with severe infection and will decrease monotonically over a week or so after starting antibacterial drugs. It is important to check the ESR daily or every other day because of 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 3-10 days, continue with antibacterials alone. If this is not the case, parenteral voriconazole should be added to cover *Aspergillus*. Failure of the ESR to decrease suggests another antimicrobial approach needs to be tried. This sequential addition of antimicrobials offers some insight into the nature of the infection. If both antibacterials and antifungal are started at the same time, one cannot know what caused a response.

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 their benefit is unclear. 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. The patient can be treated 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. Corticosteroids can also be helpful in pneumonia to shrink granulomas in the lung and promote drainage. Short (4-6 days) pulses of 1-2 mg/kg of prednisone are recommended, 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. Diagnosis by DNA is strongly recommended in suspected carriers with normal DHR who are related to a known proband, because rarely DHR testing is normal in obligate carriers and may indicate that the patient has a spontaneous mutation and the mother may not be a carrier at all. 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 two patient deaths per year per 100 cases, with the highest mortality among young children. The development of effective infection prophylaxis regimens, close surveillance for signs of infections, and aggressive surgical and medical interventions have improved the prognosis.

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Chapter 171

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, 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 hours through the first week of life. Thereafter, values are stable until 1 year 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 one confirmatory complete blood count with differential. Further evaluation then depends on whether the leukopenia represents a decreased number of neutrophils, lymphocytes, or both cell populations (Table 171.1). Treatment depends on 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 first 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 years of age, and the characteristic 70% predominance of neutrophils that occurs in adulthood is usually attained during puberty. For White children >12 months old, the lower limit of normal for the ANC is 1,500/μL; for Black children >12 months old, the lower limit of normal is 1,200/μL. The relatively lower limit of normal in Black individuals likely reflects the prevalence of the **Duffy negative** (Fy−/−) blood group, which is 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** (ANC 1,000-1,500/μL), **moderate** (ANC 500-1,000/μL), or **severe** (ANC <500/μL). ANC <200 is also termed **agranulocytosis**. This stratification aids in predicting the risk of pyogenic infection in patients who have neutropenia resulting from disorders of bone marrow production, because 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 with isolated neutropenia. *Patients with neutropenia caused by increased destruction (e.g., autoimmune) may tolerate very low ANCs without increased frequency of infection,* because of their often robust ability to generate additional neutrophils from their functioning marrow when needed.

Acute neutropenia evolves over a few days and is often a result of rapid neutrophil use and compromised neutrophil production. **Chronic neutropenia** by definition lasts longer than 3 months 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 171.2) or more rarely an inherited, intrinsic defect (Table 171.3).

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 (AINs). In contrast, children whose neutropenia is secondary to acquired disorders of production, as occurs 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 and the ability of the marrow to robustly generate new phagocytes is impaired. 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, frequent infections, aphthous stomatitis, and gingivitis. Infections frequently associated with neutropenia include cellulitis, furunculosis, perirectal inflammation, colitis, sinusitis, warts, 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 but does increase the risk of fungal pathogens causing disease. The usual signs and symptoms of local infection and inflammation (e.g., exudate, fluctuance, 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 (see Tables 171.2 to 171.6). 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 a week for 6-8 weeks to evaluate for 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 flow cytometry 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. Children of African or Arabic descent with mild to moderate neutropenia should have Duffy null, Fy(a-b-) variant, screening completed. Selection of further laboratory tests is determined by the duration and severity of the neutropenia and the associated findings on physical examination (see Table 171.1).

Acquired Neutropenia

Infection-Related Neutropenia

Transient neutropenia often accompanies or follows **viral infections** and is the most frequent cause of neutropenia in childhood (Table 171.4). Viruses causing acute neutropenia include influenzas A and B, SARS-CoV-2, adenovirus, respiratory syncytial virus, enteroviruses, human herpesvirus 6, measles, rubella, and varicella. Parvovirus B19 and hepatitis A or B may also cause neutropenia,

Table 171.1 Diagnostic Approach for Patients with Leukopenia

EVALUATION	ASSOCIATED CLINICAL DIAGNOSES
INITIAL EVALUATION	
History of acute or chronic leukopenia	
General medical history including prior serious, recurrent or unusual infections and malignancy Physical examination: stomatitis, gingivitis, dental defects, warts, lymphedema, congenital anomalies	Congenital syndromes (severe congenital neutropenia, cyclic neutropenia, Shwachman-Diamond, Wiskott-Aldrich, Fanconi anemia, dyskeratosis congenita, glycogen storage disease type Ib, disorders of vesicular transport, GATA2 haploinsufficiency, and primary immunodeficiencies)
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 wk	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 (IgG, IgA, IgM, IgE), lymphocyte subsets	Neutropenia associated with disorders of immune function
IF ANC <500/μL ON THREE SEPARATE TESTS	
Bone marrow aspiration and biopsy, with cytogenetics	Severe congenital neutropenia, cyclic neutropenia, Shwachman-Diamond syndrome, myelokathexis; chronic benign or idiopathic neutropenia; reticular dysgenesis
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 <1,000/μL	
Repeat blood counts in 3-4 wk	Transient leukopenia (e.g., viral)
IF ALC <1,000/μL THREE SEPARATE TESTS	
HIV antibody or RNA test	HIV infection, AIDS
Quantitative immunoglobulins (IgG, IgA, IgM, IgE), vaccine titers, lymphocyte subsets; qualitative lymphocyte proliferation to mitogens/antigens	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 and flow cytometry	Myelodysplasia, leukemia
Copper, vitamin B12 and folate levels	Vitamin deficiencies

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

but are more often associated with pure red cell aplasia or multiple cytopenias, respectively. Viral-associated acute neutropenia often occurs during the first 24-48 hours 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, or fungal infections (see Table 171.4). **Bacterial sepsis** is a particularly serious cause of neutropenia, especially among younger infants and 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 and certain immunodeficiencies

Table 171.2 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 "arrested" at metamyelocyte or band stage)
Reticuloendothelial sequestration	Hypersplenism	Anemia, thrombocytopenia
Bone marrow replacement	Myelofibrosis, malignancy (leukemia, lymphoma, metastatic solid tumor, etc.)	Anemia, thrombocytopenia, marrow fibrosis, malignant cells in bone marrow sites of extramedullary hematopoiesis
Cancer chemotherapy or radiation therapy	Suppression of myeloid cell production	Anemia, thrombocytopenia, bone marrow hypoplasia

Table 171.3 Acquired Disorders of Myeloid Cells

CAUSE	ETIOLOGIC FACTORS/AGENTS	ASSOCIATED FINDINGS
Aplastic anemia	Stem cell destruction and depletion	Pancytopenia
Vitamin B_{12}, copper, or folate deficiency	Malnutrition; congenital deficiency of B_{12} absorption, transport, and storage; vitamin avoidance	Megaloblastic anemia, hyper-segmented 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 birthweight <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 *PIGA* gene variant	Pancytopenia, thrombosis (hepatic vein thrombosis)

Table 171.4 Infections Associated with Neutropenia

Viral	Cytomegalovirus, dengue, Epstein-Barr virus, hepatitis viruses, HIV, influenza, measles, parvovirus B19, rubella, varicella, HHV-6, SARS-CoV-2
Bacterial	*Brucella,* paratyphoid, pertussis, tuberculosis (disseminated), tularemia, *Shigella*, typhoid; any form of sepsis
Fungal	Histoplasmosis (disseminated)
Protozoan	Malaria, leishmaniasis (kala-azar)
Rickettsial	*Anaplasma* (formerly *Ehrlichia*) *phagocytophilum,* psittacosis, Rocky Mountain spotted fever, typhus, rickettsialpox

HHV-6, Human herpesvirus-6.

such as X-linked agammaglobulinemia (XLA), hyper-IgM syndrome and AIDS. The neutropenia associated with AIDS likely 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 (Table 171.5). 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 >65 years, 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, antiepileptics, 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 week 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,

Table 171.5 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

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 (G-CSF; 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 usually and predictably follows the use of anticancer drugs or radiation therapy, especially radiation 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 weeks. 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 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 **copper, vitamin B_{12}, or folic acid deficiency**. In addition, megaloblastic pancytopenia also can result from extended use of antibiotics such as trimethoprim/sulfamethoxazole that 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. Patients receiving prolonged parenteral nutrition and supplemental lipids are additionally at risk for neutropenia given hepatosplenomegaly-related sequestration and marrow infiltration by abnormal macrophages filled with blue-staining pigment granules and atypical lipid vacuoles; these cells are termed **sea-blue histiocytes**.

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 first 2 weeks of life with skin or umbilical infections, fever, and pneumonia caused by the usual microbes that cause neonatal disease. By 7 weeks 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 G-CSF for severe infections without neutrophil recovery.

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

AIN of infancy is a benign condition with an annual incidence of approximately 1 per 100,000 among children between infancy and 10 years of age. Antineutrophil antibodies are inappropriately created by the child during an inflammatory episode, most commonly a mild viral infection. 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 months, with a range of 2-54 months. The diagnosis is often evident when a blood count incidentally reveals neutropenia in a child with a minor infection or when a routine complete blood count is obtained at the 12-month well-child visit. Occasionally, children may present with more severe infections, including abscesses, pneumonia, or sepsis. The diagnosis may be supported by the presence of antineutrophil antibodies in serum; however, the test has frequent false-negative and false-positive results, so the absence of detectable antineutrophil antibodies does not exclude the diagnosis, and a positive result does not exclude other conditions. Therefore the diagnosis is best made clinically based on a benign course and, if obtained, a 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 G-CSF 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 duration of disease ranging from 7-30 months. 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 often identified in older children and is less likely to remit spontaneously. AIN is distinguished from other forms of neutropenia by the demonstration of antineutrophil antibodies (with caveats previously discussed) 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 is generally beneficial, as is family and primary care provider education. Regular dental hygiene, always strongly recommended, is even more important. 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, G-CSF 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 from 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 can be corrected by successfully treating the underlying disease. In select 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 preoperative immunizations and may benefit from antibiotic prophylaxis after splenectomy to help mitigate the risk of sepsis. Splenectomy should be avoided in patients with common variable immunodeficiency (CVID), 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 171.6 presents a classification based on genetics (Fig. 171.1) and molecular mechanisms; other organ involvement or physical features may suggest an etiology (Table 171.7).

Primary Disorders of Granulopoiesis

Cyclic neutropenia is an 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 develop malaise, fever, oral and genital ulcers, gingivitis, periodontitis, or pharyngitis, and occasionally lymph node enlargement. More serious infections occasionally occur, including pneumonia, mastoiditis, and intestinal perforation with peritonitis leading to life-threatening clostridial sepsis. Before the availability of G-CSF, 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 pathologic variants 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 a week for 6-8 weeks. The requirement for repeated blood counts is necessary because some of the elastase variants overlap with those in patients who have **severe congenital neutropenia (SCN)**. Demonstrating oscillation or a lack thereof in the blood counts helps to identify patients' risks for progression to **myelodysplastic syndrome (MDS)/acute myelogenous leukemia (AML)**, a risk that is only associated with SCN. The diagnosis can be confirmed with genetic studies demonstrating a pathologic variant in *ELANE*. Affected patients with neutrophil nadirs <200/μL are treated with G-CSF, and their cycle of profound neutropenia changes from a 21-day period with at least 3-5 days of profound neutropenia to 9-11 days 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.

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 pathologic variants in ***ELANE***, which accounts for 60–80% of SCN cases, whereas **recessive** forms arise from variants in ***HAX1*** (the form also known as **Kostmann disease**) or *G6PC3* (encoding a myeloid-specific isoform of glucose-6-phosphatase). Pathologic alterations in *GFI1, CSF3R,* and *JAGN1* additionally may lead to the condition. *HAX1* variants 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 first few months of life. Infections often disseminate to the blood, meninges, and peritoneum and are usually caused by *S. aureus*, *Escherichia coli,* and *Pseudomonas* species. Without filgrastim therapy, most patients die of infectious complications within the first 1-2 years of life despite prophylactic antibiotics.

Table 171.6 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 *GFI1* and others)	Risk of MDS/AML
	AR *(G6PC3, HAX1, JAGN1, CSF3R)* (*HAX1* = Kostmann syndrome)	*G6PC3:* cardiac and urogenital anomalies, venous angioectasias; *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, DNAJC21, EFL1, SRP54)*	Pancreatic insufficiency, metaphyseal dysostosis, bone marrow failure, MDS/AML
Telomere biology disorders/ dyskeratosis congenita	Telomere length abnormality: XL *(DKC1)*, AD or AR *(ACD, RTEL1, TERC, TERT)*, AD *(NAF1, TINF2)*, AR *(CTC1, NHP2, NOP10, PARN, STN1, WRAP53)*	Nail dystrophy, leukoplakia, abnormal and carious teeth, lacey reticulated hyperpigmentation of the skin, bone marrow failure, various malignancies, Coats plus syndrome (*CTC1* and *STN1*)
DISORDERS OF VESICULAR TRAFFICKING		
Chédiak-Higashi syndrome	AR *(LYST)*	Partial albinism, giant granules in myeloid cells, platelet storage pool defect, impaired NK cell function, HLH
Griscelli syndrome, type II	AR *(RAB27a)*	Partial albinism, impaired NK cell function, neurologic impairment, HLH
Cohen syndrome	AR *(COH1)*	Partial albinism, pigmentary retinopathy, developmental delay, facial dysmorphism
Hermansky-Pudlak syndrome, type II	AR *(AP3B1)*	Cyclic neutropenia, partial albinism, HLH
p14 deficiency	AR *(MAPBPIP)*	Partial albinism, coarse facial features, 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
Methylmalonic/propionic acidemia/ aciduria	AR (*CLPB*) Mutase or cobalamin transporters/ propionyl coenzyme A carboxylase	Ketoacidosis, metabolic stroke, depressed consciousness, megaloblastic anemia
3-Methylglutaconic aciduria	AR (*CLPB*)	Nonspecific finding indicative of mitochondrial dysfunction or associated with known syndromes
Barth syndrome	XL *(TAZ)*	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 *(RMRP)*	Lymphopenia, short-limbed dwarfism, metaphyseal chondrodysplasia, fine sparse hair
Schimke immunoosseous dysplasia	AR *(SMARCAL1)*	Lymphopenia, pancytopenia, spondyloepiphyseal dysplasia, growth retardation, renal failure
X-linked agammaglobulinemia	XL (Bruton tyrosine kinase (*BTK*))	Agammaglobulinemia, neutropenia in ~25%
GATA2 haploinsufficiency	AD (*GATA2*)	Pulmonary alveolar proteinosis, lymphedema, monocytopenia, decreased B and NK cells, risk for severe fungal/mycobacterial/viral infections, susceptibility to leukemia/MDS, MonoMAC syndrome

AD, Autosomal dominant; AML, acute myelogenous leukemia; ANC, absolute neutrophil count; AR, autosomal recessive; HLH, hemophagocytic lymphohistiocytosis; MDS, myelodysplastic syndrome; NK, natural killer; XL, X-linked.

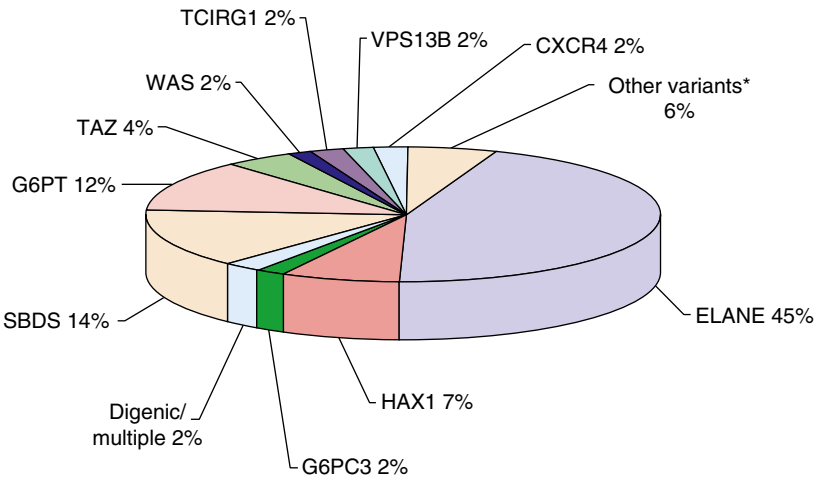

Fig. 171.1 Genes with germline variants associated with severe congenital neutropenia. Data based on 650 patients with severe congenital neutropenia registered in the European and North American Branches of the Severe Chronic Neutropenia International Registry. *Pathogenic variants in *JAGN1, LAMTOR2, GFI1, LYST, USB1,* or mitochondrial DNA. *(From Skokowa J, Dale DC, Touw IP, Zeidler C, Welte K. Severe congenital neutropenias. Nat Rev Dis Primers. 2017;3:17032. Fig. 3.)*

More than 95% of SCN patients respond to filgrastim (G-CSF) treatment with an increase in the ANC and a decrease in infections. Doses required to achieve an ANC >1,000/μL vary greatly. A starting dose of filgrastim at 5 μg/kg/day is recommended; the dose should be gradually increased, if necessary, to 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 (HSCT). Along with 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 HSCT, which is much more likely to be successful before 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 most commonly caused by pro-apoptotic pathologic variants 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 secondary to pancreatic insufficiency, which usually develops by 4 months 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 <1,000/μL. Some children have hypogammaglobulinemia, defects in chemotaxis, or a reduction 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 phenotype; approximately 90% of patients have pathologic variants identified in *SBDS* with additional disease-causing variants now recently discovered in *DNAJC21, EFL1,* and *SRP54*. SDS may progress to bone marrow hypoplasia or MDS/AML; identification of increasing *TP53* variants or cytogenetic abnormalities, particularly isochromosome i(7q) and del(20q), often precede conversion to MDS, so routine bone marrow monitoring is warranted. Treatment includes pancreatic enzyme replacement, plus G-CSF in patients with severe neutropenia.

Telomere biology disorders (TBDs), including **dyskeratosis congenita**, are disorders of telomere length that most often present as bone marrow failure rather than isolated neutropenia. Various pathologic variants have now been identified to cause such conditions (see Table 171.6), including alterations in *ACD, PARN, DKC1, RTEL1, TERC,* and *TERT*. Moreover, the classic phenotype includes nail dystrophy, leukoplakia, malformed teeth, and reticulated hyperpigmentation of the skin, although many patients, particularly young ones, do not exhibit these clinical features. Pulmonary and hepatic fibrosis is also a concern in individuals with TBDs. Patients are at risk for not only hematologic dysplasia/malignancy but additionally neoplasms involving the gastrointestinal tract, skin, and head and neck. Early and routine screening for these malignancies can be lifesaving.

Vesicular Trafficking Disorders

This group of rare **primary immunodeficiency syndromes** (see Table 171.6) derives from autosomal recessive defects in the biogenesis or trafficking of lysosomes and related endosomal organelles. 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 has characteristic giant cytoplasmic granules in neutrophils, monocytes, and lymphocytes, and is a disorder of subcellular vesicular dysfunction caused by pathologic variants 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 HSCT, but transplant does not treat all aspects of the disorder.

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 alterations in *RAB27a*, which encodes a small guanosine triphosphatase that regulates granule secretory pathways. The only curative treatment is HSCT.

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. Pathologic variants 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

Table 171.7 Main Organ Associated Features and Genetic Subtypes of Congenital Neutropenia

SYSTEM	HEMATOLOGIC OR ASSOCIATED FEATURES	DISEASE	GENE
Blood/bone marrow maturation	Maturation arrest	Severe congenital neutropenia Severe congenital neutropenia Wiskott-Aldrich syndrome *Neutropenia G6PC3* *G-CSF receptor*	*ELANE* *HAX1* *WAS* *G6PC3* Extracellular domain of *CSF3R*
	No maturation arrest	GSDIb WHIM Shwachman Diamond disease Cohen disease Hermansky-Pudlak type 2	*G6PT1* *CXCR4* *SBDS* *VPS13B* *AP3B1*
	Myelokathexis	WHIM	*CXCR4*
Pancreas	External pancreatic insufficiency	Shwachman Diamond disease	*SBDS*
Eyes	Congenital cataract	Charcot-Marie-Tooth	*Dynamin 2*
	Retinochoroidal dystrophy	Cohen disease	*VPS13B*
Heart	Heart: arrhythmias	Neutropenia G6PC3	*G6PC3*
	Dilated cardiomyopathy	Barth diseases	*TAZ*
	Cardiomyopathy	Shwachman Diamond disease	*SBDS*
	Various cardiac abnormalities	Shwachman Diamond disease WHIM Neutropenia G6PC3	*SBDS* *CXCR4* *G6PC3*
Skin	Skin xerosis eczema	Shwachman Diamond disease	*SBDS*
	Skin: prominent superficial veins	Neutropenia G6PC3	*G6PC3*
	Skin poikiloderma	SCN with poikiloderma type Clericuzio	*16ORF57*
	Skin: Partial or complete albinism	Hermansky-Pudlak type 2 AP14 defect Chédiak Higashi disease Griscelli disease	*AP3B1* *AP14* *LYST* *RAB27A*
	Hair: fine, sparse, and light-colored	Cartilage-hair hypoplasia	*RMRP*
Bone	Metaphyseal dysplasia	Shwachman Diamond disease Cartilage-hair hypoplasia	*SBDS* *RMRP*
	Facial dysmorphia	Cohen disease	*VPS13B*
Central nervous system	Mental retardation	Kostmann disease Shwachman Diamond disease Cohen disease	*HAX1* *SBDS* *VPS13B*
Muscle	Weakness	Neutropenia G6PC3 Axonal Charcot-Marie-Tooth disease	*G6PC3* *Dynamin 2*
Metabolic pathway	Fasting intolerance and glycogenosis	Glycogen storage disease type Ib	*SLC37A4*
Inner ear	Inner ear defect	GFI 1/severe chronic neutropenia Reticular dysgenesia	*GFI1* *AK2*
Urogenital tract	Uropathy	Neutropenia G6PC3	*G6PC3*
	Cryptorchidism	Cohen disease Neutropenia G6PC3	*VPS13B* *G6PC3*

G-CSF, Granulocyte colony-stimulating factor; SCN, severe congenital neutropenia; WHIM, warts, hypogammaglobulinemia, infections, myelokathexis.
From Donadieu J, Fenneteau O, Beaupain B, Mahlaoui N, Chantelot CB. Congenital neutropenia: diagnosis, molecular bases and patient management. *Orphanet J Rare Dis.* 2011;6:26. Table 2.

G-CSF 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 XLA, CVID, the severe combined immunodeficiencies (SCIDs), autoimmune lymphoproliferative syndrome, hyperimmunoglobulin M syndrome, WHIM (warts, hypogammaglobulinemia, infections, myelokathexis) syndrome, GATA2 haploinsufficiency, and a number of even rarer immunodeficiency disorders (see Table 171.6).

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 often occur during

Table 171.8 Causes of Lymphocytopenia

ACQUIRED	
Infectious diseases	AIDS, hepatitis, influenza, sepsis, tuberculosis, typhoid, COVID-19
Iatrogenic	Corticosteroids, cytotoxic chemotherapy, high-dose PUVA, immunosuppressive therapy, radiation, thoracic duct drainage/chylothorax
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.

childhood. Chronic benign neutropenia may be sporadic or inherited in either dominant or recessive form. Because of the relatively low risk of serious infection, patients usually do not require any therapy.

Idiopathic chronic neutropenia is characterized by the onset of neutropenia after 2 years of age, with no identifiable etiology. Patients with an ANC persistently <500/μL may have 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. 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 G-CSF can provide effective treatment of severe chronic neutropenia, including SCN, cyclic neutropenia, and chronic symptomatic idiopathic neutropenias. 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 AINs, to 5-100 μg/kg/day for SCN. The long-term effects of G-CSF therapy include a propensity for the development of moderate splenomegaly, reduced bone density, 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 HSCT; chemotherapy is ineffective. HSCT is also the treatment of choice for aplastic anemia or familial HLH.

LYMPHOPENIA

The definition of lymphopenia, as with neutropenia, is age dependent and can have 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 <12 months 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.

Acquired Lymphopenia

Acute lymphopenia is most often a result of infection and/or is iatrogenic from lymphocyte-toxic medications and treatments (Table 171.8). Microbial causes include viruses (e.g., respiratory syncytial virus, cytomegalovirus, influenza, measles, hepatitis, COVID-19), bacterial infections (e.g., tuberculosis, typhoid fever, histoplasmosis, 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, 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 (see Table 171.8) 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 171.8). Primary immunodeficiency may result in a severe quantitative defect, as in XLA and SCID, or a qualitative or progressive defect, as in Wiskott-Aldrich syndrome and CVID. XLA is characterized by a near-absence of mature B cells because of a pathologic alteration in *BTK* that results in a dysfunctional tyrosine kinase. SCIDs are a genetically heterogeneous group of disorders characterized by abnormalities of thymopoiesis and T-cell maturation. Newborn screening for severe T-cell deficiency, by analysis of T-cell receptor excision circles (TRECs) from dried blood spot Guthrie cards, aids 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* variants, and dyskeratosis congenita.

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Chapter 172

Leukocytosis

Thomas F. Michniacki and Kelly J. Walkovich

Leukocytosis is an elevation in the total leukocyte or white blood cell (WBC) count that is 2 standard deviations (SDs) above the mean for age. It is most often caused by elevated numbers of neutrophils (i.e., neutrophilia), although marked increases in monocytes, eosinophils, basophils, and lymphocytes can be seen. Before extensive evaluation, it is important to assess for spurious elevations in the WBC count caused by platelet clumping (secondary to insufficient sample anticoagulation or the presence of EDTA-dependent agglutinins), high numbers of circulating nucleated red blood cells (RBCs), and the presence of cryoglobulins by review of the peripheral smear.

Malignancy, namely leukemia and lymphoma, is a primary concern for patients with leukocytosis. For discussion of WBC elevation caused by immature leukocytes in acute and chronic leukemias, see Chapter 544. Nonmalignant WBC counts exceeding 50,000/μL have historically been termed a **leukemoid reaction.** Unlike leukemia, leukemoid reactions show relatively small proportions of immature myeloid cells, consisting largely of band forms, occasional metamyelocytes, and progressively rarer myelocytes, promyelocytes, and blasts. Leukemoid reactions are most often neutrophilic and are frequently associated with severe bacterial infections, including shigellosis, salmonellosis, and meningococcemia; physiologic stressors; and certain medications.

The presence of a **left shift**, defined as having >5% immature neutrophils in the peripheral blood, is consistent with marrow stress. 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. Elevated absolute neutrophil counts represent disturbances of the normal equilibrium involving bone marrow neutrophil production, migration 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 granulopoiesis. 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 an acute physical or emotional stressor (Table 172.1). Bacterial infections, trauma (especially with hemorrhage), and surgery are among the most common causes encountered in clinical practice. Neutrophilia may also be associated with heat stroke, burns, diabetic ketoacidosis, vaccines, pregnancy, or cigarette use.

Drugs commonly associated with neutrophilia include epinephrine, corticosteroids, and recombinant growth factors such as recombinant human granulocyte colony-stimulating factor (G-CSF) and recombinant human granulocyte-macrophage colony-stimulating factor (GM-CSF). 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. G-CSF and GM-CSF cause acute and chronic neutrophilia by mobilizing cells from the marrow reserves and stimulating neutrophil production.

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. Exposure of blood to foreign substances such as hemodialysis membrane activates the complement system and causes transient neutropenia, followed by neutrophilia secondary to release of bone marrow neutrophils. Reactive neutrophils often have toxic granulation and Döhle bodies present.

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 172.1). 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 hematopoietic growth factors, such as G-CSF, with a maximum response taking at least 1 week to develop.

Lifelong Neutrophilia

Congenital or acquired asplenia is associated with lifelong neutrophilia. Some patients with trisomy 21 also have neutrophilia. Uncommon genetic disorders that present with neutrophilia include leukocyte function disorders such as leukocyte adhesion deficiency and Rac2 deficiency (see Chapter 170) and systemic disorders such as familial cold urticaria, periodic fever syndromes, and familial myeloproliferative disease (see Table 172.1). Rare patients with an autosomal dominant hereditary neutrophilia have been reported.

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 almost zero, from reactive or secondary neutrophilia, which features normal to elevated levels.

ADDITIONAL FORMS OF LEUKOCYTOSIS

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 172.2). Typically, 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, and lymphomas.

Eosinophilia

Eosinophilia is defined as an absolute eosinophil count >1500 cells/μL. The majority of eosinophilic conditions are reactive, including infections (especially parasitic diseases), connective tissue disorders, allergic and hyperinflammatory diseases, pulmonary disorders, and dermatologic conditions (see Chapter 169). Drug reaction with eosinophilia and systemic symptoms (DRESS) is a particularly important condition

Table 172.1 Causes of Neutrophilia

TYPE	CAUSE	EXAMPLE
Acute acquired	Bacterial infections	
	Neutrophil disorder	Leukocyte adhesion defects
	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, cigarette exposure
	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, pregnancy, Sweet syndrome
Lifelong	Congenital asplenia	
	Hereditary disorders	Familial cold urticaria, hereditary neutrophilia, leukocyte adhesion deficiencies, periodic fever syndromes

Table 172.2 Causes of Monocytosis

CAUSE	EXAMPLE
Infections	
Bacterial	Brucellosis, subacute bacterial endocarditis, syphilis, tuberculosis, typhoid
Nonbacterial	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

to consider in those with prominent eosinophilia as severe cases are associated with significant morbidity and mortality (see Chapter 686.2). Hypereosinophilic syndrome and systemic mastocytosis are additional important causes of an elevated eosinophil count. However, persistent eosinophilia can also herald a malignancy such as leukemia, lymphoma, or carcinoma.

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.

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 months of age. Thyrotoxicosis and Addison disease are endocrine disorders associated with lymphocytosis. Persistent or pronounced lymphocytosis suggests acute lymphocytic leukemia.

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Section 4

Complement System

Chapter 173

Complement System

Anete Sevciovic Grumach

173.1 Complement Components, Pathways, and Evaluation

Anete Sevciovic Grumach

The complement system (CS) forms a network of soluble and cell surface–bound components, pattern-recognition proteins (PRPs), proteases, receptors, effectors, and regulators to perform multiple sensor and effector functions as part of the *innate* immune system (Tables 173.1 and 173.2). It represents an essential part of immunity, having a major role in host defense against pathogens, homeostasis, and inflammation, such as promoting phagocytic removal of senescent cells, molecular debris, and weak or superfluous synapses during brain formation. Complement acts not only in the extracellular space but also within cells and subcellular compartments, where it is involved in the regulation of basic processes of the cell, suggesting that complement directs both innate and adaptive immune responses. Cells are generally protected from amplification and effector insult by a group of complement regulators, which are expressed on their surface or mobilized from the circulation. However, if the equilibrium between complement activation and regulation is disturbed, complement can harm the host and precipitate or worsen adverse processes that result in diseases.

Circulating complement proteases are zymogens and, once activated, they initiate an amplification cascade through cleavage of specific targets and/or interaction with other proteins. Depending on the activating surface, the CS can be triggered by the **classical** (CP), **lectin** (LP), and **alternative** (AP) **pathways**. Each pathway is triggered by different interactions. The CP is initiated by immune complexes through binding of complement protein C1q to immune complexes containing IgM or IgG, in solution or bound to antigens on the cell surface. Certain bacteria, RNA viruses, and the lipid A component of bacterial endotoxin as **pathogen-associated molecular patterns (PAMPs)** on microbial surfaces can activate C1q directly and trigger the full complement cascade. The LP is activated when **mannose-binding lectin (MBL),** or ficolins, recognize unique carbohydrate structures present on the surface of pathogens or altered glycosylation patterns (DAMPs, danger-associated molecular patterns) on abnormal host cells. **The mannose-binding lectin-associated serine proteases (MASPs)** cleave C2 and C4, following the same sequence as CP.

The **AP** is rapidly activated after contact with pathogens, independent of antibody; however, antibody will accelerate the rate of activation. The fluid phase C3 convertase complex C3(H2O)Bb is generated with the spontaneous hydrolysis of C3, referred to as "tick over." An amplification loop leads to rapid opsonization stabilized by properdin. Therefore each of these pathways converge toward the cleavage of the abundant plasma protein C3 by a C3 convertase, followed by the formation of a C5 convertase, which cleaves C5 into C5a and C5b, and induces the activation of the common lytic effector **terminal pathway (TP).** The interaction among C5b, C6, C7, C8, and C9 is nonenzymatic and depends on changes in molecular configuration. The subsequent insertion of TP components into the cell wall leads to lysis via the **membrane attack complex (MAC),** which is composed of complement proteins C5b to C9.

Cell membrane receptors bind complement components or fragments to mediate complement activity, and a large array of serum and membrane regulatory proteins control the activation of CS (Fig. 173.1). The circulating components and regulators together comprise approximately 15% of the globulin fraction and 4% of the total serum proteins. The normal concentrations of serum complement components vary by age; newborn infants have mild to moderate deficiencies of all components.

CLASSICAL AND LECTIN PATHWAYS

The CP 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. On binding, the C1 complex changes conformation, activating the C1r and C1s protease subunits; the C1s subcomponent becomes an active enzyme, **C1 esterase**. The activation leads to cleavage of C2 and C4 and the formation of the CP C3 convertase (C4bC2a).

As part of the **innate immune response**, broadly reactive "natural" antibodies and C-reactive protein (CRP), which react with carbohydrates from microorganisms and with dying cells, can substitute for specific antibodies in the fixation of C1q and initiate reaction of the entire sequence. Endogenous substances, including uric acid crystals, amyloid deposits, DNA, and components of damaged cells, such as apoptotic blebs and mitochondrial membranes, can activate C1q directly. In this case, however, the ligand-C1q complex interacts strongly with the inhibitor's C4-binding protein and factor H, allowing some C3-mediated **opsonization** and **phagocytosis** but limiting the full inflammatory response typically triggered by microbes.

Table 173.1 Nomenclature for Complement Components

	EXAMPLES
Classical pathway components are labeled with a C and a number	C1, C2, C4
Alternative pathway components are lettered	B, P, D
Some components are called factors	Factor B, factor D
Activated components or complexes have a bar over to indicate activation	$\overline{\text{C4bC2a}}$
Cleavage fragments are designated with a small letter	C3a, C3b
Cell membrane receptor	CR1, CR2, CR3, CR4

Table 173.2 Components of 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)
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)

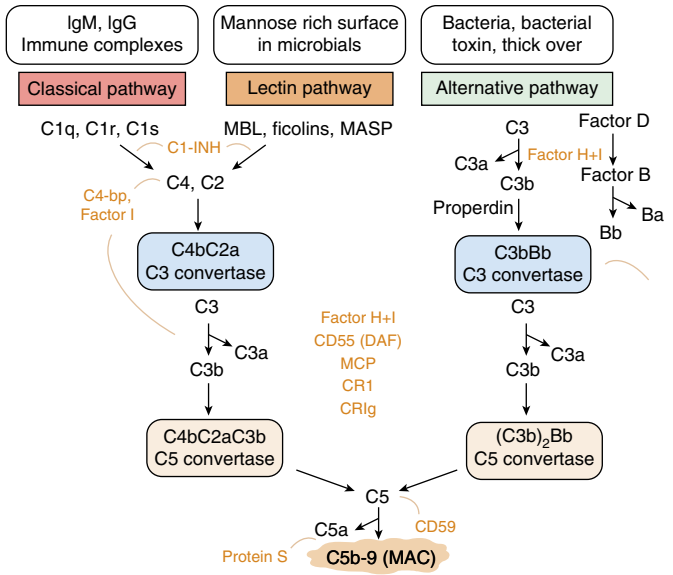

Fig. 173.1 Activation and control of the complement system. C1-INH, C1 inhibitor; C4-bp, C4-binding protein; CD59, cell membrane–associated protein; CR1 (CD35), complement receptor 1; CRIg, complement receptor of the immunoglobulin superfamily; DAF, CD55, decay-accelerating factor; MASP, mannose-binding lectin–associated serine protease; MAC, membrane attack complex; MCP, membrane cofactor protein.

C1q synthesized in the brain and retina fixes to superfluous synapses, which then can be cleared through C1q receptors on microglia, clearing the way for fresh synapses to populate the developing nervous system.

Recognition molecules in the **LP** are **MBL**, **ficolins, or collectins** (**CL-11** or kidney collectin or CL-K1; **CL-10**, collectin liver 1). MBL is the prototype of the collectin family of carbohydrate-binding proteins (**lectins**) that play an important part in innate, nonspecific immunity; its structure is homologous to that of C1q. Three ficolins have been identified in humans: **L-ficolin (ficolin-2), H-ficolin (ficolin-3),** and **M-ficolin (ficolin-1).** Ficolins show specificity for *N*-acetylglucosamine residues in complex oligosaccharides, but not for mannose or high-mannose-type oligosaccharides. Individual members display additional specificities, e.g., H-ficolin binds to *N*-acetyl-D-galactosamine and D-fucose, M-ficolin binds to sialic acid, and L-ficolin recognizes lipoteichoic acid and 1,3-β-D-glucan, the major component of yeast and fungal cell walls. These lectins, in association with **MASP-1, -2, and -3,** can bind to mannose, lipoteichoic acid, and other carbohydrates on the surface of bacteria, fungi, parasites, and viruses. There, MASPs then function 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. The activation of C3 and C5 also liberates potent chemotactic fragments (i.e., the anaphylatoxins C3a and C5a) that recruit immune cells to the site of activation and prime them. 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 CP, C142, or of the AP, $\overline{C3bBb}$. 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, especially by neutrophils, requires binding of C3 to the microbe. The severe pyogenic infections that frequently occur in C3-deficient patients illustrate this point. 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, thereby serving as a co-stimulator of antigen-induced B-cell activation.

ALTERNATIVE PATHWAY

The AP can be activated by C3b generated through CP activity or proteases from neutrophils or the clotting system. It can also be activated by a form of C3 created by a low-grade, spontaneous reaction of native C3 with a molecule of water, or 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 circulating 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 AP activation if C3b is fixed to them, including bacterial teichoic acid and 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 (RBC) membrane is such a surface, which serves as the basis for an assay of serum AP activity. Conversely, sialic acid on the surface of microorganisms or cells prevents the formation of an effective AP C3 convertase by promoting the activity of factors I and H. Significant activation of C3 can occur through the AP, and the resultant biologic activities are qualitatively the same as those achieved through activation by C142.

MEMBRANE ATTACK COMPLEX

The sequence leading to cytolysis begins with the attachment of C5b to the C5-activating enzyme from the CP, $\overline{C4b2a3b}$, or from the AP, $\overline{C3bBb3b}$. 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 unbridled consumption of components, which would generate severe, potentially lethal host damage. Cells are generally protected from amplification and effector insult by a panel of complement regulators, which are expressed on their surface or recruited from circulation At the first 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 AP enzyme that activates C3, $\overline{C3bBb}$, also has a short half-life, although it can be prolonged by the binding of **properdin** to the enzyme complex. Properdin can also bind directly to microbes and promote assembly of the AP C3 convertase.

The 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, thereby interfering with the insertion of the MAC (C5b6789). The serum proteins **vitronectin** and **clusterin** can inhibit attachment of the C5b67 complex to cell membranes, bind C8 or C9 in a full MAC, or

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 the antibody titer 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 phagocyte C1q receptor.

C4a, **C3a**, and **C5a** can bind to mast cells and thereby trigger the 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 (Fig. 173.2).

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 RBCs, 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 CS 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. The coupling of antigens to C3d allows binding to CR2 on B cells, which greatly 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. 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.

Complement Evaluation

Good quality blood sampling requires that after clotting (about 20-120 minutes), the serum must be separated by centrifugation as soon as possible, and stored under controlled conditions. In case complement testing cannot be performed on the day of blood sampling, the serum and plasma samples must be stored in a deep freezer (−20°C) for up to 3 months or in an ultra-deep freezer (−70°C) for a longer storage until analysis. If the analysis will be done by a specialized laboratory, the samples must be shipped on dry ice by courier. Repeated freezing and thawing should be avoided because of the risk of in vitro activation. The serum is sufficient for the analysis of the total function of complement proteins and regulators as well as of autoantibodies. A quantitation of activation products requires the use of EDTA plasma because it blocks the in vitro activation of the CS by way of its Mg^{2+} and Ca^{2+} complexing properties. Heparin and citrate are less useful. The utilization of the less invasive dried blood spot (DBS)-based assays can also be used for diagnosis; enzyme activities could be retained, facilitating the samples' transportation.

The indication for using assays for complement evaluation is to detect genetic, acquired, or the effect of complement inhibitory therapy. Functional assays can screen and direct the following steps for the evaluation of specific protein deficiencies (Fig. 173.3). Assays including hemolysis of RBCs **(CH50, AP50)** check the activation of classical and alternative pathways. In both cases, CH50 and AP50, the functional result is the lytic destruction of erythrocytes on membrane insertion of C5b-9 (MAC). Low but not absent CH50 results could reflect complement consumption due to active immune complex disease, diminished hepatic production due to liver disease, and immaturity of hepatic production seen in young infants. *Screening with hemolytic assays is not adequate for C9, properdin, MBL, MASP-2, or ficolin deficiencies.* In patients with these defects, the hemolytic assay value may be minimally decreased or normal. An alternative assay, popular in Europe, is a plate-based activation assay, which more specifically detects complement

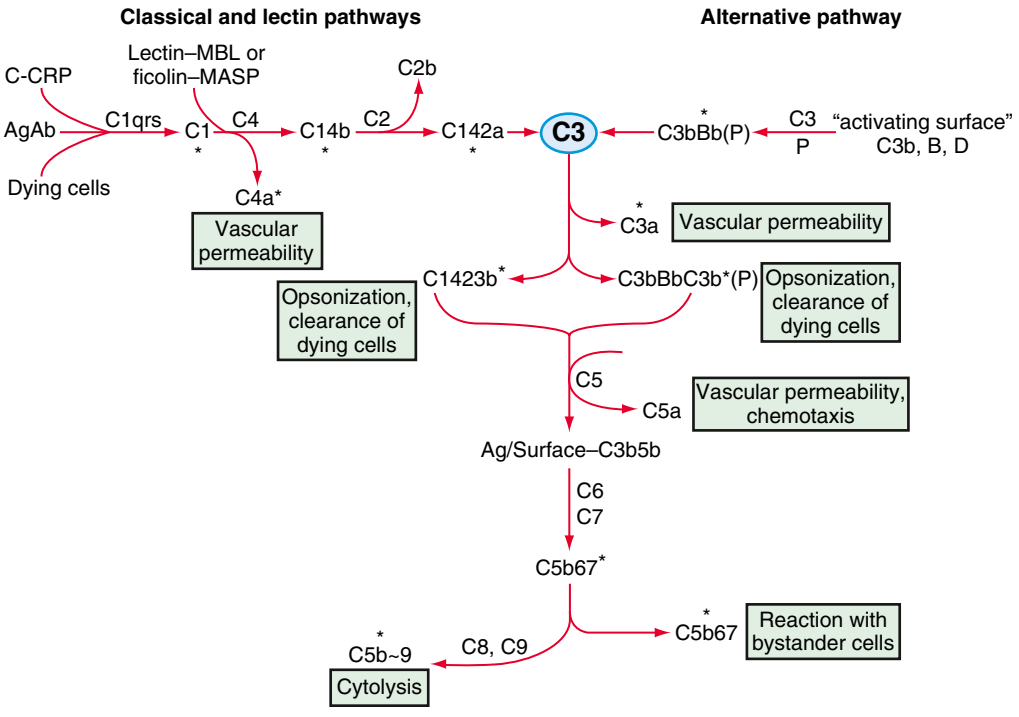

Fig. 173.2 Sequence of activation of the components of the classical and lectin pathways of complement and interaction with the alternative pathway. Functional activities generated during activation are enclosed in boxes. The multiple sites at which inhibitory regulator proteins (not shown) act are indicated by asterisks. Ab, Antibody (immunoglobulin G or M class); Ag, antigen (bacterium, virus, tumor, or tissue cell); B, D, P, factors B, D, and properdin; C-CRP, carbohydrate–carbohydrate-reactive protein; MBL, mannose-binding lectin; MASP, MBL-associated serine protease.

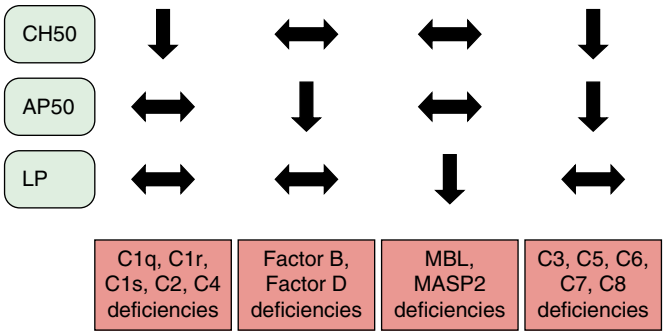

Fig. 173.3 Laboratory screening of complement system. LP, Lectin pathway; MBL, mannose-binding lectin; MASP, MBL-associated serine protease.

activation through CP, LP, and AP ("CS screen" test). Although the result target of these enzyme-linked immunosorbent assays (ELISAs) is principally the same as for the lytic assays, it is based on detecting full assembly of C5b-9 by using an antibody to a C9 neoantigen when serum is added to microtiter wells coated with the activation agent for the different pathways (e.g., IgM for CP, mannan for LP, and lipopolysaccharides for AP).

Once an abnormal CH50 or AP50 has been confirmed, immunochemical tests can be used to define the serum levels of specific components, the second step for defining complement deficiencies. Normal concentrations of single components do not exclude functional defects. The functional activity of a single component can be tested. Sera depleted of the actual component and patient's fresh serum are mixed to see whether the activity can be restored by using hemolysis as a result. Reduced functional activity of individual complement components either reflects a deficiency state, or indicates consuming complement activation. To distinguish primary or acquired defects, activation products generated by CS activation could be measured. Different approaches can be applied for this aim: detection of split fragments, generated after enzymatic cleavage of certain components, e.g., C4 (C4a, C4b/c, C4d), C3 (C3a, C3b/c, iC3b, C3d), factor B (Ba, Bb), and C5 (C5a), or the identification of protein complexes where activated components are bound to their respective regulators, like C1rs-C1-inhibitor, the properdin-containing AP convertase, C3bBbP, and sC5b-9 (soluble terminal complement complex). Detection of complement activation products like C3d and C4d on red cells using *flow cytometry* has been used to evaluate in vivo complement activation in autoimmune diseases and trauma. The terminal **C5b-9 complement complex** exists in two forms, the MAC and the soluble form (sC5b-9). The in vitro–generated surface-bound C5b-9 must not be confused with sC5b-9, which is found in plasma and if increased is a useful marker of complement activation in vivo reflecting diseases with disturbed complement function. sC5b-9 can be quantified by ELISA and is based on the same C9 neoepitope principle. In the case of efficient C5 blockade, there should ideally be no sC5b-9 present.

C4 levels have been used as a screening test for **C1-INH deficiency** in **hereditary angioedema (HAE)**; this test does not substitute quantitative and/or functional evaluation of C1-INH. C4 concentrations can be within normal range between episodes in approximately 5–10% of the patients. Also, a defective C1-INH protein can reflect only a functional assay with normal quantitative values. **Deficiency of factor I or H** permits persistence of the classical and alternative pathway convertase and thus consumption of C3, with reduction in the CH50 value. If multiple components are decreased, it is possible that sample handling was improper, a regulatory protein was deficient, or autoantibodies were present. Flow cytometry is the standard technique for the diagnosis of **paroxysmal nocturnal hemoglobinuria (PNH)** by detecting reduced levels of CD55 and CD59 on blood cells.

Autoantibodies to complement components could simulate deficiencies and assays for their detection would be relevant according to clinical information. They are often associated with specific diseases, e.g., anti-C1q antibody is associated with hypocomplementemic urticarial vasculitis and/or proliferative systemic lupus erythematosus (SLE) nephritis.

Assessment of cell surface expression of receptors and tissue deposition of complement proteins or fragments are further steps for complement evaluation. Specific gene panels are another accessible tool that could supply additional information (Table 173.3).

Table 173.3 The Steps for Complement System Evaluation

COMPLEMENT EVALUATION	EXAMPLES
Total complement activity	CH50, AP50, lectin pathway
Quantification of single components	C3, C4, MBL, properdin
Functional activity of single components	Functional C1 inhibitor
Products of complement activation	C3d; C3dg
Autoantibodies to complement components	Anti-C1q; nephritic factor
Cell surface expression	CD55; CD59; CR3/4
Tissue deposition of complement proteins or fragments	Deposition of C3 or factor H in injury burns
Genetic evaluation	Next generation sequencing or specific gene panels

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173.2 Complement Pathway Deficiencies

Anete Sevciovic Grumach

Most genetically determined complement deficiencies are inherited in an autosomal recessive fashion. Exceptions are properdin deficiency, which is X-linked, and C1-INH deficiency, which is autosomal dominant. In most cases, it is possible to predict the effects of a particular deficiency based on understanding the normal physiologic function of that protein. Increased susceptibility to **infections** caused by encapsulated bacteria and **autoimmunity** are the most common presentations of complement deficiencies. Deficiency of components of TP and properdin deficiency are associated with neisserial infections. When there is an imbalance between complement activation and regulation, complement can quickly attack the host and trigger and/or exacerbate adverse processes that result in diseases and clinical complications. Genetic variants in the **complement factor H (CFH)** and **complement factor I (CFI)** genes have been associated with **atypical hemolytic uremic syndrome (aHUS)** and **aging macular degeneration (AMD).** A distinct clinical manifestation is described for deficiency of C1-INH causing recurrent **angioedema.**

CLASSICAL PATHWAY DEFICIENCIES

Patients deficient in the initial components of the CP are prone to autoimmune connective tissue diseases (Table 173.4). Most patients with primary **C1q deficiency** have SLE; some have SLE-like syndrome without typical SLE serology, a chronic rash with underlying vasculitis, or membranoproliferative glomerulonephritis (MPGN). The association with SLE is due to compromised clearance of apoptotic debris and impaired B-cell tolerance. Some C1q-deficient children have serious infections, including septicemia and meningitis. Only a few patients with **inherited deficiencies of C1r and C1s** have been described. It is thought that neither component is stable without the other so that a pathogenic variant in one often leads to diminished levels of both. Glomerulonephritis and lupus have been reported in C1r/C1s-deficient patients.

Table 173.4 Pathway Deficiencies of Complement System

DEFICIENCY	INHERITANCE	ASSOCIATED SYMPTOMS/DISORDERS
C1q, C1r/s (often combined), C2, C4 (total C4 deficiency)	AR	SLE, systemic infections with encapsulated organisms; heterozygous C2 deficiency may have a reduced CH50 but remain asymptomatic
C4A or C4B	Complex	Susceptibility to infections and/or autoimmunity (SLE); mostly asymptomatic
C3 GOF	AD	aHUS (2–10% of the cases)
C3	AR	Pyogenic infections, neisserial infections, glomerulonephritis, AMD
C5, C6, C7, C8α–γ/C8β	AR	Neisserial infections; recurrent meningitis
C9	AR	Neisserial infections (mostly asymptomatic)
Factor B	AR*	Neisserial and pneumococcal infections, aHUS (1–4% of the cases)
Factor D	AR	Bacterial infections
MBL	Polymorphism	Bacterial infections (mostly asymptomatic) and susceptibility to autoimmunity in some cases
Ficolin-3 (H-ficolin)	Polymorphism	Various clinical phenotypes
MASP-1	AR	3MC syndrome
MASP-2	AR	Respiratory infections, mostly asymptomatic

*AR, Autosomal recessive non-codominant.
AR, Autosomal recessive; AD, Autosomal dominant; C4A and C4B, isotypes encoded by C4A and C4B genes, respectively; GOF, gain of function; SLE, systemic lupus erythematosus; aHUS, atypical hemolytic uremic syndrome; AMD, aging macular degeneration; 3MC, Mingarelli, Malpuech, Michels and Carnevale.

Complement component **C4** is a central protein in the classical and lectin pathways within the CS. **C4A** and **C4B genes** encode the two isoforms of the component C4, an essential element for the effector arm of the humoral immune response. The two isotypes of C4, which differ by only four amino acids, demonstrate differential chemical reactivities: C4A displays a higher affinity for amino group–containing antigens or immune complexes, and C4B for hydroxyl group-containing antigens. The presence of one C4A or C4B gene is called *heterozygous* C4A or C4B deficiency, whereas the presence of no functional C4A or C4B genes causes *complete* C4A or C4B deficiency and is called **homozygous C4 deficiency**. Homozygous deficiencies of complement C4A or C4B are detected in 1–10% of populations. Homozygous deficiency of C4A is associated with an increased frequency of SLE; whereas homozygous C4B deficiency has been associated with increased susceptibility to bacterial and enveloped viral infections. Within each C4 gene, there can be deletions or duplications or simple inactivating variants; therefore interpretation of a serum level is difficult.

C2 deficiency is found with a frequency of 1/10,000 in the White population. The lowest frequency of autoimmunity (10–42%), among the proteins of the CP, is observed in C2-deficient patients. Individuals with C2 deficiency also carry the risk of life-threatening septicemic illnesses, usually caused by pneumococci; however, most have not had problems, presumably because of protective effects of other complement pathways. The genes for C2, factor B (AP), 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.

Patients with C1, C2, or C4 deficiency have an increased occurrence of **autoantibodies**; antinuclear antibodies are present in 75% of patients with C1 or C4 deficiency and 25–55% of patients with C2 deficiency. Anti-dsDNA antibodies are present in 20% of patients with C1q/C4 deficiency and 33% of patients with C2 deficiency. Individuals with heterozygous C2 or C4 deficiency often remain asymptomatic. Also, there is an increased incidence of **bacterial infections** associated with deficiency of components in CP, including meningitis, pneumonia, arthritis, or septicemia. Other infections such as epiglottitis, and peritonitis have been described. The most common organisms identified in C2-deficient patients have been *Streptococcus pneumoniae* and *Haemophilus influenzae* type b.

C3 Deficiency

C3 deficiency is rare and the disease manifests early in life. Severe infections (pneumonia, meningitis, osteomyelitis, or bacteremia) caused by encapsulated bacteria *(H. influenzae*, *Neisseria meningitidis)* occur. The infections reflect the impairment in the C3b opsonization, generation of chemotactic factor, influence in B-cell stimulation, and failure of complete complement activation. **MPGN** is noted in approximately 30% of the cases of C3 deficiency. Slightly more common is a partial deficiency of C3, termed *hypomorphic* C3. This partial deficiency has been seen in some autoimmune disorders. Rare C3 gain-of-function (GOF) variants may lead to **aHUS** and endothelial damage in the glomerulus. One common and several rare variants in C3 have been associated with increased risk of AMD. A unique feature of C3 deficiency is a vasculitic rash that may appear during infections; symptoms of serum sickness may occasionally be seen. These unusual findings are due to the lack of immune complex solubilization by C3. They typically are transient in nature but can cause confusion with lupus, particularly in the presence of glomerulonephritis.

DEFICIENCY OF TERMINAL COMPONENTS (C5, C6, C7, C8, C9)

Terminal components are shared by the classical, lectin, and alternative pathways, and are ultimately responsible for the formation of the **MAC**. The risk of developing **meningococcal sepsis or meningitis** is markedly increased in people who have a deficiency of one terminal component. In contrast to the immunocompetent population (median age for meningococcal infection: 3 years), the onset of symptoms in patients with terminal deficiencies is 17 years. However, infections generally lead to lower mortality, may be recurrent, and have a milder course than in an immunocompetent person. Rarely, SLE or other autoimmune disorders has been identified in these defects. Disseminated ***Neisseria gonorrhoeae*** infections have also been described; an increased frequency of other bacterial infections is not observed. A terminal component deficiency should be suspected if there is a family history of meningococcal infections, repeated neisserial infections, or if the causative meningococcal serotype is W-135, X, Y, or Z, which less frequently cause infections in healthy individuals. Early vaccination of children could change the profile of serotypes causing infection in those patients.

C6 deficiency occurs more frequently in African Americans and in people from South Africa. Two variations of C6 deficiency have been described. In one case, a splice defect leads to a smaller than usual protein, C6SD. This protein functions less efficiently than wild-type C6; however, it is not clear whether bearing C6SD leads to compromised host defense. The other variation is combined C6 and C7 deficiency. **C7 deficiency** is rare and in the few reported cases, the clinical presentations have varied.

C8 is composed of three chains: α, β, and γ. **C8β deficiency** is more common in White people, whereas **C8α-γ deficiency** is more common among African Americans. Approximately 1 patient in 1000 carries a homozygous common nonsense variant causing **C9 deficiency** as described in Japan and Korea. It is more difficult to diagnose than most of the other complement deficiencies because the CH50 is diminished but not absent. Lytic activity can be generated in the absence of C9. The neisserial disease can occur, although the penetrance appears to be less than that with other terminal component deficiencies.

ALTERNATIVE PATHWAY DEFICIENCIES

The AP is a highly conserved surveillance system that is continuously turning over (tick over) due to a labile thioester bond in C3 and thus does not require antibodies or lectins for activation. **Properdin** is a positive regulator of AP activity and works by stabilizing AP convertases. **Properdin deficiency** is rare, hereditary, and is the only X-linked complement deficiency. A small number of patients have been identified with properdin deficiency; these patients are unusually susceptible to ***Neisseria* infections.** There is a particularly high fatality rate for meningococcal disease in properdin-deficient patients, in contrast with the protection from early death seen in patients with terminal complement component deficiencies. It manifests with either complete absence of the molecule (type I), partial deficiency (type II), or a normal level of dysfunctional protein (type III). Properdin-deficient individuals are susceptible to **meningococcal disease**, which is frequently complicated by sepsis and most commonly occurs in adolescence. **Factor D** and **Factor B deficiencies** were described in few cases and the association with *Neisseria* infections was also identified. Systemic streptococcal infections have also been involved in factor D deficiency. GOF pathogenic variants in factor B are associated with the aHUS.

LECTIN PATHWAY DEFICIENCIES

The **LP** is focused on the recognition of repetitive carbohydrate patterns found on the surface of microbial pathogens. Lectin **pattern recognition molecules (PRMs)**, which include MBL, ficolin-1, ficolin-2, ficolin-3, collectin-10, and collectin-11, activate the pathway in an analogous manner to antibodies in the CP. **MASPs**, which act in a similar fashion to C1r and C1s, associate with MBL and activate C4 and C2 by proteolytic cleavage (see Fig.173.1). Among White populations, approximately 5–7% of people have inherited MBL deficiency. LP impairment due to insufficient production of any of these components is common and may be associated with no clear clinical phenotype. However, MBL insufficiency is, in combination with other factors, associated with more severe forms of sepsis and fatal outcomes. The deficiency appears to represent a modest risk factor for infection, typically revealed in a high-risk setting. Similarly, it may subtly alter the course or contribute to the overall risk of developing several autoimmune diseases. MBL deficiency has been associated as an additional severity influence for common variable immunodeficiency, cystic fibrosis, and hepatitis. In contrast, low MBL levels have been described as protective for mycobacterial infection. MBL deficiency is not typically associated with absent levels, and it has been difficult to define the normal range in healthy people.

MASP-1, the most abundant protease of the LP, has a central role in pathway activation via MASP-2. MASP-1 may be involved in coagulation, renal, gastrointestinal, and myocardial ischemia/reperfusion-related pathology; there is no firm evidence for this type of pathology in humans.

The **Malpuech, Michels, Mingarelli, Carnevale (3MC) syndrome** is a rare, autosomal recessive genetic disorder associated with pathogenic variants in the **MASP1/3; COLEC11; or COLEC10** genes. The number of 3MC patients with known pathogenic variants in these three genes reported so far remains very small. The clinical manifestations of the 3MC syndrome consist of developmental delay, facial dysmorphia, and various skeletal anomalies. Developmental defects include cleft lip and palate, postnatal growth deficiency, cognitive impairment, and hearing loss. Excess or unusual infections and autoimmunity have not yet been described in this syndrome. The proposed mechanism was revealed by an unexpected role for these proteins in cuing neural crest cell migration.

MASP-2 deficiency was initially described in a patient with serious infections and autoimmune disease. MASP-2 deficiency has been included in the classification of primary immunodeficiencies. Asymptomatic individuals have been described; the frequency is 6/10,000, suggesting that the phenotype is mild. Healthy individuals homozygous for p.D120G have also been found by chance in genetic association studies. These findings suggest that MASP-2 deficiency could no longer be associated to a specific clinical phenotype. In contrast, increased levels of MBL or MASP-2 may contribute to poor disease outcome associated with mycobacterial infections or pneumococcal meningitis.

Complete **ficolin-3 (or H-ficolin) deficiency** was initially associated with increased susceptibility to infections and necrotizing enterocolitis. A heterogeneous range of clinical manifestations have been described in patients with complete ficolin-3 deficiency, and the first case described was later diagnosed with Wiskott-Aldrich syndrome. Respiratory and nervous system involvement in the few reported cases of FCN3 deficiency raises awareness regarding the significance of ficolin-3 in respiratory and nervous immunity.

DEFICIENCIES OF COMPLEMENT REGULATION

The CS has several levels of **regulation** at the initiation, amplification (formation of convertases), and membrane attack phases, thereby preventing inadvertent tissue damage. Deficiency of complement inhibitors leads to dysregulation either in the fluid phase or on cell surfaces and consequent recurrent infections (mostly bacterial), inflammatory disorders, and presentations with a broader clinical phenotype. These include angioedema (**C1-INH deficiency**), kidney and eye diseases (**factor H, factor I, or CD46/MCP deficiency**), **protein-losing enteropathy (CD55/DAF deficiency)**, and **PNH (CD55 + CD59 deficiency**). In addition, there are seven complement receptors (C1qR, C3aR, C5aR, CR1, CR2, CR3, and CR4). The same disease spectrum may be caused and shaped by a broad variety of different alterations in complement activators and/or regulators. The individual complement profile of a patient (sometimes referred to as **complotype**) often determines the course and severity of the disease. Disorders such as AMD, aHUS, or C3 glomerulopathy (C3G) are among the most well-described examples in this context.

Approximately 50% of patients with aHUS have genetic pathogenic variants of factors H and I, C3, factor B, and/or MCP, and deletion of complement factor H–related proteins 1 and 3 (CFHR1/CFHR3). Approximately 20% of patients with aHUS have pathologic variants in more than one gene and patients with autoantibodies to regulatory proteins also comprise a significant subset. The majority of aHUS cases are sporadic and occur in the absence of prior family history. Furthermore, even in familial forms of aHUS, penetrance is incomplete.

Thrombomodulin (CD141) also has a regulatory role and binds to factor H and C3b, thereby inhibiting complement activation. Interestingly, pathologic variants in factor H, MCP, and factor I have also been reported in **C3** MPGN, as well as preeclampsia and hemolysis, elevated liver enzyme levels, and low platelet levels (HELLP) syndrome.

Several complement proteins, their activation products, and regulators have also been related to **AMD**, particularly, C3 and factors H and I.

Hereditary Angioedema

HAE comprises a group of diseases characterized by recurrent angioedema without wheals, showing an autosomal dominant inheritance pattern. It was first recognized in patients with heterozygous **deficiencies of C1-INH** and the estimated prevalence is 1:50,000 (Chapter 189.1). Patients with angioedema without wheals have also been described with normal C1-INH levels. Several pathogenic variants

were associated with this group of patients with **primary angioedema**: factor XII (FXII-HAE), plasminogen (PLG-HAE), angiopoietin-1 (ANGPT1-HAE), kininogen-1 (KNG1-HAE), myoferlin (MYOF-HAE), and heparan sulfate-glucosamine 3-*O*-sulfotransferase 6 (HS-HAE). However, a significant proportion do not have a defined molecular explanation.

The angioedema is self-limited and recurrent, affecting the deep layers of skin and mucosa, commonly causing swelling of extremities (hands, feet, limbs), face, lips, tongue, genitalia, bowels, and the upper airway. The involvement of the gastrointestinal tract causes severe abdominal pain, distension, vomiting, and, less frequently, diarrhea. The symptoms can be misdiagnosed, and unnecessary surgery may be performed. The obstruction of upper airways due to edema of the glottis is associated with asphyxia if the attacks are not prevented. Swelling attacks are transitory and usually last from 2-5 days, but their severity and frequency vary widely from patient to patient. Approximately 5% of people who carry a C1-INH pathologic variant are asymptomatic.

In the most frequent subtype, HAE with C1-INH deficiency (HAE-C1INH, OMIM #106100), the first HAE episodes occur at a mean age of 10 years; however, the onset of symptoms may occur at an early age (Chapter 189.1). This type of HAE is classified as **type I** when there is low quantitative and functional C1-INH levels (85% of the cases) and **type II** for decreased functional C1-INH values. A typical functional level is approximately 25–40% of normal in both types. Attacks, when identified, are triggered by stress, trauma, hormones (estrogen), infections, extreme temperatures, and alcohol. Although many patients can identify triggers, many episodes have no identifiable trigger, which increases anxiety and contributes to feelings of loss of control. The symptoms are preceded by prodromes, such as erythema marginatum, irritability, nausea, and flulike symptoms. Consumption of C2 and C4 increases the risk for the development of SLE. Positive family history occurs in 75% of the cases and de novo pathogenic variants are described in 25% of the cases.

The **third type** of HAE referred to as **HAE with normal C1-INH** (previously called type III), is not a complement deficiency. It is characterized by normal serum levels and functional activity of C1-INH. It has been described primarily in females; however, both sexes are affected.

Acquired C1-INH deficiency is rarer than HAE-C1-INH (1:9) and is clinically indistinguishable from inherited C1-INH deficiency except that onset is later in life (>40 years old). Patients with acquired C1-INH deficiency require careful surveillance for malignancy; B-cell malignancies, autoimmunity, and monoclonal gammopathies are the most common. The laboratory features are similar to those of hereditary C1-INH deficiency, except that C1q levels are diminished in these patients. Anti–C1-INH can be detected in approximately 70% of the cases.

C4 Binding Protein Deficiency

C4 binding protein deficiency has been described in one family. The proband presented with angioedema, vasculitis, and arthritis. The manifestations were thought to relate to uncontrolled activation of the CP and the release of anaphylatoxins.

Factor H Deficiency

Factor H (CFH), which is present at high concentrations (500 μg/mL) in plasma, works in both the liquid and solid phases and attenuates the activity of C3 convertase in the AP and acts as a cofactor for factor I in the cleavage of C3b and C4b. It is a multifunctional molecule that has the function of decay acceleration and plays a very important role in regulating complement activation. Infections, aHUS, glomerulonephritis, and macular degeneration are the main disease phenotypes seen in patients with factor H deficiency. Infections occur due to secondary consumption of C3 with consequent partial deficiency. Diagnosis is suggestive when C3 has diminished levels and low but not absent CH50 and AP50 is found. The antigenic levels of factor H are typically low.

Several people with **MPGN** were identified with factor H deficiency. CFH deficiency was found to be the underlying basis for the pathophysiologic changes in 15–30% of patients with **aHUS**. aHUS is a thrombotic microangiopathy characterized by hemolytic anemia, thrombocytopenia, and renal failure, which occurs in the absence of its usual cause (infection with a Shiga toxin–producing organism). It is called "atypical" because it lacks the common trigger of infectious diarrhea. CFH deficiency probably affects the ability to protect the fenestrated endothelium in the glomerulus from complement-mediated damage. Recurrent aHUS also has been seen in patients with antibodies to factor H, defining an acquired form as well. This form may be slightly more amenable to therapy. Both autosomal recessive and heterozygous pathogenic variants have been seen. The age at onset is quite young in most cases, and the disease is recurrent. Mortality is not uncommon. These patients have a diminished C3 level, although the antigenic level of factor H typically is normal or elevated. Normal C3 levels are sometimes seen, and the only way in which this disorder can be identified is with direct genetic analysis.

A common tyrosine-histidine polymorphism of factor H was identified as a significant risk factor for **macular degeneration** with a higher risk of the development of macular degeneration and blindness subsequently. In macular degeneration, the central region of the retina is gradually destroyed by a process that leaves deposits of protein that contain factor H and terminal complement components. It has been hypothesized that the abnormal factor H provides less protection to the choroidal vessels, allowing smoldering complement activation with gradual damage to the endothelium.

FACTOR I DEFICIENCY

Not only factor H but also factor I is a key regulator of the AP. Deficiency of factor I results in uncontrolled activation of the AP with subsequent secondary C3 deficiency and a reduction in circulating factor H levels. Distinct clinical manifestations have been associated with **factor I deficiency.** Marked susceptibility to infections relates to the role of factor I as a cofactor for C3bBb dissociation. When factor I is lacking, C3bBb continues to cleave C3 resulting in secondary C3 deficit. Both the CH50 and the AP50 are depressed but not absent, and C3 antigen levels are low. In factor I deficiency, infections are similar to those seen in true C3 deficiency. Neisserial disease has been reported, as well as infections with encapsulated organisms such as *S. pneumoniae* and *H. influenzae.* Partial factor I deficiency has been described. aHUS, or MPGN II, has also been associated with factor I deficiency, probably related to the capacity of complement regulatory proteins to protect vascular endothelium from activating complement after microtrauma. These cases of factor I deficiency are difficult to identify because complement studies often give normal results. C3 may be depressed but is not necessarily affected. The pathogenic variants inactivate certain binding sites like surface-bound C3b and polyanion surfaces such as the fenestrated endothelium of the glomerulus, which exposes the basement membrane. A third phenotype resembles an autoinflammatory process and has been described in a small number of patients. Central nervous system inflammation has been the hallmark. Partial factor I deficiency has also been previously associated with clinical manifestations including recurrent tonsillitis, urinary infections, otitis, pyelonephritis, severe meningitis, and sepsis.

Membrane Cofactor Protein (CD46) Deficiency

MCP is a membrane protein, and its defect is intrinsic to the kidney. Deficiencies of MCP are associated with a later onset of atypical HUS compared with factor H and factor I deficiencies and it accounts for approximately 10% of all cases. There is no other known phenotype for MCP deficiency. Findings on traditional complement analysis are normal, although the mechanism is thought to be the same as for factor H and factor I deficiencies. Considering the local defect, renal transplantation can be successful.

CD59 Deficiency

CD59 is the key membrane regulator of the TP that prevents insertion of the MAC into host tissue. It is expressed on most hematopoietic cells and endothelial cells, where it confers protection from intravascular complement-mediated lysis. Isolated CD59 deficiency manifests by chronic hemolytic anemia, recurrent stroke, and severe Guillain-Barré–like neurologic symptoms with hemolysis. This defect

Table 173.5 Protein Regulators and Receptor Deficiencies of Complement System

DEFICIENCY	INHERITANCE	ASSOCIATED SYMPTOMS/DISORDERS
C1 inhibitor	AD	HAE with C1-INH deficiency
C4-binding protein	Unknown	Atypical Morbus Behçet, angioedema, protein S deficit
Properdin	X-linked recessive	Meningitis (*Neisseria*)
Factor H	AR	Membranoproliferative glomerulonephritis, AMD, aHUS (20–30% of the cases)
Factor I	AR	Pyogenic infections, neisserial infections, glomerulonephritis, aHUS (5–10% of the cases), central nervous system inflammation
CFHR1 (FHR3)	Complex	aHUS, C3G, AMD, RA, SLE
Thrombomodulin (CD141)	AD	aHUS (3–5% of the cases)
CD46/MCP	Most often heterozygous or compound heterozygous pathogenic variants	aHUS (10–15% of the cases)
CD55/DAF	AR	Protein losing enteropathy
CD55 (DAF) or CD59	AR	PNH
CD59	AR	Chronic hemolysis and relapsing peripheral demyelinating disease, cerebral infarction
CR2 (CD21)	AR	Infections, associated with CVID
CR3 (CD18/CD11b); CR4 (CD18/CD11c, LFA-1)	AR	LAD

CFHR1, Complement factor H related 1; MCP, membrane cofactor protein; DAF, decay-accelerating factor; LFA-1, integrin called lymphocyte function-associated antigen 1; AR, autosomal recessive; AD, autosomal dominant; aHUS, atypical hemolytic uremic syndrome; C3G, C3 glomerulopathy; SLE, systemic lupus erythematosus; AMD, aging macular degeneration; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; PNH, paroxysmal nocturnal hemoglobinuria; CVID, common variable immunodeficiency; LAD, leukocyte adhesion deficiency.

in CD59 was suspected in cases of chronic hemolysis because of the phenotypic resemblance to **PNH**. PNH is caused by acquired somatic variants of phosphatidylinositol glycan class A (PIG-A) or phosphatidylinositol glycan class M (PIG-M) in a clone of bone marrow progenitor cells. The protein product of PIG-A is an anchoring structure for C8 binding protein, DAF (CD55), and CD59. Glycosylphosphatidylinositol (GPI)-anchored proteins protect hematopoietic cells from complement-mediated lysis. PNH is characterized by recurrent episodes of hemoglobinuria secondary to intravascular hemolysis and can be associated with thrombosis and aplastic anemia. The red cells are the most vulnerable because they have no ability to repair membrane damage. When the cells develop from the variant-bearing progenitor, they lack all GPI-anchored membrane proteins, although the major features relate to loss of CD59. The diagnosis of PNH is made by flow cytometry for CD59 or CD55 (DAF).

Decay-Accelerating Factor (CD55) Deficiency

DAF (CD55) is a membrane-bound regulator that dissociates both classical and alternative C3 convertases. In certain kindreds, DAF deficiency has been associated with protein-losing enteropathy, whereas in others, all of the members have been completely healthy, with the deficiency being identified at the time of blood donation or cross matching for a transfusion. The *Cromer blood group* antigens reside on DAF. The RBCs of people with the Cromer-null phenotype, Inab, lack DAF but do not appear to show increased susceptibility to hemolysis. This finding suggests that CD59 is substantially more important in regulating red cell lysis by complement.

DEFICIENCIES OF COMPLEMENT RECEPTORS

CR1 Deficiency

CR1 (CD35) is a multiple modular protein that binds C3b/C4b-opsonized foreign antigens, mediating the immune adherence phenomenon. No cases of complete inherited CR1 deficiency have been reported; however, acquired mild C1R deficiency is quite common in patients with immune complex diseases and serum sickness. Similarly, a polymorphic variant of CR1 with diminished levels and function has been described, although it does not appear to be a risk factor for autoimmune disease.

CR3/CR4 Deficiency

CR3/CR4 deficiency (LFA-1) is a defect in the 3 β_2-integrin adhesion molecules. Pathogenic variants in the common β chain (CD18) lead to failure to express adequate α chains: CD11a, CD11b, and CD11c. **Leukocyte adhesion deficiency (LAD)** is an autosomal recessive disorder of neutrophil function resulting from a deficiency of β_2-integrin subunit of the leukocyte cell adhesion molecule (Table 173.5; see Chapter 170). The leukocyte cell adhesion molecule is present on the surface of peripheral blood mononuclear leukocytes and granulocytes and mediates cell-cell and cell-extracellular matrix adhesion. LAD is characterized by a delayed separation of the umbilical cord, recurrent bacterial and fungal infections, and impaired pus formation and wound healing associated with heavy mortality; bone marrow transplantation often is recommended. The infections are characteristic in that necrosis predominates, with little neutrophilic infiltrate. With some residual β_2-integrin expression, the patient may be able to survive without a bone marrow transplant and infections are common.

The manifestations of the disorder are due to the combined effects of ineffective opsonization and an inability to traverse the vascular endothelium to phagocytose bacteria. β_2-Integrins are essential for the firm adhesion step and diapedesis. Lacking β_2-integrins, the neutrophils remain in the vascular space, where they are unable to participate in the defense against bacteria. This explains the lack of pus at sites of active infection.

Two other forms of LAD are recognized: **LAD type II** is due to a defect in fucosylation of selectin ligands and **LAD type III** is due to an activation defect of integrins. The major manifestations are the infection pattern just described and a moderate to severe bleeding tendency secondary to impaired activation of platelet adhesion molecules. LAD-III results from pathogenic variants in FERMT3, or KINDLIN3, which encodes an intracellular protein that interacts with β-integrins in hematopoietic cells. In LAD-III, the adhesive functions of integrins on both leukocytes and platelets are disrupted, most likely due

to defects in activation-dependent alterations of surface integrins that enable high-avidity binding to ligands on target cells, a process termed inside-out signaling.

MANAGEMENT OF COMPLEMENT DEFICIENCIES

Prophylactic antibiotics may offer additional protection from serious infection. With the onset of unexplained fever, cultures should be obtained and antibiotic therapy instituted rapidly and with less stringent indications than in an unaffected child. The parent or patient should be given a written action plan describing any predisposition to systemic bacterial infection or autoimmune disease associated with the patient's deficiency, along with the recommended initial approach to management, for possible use by school, camp, or emergency department physicians. Therapy for infection is not standardized, but it is usually directed to prevent infections caused by encapsulated bacteria. Early complement component deficiencies have major risks to acquire infections caused by *S. pneumoniae* and *H. influenzae.*

Patients should also be vaccinated against encapsulated organisms to maintain high titers. In the case of terminal component, factor D, and properdin deficiencies, high levels of antibody after vaccination may partially compensate for the complement deficiency. Effective vaccines are available; high titers of antibody may offer protection. Repeat immunization of patients is advisable because complement deficiency can be associated with a blunted or shorter-lived antibody response than normal. Immunization of household members may reduce the risk of exposing patients to these pathogens.

Patients under immunosuppression for rheumatologic disorders such as SLE will require more vigilance for severe infection. Individuals with SLE and a complement defect generally respond as well to therapy as do those without complement deficiency. Management of cardiac risk factors is of heightened importance in early complement component–deficient individuals because of their accelerated atherosclerosis. C1q deficiency has a poor prognosis and this protein is produced to a large extent by myeloid cells. Bone marrow transplantation has been curative and should be considered for C1q deficiency.

MBL purified from plasma or recombinant material has been administered in trials; however, no prospective study has been performed. In addition, the role of MBL deficiency in significant infections is not well established.

The treatment of **HAE with C1-INH deficiency** is noted in Chapter 189.1. General guidance includes avoiding the use of estrogens or drugs that can induce angioedema, such as angiotensin-converting enzyme inhibitors (ACEis) and gliptins. If possible, trigger factors could be avoided. Vaccination is not contraindicated, and hepatitis A and B vaccinations are recommended. The approach includes long-term prophylaxis (LTP), short-term prophylaxis (STP), and on-demand therapy (Table 173.6; see Chapter 189.1).

STP is used for dental procedures, surgical procedures, endoscopies, or other situations in which significant trauma may be expected. Attenuated androgens can be used for this indication; C1-INH concentrates have largely supplanted androgens in this setting. A recombinant C1-INH, conestat alfa, is effective for both HAE attacks and for STP. Fresh-frozen plasma (FFP) is another alternative in this setting.

Despite prophylaxis, breakthrough episodes do occur. **On-demand therapy** should also be an option for patients with sporadic attacks or who may not be on any active prophylaxis. There are several options to treat the attacks: C1-INH concentrate; ecallantide, a kallikrein inhibitor; and icatibant, a bradykinin β_2-receptor antagonist.

On-demand treatment and STP is the same for **HAE with normal C1-INH**. LTP shows improvement with tranexamic acid and progestins.

PNH/aHUS Treatment

Eculizumab, a humanized monoclonal IgG2/4-antibody targeting C5, prevents the generation of the MAC C5b9 and is an effective treatment for PNH and aHUS.

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Table 173.6 Therapies for Hereditary Angioedema with C1 Inhibitor Deficiency

LONG-TERM PROPHYLAXIS	
Androgens (danazol, oxandrolone, stanozolol)	Avoid use If necessary: Danazol: 10 mg/kg/day (max 200 mg/day) Oxandrolone: ≤ 0.1 mg/kg/day (no max) Stanozolol: 2-6 mg/day (dose and max) after puberty (Tanner 5) Oral
Antifibrinolytics (tranexamic acid, epsilon aminocaproic acid)	Tranexamic acid: 10 mg/kg/day bid to 25 mg/kg/day tid Limit dosage 3 g/day Oral
pdC1-INH nanofiltrated*	Approved for ≥12 yr in some countries, ≥6 yr in others 1,000 IU in ≥12 yr 6-12 yr 500 IU q 3-4 days IV
SC pdC1-INH nanofiltrated	60 IU/kg twice weekly >12 yr SC
Lanadelumab	300 mg every 2 wk After 6 mo, if no attacks: 300 mg every 4 wk >12 yr SC
Berotralstat	Approved in some countries for 12 yr or older 150 mg/day Oral
SHORT-TERM PROPHYLAXIS	
pdC1-INH nanofiltrated*	20 IU/kg IV (no age limits) 1-6 hr before procedure/trigger IV
rhC1-INH/conestat alfa	Approved for ≥12 yr in some countries, ≥2 yr in others 50 IU/kg, max. 4,200 IU (50 IU/kg <84 kg, 4,200 IU >85 kg) IV
Androgens (danazol, oxandrolone, stanozolol)	Avoid use Danazol: 10 mg/kg/day (max 200 mg/day) Oxandrolone: ≤0.1 mg/kg/day (no max) Stanozolol: 2-6 mg/day (dose and max) 5 days before and 2-3 days after procedure/trigger Oral
Fresh-frozen plasma	May be used, if other STP medications not available 10 mL/kg IV No age limits
ON-DEMAND THERAPY	
Ecallantide	Approved in some countries for ≥12 yr 30 mg SC Self-administration is not allowed due to anaphylaxis
Icatibant	Approved for ≥18 yr in some countries, ≥2 yr in others 30 mg/3 mL Dose adjustment is needed for adolescent/children <65 kg/≥2 yr SC
pdC1-INH nanofiltrated*	20 IU/kg IV (no age limits)
rhC1-INH/conestat alfa	Approved for ≥12 yr in some countries, ≥2 yr in others 50 IU/kg, max. 4,200 IU (50 IU/kg <84 kg, 4,200 IU >85 kg) IV
Fresh-frozen plasma	May be used if other on-demand medications are not available 10 mL/kg IV No age limits

*Commercial name for pdC1-INH nanofiltered indicated for LTP is Cinryze and for STP is Berinert.
IV, Intravenous; LTP, long-term prophylaxis; pd, plasma derived; rh, recombinant; SC, subcutaneous; STP, short-term prophylaxis.

Section 5

Immune Dysregulation

Chapter 174

Immune Dysregulation

Danielle E. Arnold and Jennifer W. Leiding

Primary immune dysregulatory diseases (PIRDs) are a recognized subset of primary immunodeficiencies that are characterized by hyperinflammation, organ-specific and systemic autoimmunity, endocrinopathy, enteropathy, and nonmalignant lymphoproliferation. Clinical manifestations of immune dysregulation should lead to a consideration of PIRD. Genetic testing can confirm a diagnosis. Targeted treatments are available for many PIRDs and hematopoietic cell transplant (HCT) is often curative.

174.1 Tregopathies

Danielle E. Arnold and Jennifer W. Leiding

Tregopathies are a subset of primary immunodeficiency diseases recognized by the International Union of Immunologic Societies. The clinical manifestations of these diseases are variable, but all involve some degree of immune dysregulation manifesting as autoimmunity, hyperinflammation, cancer predisposition, and/or lymphoproliferative disease.

PATHOPHYSIOLOGY

T regulatory (Treg) cells are specialized T cells responsible for the maintenance and self-tolerance of immune responses (Fig. 174.1). These cells are responsible for suppressing production of proinflammatory cytokines and growth factors and suppressing T-cell proliferation. The transcription factor FOXP3 is essential for the regulatory function of Treg cells. Several subsets of Treg cells exist, each characterized by unique features. Thymic-derived Treg cells (tTreg) ($CD4^+CD25^+FOXP3^+$) account for ~5% of total $CD4^+$ T cells in the peripheral blood. $FOXP3^+$ Treg cells can also differentiate outside of the thymus in peripheral tissues. These cells are known as peripherally induced regulatory (pTreg) cells. A number of monogenic diseases (Table 174.1) of the immune system that affect the number and/or function of Treg cells have been described. By reducing the effect of Treg cells, T-cell activation and proliferation are unrestrained. This lack of regulation or inhibition manifests as immune dysregulation. Clinical symptoms of these disorders include early onset multiorgan autoimmunity, endocrinopathy, enteropathy, colitis, and lymphoproliferation.

Diagnosis

In a patient with early-onset, severe, or difficult to control autoimmunity, endocrinopathy, colitis, or nonmalignant lymphoproliferative disease, a diagnosis of a Tregopathy should be considered. Next generation sequencing via a targeted panel and/or whole exome sequencing is necessary to establish a genetic diagnosis.

Treatment

Targeted treatment is available for several Tregopathies (see Table 174.1). Abatacept, a CTLA4-Ig fusion protein, has been used successfully in the treatment of refractory cytopenias, interstitial lung disease, and lymphoproliferation in CTLA4 haploinsufficiency and lipopolysaccharide-responsive and beigelike anchor protein (LRBA) deficiency. Jakinibs are a class of medications that inhibit Janus kinase activation of certain STAT transcription factors. Jakinibs have been used successfully to treat immune dysregulatory and autoimmune symptoms in gain-of-function of STAT1 and STAT3 diseases. HCT can provide a curative option for many Tregopathies.

IMMUNE DYSREGULATION POLYENDOCRINOPATHY, ENTEROPATHY, X-LINKED SYNDROME

This immune dysregulation syndrome is characterized by onset within the first few weeks or months 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 pathogenic variant in the *FOXP3* gene, which encodes a forkhead-winged helix transcription factor *(scurfin)* involved in the function and development of $CD4^+$ $CD25^+$ Tregs. The absence of Tregs may predispose to abnormal activation of effector T cells. Variants in multiple other genes also produce an **IPEX-like syndrome** (see Table 174.1; Fig. 174.2).

Clinical Manifestations

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

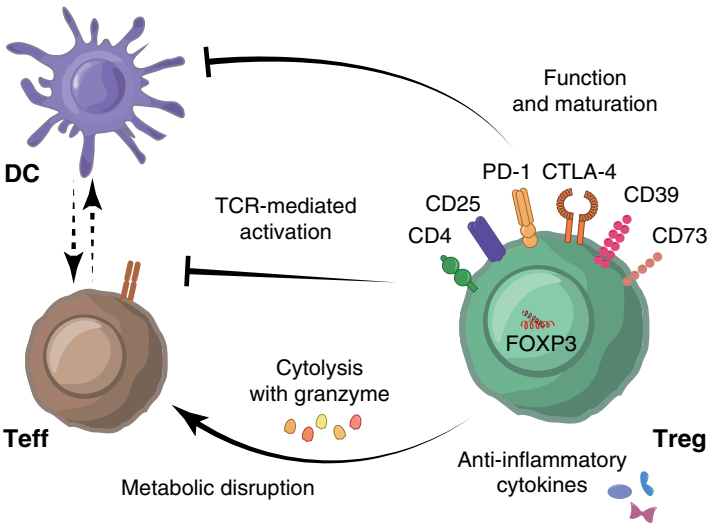

Fig. 174.1 Immunosuppressive mechanisms underlying Treg-mediated immune suppression. Tregs are characterized by expression of the cell surface markers $CD4^+$, CD25high and $CD127^{low/-}$, and transcription factor FOXP3. Tregs modulate the immune system using their suppressive molecules PD-1, CTLA-4, and CD39, and various surface receptors through inhibition of dendritic cell (DC) function and maturation, through the secretion of anti-inflammatory cytokines such as IL-10, TGF-β, and IL-35, and/or through direct inhibition of Teff via induction of cytolysis using granzyme and metabolic disruption. Moreover, Tregs can reduce Teff activation by limiting TCR-ligand binding. DC, dendritic cell; TCR, T cell receptor; Teff, effector T cell; Treg, regulatory T cell. (*From Kempkes RWM, Joosten I, Koenen HJPM, He X. Metabolic pathways involved in regulatory T cell functionality. Front Immunol. 2019;10:2839. Fig. 1.*)

Table 174.1 Tregopathies

GENE (PROTEIN)	DISORDER	INHERITANCE	CLINICAL PHENOTYPE	DEFINITIVE OR DISEASE-SPECIFIC TREATMENT
FOXP3	IPEX syndrome	XL	Enteropathy, type 1 diabetes, eczema, FTT, autoimmune cytopenias, thyroiditis, hepatitis	Tacrolimus, cyclosporine Allogeneic HCT
IL2RA	CD25 deficiency	AR	Enteropathy, eczema, lymphoproliferation, recurrent infections	Allogeneic HCT
CTLA-4 *ALPSV*	CTLA4 haploinsufficiency	AD	Enteropathy, type 1 diabetes, autoimmune cytopenias, interstitial lung disease	Sirolimus Abatacept, belatacept Allogeneic HCT
LRBA	LRBA deficiency	AR	Enteropathy, type 1 diabetes, autoimmune cytopenias, interstitial lung disease	Abatacept, belatacept Allogeneic HCT
BACH2	BACH2 deficiency	AD	Enteropathy, lymphoproliferation, recurrent respiratory tract infections, infections	Allogeneic HCT
STAT3	STAT3 GOF	AD, GOF	Enteropathy, autoimmune cytopenias, lymphoproliferation, type 1 diabetes, recurrent infections	Jakinibs Allogeneic HCT
STAT5B	STAT5B	AD, AR	Eczema, growth hormone deficiency, infections, enteropathy, JIA, ITP, chronic lung disease	Symptom specific therapy, HCT

IPEX, Immune dysregulation, polyendocrinopathy, enteropathy, X-linked; XL, X-linked; FTT, failure to thrive; HCT, hematopoietic cell transplant; AR, autosomal recessive; CTLA, cytotoxic T-lymphocyte protein; ALPSV, autoimmune lymphoproliferative disease V; AD, autosomal dominant; LRBA, lipopolysaccharide-responsive and beigelike anchor protein; BACH, broad complex-tramtrack-bric a brac and Cap'n'collar homology; STAT, signal transducer and activator of transcription; GOF, gain of function; JIA, juvenile idiopathic arthritis; ITP, immune thrombocytopenic purpura.

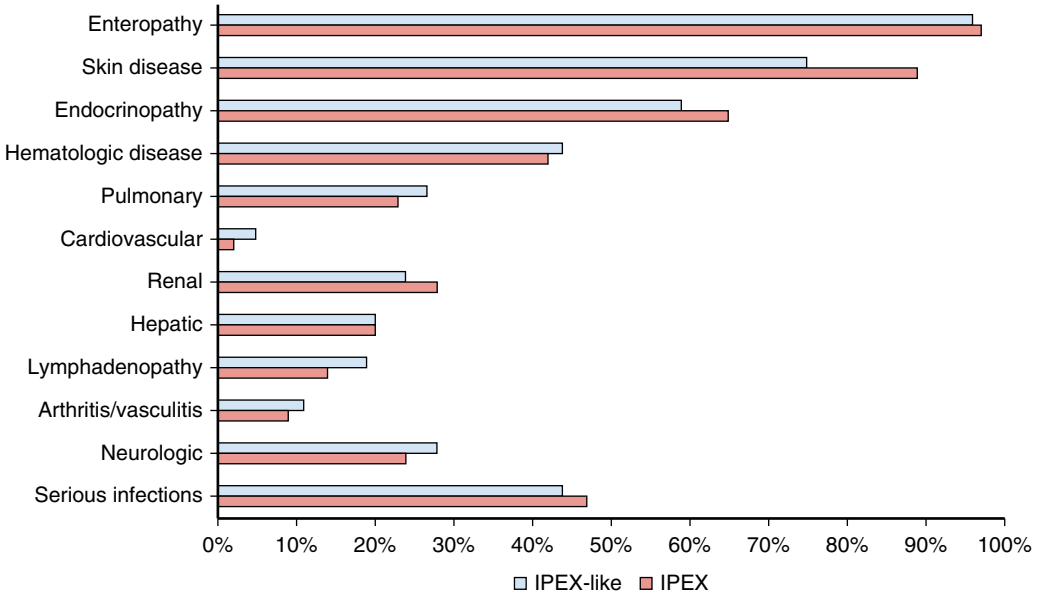

Fig. 174.2 Clinical manifestations in the IPEX-like cohorts. (*Modified from Gambineri E, Ciullini Mannurita S, Hagin D, et al. Clinical, immunological, and molecular heterogeneity of 173 patients with the phenotype of immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome. Front Immunol. 2018;9:2411. Fig. 5.*)

with normal levels of IgM, IgG, and IgA. The diagnosis is initially made clinically and confirmed by genetic testing (exome or panels).

Treatment

Inhibition of T-cell activation by cyclosporine, tacrolimus, or sirolimus with corticosteroids is the treatment of choice, along with the specific care of the endocrinopathy and other manifestations of autoimmunity. These agents are typically used as a bridge to transplant. HCT is the only possibility for curing IPEX. Janus kinase inhibitors have been used in patients with IPEX-like syndromes.

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174.2 Hemophagocytic Lymphohistiocytosis

Danielle E. Arnold and Jennifer W. Leiding

Hemophagocytic lymphohistiocytosis (HLH) is a severe systemic hyperinflammatory syndrome that can be aggressive and life-threatening. Classic features include fever, cytopenia, hepatosplenomegaly, coagulopathy, and elevations in inflammatory markers.

Primary or genetic HLH is due to pathogenic variants in genes that predispose patients to HLH by a variety of mechanisms and includes classic familial HLH due to pathogenic variants in *PRF1*, *UNC13D*, *STX11*, and *STXBP2*; certain pigmentary disorders; and other primary

immunodeficiencies or immune regulatory disorders (see Chapter 556.2; Fig. 174.3). Primary HLH is seen most frequently in pediatric patients but may occur at all ages.

Secondary HLH occurs in the setting of a medical condition that results in intense immune activation such as severe infection, malignancy, or rheumatologic disease. Many primary immune deficiencies (PIDs) are also associated with an increased risk of HLH, usually in the setting of infection. HLH has been reported in patients with severe combined immune deficiency and chronic granulomatous disease, but secondary HLH has been seen in a wide variety of PID. Several inborn errors of metabolism can also present with secondary HLH.

Of note, patients with primary or genetic HLH often present with HLH triggered by or "secondary" to infection or other immune activating events.

For more details see Chapter 556.2.

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174.3 Epstein-Barr Virus Susceptibility Disorders

Danielle E. Arnold and Jennifer W. Leiding

Epstein-Barr virus (EBV) is a gamma-herpes family virus with a marked tropism for B cells. Most individuals experience asymptomatic infection or infectious mononucleosis, a self-limiting lymphoproliferative disease that is particularly common in adolescents. EBV is also an oncogenic virus and may induce several types of neoplasms, including B-cell, T-cell, and natural killer (NK) cell lymphomas; nasopharyngeal and gastric carcinomas; and EBV-associated smooth muscle cell tumors.

During primary infection, EBV-infected B cells are eliminated by EBV-specific cytotoxic T cells as well as other innate cytotoxic lymphocytes such as NK cells, γδ T cells, and invariant natural killer T (iNKT) cells. However, some EBV-infected B cells escape the immune response, establishing a reservoir for EBV that may reactivate

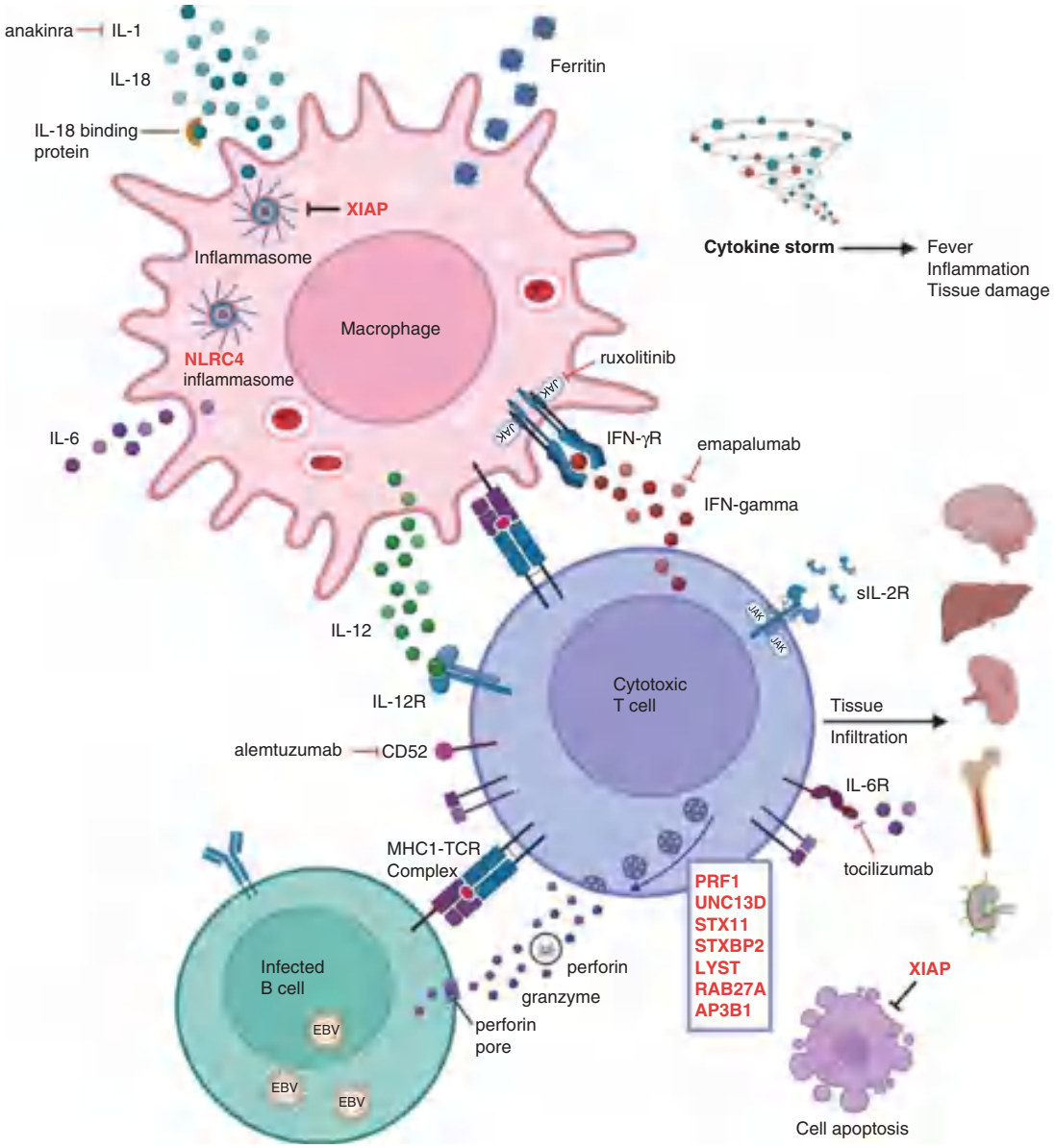

Fig. 174.3 Hemophagocytic lymphohistiocytosis (HLH). HLH is a severe systemic inflammatory syndrome due to abnormal reciprocal macrophage and cytotoxic lymphocyte hyperactivation, resulting in cytokine storm, hemophagocytosis, and tissue infiltration by activated immune cells. Primary HLH genes associated with defective granule-mediated cytotoxicity or inflammasome dysregulation are shown in red. Common nonsteroidal immunosuppressive agents frequently used to treat HLH are also shown. EBV, Epstein-Barr virus; IFN, interferon; IL, interleukin; MHC, major histocompatibility complex; TCR, T-cell receptor; XIAP, X-linked inhibitor of apoptosis.

throughout an individual's life. These reactivations are typically asymptomatic in healthy individuals; however, in immunocompromised persons, EBV reactivations and persistence and expansion of latently infected B lymphoblasts may result in symptomatic and often severe disease.

PATHOPHYSIOLOGY

There are several primary combined immunodeficiencies characterized by a very high predisposition to EBV infection, some of which are listed in Table 174.2. These disorders are due to defects in pathways involved in T- and B-cell interaction and crosstalk (Fig. 174.4). Disruption of these pathways results in aberrant cytotoxic T-cell activation, migration, proliferation, and/or cytolytic activity in response to antigenic stimulation and, thus, impaired immune surveillance of B cells by T cells. Marked decrease or absence of iNKT cells, mucosal-associated invariant T (MAIT) cells, and/or NK cells and impaired NK cell function are also often observed.

Clinical Manifestations, Diagnosis, and Treatment

More than 50% of patients with EBV susceptibility disorders experience at least one episode of EBV lymphoproliferative disease. Patients are also susceptible to other EBV-driven pathologies, including HLH and both Hodgkin and non-Hodgkin lymphoma. Other severe viral infections (e.g., other herpesviruses, human herpesvirus 6 [HHV-6]), bacterial infections, particularly recurrent pulmonary infections, and hypogammaglobulinemia and/or dysgammaglobulinemia are also common. Diagnosis for these disorders is with a full immune evaluation and genetic testing. Treatment includes rituximab (anti-CD20 antibody) to eliminate EBV-infected B cells, treatment of infections, and immunoglobulin

Table 174.2 Primary or Genetic EBV Susceptibility Disorders

GENE (PROTEIN)	DISORDER	INHERITANCE	PATHOGENESIS	ADDITIONAL FEATURES	DEFINITIVE OR DISEASE-SPECIFIC TREATMENT*
MAGT1	XMEN (X-linked immunodeficiency w/Mg^{2+} defect, EBV infection and neoplasia)	XL	Defective Mg^{2+} transporter; ↓ NKG2D expression results in defective cytotoxicity	Chronic EBV infection rather than full-scale HLH, viral infections, lung infections, autoimmune cytopenia, lymphoma	Allogeneic HCT
ITK	Lymphoproliferative syndrome 1	AR	Defective tyrosine kinase function; defective cytotoxic T-cell expansion, and cytolytic capacity; ↓ iNKT cells	Chronic EBV infection, lung infections, PJP, autoimmune cytopenia, lymphoma	Allogeneic HCT
CD27	Lymphoproliferative syndrome 2	AD	CD27 is a co-stimulatory molecule on T cells; required for normal T-cell proliferation and cytotoxicity against EBV-infected B cells; ↓ iNKT cells	Chronic EBV infection, lung infections, uveitis, oral and anal ulcers, hypogammaglobulinemia, lymphoma	Allogeneic HCT
CD70	Lymphoproliferative syndrome 3	AR	CD70 expressed by EBV-infected B cells interacts with CD27 on T cells; required for normal expansion and cytotoxicity of T cells; ↓ NKG2D and 2B4 expression; ↓ iNKT cells	Chronic EBV infection, lung infections, lymphoma	Allogeneic HCT
CTPS1	CTPS1 deficiency	AR	Enzyme involved in de novo synthesis of cytidine nucleotide triphosphate (CTP); deficiency leads to impaired T-cell proliferation; ↓ iNKT cells	Chronic EBV infection, viral infections, lung infections, meningitis, eczema, lymphoma	Allogeneic HCT
CORO1A	CORO1A deficiency	AR	Actin regulator; T lymphopenia, impaired immunologic synapse formation and intracellular signaling; ↓ iNKT cells	Chronic EBV infection rather than HLH, viral infections, lung infections, neurologic involvement, lymphoma	Allogeneic HCT
RASGRP1	RASGRP1 deficiency	AR	Activates RAS, which leads to MAPK pathway activation; defects in T-cell activation, proliferation, and migration; ↓ iNKT cells	Chronic EBV infection, viral infections, lung infections, autoimmune cytopenia, EBV negative lymphoproliferative disease, lymphoma	Allogeneic HCT

*Treatment should include HLH-directed therapy, treatment of infections and malignancy, and other supportive care measures as appropriate.
EBV, Epstein-Barr virus; AR, autosomal recessive; XL, X-linked; AD, autosomal dominant; TNF, tumor necrosis factor; iNKT, invariant NK T cell; CNS, central nervous system; HSM, hepatosplenomegaly; PJP, *Pneumocystis jiroveci* pneumonia; HCT, hematopoietic cell transplantation.

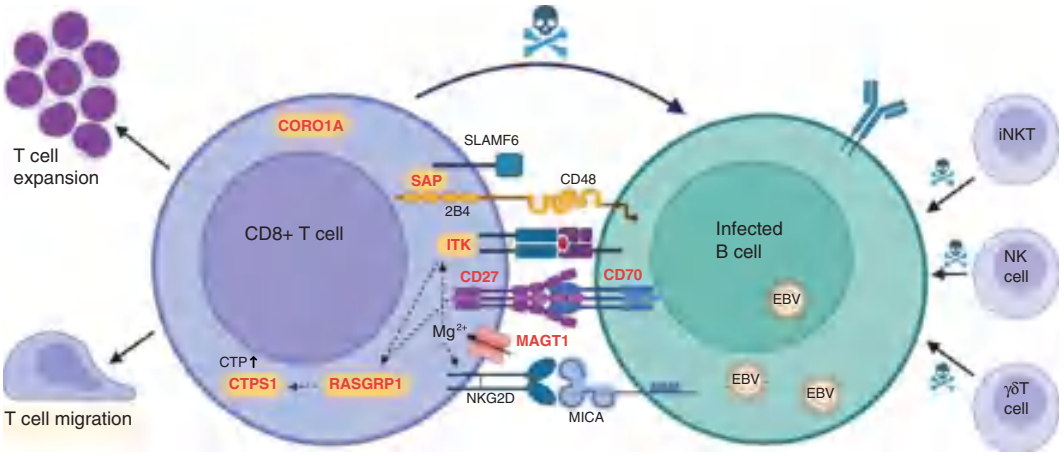

Fig. 174.4 Epstein-Barr virus (EBV) susceptibility disorders. Combined immunodeficiencies characterized by a very high predisposition to EBV lymphoproliferative disease are shown in red. These genes/proteins play essential roles in the recognition of EBV-infected B cells by T cells and in cytotoxic T-cell activation, migration, proliferation, and/or cytotoxic activity. As such, defects in any of these components allow for EBV-infected B-cell immune escape. Invariant natural killer T (iNKT) cell, NK cell, and γδT-cell numbers and/or function may also be low or aberrant, respectively.

replacement when indicated. Allogeneic HCT is the only curative treatment available.

Other Primary Immunodeficiencies Associated with Epstein-Barr Virus Lymphoproliferative Disease

Herpesvirus infections and EBV lymphoproliferative disease are also seen to a lesser extent in several other combined immunodeficiencies associated with T-cell defects, particularly those affecting T-cell survival and mobilization. Classic examples include Wiskott-Aldrich syndrome, DOCK8 deficiency, GATA2 haploinsufficiency, and activated PI3K-delta syndrome, among others. Severe EBV infections may also be seen in patients with hypomorphic or leaky severe combined immunodeficiency.

Any patient who presents with prolonged and/or severe EBV lymphoproliferative disease or EBV-positive lymphoma warrants evaluation for an underlying primary immunodeficiency.

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174.4 Chronic Active Epstein-Barr Virus

Danielle E. Arnold and Jennifer W. Leiding

Chronic active EBV (CAEBV) is a rare systemic EBV lymphoproliferative disorder characterized by fever, persistent lymphadenopathy, hepatosplenomegaly, and hepatitis in the absence of an underlying primary or secondary immunodeficiency, malignancy, or autoimmune disorder.

GENETIC PREDISPOSITION

CAEBV is seen primarily in persons of East Asian (Japan, Korea, China, and Taiwan) or Latin American (Indigenous people in Mexico and Central/South America) ancestry; in these patients, EBV is predominantly present in T cells or NK cells. Conversely, while rare, persons of Western European descent typically have B-cell CAEBV. The uneven geographic distribution of CAEBV suggests that underlying genetic factors may contribute to the development of CAEBV; heterozygous pathogenic variants in HLH predisposing genes (e.g., perforin) have been identified in patients with CAEBV. Causative genetic defects have not been identified in most cases.

Pathophysiology

The mechanism of EBV entry into T cells or NK cells is unclear, but T cells and NK cells can express low levels of CD21, the EBV receptor, during primary infection. The pathogenesis of CAEBV is less clear. Evidence suggests that EBV infection directly induces T-cell or NK cell survival via activation of several survival-promoting molecules or pathways, including upregulation of co-stimulatory molecules that suppress apoptosis, activation of the NF-κB pathway, and upregulation of activation-induced cytidine deaminase, which acts as a genomic disruptor and has been shown to play a role in EBV-induced lymphomagenesis in B cells.

Table 174.3 Chronic Active EBV (CAEBV) Diagnostic Criteria

All 4 criteria must be present:

1. Sustained or recurrent infectious mononucleosis-like symptoms persisting for >3 mo
2. EBV PCR >$10^{2.5}$ copies/μg DNA in the peripheral blood or tissue lesion
3. Evidence of EBV infection of T or NK cells in the peripheral blood or affected tissues
4. Exclusion of other diagnoses: primary EBV infection, primary or secondary immunodeficiency, malignancy, autoimmune disease

EBV, Epstein-Barr virus; NK, natural killer; PCR, polymerase chain reaction.

Clinical Manifestations and Diagnosis

Clinical manifestations of CAEBV are heterogenous, ranging from a mild and indolent clinical course to a more aggressive and potentially fatal illness due to complications such as HLH, multisystem organ failure, and/or progression to leukemia or lymphoma. Clinical manifestations may by episodic, but patients typically have persistently and markedly elevated levels of EBV in the blood throughout their disease course. Infiltration of tissues by EBV-positive lymphocytes may result in organ failure (liver failure is commonly seen), and EBV-infected T cells and NK cells may undergo malignant transformation. The diagnostic criteria for CAEBV are listed in Table 174.3; CAEBV should be suspected in any patient with sustained inflammation of unknown origin and chronically elevated EBV polymerase chain reaction (PCR) levels.

Evaluations to determine whether EBV is predominantly present in T cells or NK cells should be undertaken, if possible, in patients with CAEBV. One method is EBV PCR on peripheral blood mononuclear cells that have been sorted by flow cytometry, although this test is not widely available. Histologic examination of tissue that has been infiltrated by EBV-infected lymphocytes by immune staining and in situ hybridization of EBV-encoded mRNA (EBER) is another approach.

Treatment

Treatment options in severe cases are limited, and clinical responses are mostly transient. Some therapeutic approaches include

immunomodulatory therapy, combination bortezomib and ganciclovir, and EBV-specific T cells. Patients with HLH should receive HLH-directed therapy. Standard antiviral therapy is not effective. Cytotoxic chemotherapy is also used to reduce disease activity and burden of EBV-infected lymphocytes, primarily as a bridge to HCT. Allogeneic HCT is the only definitive therapy available with overall survival rates as high as 87% in some reports. Patients with progressive disease remain difficult to transplant. As such, some advocate rapidly proceeding to HCT early in the disease process, although the timing of HCT remains controversial.

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174.5 Very Early Onset Inflammatory Bowel Disease

Danielle E. Arnold and Jennifer W. Leiding

Inflammatory bowel disease that presents in children less than 6 years of age is known as very early onset inflammatory bowel disease (VEO-IBD). Monogenic defects involved in primary immunodeficiency and intestinal barrier processes are enriched in children with VEO-IBD (Fig. 174.5). Targeted therapies in children with VEO-IBD with a monogenic defect have been successful in treating disease manifestations (see Chapter 382.3).

DISEASE CLASSIFICATION AND CLINICAL PRESENTATION

Children diagnosed with IBD <2 years of age are referred to as *infantile*-onset IBD and those 2-6 years as VEO-IBD. Children present with classic symptoms of IBD including weight loss, failure to thrive, abdominal pain, fever, constipation, diarrhea, hematochezia. The phenotype is heterogenous with some children having mild disease and others presenting with or developing more severe disease over time. Approximately 40% have extensive pancolonic disease at presentation. Extent, location, and histology can progress or change over time.

For more details see Chapter 382.3.

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174.6 Autoimmune Cytopenias

Danielle E. Arnold and Jennifer W. Leiding

Autoimmune cytopenias are a group of disorders in which there is immune destruction of differentiated hematopoietic cells. Immune destruction can be autoantibody mediated or non-autoantibody mediated. Single lineage disease can affect red cells (autoimmune hemolytic anemia [AIHA]), platelets (idiopathic thrombocytopenia purpura [ITP]), or neutrophils (autoimmune neutropenia [AIN]). Bilineage or trilineage disease can affect any combination of these cell lines. **Evan disease** is a combination of AIHA and ITP.

PATHOPHYSIOLOGY

The etiology of autoimmune cytopenias as a manifestation of an inborn error of immunity is often multifactorial with autoantibody-mediated destruction or cellular-mediated destruction of red blood cells, platelets, or neutrophils as the major causes of hemolysis (Table 174.4). In disorders with intrinsic B-cell defects and disrupted T- and B-cell interactions, autoantibody production toward hematopoietic cells can

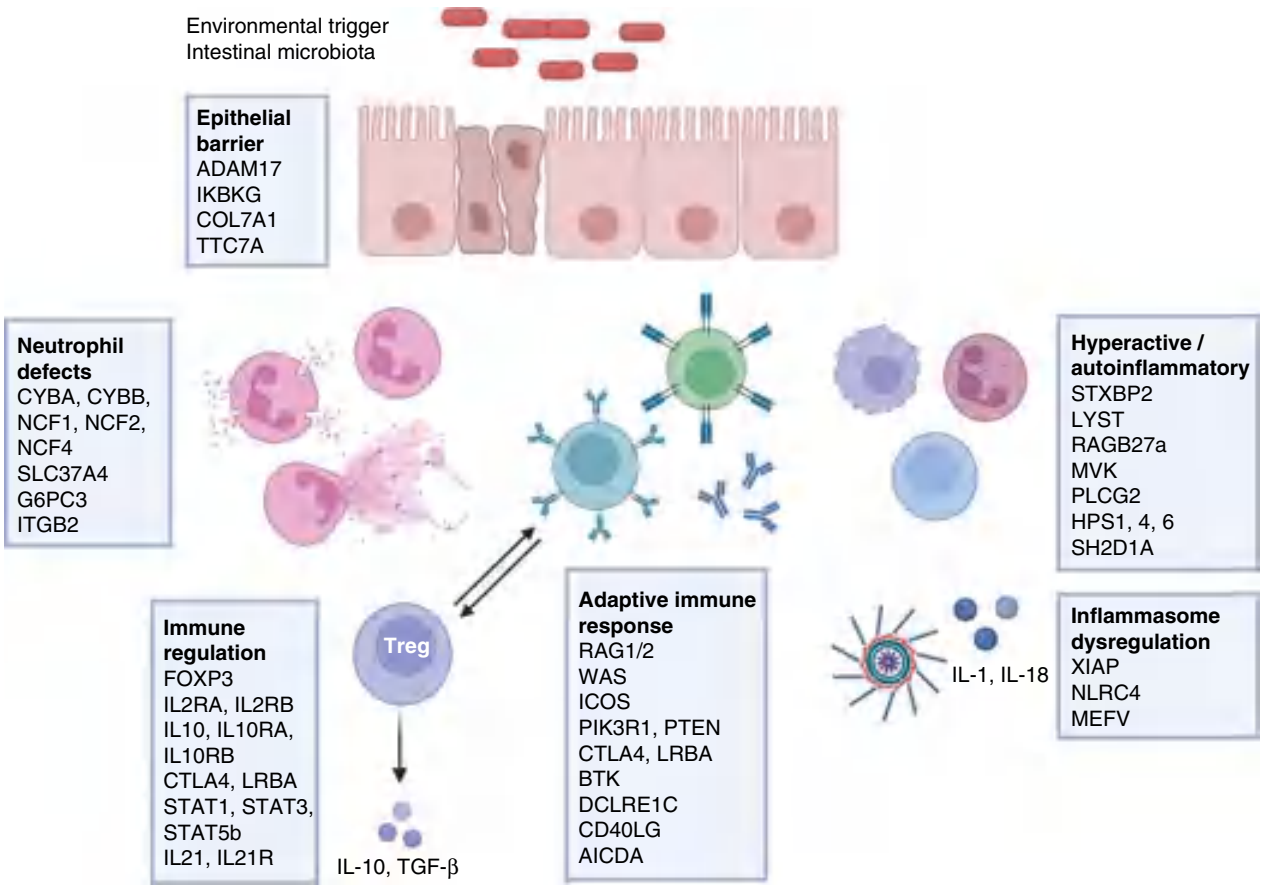

Fig. 174.5 Very early onset inflammatory bowel disease. Complex host interactions between the environment, intestinal microbiota, and immune-related genes maintain gut health. Mutations in genes involved in epithelial barrier, neutrophil function, control of inflammation, and T- and B-cell function can manifest as very early onset inflammatory bowel disease. IL, Interleukin; TGF, transforming growth factor; Treg, T regulatory cell.

Table 174.4 Monogenic Causes of Autoimmune Cytopenias and Primary Immunodeficiency

GENE (PROTEIN)	DISORDER	MOI	CLINICAL PHENOTYPE	IMMUNE FEATURES	DEFINITIVE OR DISEASE-SPECIFIC TREATMENT
PIK3 defects	Activated PI3K-delta syndrome	AD, LOF AD, GOF AD	Insulin resistance, short stature, nodular lymphoid hyperplasia, lymphoma, bronchiectasis	High IgM, low IgG, low CD4/CD45RA	Allogeneic HCT *Leniolisib, sirolimus
STAT3	STAT3 GOF	AD, GOF	Enteropathy, autoimmune cytopenias, lymphoproliferation, recurrent infections	Elevated DNTs Variable decreases in IgG, IgA, IgM, B- and T-cell quantities	Jakinibs Allogeneic HCT
STAT1	STAT1 GOF	AD, GOF	Chronic mucocutaneous candidiasis, cerebral aneurysms, interstitial lung disease, enteropathy, colitis	Variable decreases in IgG, IgA, IgM, B- and T-cell quantities	Jakinibs Allogeneic HCT
CTLA-4	CTLA4 haploinsufficiency	AD	Enteropathy, type 1 diabetes, autoimmune cytopenias, interstitial lung disease	Low IgG, low T-cell quantities	Sirolimus Abatacept, belatacept Allogeneic HCT
LRBA	LRBA deficiency	AR	Enteropathy, type 1 diabetes, autoimmune cytopenias, interstitial lung disease	Low IgG, low T-cell quantities	Abatacept, belatacept Allogeneic HCT
TNFRSF6 *TNFSF6* *FADD* *CASP8* *CASP10*	ALPS	AR GOF	Lymphadenopathy, lymphoma	Elevated DNTs	Mycophenolate mofetil Sirolimus

PI3K, Phosphoinositide 3 kinase; AD, autosomal dominant; LOF, loss of function; AD, autosomal dominant; GOF, gain of function; HCT, hematopoietic cell transplant; STAT, signal transducer and activator of transcription; CTLA, cytotoxic T-lymphocyte protein; LRBA, lipopolysaccharide-responsive and beigelike anchor protein; ALPS, autoimmune lymphoproliferative syndrome; DNT, double negative T cell.

occur. When B-cell maturation is impaired, vital steps in the induction of tolerance are omitted. In addition to the humoral B-cell defects that can lead to autoimmune cytopenias, intrinsic defects in T-cell effector function can lead to cellular autoimmunity. Impaired T-cell development can cause a lack of functional effector cells against non-self or "dangerous" antigens while allowing production of autoreactive clones with T-cell receptors directed against self-antigens. Additionally, T-cell defects may lead to a reduction in $FOXP3^+$ Treg cells.

Clinical Manifestations and Diagnosis

The clinical presentation of AIHA commonly includes dizziness, fatigue, pallor, jaundice, and exertional dyspnea (see Chapter 513). Complete blood count will show anemia and reticulocytosis. Additional features of hemolysis include hyperbilirubinemia, elevated lactate dehydrogenase, and decreased haptoglobin levels. Direct antiglobulin testing is most often positive. ITP typically presents with bleeding episodes that can range from mild bruising, petechiae, and epistaxis to oral purpura, hematuria, menorrhagia, gastrointestinal hemorrhage, or intracranial bleeding (see Chapter 533.1). Severe life-threatening bleeding is rare. Laboratory findings include acute thrombocytopenia. Mean platelet volume is elevated or variable indicating that large new platelets are being generated to compensate for loss. Autoantibodies against platelet glycoproteins may be positive but are not helpful in elucidating immune thrombocytopenia as they are positive in less than 65% of patients with immune thrombocytopenia and are not predictive, specific, or prognostic. AIN presents with low absolute neutrophil count (see Chapter 171). Clinical manifestations include aphthous stomatitis, periodontal disease, and increased frequency of soft tissue infections. Invasive infections and sepsis are rare. Antigranulocyte antibodies can be present.

Immunodeficiencies Associated with Autoimmune Cytopenias

Autoimmune cytopenias, especially those that include bilineages and trilineages, are often a presenting symptom of or associated with primary immunodysregulatory disorders. Other organ-specific immunodysregulatory and autoimmune conditions are often present. Next generation sequencing via whole exome sequencing or panel-based sequencing can aid in establishing a diagnosis. When an inborn error of immunity is suspected with the presence of autoimmune cytopenias, a general immune screen should be performed including serum quantities of IgG, IgM, IgA, and IgE. Quantities of T cell, B cell, and NK cells should also be measured. Additional labs that may be helpful in narrowing a diagnosis of immunodeficiency include quantification of $\alpha\beta^+$double negative T cells ($CD4^-CD8^-$), $CD27^+IgD^+$ and $CD27^+IgD^-$ memory B cells, serum ferritin, soluble interleukin (IL)-2 receptor, IL-18, soluble Fas ligand, vitamin B_{12}, and folate.

Treatment

Targeted treatment of the primary immunodysregulatory disorder can control or resolve autoimmune cytopenias. Standard treatment of autoimmune cytopenias with or without a primary immunodysregulatory disorder include corticosteroids, intravenous immunoglobulin (IVIG), and biologic therapies such as rituximab and daratumumab (monoclonal antibody against CD38 expressed on long-lived plasma cells). Control of symptoms is often more difficult and may increase the suspicion for an underlying primary immunodysregulatory disorder.

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174.7 Autoimmune Lymphoproliferative Syndrome

Danielle E. Arnold and Jennifer W. Leiding

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 co-receptors ($CD3^+$ 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 pathologic variant in the *FAS* gene, which produces a cell surface receptor of the tumor necrosis factor (TNF) receptor superfamily (TNFRSF6), which, when stimulated by its ligand, will produce programmed cell death (Table 174.5). 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, Fas-associated protein with death domain deficiency (FADD), and protein kinase C delta deficiency (PRKCD). These disorders have varying degrees of immunodeficiency, 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 first year of life, and most are symptomatic by age 5 years. Lymphadenopathy can be striking (Fig. 174.6). Splenomegaly

Table 174.5 Revised Diagnostic Criteria for Autoimmune Lymphoproliferative Syndrome*

REQUIRED

1. Chronic (>6 mo), nonmalignant, noninfectious lymphadenopathy, splenomegaly or both
2. Elevated $CD3^+$ $TCR\alpha\beta^+$ $CD4^-CD8^-$ DNT cells (≥1.5% of total lymphocytes or 2.5% of $CD3^+$ lymphocytes) in the setting of normal or elevated lymphocyte counts

ACCESSORY

Primary

1. Defective lymphocyte apoptosis (in two separate assays)
2. Somatic or germline pathogenic mutation in *FAS*, *FASLG*, or *CASP10*

Secondary

1. Elevated plasma sFasL levels (>200 pg/mL) OR elevated plasma interleukin-10 levels (>20 pg/mL) OR elevated serum or plasma vitamin B_{12} levels (>1500 ng/L) OR elevated plasma interleukin-18 levels >500 pg/mL
2. Typical immunohistologic findings as reviewed by an experienced hematopathologist
3. Autoimmune cytopenias (hemolytic anemia, thrombocytopenia, or neutropenia) AND elevated immunoglobulin G levels (polyclonal hypergammaglobulinemia)
4. Family history of a nonmalignant/noninfectious lymphoproliferation with or without autoimmunity

*A *definitive* diagnosis is based on the presence of both required criteria plus one primary accessory criterion. A *probable* diagnosis is based on the presence of both required criteria plus one secondary accessory criterion.

DNT, Double-negative T cell; TCR, T-cell receptor.

From Petty RE, Laxer RM, Lindsley CB, Wedderburn LR, eds. *Textbook of Pediatric Rheumatology*. 7th ed. Philadelphia: Elsevier; 2016. Box 46-2.

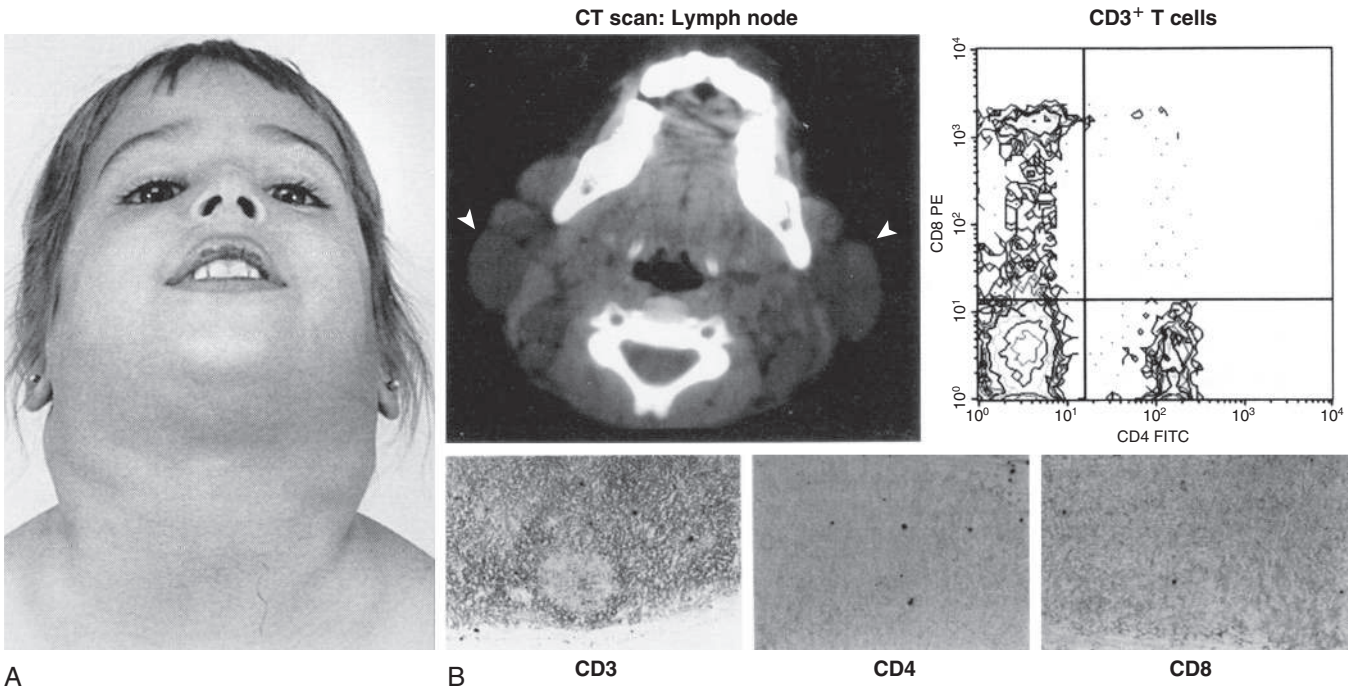

Fig. 174.6 Clinical, radiographic, immunologic, and histologic characteristics of the autoimmune lymphoproliferative syndrome. **A,** Front view of the National Institutes of Health patient. **B,** *Top left,* CT scan of the neck is shown demonstrating enlarged preauricular, cervical, and occipital lymph nodes. *Arrowheads* denote the most prominent lymph nodes. *Top right,* 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. *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. *Bottom,* CD3, CD4, and CD8 staining on serial sections of a lymph node biopsy specimen from a patient with ALPS. 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. 1999;103[5 Pt 1]:729–738.*)

may produce hypersplenism. 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 regress and is characterized by frequent exacerbations and recurrences. Other autoimmune features include urticaria, uveitis, glomerulonephritis, hepatitis, vasculitis, panniculitis, arthritis, premature ovarian failure, thyroiditis, myocarditis, pancreatitis, and CNS involvement (seizures, headaches, encephalopathy, transverse myelitis, Guillain-Barré syndrome, ataxia).

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 174.5 lists the criteria for the diagnosis. Flow cytometry helps identify the lymphocyte type (see Fig. 174.6). Functional genetic analysis for the *TNFRSF6* gene often reveals a heterozygous mutation. The differential diagnosis of ALP-related syndromes is noted in Table 174.6.

Table 174.6 Autoimmune Lymphoproliferative Syndrome (ALPS)-Related Syndromes That Are Potentially Similar to But Genetically Distinct from ALPS or Meet Characteristics of ALPS with Undetermined Genetic Defects (ALPS-U)

DISEASE	NOMENCLATURE	MUTATION	CLINICAL FEATURES	LABORATORY BIOMARKERS	POTENTIAL TARGETED THERAPIES
Ras-associated autoimmune leukoproliferative disorder	RALD	Germline or somatic *NRAS* and *KRAS* pathogenic variants RAS markedly decreases Bim protein expression leading to impaired lymphoid withdrawal and T-cell receptor (TCR)-induced apoptosis	Primary immunodeficiency disorder of defective apoptosis leading to lymphadenopathy, massive splenomegaly, increased circulating B cells, hypergammaglobulinemia, and autoimmunity increased risk for hematopoietic malignancies	Persistent absolute or relative monocytosis, hypergammaglobulinemia, B lymphocytosis Does not exhibit elevated "double-negative T cells" (DNTs), vitamin B_{12} Activating somatic mutations in *KRAS* or *NRAS*	Mitogen-activated pathway kinase (MAPK) inhibitors (for example, trametinib), mammalian target of rapamycin (mTOR) inhibitors (sirolimus, everolimus)
Dianzani autoimmune lymphoproliferative disease	DALD	No causative genes identified Overexpression of the cytokine osteopontin Perforin	Exhibit autoimmunity, lymphoproliferation, splenomegaly, and defective Fas without expansion of DNT cells	Absent DNTs FAS resistance but without *FAS* or *FASL* mutations	
Caspase-8 deficiency state	CEDS	Loss-of-function pathogenic variants in *CASP8* thought to play a dual role in the induction of the nuclear factor-kappa B (NF-κB) transcription factor during lymphocyte activation as well as in apoptosis mediated by the Fas death-inducing signaling complex (DISC)	Exhibits lymphoproliferation and apoptosis defects observed in ALPS, but manifests immunodeficiency rather than autoimmunity; recurrent sinopulmonary infections Increased risk for malignancy	Serum Ig levels, antibody function, lymphocyte activation Defective activation of T, B and natural killer (NK) cells *CASP8* deficiency	
Fas-associated death domain deficiency	*FADD* deficiency	Autosomal recessive (AR) *FADD* deficiency	Characterized by severe bacterial and viral infections, congenital heart defects, and recurrent episodes of fever, liver, dysfunction, and seizures	*FADD* deficiency	
Common variable immunodeficiency 9	Protein kinase C delta *(PRKCD)* deficiency	AR *PRKCD* primary immunodeficiency	Characterized by recurrent infections, lymphadenopathy, hepatosplenomegaly, autoimmunity, and NK cell dysfunction	IL-10 overexpression by B cells	

Table 174.6 Autoimmune Lymphoproliferative Syndrome (ALPS)-Related Syndromes That Are Potentially Similar to But Genetically Distinct from ALPS or Meet Characteristics of ALPS with Undetermined Genetic Defects (ALPS-U)—cont'd

DISEASE	NOMENCLATURE	MUTATION	CLINICAL FEATURES	LABORATORY BIOMARKERS	POTENTIAL TARGETED THERAPIES
Activated PI3K delta syndrome	APDS, also known as PASLI	Heterozygous gain-of-function pathogenic variants in *PI_3KCD* or *PI_3KR1*	Recurrent respiratory infections and increased susceptibility to viral infections with both B- and T-cell defects	Decreased naïve T cells, low IgG, IgA, and normal or elevated IgM	mTOR inhibitors, PI3K inhibitors
X-linked immunodeficiency with magnesium defect, Epstein-Barr virus (EBV) infection and neoplasia	XMEN disease	Loss-of-function pathogenic variants in magnesium transporter 1 *(MAGT1)*; X-linked	Chronic high-level EBV with increased EBV-infected B cells and increased susceptibility to EBV-associated lymphomas	Mg deficiency	Magnesium
Gain-of-function mutations in signal transducer and activator of transcription 1 defect	GOF *STAT1* defect	*STAT1* gain-of-function pathogenic variants	Chronic mucocutaneous candidiasis, recurrent *Staphylococcus aureus* infections, cerebral aneurysms, and multiple autoimmune features	Decreased TH17 response	JAK/STAT inhibitors (for example, ruxolitinib)
Gain-of-function mutations in signal transducer and activator of transcription 3	GOF *STAT3*-mutations	*STAT3*-gain of function pathogenic variants	Lymphoproliferation and childhood-onset autoimmunity thought to result from dysregulated cytokine signaling and interstitial lung disease		Anti–IL-6R monoclonal antibody (tocilizumab)
Cytotoxic T lymphocyte antigen *(CTLA4)* haploinsufficiency with autoimmune infiltration	CHAI	Heterozygous loss-of-function pathogenic variants in *CTLA4*	Hypogammaglobulinemia and autoantibody-mediated cytopenias, lymphadenopathy, splenomegaly, organ-specific autoimmunity, and lymphocytic infiltration of nonlymphoid organs CHAI more commonly seen in older children or young adults, whereas disease onset in LATAIE is typically earlier		CTLA4-Ig fusion drug (Abatacept) mTOR inhibitors
Common variable immune deficiency caused by defect in lipopolysaccharide-responsive and beigelike anchor protein LRBA deficiency with autoantibodies, regulatory T-cell defects, autoimmune infiltration, and enteropathy	*LRBA* deficiency LATAIE	*LRBA* encodes the lipopolysaccharide-responsive and beigelike anchor protein, thought to regulate CTLA4	Antibody deficiency, infection, autoimmunity, and lymphoproliferation, often linked with enteropathy or inflammatory bowel disease Lymphocyte infiltration also seen in lungs and brain		CTLA4-Ig fusion drugs Hydroxy-chloroquine or chloroquine mTOR inhibitors

Note: The majority of these syndromes have been defined based on the genomic defect with associated symptoms.
From Bride K, Teachey D. Autoimmune lymphoproliferative syndrome: more than a FAScinating disease. *F1000Res.* 2017;6:1928. Table 1.

Treatment

Rapamycin (sirolimus) will often control the adenopathy and autoimmune cytopenias. 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.

174.8 Nuclear Factor-κB Pathway Defects

Danielle E. Arnold and Jennifer W. Leiding

The NF-κB pathways consist of canonical (NF-κB1) and noncanonical (NF-κB2) pathways. On cellular activation, both pathways lead to activation and translocation of NF-κB proteins into the nucleus, where they initiate downstream inflammatory responses. Defects in many proteins in both pathways have been described. Table 174.7 describes immune defects of the NF-κB pathways that cause symptoms of immune dysregulation or autoimmunity. Treatment of NF-κB defects includes prevention of infections and replacement of immunoglobulin and has included HSCT.

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Table 174.7 Defects of Nuclear Factor-κB Pathways Associated with Immune Dysregulation

PROTEIN	INHERITANCE	AUTOIMMUNE OR INFLAMMATORY COMPLICATIONS	OTHER MANIFESTATIONS	IMMUNOLOGIC PHENOTYPE
IKBKG (NEMO)	XL	Colitis	• Ectodermal dysplasia • Osteopetrosis • Lymphedema • Bacterial infections • Opportunistic infections • DNA viral infections	• Hypogammaglobulinemia • Hyper-IgM • Hyper-IgA • Hyper-IgD • Poor antibody responses • Decreased NK cell function • Decreased TLR responses
NF-κB1	AD	• Pyoderma gangrenosum • Lymphoproliferation • Cytopenia • Hypothyroidism • Alopecia areata • Enteritis • LIP • NRH	• Atrophic gastritis • Squamous cell carcinoma • Respiratory tract infections • Superficial skin infections • Lung adenocarcinoma • Respiratory insufficiency • Aortic stenosis • Non-Hodgkin lymphoma	• Hypogammaglobulinemia • IgA deficiency
NF-κB2	AD	• Alopecia totalis • Trachyonychia • Vitiligo • Autoantibodies: thyroid peroxidase, glutamate decarboxylase, thyroglobulin • Central adrenal insufficiency	• Viral respiratory infections • Pneumonias • Sinusitis • Otitis media • Recurrent herpes • Asthma • Type 1 Chiari malformation • Interstitial lung disease	• Early-onset hypogammaglobulinemia • Low vaccine responses • Variable B-cell counts • Low switched memory B cells ($CD19^+CD27^+IgD^-$) • Low marginal zone B cells ($CD19^+CD27^+IgD^+$)

XL, X-linked; AD, autosomal dominant; LIP, lymphocytic interstitial pneumonitis; NRH, nonregenerative hyperplasia; TLR, toll like receptor.

Chapter 175

Defects of Innate Immunity

Jenna R.E. Bergerson and Alexandra F. Freeman

The innate immune system is the body's first defense against pathogens, and includes barriers such as the skin as well as neutrophils, natural killer (NK) cells, the toll-like receptors (TLRs) for microbial pathogen recognition, cytokines, and the complement system. Breakdown of different parts of this system can predispose primarily to different pathogens, such as viruses, fungi, bacteria, and mycobacteria. The innate immune system also plays an important role in engaging the adaptive immune response.

175.1 Predisposition to Fungal Infections

Jenna R.E. Bergerson and Alexandra F. Freeman

Despite constant exposure to environmental fungi at sites like the respiratory and gastrointestinal tracts and the skin, immunocompetent individuals do not develop invasive fungal disease because highly sophisticated host defenses have evolved with time. The genetic basis for inborn errors of immunity (IEIs) presenting with mucocutaneous and/or invasive fungal disease have provided valuable insight into the immunologic mediators necessary for antifungal host defense. Certain IEIs whose phenotype includes fungal disease, such as chronic granulomatous disease (CGD), APECED, GATA2 deficiency, and dominant negative STAT3 pathogenic variants (Job syndrome), are examples.

Candida and *Aspergillus* are the two most commonly encountered opportunistic fungi in clinical practice; both of these fungi are recognized in host tissues by pattern recognition receptors (PRRs) on the cell surface. When triggered by a relevant ligand, activation of these receptors results in pathogen uptake and killing. Most relevant to antifungal immunity is the C-type lectin receptor (CLR) family, which recognizes specific fungal cell wall components called pathogen-associated molecular patterns, like β-glucans or mannans. When CLRs like Dectin-1 bind ligand, the CARD9/BCL10/MALT1 complex (BCM complex) is formed. Signaling via downstream pathways ultimately results in production of proinflammatory cytokines and promotes fungal uptake and killing by myeloid phagocytes.

The molecular mechanisms that protect against host *mucosal* infections with *Candida* spp. are vastly different than those that confer protection against *systemic* infection. Neutrophils, monocytes, and macrophages are seemingly dispensable for immunity to mucosal *Candida* infection; chronic mucocutaneous candidiasis (CMC) is not seen in neutropenic patients or those with CGD. Instead, mucocutaneous candidiasis seems to correlate with impairments in T-lymphocyte number or function. Interleukin (IL)-17 signaling is also a critical pathway for protection against CMC. On receptor activation, the adaptor molecule ACT1 is recruited to the IL-17 receptor and mediates the induction of signaling pathways that upregulate the transcription of cytokines and antimicrobial peptides (AMPs) that help clear *Candida* from the mucosal surfaces. Control of endemic fungi, such as *Histoplasma,* is dependent on the IL-12/IFNg/STAT1 pathway.

Chronic mucocutaneous candidiasis is characterized by severe, persistent, or recurrent symptomatic infection of the nails, skin, oral, or genital mucosa by the *Candida* genus. CMC has been associated with a number of IEIs, in which it is one of many disease features along with other infections and/or autoimmune manifestations. However, CMC can also be a main feature of a primary immunodeficiency disease (PIDD) (Table 175.1).

Antifungal therapy is the hallmark of treatment in these diseases. Episodes of CMC typically respond to either topical or oral therapy. Recurrences are common without secondary prophylaxis. Prophylaxis should be initiated in those patients with frequent and early recurrences after discontinuation of antifungal therapy. Prophylaxis is important not only to reduce the morbidity associated with recurrent episodes of CMC, but also to prevent mucosal inflammation, which can increase the risk of squamous cell carcinoma. Repeated courses of antifungal therapy increase the risk of developing resistance to antifungal therapy. All cases of CMC should be confirmed with culture, and susceptibility testing should guide the choice of antifungal if a therapeutic response is not observed.

Systemic fungal disease should be guided by culture and susceptibility data with consideration of antifungal penetration in the affected tissue. Additional factors to consider include concomitant medications (triazoles are metabolized by P450 and prolong the QT interval with the exception of isavuconazole, which shortens it), liver function, and kidney function (amphotericin use). It is important to also consider that voriconazole is associated with additional toxicities including an increased risk of squamous cell carcinoma of the skin, fluorosis, peripheral neuropathy, and visual disturbances. Survival of life-threatening fungal infection should also mandate secondary antifungal prophylaxis unless the underlying immunodeficiency is cured by hematopoietic stem cell transplantation (HSCT).

CARD9 DEFICIENCY

CARD9 deficiency is caused by biallelic loss-of-function (LOF) pathogenic variants in *CARD9.* CARD9 contributes to antifungal host defense in a pathogen- and organ-specific manner with a striking predilection for *Candida albicans* central nervous system (CNS) infections. CARD9 deficiency is the only known IEI in which patients are predisposed to both mucocutaneous and systemic candidiasis, with *C. albicans* typically isolated. The CNS is the most common site of systemic involvement, with CNS candidiasis often presenting as either meningoencephalitis or an intracranial abscess ± obstructive hydrocephalus. The next most common site of systemic involvement is bone. Neutrophils are absent in all involved exudates and tissues.

Deep dermatophytosis and subcutaneous phaeohyphomycosis infections can also be seen in CARD9 deficiency. *Trichophyton rubrum* and *Trichophyton violaceum* were the most common dermatophyte species. Severe complications like lymphadenitis, extension into adjacent organs with fistula formation, and dissemination to the CNS have been seen. Dermal biopsies show necrotizing granulomatous inflammation, subcutaneous nodules, and severe ulceration of the superficial tissues. Subcutaneous phaeohyphomycosis with a predilection for facial involvement has also been reported. Granulomatous inflammation with scattered lymphocytes and eosinophils are seen on biopsy. Extrapulmonary aspergillosis and a variety of dematiaceous fungi have also been reported including *Phialophora verrucosa, Exophiala spinifera, Ochroconis musae,* and *Corynespora cassiicola.*

Clinical manifestations of CARD9 deficiency are fully penetrant by the fourth or fifth decade of life with about 40% of patients presenting in adulthood. Sequencing of CARD9 is required to establish the diagnosis, and determination of functional consequences of CARD9 variants is difficult. Lymphocyte phenotyping is usually normal, as are absolute neutrophil and monocyte counts despite a lack of neutrophils in infected CSF. Nearly 60% of affected patients have findings of elevated serum IgE and/or hypereosinophilia. Treatment of fungal infection follows the tenets outlined earlier, frequently with infectious diseases consultation followed by lifelong antifungal prophylaxis unless HSCT is successfully performed. Two patients with CARD9 deficiency have been successfully treated with HSCT leading to clinical remission. There is a potential role for treatment of fungal disease with granulocyte-macrophage colony-stimulating factor (GM-CSF) therapy in CARD9 deficiency, but there is variability in response that may relate to the underlying pathogenic variant(s) responsible for disease; thus seeking expert advice is recommended.

Table 175.1 Medelian Susceptibility to Mycobacterial Disease Defects

	GENE/INHERITANCE	CLINICAL PHENOTYPE	TREATMENT
Complete IFNgR1/R2 deficiency	*IFNgR1* or I*FNgR2*/AR	Early-onset disseminated NTM or BCG	Antimycobacterials; HSCT
Autosomal dominant IFNgR1 deficiency	IFNgR1/AD	NTM or BCG osteomyelitis, disseminated *Salmonella,* disseminated endemic mycoses	Antimycobacterials; adjuvant IFN-γ
IL-12RB1 deficiency	*IL12RB1*/AR	Disseminated NTM, BCG, *Salmonella* Mucocutaneous candidiasis Variable penetration	Antimycobacterials; consider IFN-γ with careful monitoring
IL-12p40 deficiency	*IL12B*/AR	Disseminated NTM, BCG, *Salmonella* Variable penetration	Antimycobacterials; consider IFN-γ with careful monitoring
IL-12Rb2 deficiency	*IL12RB2*/AR	NTM, BCG, and tuberculosis	Antimycobacterials
IL-23R deficiency	*IL23R*/AR	NTM, BCG, and tuberculosis	Antimycobacterials
STAT1 LOF	*STAT1*/AD	Disseminated BCG/NTM, often osteomyelitis	Antimycobacterials; consider IFN-γ
SPPL2a deficiency	*SPPL2A*/AR	Disseminated BCG	Antimycobacterials
TYK2 deficiency	*TYK2*/AR	Disseminated BCG, tuberculosis, viral infections	Antimycobacterials
Macrophage gp91 phox deficiency	*CYBB*/XL; distinct variants than those causing CGD	Disseminated BCG	Antimycobacterials
IRF8 deficiency (dominant)	*IRF8*/AD	Disseminated BCG, NTM	Antimycobacterials
IRF8 deficiency (recessive)	*IRF8*/AR	Viral, mycobacterial, mucocutaneous candidiasis	Antimicrobials, consider HSCT
ISG15 deficiency	*ISG15*/AR	Disseminated BCG	Antimycobacterials
RORγt deficiency	*RORC*/AR	Disseminated BCG and mucocutaneous candidiasis	Antimicrobials
JAK1 LOF	*JAK1*/AR	Bacterial, viral, and disseminated NTM	Antimicrobials

AD, Autosomal dominant; AR, autosomal recessive; BCG, bacilli Calmette-Guérin; CGD, chronic granulomatous disease; HSCT, hematopoietic stem cell transplantation; IFN, interferon; LOF, loss of function; NTM, nontuberculous mycobacteria.

STAT1 GOF

STAT1 gain-of-function (GOF) pathogenic variants present with CMC, autoimmunity, intracranial aneurysms, and/or squamous cell carcinoma. This condition likely accounts for more than 50% of CMC cases; CMC affects most patients with this diagnosis and typically presents in the first year of life. *Candida* involvement of the oropharynx is most common, but esophagitis, genital, and skin and nail disease are also common. *C. albicans* is the most common cause of CMC, but other *Candida* species have also been isolated. Azole resistance is a major challenge over time making treatment difficult.

Invasive fungal infections are less common in this disease but can be quite severe. Disseminated *Histoplasmosis, Cryptococcus, Coccidioides,* and *Paracoccidioides* can be difficult to treat and, in some cases, have been fatal. Pulmonary and disseminated mold infections have been reported infrequently and include organisms such as *Aspergillus, Nannizziopsis,* and *Mucorales. Pneumocystis jiroveci* pneumonia has been reported rarely.

A wide range of other types of pathogens cause infections in this patient population as well including recurrent bacterial sinopulmonary infections, typically due to *Streptococcus pneumoniae*, *Haemophilus influenzae,* and *Staphylococcus aureus*. Bronchiectasis, when present, may further produce susceptibility to pathogens such as *Pseudomonas*. Less commonly skin infections such as folliculitis or cellulitis are also observed. Mycobacterial infections are typically due to BCG in those from countries that routinely immunize against tuberculosis (TB), and nontuberculous mycobacteria (NTM) adenitis or TB, or NTM lung infections. NTM infections do not usually disseminate widely in STAT1 GOF as they do in autosomal recessive or dominant STAT1 LOF.

Severe or recurrent viral infections, most commonly due to herpesviruses (herpes simplex virus [HSV], varicella-zoster virus [VZV], Epstein-Barr virus (EBV), cytomegalovirus [CMV], BK, and JC), are also troublesome in over 30% of patients. Recurrent oral mucocutaneous disease due to HSV or recurrent VZV infection are the most frequent viral disease manifestations. EBV and CMV viremias are commonly detected, but CMV disease is infrequent as is symptomatic EBV disease. Human papillomavirus (HPV)-driven warts and molluscum are seen in a small number of these patients and are difficult to treat. Although rare, progressive multifocal leukoencephalopathy (PML) from JC virus is of particular concern due to its high mortality. PML has been seen with and without additional immune modulation; therapies that are sometimes indicated for the autoimmunity seen in STAT1 GOF, such as rituximab, need to be used with caution.

Additional disease manifestations include autoimmunity, vasculopathy, and malignancy. Autoimmune thyroid disease is most common, but type 1 diabetes mellitus, vitiligo, alopecia, pernicious anemia, autoimmune cytopenias, inflammatory bowel disease, and lupus-like disease have all been observed and, in many cases, the autoimmune manifestations can be quite refractory and difficult to control. Aphthous ulcers are also especially common and can be very painful. Cerebral aneurysms are the most common vasculopathy seen, but extracerebral vascular abnormalities occur as well. These aneurysms may be the result of vasculitis, perhaps from pathogens like VZV; serial

prospective imaging should be a part of routine screening. The most common malignancy observed is squamous cell carcinoma, mainly of the skin, oropharynx, and esophagus. Chronic inflammation caused by mucosal *Candida* infections may play an important role, as well as inflammation driven by increased STAT1 activity.

Management has been largely targeted against the infections and treatment of autoimmunity when present. Many of the patients need antifungal prophylaxis, and azole resistance may emerge and limit therapeutic choices to topical nystatin or amphotericin washes, or IV echinocandins. It is worth highlighting that voriconazole is not recommended in this patient population due to its photosensitivity and long-term skin cancer risk. In those patients with recurrent sinopulmonary infections and/or bronchiectasis, antibiotic prophylaxis is likely to be beneficial. Azithromycin prophylaxis, if pulmonary NTM is not present, may be beneficial not only for prevention of recurrent airway infections, but also will yield some antiinflammatory benefits. Recurrent HSV or VZV infections suggest the need for prophylaxis with acyclovir or valacyclovir. The autoimmunity is typically treated with immune suppression, and many have received long courses of corticosteroids. However, there are positive reports of success controlling this inflammation and autoimmunity with JAK inhibition. Ruxolitinib has been used in STAT1 GOF to treat alopecia, enteropathy, autoimmune cytopenias, and hepatitis. There is one report of JAK inhibition being used early in the course of associated insulin-dependent diabetes, with resolution of the need for insulin and remission of the diabetes. JAK inhibition also can be highly effective in the treatment of CMC because there is growing evidence that the CMC observed in this disease is due to exuberant inflammation rather than infection susceptibility. *Severe or disseminated infections have progressed while on JAK inhibition, thus, it is best to start this treatment only when invasive infections are adequately controlled.* Some patients develop hypogammaglobulinemia over time; immune globulin replacement may be indicated. HSCT is not yet the preferred option for treatment of STAT1 GOF. HSCT in this population of patients has been difficult with high morbidity and mortality, although it is important to note that many of these transplants were done before the genetic diagnosis was known and a variety of conditioning regimens were used.

IL-17F DEFICIENCY

A dominant-negative missense pathogenic variant in *IL17F* was reported in multiple patients from one kindred with CMC. About 65% of these patients had CMC manifesting as persistent thrush, vulvovaginal candidiasis, and interdigital intertrigo. Lymphocyte phenotyping and quantitative immunoglobulin levels were normal in the one patient who had such testing. Diagnosis relies on sequencing of IL-17F, but can also be suspected if flow cytometry shows absent intracellular IL-17F producing $CD3^+$ cells in patients with detectable IL-17A and IL-22 producing $CD3^+$ cells. Although there is insufficient clinical information to suggest ideal management of patients with IL-17F deficiency, we recommend a similar approach as outlined for management of CMC.

IL-17RA DEFICIENCY

IL-17RA deficiency also presents with CMC, but usually with onset within the first year of life. Candidiasis involved the oropharynx in 95% of patients, the genitals in 38% (60% females), the skin or scalp in 67%, and the nails in 19%. Episodes of CMC seemed to respond to topical or oral therapy. Staphylococcal skin infections were seen in 65% of the cohort, with such lesions also manifesting in the first year of life. Bacterial recurrent sinopulmonary infections occur in just over one-third of these patients, and all responded to antibiotic therapy.

Lymphocyte phenotyping is normal, and diagnosis should be made by sequencing of the *IL17RA* gene, particularly when early-onset CMC and concurrent *S. aureus* skin infections are present.

As CMC is a presenting feature of all reported patients with IL-17RA deficiency, oral antifungal prophylaxis should be initiated. Strong consideration should be given to also initiating antibiotic prophylaxis in those who have culture-proven bacterial infections that are recurrent or severe. In those with recurrent sinopulmonary infections, although the spectrum of organisms is not known, covering for common bacterial etiologies like *S. pneumoniae, H. influenzae,* and *Moraxella catarrhalis* should be sufficient to prevent disease.

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175.2 Innate Immunity Defects with Predominant Susceptibility to Viral Infections

Jenna R.E. Bergerson and Alexandra F. Freeman

Defects in innate immunity that predispose to viral infections are divided into three main groups: those primarily predisposing to HPV, those predisposing primarily to HSV encephalitis, and those predisposing to other viruses, many of which interfere with interferon (IFN) signaling. Some of these defects are described in the following sections along with other rare defects highlighted in Table 175.2.

PREDOMINANT HPV SUSCEPTIBILITY

Epidermodysplasia verruciformis (EV) is the main clinical presentation for diseases with autosomal recessive pathogenic variants in the transmembrane channel-like 6 and 8 (*TMC6* and *TMC8*) genes and more recently described in the calcium- and integrin-binding protein 1 *(CIB1)* gene, encoding for the proteins EVER1, EVER2, and CIB1, respectively. EVER1, EVER2, and CIB1 complex together for keratinocyte intrinsic immunity, and disruption of this complex leads to HPV susceptibility. The typical warts affecting healthy individuals are from α-HPV types; however, in EV, β-HPV causes symptomatic disease, which is usually asymptomatic in healthy individuals but associated with cancer in some immune compromised individuals. The warts are frequently not the typical verrucous appearance seen in healthy children, but are usually flat warts, and can look like tinea versicolor with pigment changes. The warts appear in sun-exposed areas and have a high incidence of cancer transformation. Individuals with EV do not usually have increased risk of other infections; they have normal immune evaluations including normal lymphocyte number and function. Diagnosis is with genetic testing after suspicion with atypical widespread HPV disease. There is no specific treatment, although warts are treated with standard therapies (see Chapter 708). Patients needed to be counseled to avoid UV and radiation exposure, and these individuals need frequent screening for skin cancer.

WHIM (wart, hypogammaglobulinemia, infections, myelokathexis) syndrome is an autosomal dominant (AD) disease caused by GOF pathogenic variants in *CXCR4*. Increased responsiveness of the CXCR4 receptor to its ligand CXCL12 (also known as SDF-1) results in increased retention of the neutrophils in the bone marrow and thus the finding of myelokathexis (neutropenia related to the inability of neutrophils to leave the marrow). Patients also have lymphopenia with decreased B-, T- and NK lymphocytes, along with hypogammaglobulinemia. Although recurrent infections are common, they tend not to be as severe as expected from the neutropenia because the neutrophils often are released from the bone marrow with infection; dental issues likely related to the neutropenia are common. Recurrent sinopulmonary infections likely relate more to the hypogammaglobulinemia, and some patients develop bronchiectasis. Warts typically start in childhood or adolescence and are often particularly severe with poor response to therapy. Evolution into squamous cell carcinomas can occur; patients require monitoring. Treatment traditionally has been supportive in treating infections and preventive with immune globulin therapy and G-CSF, which usually needs to be dosed at lower concentrations due to frequently experienced debilitating bone pain. Plerixafor, an antagonist of CXCR4, may provide a specific therapy.

There are several other PIDDs that primarily affect lymphocytes that have HPV susceptibility as a major component and are discussed in

other chapters. Many of these diseases, such as DOCK8 deficiency and GATA2 deficiency, have broader susceptibility than just HPV. CD28 deficiency has susceptibility specific for HPV resulting in warts and cutaneous horns. Compared to EV, those with CD28 deficiency have predisposition to the more common α- and γ-HPV types.

Predisposition to Severe Viral Infections

Host control of viral infections is predominately dependent on normal type 1 IFN signaling (Fig. 175.1; see Table 175.2). Type 1 IFNs, including the IFN-α subtypes and IFN-β, bind to their heteroreceptor comprising IFNAR1 and IFNAR2 leading to phosphorylation of TYK2 and JAK1. Activation of TYK2 and JAK1 leads to phosphorylation of STAT1 and STAT2, which then cause upregulation of **interferon-stimulated genes (ISGs)**. There are multiple potential defects along this pathway that can lead to viral susceptibility. The role of this pathway has been highlighted with the COVID-19 pandemic, with not only genetic defects but also autoantibodies against type I IFNs leading to more severe disease.

Autosomal recessive pathogenic variants in *IFNAR1* and *IFNAR2* lead to a lack of TYK2 phosphorylation for IFNAR1 defects, and both TYK2 and JAK1 phosphorylation for IFNAR2 with subsequent downstream deficiency of ISG upregulation. Despite the severe in vitro findings, the viral infection susceptibility appears more limited. Both are rare diseases, with most patients developing severe or fatal illness after live viral vaccination with the measles mumps rubella (MMR) vaccine (largely measles component) or yellow fever vaccine. Herpes viral control is variable, with a fatal case of herpes encephalitis reported in IFNAR1 deficiency, and poor control of human herpesvirus 6 (HHV6) in IFNAR2. Variants have been described with severe SARS-CoV-2 infection. These diseases appear to have incomplete penetrance, with some affected individuals having better control of viral infections or vaccination. Naturally acquired viral infections have been controlled much more than live viral vaccinations. These diseases are rare and therapy remains unclear, but avoiding live viral vaccines, considering antiviral prophylaxis for HSV/VZV infections, and vaccination of affected individuals and close contacts for influenza and COVID-19 appears prudent.

Genetic defects in *STAT1* can be activating (STAT1 GOF) or can be heterozygous or recessive with LOF. Autosomal recessive complete STAT1 deficiency is the most severe defect with most cases being fatal early in life. As IFN-α, IFN-β, and IFN-γ all signal through STAT1, completely impaired signaling predisposes individuals to both severe early-onset viral disease in addition to disseminated mycobacterial disease. Herpes family infections are common as well as live viral disseminated infection. The disease is fatal without HSCT early in life, but HSCT outcomes have been poor with several children having herpes family inflammatory complications after HSCT, such as with hemophagocytic lymphohistiocytosis (HLH) or severe CMV disease. There are also patients with autosomal recessive hypomorphic *STAT1* pathogenic variants who have some residual STAT1 disease that appears to have a less severe phenotype. Treatment is with aggressive antimicrobials to treat presenting infections and prevent new infections until HSCT is performed.

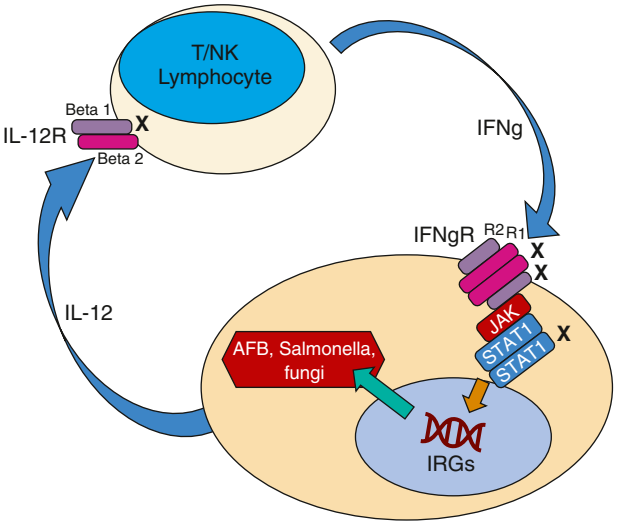

Fig. 175.1 Host control of mycobacteria. Macrophages ingest mycobacteria leading to secretion of cytokine IL-12, which then binds to its heterodimer receptor on the T lymphocytes and NK cells leading to the secretion of IFN-γ. IFN-γ binds to its heterodimer receptor, IFN-γR1 and IFN-γR2, leading to JAK1 and JAK2 phosphorylation, and then STAT1 phosphorylation. Where defects lead to MSMD are marked by an X.

Autosomal recessive complete STAT2 deficiency presenting early in life with severe viral infections is not as severe as STAT1 deficiency due to maintenance of IFN-γ signaling. Compared to IFNAR1 and IFNAR2 deficiency, there is more severe disease with naturally acquired viral infections such as respiratory syncytial virus (RSV) and enteroviruses, but similarly severe disease has been seen with MMR vaccine. Some children have been described to have a Kawasaki-like inflammatory presentation. The phenotype has been variable with some deaths early in life and some surviving to adulthood. Treatment remains uncertain with few patients reported, but live viral vaccines should be avoided, antiviral prophylaxis provided, and influenza vaccination given to those affected and close contacts.

Autosomal recessive IRF9 deficiency appears to present similarly to STAT2 deficiency. After IFN-α or IFN-β stimulation leads to STAT1 and STAT2 phosphorylation, these STAT proteins can heterodimerize with IRF9 to lead to ISG upregulation. This is a very rare defect presenting with naturally occurring or vaccine strain viruses. Life-threatening influenza and severe enterovirus infections have been described in addition to vaccine strain varicella and MMR dissemination. Treatment remains uncertain with few patients reported, but live viral vaccines should be avoided, antiviral prophylaxis considered, and influenza and COVID-19 vaccination given to those affected and close contacts.

Defects have been described in cytosolic sensors of viral DNA or RNA replication by-products that lead to fairly specific viral susceptibility. Melanoma differentiation-associated protein 5 (MDA5), encoded by the *IFIH1* gene, is a cytosolic sensor of double-stranded RNA by-products of RNA viral replication. Several patients have been described with LOF variants, either autosomal recessive or dominant, with presumed dominant negative effect, resulting in severe susceptibility to respiratory viruses including rhinovirus and influenza. Retinoic acid-inducible gene I (RIG-I), encoded by the *DDX58* gene, plays a similar role, and a patient has been described with LOF variants having severe influenza infection. RNA polymerase III deficiency (POL III) is a cytosolic DNA sensor detecting replication by-products of DNA viruses. AD pathogenic variants have been reported in POL III in children and adults with severe varicella-zoster disease causing pneumonitis, encephalitis, and CNS vasculitis. Treatment is not defined, but avoiding live viral vaccines, providing antiviral prophylaxis, and providing non-live annual influenza and COVID-19 vaccination to affected individuals and family members appear prudent.

NK functional and quantitative defects can occur on their own or as part of combined immune deficiencies and are associated with viral infections (see Chapter 167). Pathogenic variants in the *FCGR3A* gene, encoding CD16, which is a Fc receptor on NK cells, impair NK cytotoxicity. A few patients have been described who have susceptibility to herpes family viruses with EBV-related disease such as Castleman disease or HSV and VZV infections. Patients also develop significant warts from HPV infection. Antiviral prophylaxis should be given to prevent HSV/VZV infections, in addition to HPV vaccination.

Predominant HSV Encephalitis

Defects that affect TLR3 signaling predispose quite specifically to HSV encephalitis due to their role in the activation of type 1 IFNs in the CNS (Fig. 175.2; see Table 175.2). Double-stranded RNA is detected by TLR3, which then recruits the adaptor TRIF to activate TRAF3 to induce IFN-α, IFN-β, and inflammatory cytokines through TBK1 and IRF3 and other proteins. UNC93B1 acts as a transporter protein to

Table 175.2 Defects with Predominant Susceptibility to Viral Infections

GENE/INHERITANCE	CLINICAL PHENOTYPE	SPECIFIC TREATMENT	GENE/INHERITANCE
Epidermodysplasia verruciformis	*EVER1, EVER2, CIB1*/AR	Diffuse flat warts, with increased skin cancers	Avoid UV/radiation exposure, skin cancer screening.
WHIM syndrome	*CXCR4*/AD	Warts, squamous cell cancer, sinopulmonary infections, neutropenia, hypogammaglobulinemia	G-CSF, IgRT, plerixafor
IFNAR1 deficiency	*IFNAR1*/AR	Severe disease after live viral vaccination (MMR, yellow fever), herpesviruses	Avoid live viral vaccination, consider HSV/VZV prophylaxis
IFNAR2 deficiency	*IFNAR2*/AR	Severe disease after live viral vaccination (MMR, yellow fever), herpesviruses	Avoid live viral vaccination, consider HSV/VZV prophylaxis
Complete STAT1 deficiency	*STAT1*/AR	Early-onset severe viral and disseminated *Mycobacteria*	Early HSCT
STAT2 deficiency	*STAT2*/AR	Severe respiratory viruses, enterovirus; some live viral vaccine disease	Avoid live viral vaccines
IRF9 deficiency	*IRF9*/AR	Severe respiratory viruses, enterovirus; some live viral vaccine disease	Avoid live viral vaccines
IRF7 deficiency	*IRF7*/AR	Severe influenza	Influenza vaccination*
MDA5 deficiency	*IFIH1*/AR or AD	Severe respiratory tract infections	Influenza vaccination
RNA polymerase III deficiency	*POL3A,POL3C, POL3F*/AD	Severe varicella-zoster	Antiviral prophylaxis
CD16 deficiency	*FCGR31*/AR	Herpes family infections, HPV	Antiviral prophylaxis
IL-18BP deficiency	*IL18BP/AR*	Fulminant hepatitis A	Hepatitis A vaccination
TLR3 deficiency	*TLR3*/AD and AR	HSV encephalitis, severe influenza, zoster	Antiviral prophylaxis
TRAF3 deficiency	*TRAF3*/AD	HSV encephalitis	Antiviral prophylaxis
TRIF deficiency	*TRIF*/AD and AR	HSV encephalitis	Antiviral prophylaxis
UNC93B1 deficiency	*UNC93B1*/AR	HSV encephalitis	Antiviral prophylaxis
TBNK1 deficiency	*TBNK1*/AD	HSV encephalitis	Antiviral prophylaxis
IRF3 deficiency	*IRF3*/AD	HSV encephalitis	Antiviral prophylaxis
DRB1 deficiency	*DRB1*/AR	Brainstem encephalitis	Antiviral prophylaxis

*Although influenza vaccination is highlighted for certain inborn errors of immunity (IEIs), influenza vaccination should be given to all those with IEIs and their close contacts unless there is a contraindication. In addition, HPV vaccination should be given per the recommended schedule. Vaccination at an earlier age can be considered for certain defects with HPV predisposition.

AD, Autosomal dominant; AR, autosomal recessive; G-CSF, granulocyte colony-stimulating factor; HPV, human papillomavirus; HSCT, hematopoietic stem cell transplantation; HSV, herpes simplex virus IFN, interferon; MMR, measles mumps rubella; UV, ultraviolet; VZV, varicella-zoster virus; WHIM, (wart, hypogammaglobulinemia, infections, myelokathexis) syndrome.

transport TLR3 and other TLRs from the endoplasmic reticulum to the endosome to allow RNA binding. The TLR3 pathway is redundant for leukocyte immunity, but it is essential for CNS host viral immunity; thus the infection susceptibility of these defects is primarily CNS HSV disease. The defects in signaling are not found in leukocytes but required fibroblasts and inducible pluripotent stem cell generation of CNS cells to demonstrate abnormal IFN-α responses with HSV infection.

Pathogenic variants in multiple genes along this pathway have similar presentations with HSV encephalitis including autosomal recessive and dominant LOF variants in *TLR3*, dominant pathogenic variants in *TRAF3*, dominant and recessive pathogenic variants in *TRIF*, recessive pathogenic variants in *UNC93B1*, and dominant pathogenic variants in *TBK1* and *IRF3*. The HSV encephalitis tends to present in infancy and early childhood on HSV exposure, with frontal and temporal lobes predominantly affected. Dominant pathogenic variants in *TLR3* have also been associated with severe influenza and varicella-zoster encephalitis in a few adults. Genetic diagnosis is essential as routine immunologic studies are normal. Treatment is supportive with acyclovir or similar prophylaxis.

Rarely children can have brainstem CNS infections, including HSV; defects in the TLR3 pathway have not been found in these cases. Autosomal recessive hypomorphic pathogenic variants in *DBR1* (debranching enzyme 1) have been identified in children with brainstem encephalitis caused by HSV, norovirus, and influenza virus. DBR1 is an RNA lariat-debranching enzyme that degrades spliced RNA introns, which is ubiquitously expressed in humans but with highest amounts in the brainstem and peripheral nervous system. With decreased function, there is increased accumulation of lariat introns that presumably interfere with viral recognition and control. Genetic diagnosis can allow prophylaxis with antivirals such as acyclovir and influenza vaccination of the affected individual and close contacts.

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175.3 Susceptibility to Invasive Bacterial Infections

Jenna R.E. Bergerson and Alexandra F. Freeman

Inborn errors of immunity (IEIs) with predominant susceptibility to invasive bacterial infections such as meningitis, sepsis, arthritis, osteomyelitis, and deep-seated abscesses are rare, and are mostly due to neutrophil defects or defects in innate immunity. Inherited disorders of the Toll and IL-1 receptor (TIR)-pathway are innate immunity defects with a very distinct phenotype with invasive pyogenic bacterial infections and usually the absence of fever and inflammatory markers. TLRs on white blood cell surfaces sense bacterial peptides leading to activation of the NF-κB and MAPK pathway leading to inflammatory mediators (Fig. 175.3). IEIs associated with impaired TLR signaling include pathogenic variants in *NEMO, IKBA, MyD88,* and *IRAK4* (Table 175.3).

IRAK4 DEFICIENCY

IRAK4 deficiency presents in infancy and early childhood with severe, recurrent bacterial infections, specifically due to *S. pneumoniae, S. aureus*, and *Pseudomonas aeruginosa*. Unique to this disorder, clostridial infections have also been reported. An impairment in mounting a fever at the beginning of infection with a corresponding rise in CRP are also hallmark features of this disease. Most patients with IRAK4 deficiency present with their first bacterial infection before 2 years of age; there is a high mortality rate in the early years. However, the frequency and severity of infections in IRAK4 deficiency improves with age, with none of the reported patients having invasive bacterial infections after the onset of adolescence, even those not on prophylactic antibiotics. Approximately 50% of IRAK4-deficient patients continue to have noninvasive skin and upper respiratory infections after adolescence. Delayed separation of the umbilical cord has been reported in IRAK4-deficient patients due to an unclear mechanism.

Diagnosis relies on clinical suspicion and genetic testing because other immunologic studies are variable or require research laboratory testing. All T- and B-cell and NK cell subsets are unremarkable, but there may be a deficiency of unswitched memory B cells with normal levels of switched memory B cells. Specific antibody levels to pneumococcal and allohemagglutinins of the ABO system are impaired in up to 30% of patients. Serum IgE and IgG4 concentrations are elevated in up to 65% and 30%, respectively. Defective IL-6 production leads to the inability to increase plasma CRP or mount fevers. Without the clinical findings of fever and inflammatory markers, there may be a low threshold for diagnostic imaging and initiating empiric parenteral antibiotic treatment against *S. pneumoniae, S. aureus,* and *P. aeruginosa*. Antibiotic prophylaxis should be implemented with agents like clotrimazole plus penicillin, and immunizations against pneumococcus serotypes, *H. influenzae,* and *Neisseria meningitidis* given. If patients have a poor response to vaccination, immunoglobulin replacement should be considered. There is a paucity of data to support the duration of antibiotic prophylaxis, but given that invasive pyogenic infections seem to resolve by adolescence a trial discontinuation could be considered at this time. Nonetheless these patients continue to have skin and upper respiratory infections and may benefit from lifelong antibiotic prophylaxis targeting pyogenic bacteria.

MYD88 DEFICIENCY

MyD88 deficiency resembles the clinical and laboratory findings in IRAK4 deficiency (Fig. 175.4; see Table 175.1). These patients have a susceptibility to serious bacterial infections due primarily to *S. pneumoniae, S. aureus,* and *P. aeruginosa*, including an inability to mount fever at the beginning of infection. CRP does not rise early during infection, likely due to impaired IL-6 production. Invasive bacterial infections begin before age 2 years and seem to improve with age, although noninvasive bacterial infections similarly persist after adolescence. Diagnosis is similar to IRAK4 deficiency relying on genetics, as routine immunologic testing is nondiagnostic. MyD88-deficient patients may have elevated serum IgE and IgG4 concentrations in up to 50% and

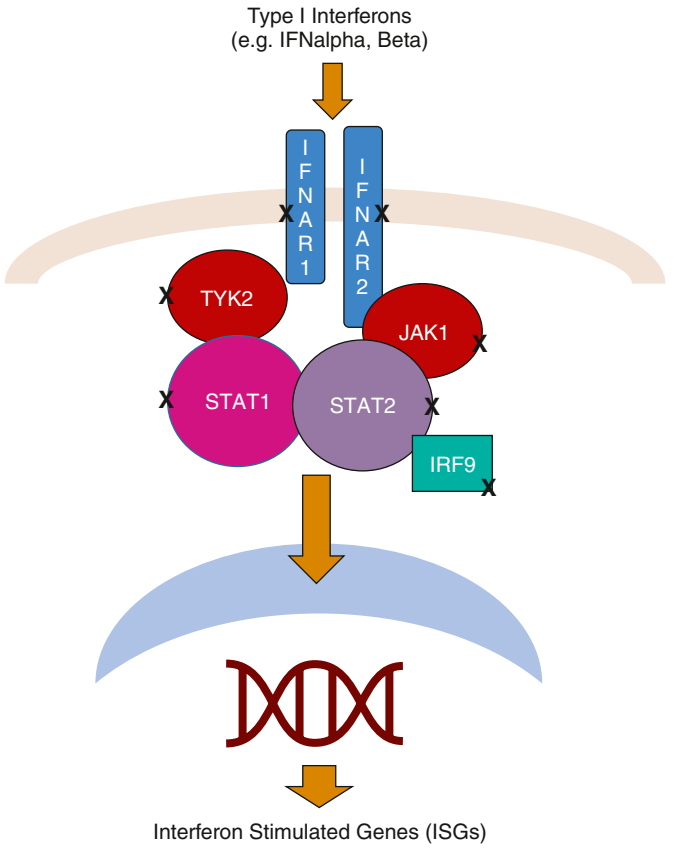

Fig. 175.2 Defects along type 1 interferon (IFN) signaling lead to viral susceptibility. Type 1 IFNs bind to their heteroreceptor comprising IFNAR1 and IFNAR2 leading to TYK2 and JAK1 phosphorylation followed by phosphorylation of STAT1 and STAT2, which then cause upregulation of IFN-stimulated genes (ISGs). IRF9 can also heterodimerize with STAT2 leading to ISG upregulation. Multiple genetic defects along this pathway (marked with X) can lead to viral susceptibility.

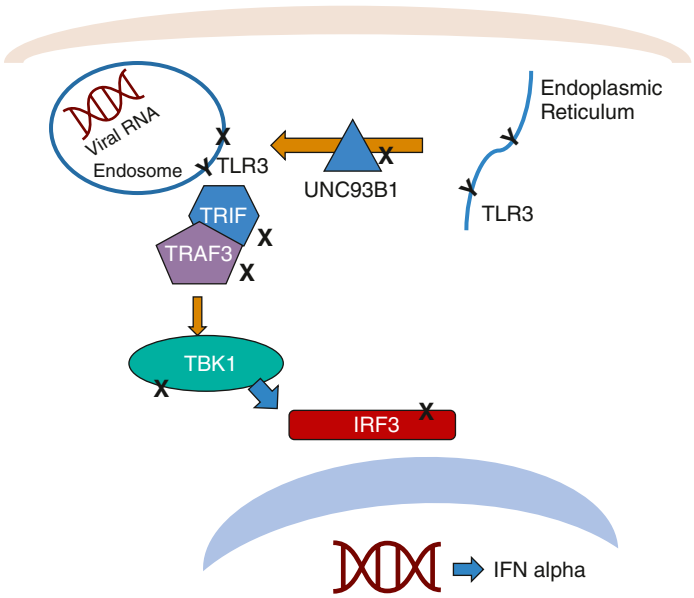

Fig. 175.3 Defects that affect toll-like receptor (TLR) 3 signaling predispose to HSV encephalitis by impairing type I interferon (IFN) activation. Double-stranded RNA is detected by TLR3, which then recruits the adaptor TRIF to activate TRAF3 and then through TBK1 and IRF3 to induce IFN-α and other inflammatory cytokines. UNC93B1 transports TLR3 from the endoplasmic reticulum to the endosome.

Table 175.3 Innate Defects with Bacterial Susceptibility

DISEASE	GENE/INHERITANCE	CLINICAL PHENOTYPE	LABORATORY PARAMETERS
IRAK4 deficiency	*IRAK4*, AR	Early-onset invasive pyogenic bacterial infections resolving in adolescence Persistence of noninvasive skin and URT infections	↓ IL-6, undetectable CRP in setting of infection ↓ CSM B cells Poor specific antibody levels to pneumococcus
MyD88 deficiency	*MYD88*, AR	Early-onset invasive pyogenic bacterial infections resolving in adolescence Persistence of noninvasive skin and URT infections	↓ IL-6, undetectable CRP in setting of infection ↓ CSM B cells
IRAK1 deficiency	*IRAK1*, XL	Undefined as reported in only one patient with Rett syndrome	Unknown
TIRAP deficiency	*TIRAP*, AR	Undefined Identified in nine members of one family with only one affected (pneumonia and sepsis from PVL-associated *Staphylococcus aureus*	Selectively ↓CSM B cells
Isolated congenital asplenia	*RPSA*, AD	Sepsis with encapsulated bacteria, absent spleen	HJB on blood smear
	PBX1, NKX2-5, BAPX1, POD1, AR	Sepsis with encapsulated bacteria, absent spleen	HJB on blood smear

AD, Autosomal dominant; AR, autosomal recessive; CSM; class switched memory; HJB; Howell-Jolly bodies; IL, interleukin; PVL, Panton-Valentine leukocidin; URT, upper respiratory tract; XL, X-linked.

33% of patients tested (respectively), as well as a specific deficiency of unswitched memory B cells. Treatment of MyD88 deficiency should follow the same principles as outlined previously for IRAK4 deficiency.

Other inherited disorders of the TIR pathway like IRAK1 deficiency and TIRAP deficiency will be addressed in Table 175.3.

ISOLATED CONGENITAL ASPLENIA

Asplenia refers to the complete lack of splenic tissue and includes a heterogenous group of conditions ranging from surgical asplenia to congenital asplenia. Congenital asplenia can be part of a syndrome of multiple congenital anomalies (see Chapter 480.11) or, less often, it can be isolated (see Table 175.3).

A diagnosis of isolated congenital asplenia (ICA) is made on the basis of the presence of Howell-Jolly bodies (HJBs) on blood smear and the lack of a detectable spleen at ultrasound in the absence of cardiovascular malformations. Some cases are due to an AD inheritance; relatives of those with ICA should be evaluated because the outcome is typically poor without initiation of antibiotic prophylaxis and pneumococcal vaccination. Half of all isolated cases are due to pathogenic variants in *RPSA*, a protein component of the small ribosomal subunit. Involvement of related key spleen patterning genes involved during embryogenesis can also result in splenic agenesis.

Presentation is typically with overwhelming, refractory infections due to encapsulated bacteria, particularly *S. pneumoniae*, but also other encapsulated bacteria like *H. influenzae* and *N. meningitidis*. Diseases like malaria and babesiosis also affect asplenic patients more severely due to defective removal of intra-erythrocytic parasites. In all cases of pneumococcal sepsis, a blood smear should be evaluated for HJBs in addition to an abdominal ultrasound to identify patients with ICA.

Immunization against pneumococcal serotypes and meningococcal serotypes is essential. Conjugated vaccines are preferred to unconjugated vaccines. Influenza vaccination should also occur yearly due to the risk of pneumococcal superinfection. Long-term oral penicillin prophylaxis (amoxicillin 10 mg/kg twice daily to max 250 mg OR ≤3 years: penicillin V 125 mg twice daily, ≥3 years: penicillin 250 mg twice daily) is recommended, as is early initiation of IV antibiotics in the setting of febrile illnesses. Patient education is a critical part in management. Patients should recognize and react to fever as a life-threatening emergency with initiation of antibiotic therapy at home (pediatric dosage of amoxicillin-clavulanate 45 mg/kg twice daily or levofloxacin 10 mg/kg for penicillin allergic patients) even before seeking medical care. Animal bites (risk of *Capnocytophaga*) also should be recognized as a medical emergency requiring local wound care and debridement, and a short course of antibiotic therapy (amoxicillin-clavulanate for 3-5 days). Lastly, when traveling patients should know what to do in case of fever, and if in a tropical area recognize the increased risk for malaria.

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175.4 Mendelian Susceptibility to Mycobacterial Diseases

Jenna R.E. Bergerson and Alexandra F. Freeman

The group of diseases referred to as mendelian susceptibility to mycobacterial diseases (MSMDs) centers around the synthesis and signaling of IFN-γ required for the ability of macrophages to control intracellular infections including mycobacteria as well as some other intracellular bacteria, fungi and viruses (see Table 175.1).

Control of mycobacterial infections relies on the IL-12/IFN-γ/STAT1 pathway (see Fig. 175.4). When the macrophages ingest mycobacteria or other intracellular organisms, they secrete the cytokine IL-12, which binds to its receptor, a heterodimer comprising IL-12RB1 plus IL-21RB2, on the T lymphocytes and NK cells. This then leads to the secretion by the T/NK lymphocytes of IFN-γ. IFN-γ binds to its heterodimer receptor, IFN-γR1 and IFN-γR2, leading to JAK1 and JAK2 phosphorylation, and then STAT1 phosphorylation. STAT1 is a transcription factor that leads to the upregulation of IFN-regulated genes (IRGs), which leads to the clearance of these infections. Control of mycobacteria relies on this pathway, but also other intracellular microorganisms such as endemic fungi (e.g., *Histoplasma* and *Coccidioides*), *Salmonella,* leishmaniasis, and, in part, some viruses, such as those in the herpes virus family.

The MSMD defects typically present with disseminated BCG or with extrapulmonary nontuberculous and environmental mycobacteria (NTM); individuals with disseminated mycobacterial disease with either bone or visceral involvement should be evaluated. Depending on the type of defect, the infection may be more localized, such as the osteomyelitis seen frequently with dominant LOF defects in *IFN-γR1* or *STAT1*,

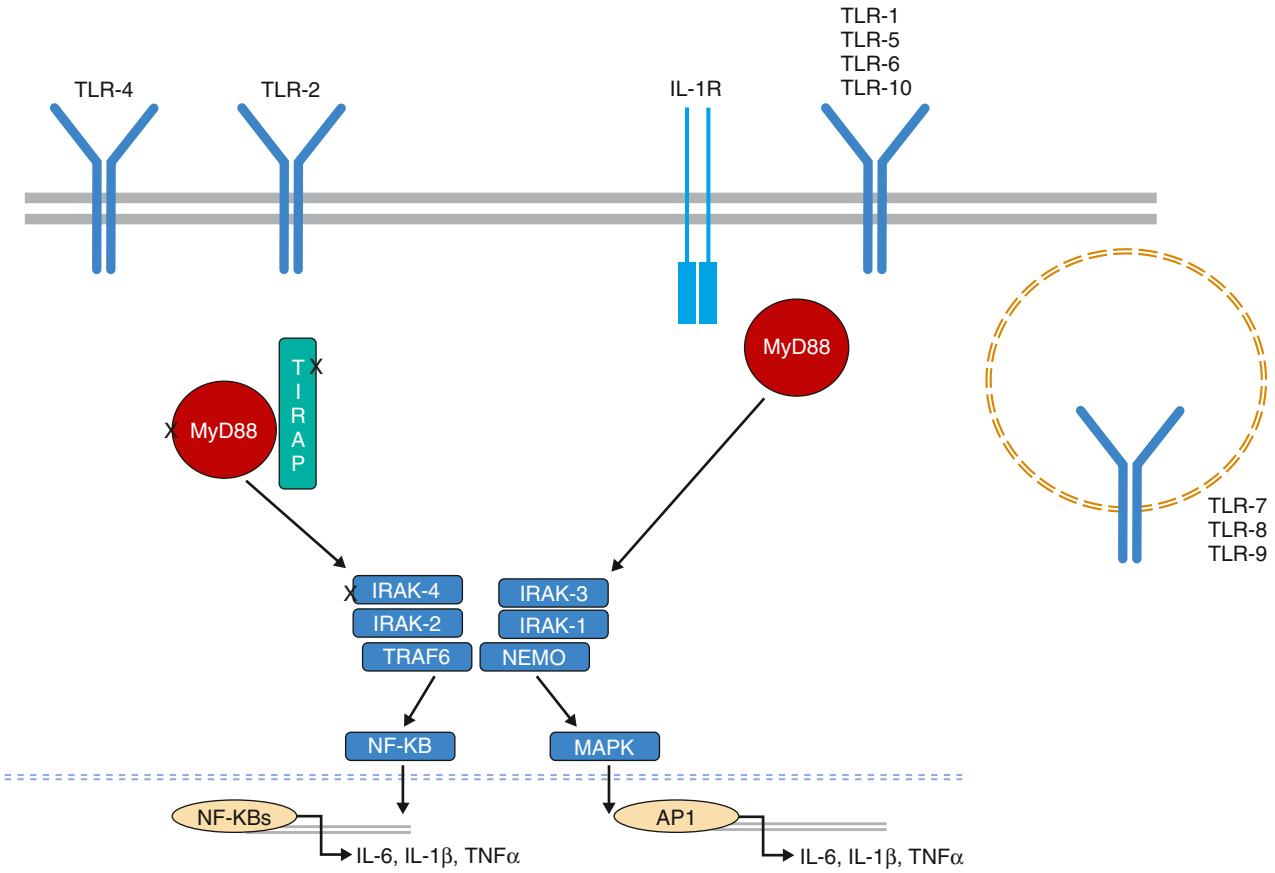

Fig. 175.4 TLR/IL-1R pathways. MyD88 is a cytosolic adaptor protein that bridges TLRs and IL-1Rs to the IRAK complex and subsequently allows for the downstream production of cytokines and interferons (IFNs) through the NF-κB and MAPK pathways. All TLRs, except TLR3, as well as multiple IL-1Rs use MyD88 and IRAK4. Where defects lead to predominant susceptibility to invasive bacterial infections are marked by an X.

or with more disseminated disease often with lymph node, bowel, and hepatosplenic involvement. Extrapulmonary TB should also raise suspicion of MSMD in young BCG-vaccinated children. Mycobacterial disease restricted to the lungs is much less frequently associated with MSMD, but more often with diseases predisposing to bronchiectasis. In addition, young children with isolated cervical adenitis from NTM do not usually have MSMD; the evaluation can be limited to those with recurrent or difficult to treat disease.

Therapy relies on targeted antimicrobials, but cytokine adjuvants, such as IFN-γ, and consideration of HSCT varies based on the defect. Related defects that predispose to CMC are noted in Table 175.4.

IFN-γR Defects

The IFN-γ receptor is a heterodimer comprised of IFN-γR1 and IFN-γR2, and defects in both components lead to abnormal signaling. There are biallelic and heterozygous pathogenic variants that lead to differing presentations.

Autosomal Recessive Complete IFN-γR1/IFN-γR2 Deficiency

The most severe defect of the IFN-γR defects are homozygous or compound heterozygous pathogenic variants that block all IFN-γ signaling. The variants are in the extracellular domains of the protein and lead to no surface receptor expression. In countries where BCG is given, these patients typically present in infancy with disseminated BCG; in other countries affected patients present usually in early childhood with disseminated NTM, such as *Mycobacterium avium* complex (MAC). *Salmonella* and *Listeria* can also cause severe infection; there may be more severe disease with common respiratory viruses and herpes family viruses. Diagnosis is with genetic testing, but some laboratories can also suggest the diagnosis by performing flow cytometry showing no surface expression of the IFNg-γ on monocytes or lack of intracellular STAT1 phosphorylation after stimulation with IFN-γ.

Treatment of complete IFN-γR1 deficiency is aggressive antimicrobial therapy until HSCT. Adjuvant IFN-γ is not helpful because signaling is blocked; addition of IFN-α has been used successfully in some cases of disseminated MAC. These patients usually have disseminated NTM or BCG and require combination antibiotics through HSCT, with breakthrough infections being seen often if antibiotics are withdrawn. High serum IFN-γ levels in the blood are typical when infection is present and has been correlated with a poor HSCT outcome; these levels can be followed and HSCT optimally performed when they decline.

Autosomal Dominant IFN-γR1 Deficiency

Compared with complete γ/2 deficiency, AD IFN-γR1 deficiency allows partial IFNg signaling, and thus a typically less severe clinical course. Most pathogenic variants are small frameshift deletions in the intracellular domain of the *IFNGR1* gene, thus blocking both the JAK binding site as well as the receptor recycling domain, eliminating the removal of the nonfunctional receptor from the cell surface. Clinical presentation is usually later in childhood or adolescence with more focal NTM infections, which is usually osteomyelitis. BCG can present with osteomyelitis as well, at a younger age than is usually seen for the environmental NTM. Disseminated endemic fungi infections with *Histoplasma* and *Coccidioides* are seen, in addition to disseminated *Salmonella* infections. Diagnosis relies on genetic testing, but in laboratories able to perform flow cytometry for IFN-γR expression, diagnosis is suspected by increased IFN-γR expression due to the inability to recycle the receptor. Intracellular STAT1 phosphorylation is reduced after IFN-γ stimulation, although not absent such as with the complete defects.

Treatment involves antimicrobials guided by the specific infection, with combination antibiotics needed for NTM/BCG. The addition of IFN-γ is

Table 175.4 Chronic Mucocutaneous Candidiasis Associated Inborn Errors of Immunity

SYNDROME	GENE	INHERITANCE	FUNGAL SPECIES	OTHER MANIFESTATIONS
CARD9 deficiency (30% CMC)	*CARD9*	AR	*Candida* spp. (often CNS involvement), CMC *Aspergillus* spp. (extrapulmonary), dermatophytes, phaeohyphomycosis	Some with increased IgE and eosinophilia
IL-17F deficiency (67% CMC)	*IL17F*	AD	CMC	Asthma, folliculitis
IL-17RA deficiency (100% CMC)	*IL17RA*	AR	CMC	Folliculitis, susceptibility to *Staphylococcus aureus* (skin) bacterial infections
IL-17RC (100% CMC)	*IL17RC*	AR	CMC	None
ACT1 (100%)	*TRAF3IP2*	AR	CMC	Seborrheic dermatitis
STAT1 GOF (95% CMC)	*STAT1*	AD	CMC, *Histoplasma capsulatum*, *Coccidioides* spp. *Talaromyces marneffei*, *Trichophyton*, *Cryptococcus*, *Aspergillus*, *Mucorales*	Herpes viral infections, bacterial sinopulmonary and skin infections, mycobacterial pulmonary and disseminated infections, CNS aneurysms, autoimmunity

AD, Autosomal dominant; AR, autosomal recessive; CMC, chronic mucocutaneous candidiasis; CNS, central nervous system; GOF, gain of function; IL, interleukin.

often helpful to clear the infection because some IFN-γ signaling remains. After clearance of the infection, lifelong prophylaxis is suggested such as with azithromycin therapy, and consideration of fluconazole for *Coccidioides* endemic regions. IFN-γ is not usually long term for prophylaxis. HSCT has been performed in rare cases but is typically not considered necessary.

Autosomal Recessive IL-12 Receptor Beta 1 (IL-12RB1) Deficiency

Biallelic typically missense or nonsense pathogenic variants in *IL-12RB1* result in complete loss of IL-12 signaling leading to disseminated NTM or other intracellular infections. Compared with complete IFN-γR deficiency, the penetration and expressivity of IL-12RB1 deficiency is much more variable. Some patients are asymptomatic, even if BCG is given, whereas others develop severe disease early in life with early mortality; even within families the disease can have very different presentations. This defect is also more common than IFN-γR deficiency. Disseminated BCG is common in countries in which the vaccine is given and disseminated environmental NTM presents at much more variable ages in other countries. Although there is increased childhood mortality from this defect, patients who clear disseminated BCG infection have lower rates of subsequent NTM infection than those who did not have a BCG infection. Disseminated *Salmonella* is seen frequently. IL-12RB1 forms a heterodimer with IL-23R, so perturbation of this signaling cascade also results in an increased rate of mucocutaneous candidiasis. Diagnosis is confirmed with genetic testing, but some laboratories can test the lymphocyte response to IL-12 signaling, noting absence of STAT4 phosphorylation or IFN-γ secretion.

Treatment is aimed at antimicrobials for the diagnosed infection. Secondary prophylaxis is suggested after clearance of mycobacterial infections, such as with azithromycin. Adjuvant IFN-γ therapy has been used in cases where antimicrobials do not adequately clear the infection. Increased doses than are used in CGD may be needed, with prudence being to titrate up the dose slowly as hyperinflammatory presentations can complicate the therapy. There is very little experience with HSCT in IL-12RB1 deficiency.

AD STAT1 Loss of Function

Although GOF and complete LOF *STAT1* defects can be associated with NTM infections, NTM infections occur with the highest frequency in AD *STAT1* LOF, which is to be expected because STAT1 is downstream of the IL-12/IFN-γ pathway. Presentation is typically with more focal NTM or BCG infections, often with osteomyelitis, similar to that seen with AD IFN-γR1 deficiency. Diagnosis requires genetic testing. Patients typically respond well to combination antimicrobials and can then be placed on long-term prophylaxis. Infants with complete *STAT1* deficiency have had disseminated BCG; this defect also has severe viral infections.

TYK2 Deficiency

JAK proteins and TYK2 are part of the JAK/STAT signal transduction pathway. TYK2 is downstream of IFN-α and -β, as well as IL-12/IL-23, with its activation leading to STAT1 phosphorylation. Patients have had disseminated BCG, TB, and viral infections.

DIFFERENTIAL DIAGNOSIS FOR MSMD

MSMD centers around the control of intracellular organisms including *Mycobacteria* by the lymphocyte/macrophage interactions involving the IL-12/IFN-γ/STAT1 pathway. However, other primary and secondary immune deficiencies should be included in the differential diagnosis of those presenting with disseminated NTM. Disseminated NTM is a common infection for those with **GATA2 deficiency**, which typically presents in adolescence or adulthood, and is often associated with monocytopenia and myelodysplasia, susceptibility to HPV, and pulmonary alveolar proteinosis. **Nuclear factor-κ-B (NEMO)** deficiency and other genetic defects involved in NF-κB activation, such as defects in IkBα, are combined immune deficiencies that present with recurrent bacterial, viral, and disseminated mycobacterial disease; NEMO and IKBα may both have ectodermal dysplasia as part of the phenotype. Disseminated NTM is a less frequent complication for other myeloid and lymphocyte IEIs such as CGD, NFKB1 deficiency, and severe combined immune deficiency (SCID). Disseminated NTM is also associated with **autoantibodies against IFN-γ;** these should be considered for adult-onset disease. In the United States, anti–IFN-γ autoantibody disease with disseminated NTM is much more common in Asian females but is seen in males and females in East Asian countries. HIV/AIDS should always be ruled out for those with disseminated NTM. Disseminated NTM can also be seen secondary to immune suppressive medications, with TNF-α blockade being the most common cause. Hairy cell leukemia has an increased incidence of disseminated NTM.

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Chapter 176

Approaches to Treatment of Primary Immune Deficiency Diseases

Alissa McInerney, Stefani Su, and Artemio M. Jongco III

GENERAL INFECTION PREVENTION AND MANAGEMENT STRATEGIES

Whenever possible, precautionary measures to reduce or minimize exposure to infection should be implemented. Whereas patients with severe immunologic defects (e.g., severe combined immunodeficiency [SCID]) would benefit from strict isolation, patients with other, less severe types of primary immunodeficiency disease (PID) usually do not require such restrictive measures. It is imperative to maximize the patient's quality of life while implementing appropriate infection mitigation strategies. Using shared decision-making, the clinician, patient, and caregivers should regularly discuss the risks, benefits, and alternatives of infection mitigation strategies, as the patient's clinical situation and risk change over time. Universal precautions, including but not limited to proper and thorough hand hygiene, should be frequently practiced by patients as well as their close contacts. The use of masks that cover the nose and mouth should be considered to avoid infection, especially when highly transmissible infections (e.g., SARS-CoV-2) are prevalent in the community. This is especially important in those PID patients before hematopoietic stem cell transplant (HSCT) while on immunosuppressive medications and afterward while awaiting immune reconstitution. *There is a low threshold to do further diagnostic testing to identify acute infections early and to start antimicrobial therapy or admit the patient to hospital for aggressive treatment if needed.*

It is also important to practice standard routine *oral* hygiene. Guidelines for antibiotic prophylaxis prior to dental procedures in PID patients has not been well established. Antibiotic prophylaxis is recommended for patients with PIDs requiring invasive dental procedures such as root canals and tooth extraction. In particular, those patients with PID with ongoing odontogenic infections require antibiotics before and during dental treatment. There is not enough evidence for antibiotic prophylaxis for noninvasive dental procedures such as oral examinations.

IMMUNIZATIONS

Some PID patients *will not* mount an adequate immune response to vaccinations because of their underlying immunologic defect. Nonetheless, immunizations should be given to prevent infections to PID patients who are able to respond to vaccination. Specific immunization practices are covered in Chapter 215. Immunization with live viral or bacterial vaccines (BCG) is contraindicated in many PIDs due to the risk of acquiring the live vaccine–related disease. Specific recommendations for vaccines in PID are shown in Table 176.1.

Patients who are on immunoglobulin G (IgG) replacement therapy (IgRT) do not require routine vaccinations because they receive *passive* immunization. Protective levels of antibodies against tetanus toxoid, diphtheria toxoid, measles, varicella, pertussis, pneumococci, and three meningococcal serotypes are documented in patients receiving IgRT.

GUIDANCE FOR CLOSE CONTACTS

Household members and other close contacts should not receive live oral polio virus or live influenza vaccine because they may shed the virus and transmit infection. Household members should generally be vaccinated to all recommended vaccines, including MMR and varicella, to facilitate herd immunity. Transmission of MMR vaccine viruses has not been reported. The risk of transmission of varicella vaccine virus from a healthy person to an immunocompromised person is rare. If a close contact develops varicella rash after immunization with the varicella or zoster vaccines, isolation of the patient and administration of varicella-zoster immune globulin is recommended.

COVID-19 VACCINE

The impact and severity of SARS-CoV-2 infection likely varies depending on the underlying immune defect. Small case series have suggested that B-cell lymphopenia (such as in X-linked agammaglobulinemia [XLA]) may actually be a protective factor and correlates with milder COVID-19 course. Meanwhile, patients with biallelic loss-of-function variants in *AIRE,* who have autoimmune polyendocrine syndrome type-1 (APS-1), appear to have higher risk for life-threatening COVID-19 pneumonia due to the presence of autoantibodies to type I interferons (IFNs). Although all PID patients will benefit from infection prevention and mitigation practices, it is becoming apparent that morbidity and mortality is variable among PID patients.

The most effective COVID prevention practices include the standard infection prevention strategies for all diseases including frequent handwashing, minimizing exposure to sick contacts, self-isolation/quarantining while ill, and mask wearing when in crowded public areas or areas with suboptimal ventilation. The most effective prevention strategy against COVID-19 is vaccination. Although this is a rapidly changing situation, a variety of organizations have created recommendations for immunodeficiency patients. The consensus is that PID patients should be vaccinated with non-live vaccines based on what has been approved for the age-group in their country. Patients with humoral deficiencies who do not respond with measurable antibody titers should still be considered for vaccination as vaccines can induce cellular immunity as well.

In the United States, the Centers for Disease Control and Prevention (CDC) recommends administration of a third or fourth dose in high-risk patients, such as immunocompromised patients, including PID patients with moderate to severe immunodeficiency and patients on chronic immunosuppressive therapy.

PROPHYLAXIS

Antimicrobial Prophylaxis

Prophylactic antibiotics are one of the mainstays for infection prevention in patients with PID. The specific antimicrobial prophylaxis recommended differs depending on the type of PID because patients with different PIDs are susceptible to different pathogens.

IMMUNODEFICIENCIES AFFECTING CELLULAR AND HUMORAL IMMUNITY

Severe Combined Immunodeficiency

Patients with SCID will require definitive treatment with allogeneic HSCT to correct the immune defect. It is crucial that patients remain infection free to maximize chances of long-term survival. With the implementation of newborn screening for SCID, infants with SCID are being detected before they develop infections. When SCID is suspected, the number of people in contact with the infant should be limited. Due to risk of transmission of cytomegalovirus (CMV) through breast milk, many PID transplant centers recommend cessation of breastfeeding until the CMV status of both the mother and infant is established.

Antimicrobial prophylaxis should be directed toward pneumonia caused by *Pneumocystis jiroveci* with a combination of sulfamethoxazole and trimethoprim. However, in infants under 2 months of age, there is a concern for bilirubin displacement from albumin and subsequent risk of kernicterus. In these young infants, close monitoring of bilirubin levels is recommended or alternatives such as atovaquone, dapsone, and pentamidine can be considered. Fluconazole to prevent mucocutaneous candidiasis and acyclovir for viral prophylaxis can be considered as well. In countries where BCG vaccine is commonly administered in early infancy, daily chemoprophylaxis until definitive treatment with HSCT and immune reconstitution is needed with isoniazid and rifampin due to the risk of disseminated BCG infection.

Table 176.1 Immunizations in Patients with Primary Immunodeficiency Diseases

PRIMARY DEFECT	EXAMPLE OF SPECIFIC IMMUNODEFICIENCY	NOT RECOMMENDED	RECOMMENDED
Predominantly antibody deficiencies	Hypogammaglobulinemias (X-linked agammaglobulinemia, common variable immunodeficiency) Other antibody deficiencies (selective IgA deficiency, IgG subclass deficiencies, specific antibody deficiency with normal immunoglobulins)	Live-attenuated vaccines excluding BCG Live-attenuated influenza, OPV, adenovirus, typhoid, yellow fever	Inactivated vaccines All vaccines likely effective Pneumococcal and *Hib*
Combined immunodeficiencies	Complete defects (SCID, complete DiGeorge syndrome) Partial defects (partial DiGeorge syndrome, Wiskott-Aldrich syndrome, ataxia telangiectasia)	All live vaccines Live-attenuated influenza, OPV, rotavirus, adenovirus, smallpox, typhoid, yellow fever, BCG	All vaccines likely ineffective Inactivated vaccines, live-attenuated MMR, varicella, and herpes zoster if documentation of adequate T-cell number*
Complement		None	All routine vaccines, especially pneumococcal and meningococcal vaccines
Phagocytic function	Chronic granulomatous disease, leukocyte adhesion defects	Live-attenuated influenza, adenovirus, typhoid, BCG	All inactivated vaccines, other live-attenuated viral vaccines
IFN-γ-IL-12 pathway defects		BCG	

*Age-related levels of immunocompetence proposed by the CDC: <1 yr, 1500; 1-5 yr, 1,000; and >6 yr, 500 $CD4^+$ T cells/mm^3 for HIV may also be used.
BCG, Bacille Calmette-Guérin; OPV, oral poliovirus vaccine; SCID, severe combined immune deficiency; MMR, measles, mumps, rubella; IFN-γ, interferon gamma; IL-12, interleukin-12.
Data from Medical Advisory Committee of the Immune Deficiency Foundation, Shearer WT, Fleisher TA, et al. Recommendations for live viral and bacterial vaccines in immunodeficient patients and their close contacts. *J Allergy Clin Immunol*. 2014;133(4):961–966.

Palivizumab, a humanized monoclonal antibody against respiratory syncytial virus (RSV), can be considered for children under 2 years of age with SCID during the RSV season to prevent serious disease. The specific RSV seasonal patterns differ between countries.

HYPER-IgM/*CD40LG* DEFICIENCY

Patients with hyper-IgM or CD40LG deficiency are especially susceptible to *P. jiroveci* pneumonia (PJP) and require prophylaxis with a combination of sulfamethoxazole and trimethoprim. These patients are also at special risk for developing sclerosing cholangitis, which can be associated with *Cryptosporidium parvum* infection. To prevent the risk of cryptosporidium infection, steps need to be taken to avoid drinking contaminated water and places where risk of infection is higher, such as at recreational water parks.

COMBINED IMMUNODEFICIENCIES WITH ASSOCIATED OR SYNDROME FEATURES

DiGeorge Syndrome/22q11 Deletion Syndrome

Most patients with DiGeorge syndrome do not require antimicrobial prophylaxis as most patients do not have severe immunodeficiency (i.e., partial DiGeorge syndrome). Less than 1% of patients have significant thymic aplasia and profound T- and B-cell lymphopenia (i.e., complete DiGeorge syndrome), putting them at risk of PJP and CMV; PJP prophylaxis is recommended.

Wiskott-Aldrich Syndrome

Patients with Wiskott-Aldrich syndrome (WAS) are susceptible to a variety of viral and bacterial infections. *Prophylactic antimicrobials against infection by PJP and herpes simplex virus are often recommended.* If splenectomy is necessary for severe refractory thrombocytopenia, those patients would then require penicillin prophylaxis to protect against infection by encapsulated organisms.

Ataxia Telangiectasia

Opportunistic infections in patients with ataxia telangiectasia are infrequent; however, sinopulmonary infections are common. Prophylactic azithromycin is commonly used empirically, however, efficacy data are sparse.

STAT3 HYPER-IgE SYNDROME (JOB SYNDROME)

These patients are susceptible to skin infections predominantly with *Staphylococcus aureus* causing "cold" abscesses with diminished inflammatory response. Chronic mucocutaneous candidiasis occurs in over 70% of patients. Pneumonia is a frequent infection with risk of leading to bronchiectasis and pneumatoceles. Common causative pathogens include *Staphylococcus, Streptococcus pneumoniae, Haemophilus influenzae,* and fungal organisms such as *Aspergillus* and *P. jiroveci*. *Antimicrobial prophylaxis with a combination of sulfamethoxazole and trimethoprim and antifungal medications such as itraconazole is recommended.*

NF-κB ESSENTIAL MODULATOR (NEMO) DEFICIENCY

Patients with NF-κB essential modulator (NEMO) deficiency are susceptible to nontuberculous mycobacteria (NTM), similar to patients with IFN-γ and interleukin (IL)-12 defects. Prophylaxis with azithromycin should be considered. However, these patients are also at risk for many bacterial infections, viral infections such as herpesviruses, and opportunistic infections such as PJP. *Acyclovir for viral prophylaxis and a combination of sulfamethoxazole and trimethoprim for PJP prophylaxis should be considered as well.*

PREDOMINANTLY ANTIBODY DEFICIENCIES

Hypogammaglobinemias

Lifelong IgRT is the mainstay of infection prevention for patients with major antibody deficiencies such as agammaglobulinemia and common variable immunodeficiency (CVID). Prophylactic antibiotics can be used in conjunction with IgRT for patients who develop recurrent respiratory tract infections, which can lead to severe complications of bronchiectasis. Macrolide antibiotics such as azithromycin are commonly used for prophylaxis due to their anti-inflammatory properties in chronic lung disease. Low-dose oral azithromycin reduces the number of exacerbation episodes per patient-year, with a consequent reduction in additional courses of antibiotics and risk of hospitalization.

Other Antibody Deficiencies

Patients with minor antibody deficiencies such as **transient hypogammaglobulinemia of infancy (THI),** selective IgA deficiency, IgG

subclass deficiency, or specific antibody deficiency with normal immunoglobulins can usually be managed without need for IgRT. Patients who experience chronic or recurrent infections may benefit from prophylactic antibiotics. Prophylactic antibiotics and IgRT are equally effective as first-line treatment in preventing infections in specific antibody deficiency patients.

CONGENITAL PHAGOCYTE DEFECTS

Chronic Granulomatous Disease

Patients with chronic granulomatous disease (CGD) are susceptible to severe bacterial and fungal infections. The most common bacterial organisms include *S. aureus*, *Serratia marcescens, Burkholderia cepacia,* and *Nocardia* species. The majority of fungal infections in CGD are attributed to *Aspergillus* species causing invasive aspergillosis. *Prophylaxis with a combination of sulfamethoxazole and trimethoprim and itraconazole is recommended.*

Leukocyte Adhesion Deficiency

Antibiotic prophylaxis to protect against infections with *S. aureus* or gram-negative bacilli is recommended.

DEFECTS IN INTRINSIC AND INNATE IMMUNITY

Interferon-γ/IL-12 Pathway Defects

Patients with IFN-γ/IL-12 pathway defects are at special risk for infections with intracellular pathogens such as nontuberculosis *Mycobacterium* species as well as *Salmonella*. *Prophylaxis with daily azithromycin or clarithromycin is recommended.*

COMPLEMENT DEFICIENCIES

Deficiency of terminal pathway components can lead to recurrent neisserial infections. Antibiotic prophylaxis with penicillin can be considered. *Immunization against S. pneumoniae, H. influenzae, and Neisseria meningitidis is strongly recommended.*

IMMUNOGLOBULIN G REPLACEMENT THERAPY

Human immunoglobulin preparations, derived from the plasma of paid donors, can be administered intravenously (IVIG), subcutaneously (SCIG), or intramuscularly (IMIG) to treat a variety of disorders, including inborn errors of immunity, acquired immunodeficiency, and autoimmune and inflammatory disorders. IgRT provides *passive immunity* through preformed antibodies against a wide range of pathogens that are encountered by the general population, leading to immediate but transient protection; IgRT has an integral role in the treatment of patients with defects in the humoral immune system. IgRT is also used for a variety of medical conditions because of its anti-inflammatory and immunomodulating effects.

Products

Although most products are approved for a specific administration route, several 10% **IVIG** solutions can be administered subcutaneously with good patient tolerability. More concentrated 20% **SCIG** and 16% **IMIG** products should not be used intravenously. Available products and their key properties are summarized in Table 176.2. **IMIG** is rarely used because of its inferior safety and tolerability profile. Injections are painful, the injectable volume is limited, and the risk of local injury and adverse reactions is higher. Both **IVIG** and **SCIG** products are effective in treating humoral immunodeficiencies, without significant differences in the infection rates between the two routes. Incidence of infection is inversely correlated with dose regardless of route.

INDICATIONS FOR IgRT

IgRT is indicated for the treatment of primary immunodeficiencies characterized by absent or deficient antibody production, which comprises the majority of PIDs. The utility of IgRT in decreasing the frequency and severity of infection is well accepted for agammaglobulinemia (e.g., XLA) and hypogammaglobulinemia (e.g., CVID). There are six distinct phenotypes of primary immunodeficiency for which IgRT is or may be indicated: (1) agammaglobulinemia due to absence of B cells, (2) hypogammaglobulinemia with poor antibody function, (3) normal immunoglobulin levels with impaired specific antibody production, (4) hypogammaglobulinemia with normal antibody function, (5) isolated IgG subclass deficiency with normal immunoglobulin levels and normal quality antibody responses, and (6) recurrent infections related to an unknown immune mechanism.

Agammaglobulinemia Due to Absence of B cells

IgRT reduces both acute and chronic infections in this patient population; the number and severity of infectious complications are inversely correlated with IgRT dose. When IgG trough levels are maintained above 800 mg/dL, serious bacterial illness and enteroviral meningoencephalitis are prevented; increasing trough levels up to 1,000 mg/dL are associated with decreased risk for pneumonia. In the setting of SCID, IgRT is warranted at diagnosis because maternally derived IgG wanes after birth, during the posttransplant period, or gene therapy or enzyme replacement (for adenosine deaminase [ADA] deficiency) until B-cell function reconstitution, or indefinitely if B-cell function is not restored.

Hypogammaglobulinemia with Poor Antibody Function

Patients with recurrent infections who demonstrate decreased immunoglobulin concentrations and/or impaired response to protein and/or polysaccharide vaccines benefit from IgRT. CVID falls in this category. Initiation of IgRT is associated with decreased infection rate compared with pretreatment. Adequate IgRT dosing is associated with decreased frequency of sinopulmonary infections, which can mitigate the development of lung inflammation, bronchiectasis, and chronic lung disease. Growing evidence and expert consensus support individualizing IgRT dosing to keep the patient relatively infection free, achieving a "biologic trough or biologic steady-state level," and following clinical outcomes rather than using a standardized dose in all patients by disease. In addition to CVID, patients with class-switching defects, such as autosomal recessive and X-linked hyper-IgM syndromes, also demonstrate decreased infection rates from a variety of pathogens.

NORMAL IMMUNOGLOBULIN LEVELS WITH IMPAIRED SPECIFIC ANTIBODY PRODUCTION

Determining whether and when IgRT is indicated for these patients can be challenging. Available evidence and expert consensus suggest that IgRT should be given when there is well-documented nonresponsiveness to polysaccharide vaccines and recurrent infections that are inadequately managed by antibiotic prophylaxis. Protective concentration of antibody to polysaccharide antigens is considered 1.3 μg/mL and conversion from nonprotective to protective titers. In children 2-5 years, >50% of concentrations tested are considered protective, with an observed increase of at least twofold postvaccination, while the threshold is >70% in patients aged 6-65 years. Selective antibody deficiency has been categorized into four phenotypes—mild, moderate, severe, and memory (where the patient can mount an adequate initial response that wanes within 6 months). If an IgRT trial is started, it should be discontinued after a period of time so that antibody responses can be reevaluated a minimum of 3 months after discontinuation. Some children can demonstrate clinical improvement and improved response after pneumococcal polysaccharide vaccine challenge after a short trial of IgRT, whereas others continue to have recurrent infections and restart IgRT.

Hypogammaglobulinemia with Normal Antibody Function

Age-specific normal ranges differ among laboratories and having IgG levels below the lower limit of normal for age without accompanying infections may not be clinically significant. The IgG levels of children experiencing **THI** normalize with time. THI may be exacerbated by preterm birth. In the absence of significant infections, IgRT is not routinely recommended for these children. Acquired hypogammaglobulinemia arising from medication (e.g., seizure medications, B-cell depletion therapy) can also fall in this category. Severe hypogammaglobulinemia, conventionally defined as IgG levels ≤150 mg/day, is considered a risk

Table 176.2 Available Immunoglobulin Replacement Therapy Products

ROUTE	PRODUCT	DOSAGE FORM	DILUENT	REFRIGERATION REQUIRED?	FILTRATION REQUIRED?	OSMOLALITY (mOsm/kg)	SODIUM	PH	IgA (mcg/mL)	STABILIZER OR REGULATOR*	PATHOGEN INACTIVATION/ REMOVAL†
IV	Asceniv	10% liquid	NA	Yes	No	Not available	0.100-0.140 mol/L	4.0-4.6	<200	Glycine and polysorbate 80	FP, S/D, VF
	Bivigam	10% liquid	NA	Yes	No	<510	100-140 mM	4.0-4.6	≤200	Glycine	FP, S/D, NF
	Flebogamma DIF 5%	5% liquid	NA	No‡	Optional	240-370	Trace	5.0-6.0	<50	D-sorbitol	Past, S/D, dsNF, FP, PEG, pH 4
	Flebogamma DIF 10%	10% liquid	NA	No‡	No	240-370	Trace	5.0-6.0	<100	D-sorbitol	Past, S/D, dsNF, FP, PEG, pH 4
	Gammagard 5% S/D	Lyophilized	Sterile water	No	Yes	636	8.5 mg/mL	6.8	<1	2% glucose and glycine	CEF, CHROM, S/D
	Gammaplex	5% liquid	NA	No‡	15-20-μm filter preferred	420-500	30 to 50 mmol/L	4.8-5.0	<4	Sorbitol and glycine and polysorbate 80	S/D, VF, low pH
	Gammaplex	10% liquid	NA	No‡	No	≥280	<30 mM/L	4.9-5.2	<20	Glycine and polysorbate 80	S/D, VF, low pH
	Octagam	5% liquid	NA	No‡	Optional	310-380	0.03 mEq/mL	5.1-6.0	<200	Maltose	CEF, UF, CHROM, S/D, pH 4
	Octagam	10% liquid	NA	No‡	Optional	310-380	<30 mmol/L	4.5-5.0	106	Maltose	CEF, S/D, pH 4, UF, CHROM
	Panzyga	10% liquid	NA	No§	Optional	240-310	Trace	4.5-5.0	100	Glycine	S/D, CEF, NF, CHROM
	Privigen	10% liquid	NA	No**	No	240-440	Trace	4.6-5.0	<25	L-proline	CEF, CHROM, pH 4, DF, NF, OAF
IV or SC	Gammagard liquid	10% liquid	NA	No‡	Optional	240-300	None added	4.6-5.1	37	Glycine	CEF, CHROM, S/D, pH 4, NF
	Gammaked	10% liquid	NA, incompatible with saline	No**	No	258	None added	4.0-4.5	46	Glycine	CEF, pH 4.2, DF, CAP, CHROM, NF
	Gamunex-C	10% liquid	NA, incompatible with saline	No**	No	258	None added	4.0-4.5	46	Glycine	CEF, pH 4.2, DF, CAP, CHROM, NF

Continued

Table 176.2 Available Immunoglobulin Replacement Therapy Products—cont'd

ROUTE	PRODUCT	DOSAGE FORM	DILUENT	REFRIGERATION REQUIRED?	FILTRATION REQUIRED?	OSMOLALITY (mOsm/kg)	SODIUM	PH	IgA (mcg/mL)	STABILIZER OR REGULATOR*	PATHOGEN INACTIVATION/ REMOVAL†
SC	Cutaquig	16.5% liquid	NA	Yes¶	No	310-380	<30 mmol/L	5.0-5.5	≤600	Maltose	CEF, UF, CHROM, S/D, pH 4
	Cuvitru	20% liquid	NA	No***	No	208-290	None	4.6-5.1	80	Glycine	CEF, CHROM, NF, S/D
	Hizentra	20% liquid	NA	No	No	380	Trace, <10 mmol/L	4.6-5.2	≤50	Proline	CEF, CHROM, pH 4.2, DF, NF, VF, OAF
	HyQvia	10% liquid + recombinant human hyaluronidase	NA	No	No††	240-300	None added	4.6-5.1	37	Glycine	CEF, CHROM, S/D, pH 4, NF
	Xembify	20% liquid	NA	2-8°C	No	280-404	None	4.1-4.8	≤70	Glycine	CEF, CHROM, CAP, NF, DF, low pH
IM	GamaSTAN	16.5% liquid	NA	2-8°C	No	Not available	Not measured	4.1-4.8	Not measured	Glycine	CEF, CAP, CHROM, NF, low pH, DF
	GamaSTAN S/D‡‡	15–18% liquid	NA	2-8°C	No	Not available	0.4-0.5%	6.4-7.2	Not measured	Glycine	CEF, S/D, UF

*Precautions and laboratory abnormalities associated with specific stabilizers include the following:
- Glucose: May alter glycemic control in patients with diabetes mellitus.
- L-proline: Cannot be used in patients with hyperprolinemia.
- Maltose: Falsely elevates glucose readings in certain blood glucose monitoring systems, may contain trace corn protein (potential allergen), and may increase plasma osmolality (usually not clinically important).
- Polysorbate 80: Some patients may be hypersensitive (also known as Tween 80); reactions can be delayed type.
- Sorbitol, D-sorbitol: Cannot be used in patients with hereditary fructose intolerance.
- Sucrose: Avoid in patients with renal impairment or increased risk of acute kidney injury.

†Pathogen inactivation/removal using CEF, DF, UF, CAP, CHROM, Nano, dsNF, VF, S/D, Past, FP, or OAF.
‡Not required (+2 to 25°C).
§Storage is 2-8°C for 24 months or 25°C for 9 months.
**Storage is 2-8°C for 36 months or 25°C for 6 months.
¶Storage is 2-8°C for 24 months or 25°C for 6 months.
***Storage is 2-8°C for 36 months or 25°C for 12 months.
††Storage is 2-8°C for 36 months or 25°C for 3 months.
‡‡GamaSTAN S/D has been discontinued in the United States.

Note: Brand names and descriptions refer to products available in the United States and some other countries; product availability, specific composition, and other details regarding individual products vary in other countries.

IgA, Immunoglobulin A; IV, intravenous; NA, not applicable; FP, fraction precipitation; S/D, solvent detergent; VF, virus filtration; Nano, NF, nanofiltration; DIF, dual inactivation and filtration; Past, pasteurization; dsNF, double sequential nanofiltration; PEG, polyethylene glycol precipitation; CEF, cold ethanol fractionation; DF, depth filtration; UF, ultrafiltration; CHROM, chromatography; SC, subcutaneous; CAP, caprylate; OAF, octanoic acid fractionation; IM, intramuscular.

Adapted from Perez EE, Orange JS, Bonilla F, et al. Update on the use of immunoglobulin in human disease: A review of evidence. *J Allergy Clin Immunol*. 2017;139(3S):S1–S46; with data from Immune Deficiency Foundation. Characteristics of Immunoglobulin Products Used to Treat Primary Immunodeficiencies. Accessed 8/10/21. https://primaryimmune.org/sites/default/files/publications/IDF_IG%20Booklet%202020.pdf

factor for infection, and empiric trial of IgRT is reasonable. However, patients with levels between 150 and 250 mg/dL deserve further consideration of antibody function and individual clinical history.

Isolated IgG Subclass Deficiency with Normal Immunoglobulin Levels and Normal Quality Antibody Responses

Most patients with subclass deficiency are asymptomatic, but a few may have recurrent infections and poor antibody responses to specific antigens. *First-line management includes prophylactic antibiotics and treatment of other comorbidities, such as allergic rhinitis, that can contribute to the development of sinopulmonary infections.* IgRT is not routinely recommended for these patients; some case studies have demonstrated reduced infection rate, decreased antibiotic use, and improved quality of life among patients on therapy.

Recurrent Infections Related to an Unknown Immune Mechanism

There are defined immunodeficiencies, such as ataxia telangiectasia, WAS, and *STAT3* deficiency, as well as syndromic immunodeficiencies, such as Jacobsen syndrome, which can present with variable humoral immune defects. IgRT can prevent infections in select patients, and the decision to start IgRT and dosing considerations should be tailored to individual needs.

INDIVIDUALIZING IgRT

Clinicians, patients, and caregivers need to consider each patient's specific clinical situation and comorbidities, incorporate patient and caregiver preferences, and consider flexibility in dosing route and frequency. Children and adolescents may object to the multiple and more frequent needlesticks associated with SCIG. Once the decision is made to start IgRT, the clinician, patient, and caregivers need to periodically reassess and adjust as needed. Available IgRT products differ from one another and are not interchangeable; the product used should be matched carefully to the patient characteristics to maximize patient safety. There are eight guiding principles on the safe, effective, and appropriate use of IgRT in patients with primary immunodeficiency (Table 176.3).

Table 176.3 Guiding Principles for Effective Use of IgRT for Patients with Primary Immunodeficiency

GUIDING PRINCIPLE	RATIONALE
Indication for IgRT	IgG is indicated as replacement therapy for patients with PI characterized by absent or deficient antibody production; PI is an FDA-approved indication for IgRT
Diagnoses	A large number of PI diagnoses exist for which IgRT is indicated and recommended; many diagnoses have low total IgG levels, but some have a normal level with documented specific antibody deficiency
Frequency of IgRT	Treatment is indicated as ongoing replacement therapy for PI; treatment should not be interrupted once a definitive diagnosis has been established
Dose	IVIG is indicated for PI patients at a starting dose of 400-600 mg/kg every 3-4 wk; SCIG is generally used at a starting dose of 100-200 mg/kg/wk; SCIG dosing frequency is flexible
IgG trough levels	IgG trough levels can be useful in some diagnoses to guide care but should not be a consideration in access to IgRT
Site of care	The decision to infuse IgRT in a hospital, outpatient infusion center, community office, or home-based setting must be based on patient clinical characteristics
Route	Administration route must be based on patient characteristics; throughout life, certain patients may be more appropriate for IV or SC therapy depending on many factors, and patients should have access to either route as needed
Product	IVIG/SCIG are not generic drugs and products are not interchangeable; a specific product needs to be matched to patient characteristics to ensure patient safety; product change should only occur with active participation of the prescribing physician

IgRT, Immunoglobulin replacement therapy; IgG, immunoglobulin G; PI, primary immunodeficiency; FDA, US Food and Drug Administration; SCIG, subcutaneous immunoglobulin; IV, intravenous; SC, subcutaneous; IVIG, intravenous immunoglobulin.
Data from Perez EE, Orange JS, Bonilla F, et al. Update on the use of immunoglobulin in human disease: A review of evidence. *J Allergy Clin Immunol.* 2017;139(3S):S1–S46; with data from Yong PL, Boyle J, Ballow M, et al. Use of intravenous immunoglobulin and adjunctive therapies in the treatment of primary immunodeficiencies: A working group report of and study by the Primary Immunodeficiency Committee of the American Academy of Allergy Asthma and Immunology. *Clin Immunol.* 2010;135(2):255–263.

CONSIDERATIONS FOR PRODUCT SELECTIONS

IVIG

IgA Content

The amount of IgA in various products varies. Rarely, severe allergic reactions, including anaphylaxis, have been reported in patients with IgE anti-IgA or IgG anti-IgA. In these cases, use of low IgA-containing IVIG products or SCIG, which appears to be tolerated by these patients despite having higher IgA content, is recommended. Anaphylaxis due to IgA in SCIG has not been reported.

Adverse Reactions

All IgRT products are associated with a potential risk for adverse reactions, but historically IVIG is associated with higher risk. Most IVIG adverse reactions are rate related, mild, and occur in 5–15% of infusions. Slowing or stopping the infusion for 15-30 minutes usually leads to complete resolution. Premedication regimens can also help. Ensuring adequate hydration or switching to SCIG has been used successfully to mitigate this risk. Risk factors for experiencing adverse reactions include (1) having IVIG for the first time, (2) having or recently having a bacterial infection, (3) having underlying chronic inflammation, (4) using higher concentration products, (5) using lyophilized product, and (6) fast infusion rates. Future reactions become less likely after subsequent infusions with the same product. However, patients can develop adverse reactions at any point even to products they have tolerated previously; clinicians and patients need to remain vigilant. For enhanced safety, patients who have experienced prior adverse reactions may benefit from getting infusions at a medical facility, instead of at home with an infusion nurse.

Serious adverse events, including acute renal failure, neurodegeneration, and thromboembolic events, can occur during or soon after infusion. Thromboembolic events such as myocardial infarction, stroke, deep vein thrombosis, and pulmonary embolism are rare, but they need to be watched for and require timely intervention when they occur. Risk factors include preexisting cardiovascular disease, diabetes mellitus, dehydration, sepsis, increased blood viscosity, hypercholesterolemia, and hypertension. The use of indwelling venous catheters solely for IVIG administration is not recommended due to the increased risk for thromboembolism and infection with these devices.

SCIG

Products

Available products range from 10–20% concentration and offer much dosing flexibility for patients. Facilitated SCIG (fSCIG) involves recombinant human hyaluronidase to facilitate the SC administration of large volumes of IgG among multiple sites and a variety of dosing schedules. Many studies demonstrate equivalence and noninferiority of SCIG and IVIG for management of PIDs.

Adverse Reactions

SCIG is well tolerated by many patients, including children and IgA-deficient patients, and its safety profile is well documented. The most common adverse reaction is local infusion site reactions that can range from mild to severe, but severe local reactions are rare. The prevalence of these local site reactions appears to diminish when infusions are continued. Carefully cleaning the skin of the infusion site with alcohol and using appropriately sized infusion needles or catheters can further decrease risk of local reactions. IV administration of 10% products that are approved for both IV and SC administration is unlikely to be problematic, but 20% products should not be used intravenously. Premedication is usually not needed for SCIG, but pretreatment of the infusion site with local anesthetic creams may improve tolerability in children.

In the United States, patients are routinely provided epinephrine autoinjectors as part of an anaphylaxis kit for home infusions, regardless of prior history of allergic reactions to IgRT.

DOSING CONSIDERATIONS

The IgRT dose that keeps a patient relatively infection free varies between patients and can vary in the same patient over time, so the goal of IgRT should be to maximize clinical outcomes and not to achieve a specific IgG level.

Conversion from IVIG to SCIG

The bioavailability of SCIG is approximately 67% lower compared to IVIG. Thus the monthly dose of SCIG required to achieve an equivalent monthly area under the curve (AUC) is 1.37 times the IVIG dose for 16% products and 1.53 for 20% products. No significant differences in infection incidence or outcome have been shown between studies that do not utilize this dose adjustment compared to studies with this dose adjustment. In clinical practice, AUC dose adjustment is rarely used.

IVIG Dosing

For IVIG, many clinical immunologists use 400-600 mg/kg every 3-4 weeks as an acceptable starting point for maintenance therapy, while continuing to check annual trough levels. Infusion rates start slowly (e.g., 0.01 mL/kg/min) to minimize adverse reactions, and the rate can be increased as tolerated. Clinicians should monitor weight changes and adjust dosing accordingly. Also, IgG levels may need to be checked more frequently if the patient experiences breakthrough infections, develops new medical conditions (e.g., protein losing conditions), or is not responding to treatment as expected. Because pharmacokinetics also differs among patients, a specific IVIG dose can result in different trough levels in patients with similar body mass. There is insufficient evidence to routinely recommend higher loading IVIG doses in patients with low IgG levels at presentation; this practice has been associated with higher risk for adverse reactions at IgRT start. There is limited data on optimal dosing intervals for IVIG, and current practices vary widely.

SCIG Dosing

For traditional **SCIG**, a starting dose of 100-200 mg/kg of body weight per week is commonly used. For hyaluronidase fSCIG, a starting dose of 400-600 mg/kg via one or two sites every 3-4 weeks is common. When fSCIG is given every 3-4 weeks, the initial peak will still be lower than that of IVIG given at the same intervals, but the trough serum levels will be similar. Patients have more dosing frequency flexibility because there are products approved for daily, weekly, biweekly, or monthly dosing. Infusion rates generally range from 10-35 mL/hr per site by pump with volumes of 15-40 mL per site. The number of sites depends on the total volume for the target dose, and typical infusion sites include abdomen, outer thigh, upper arm, and buttocks. Manual rapid-push protocols that do not require infusion pumps have been reported to be safe and tolerable by patients in small nonrandomized trials. Steady-state serum IgG levels should be monitored periodically after approximately 3 months and can be used to assess patient adherence.

Facilitated SCIG

The dosing of hyaluronidase fSCIG is similar to IVIG. In the United States, fSCIG is approved for use in patients 2 years or older. Unlike traditional SCIG, a four-dose/7-week "ramp-up" period is recommended when starting fSCIG, even in patients who have used other IgRT products successfully. Once established on therapy, **fSCIG** infusion rates can be increased as tolerated by the patient from 50 mL/hr up to 300 mL/hr. The IgG is infused via peristaltic pump or large volume battery-operated pump, similar to IVIG, which has been programmed to account for the higher pressure of fSCIG compared with IV.

ADMINISTRATION DETAILS

Premedication

Many patients tolerate IVIG infusions without premedication. Pediatric pretreatment regimens include oral acetaminophen or ibuprofen, oral or IV or IM diphenhydramine, or alternatively a nonsedating antihistamine and/or a glucocorticoid such as oral prednisolone or IV hydrocortisone. Maintaining adequate hydration before infusion orally or via IV fluids with normal saline may be beneficial, especially for patients with preexisting renal disease or other risk factors (e.g., concomitant use of nephrotoxic agents). *Premedication is usually not required for SCIG.*

VACCINATION WHILE ON IgRT

Administration of IgRT may interfere with vaccination efficacy because the antibodies in the product might bind to the antigens in the vaccine and inhibit the immune response. The IgG in the IgRT product may hinder the viral replication that is needed to induce the desired immune response in live-virus vaccines such MMR or varicella (varicella-zoster virus [VZV]). Antibody-containing blood products from the United States do not interfere with the immune response to yellow fever vaccine and are not believed to interfere with the response to live typhoid, live-attenuated influenza, rotavirus, or zoster vaccines. The duration of inhibition ranges from 3-11 months and is related to the amount of antigen-specific antibody contained in the immune globulin or blood product. *For patients on IgRT, 8 months since last IVIG infusion is the suggested waiting time before administering live vaccines.* Although no specific recommended waiting time has been suggested for SCIG, many clinicians will also wait for 8 months since last infusion.

- If the antibody-containing product is administered *before* the vaccine is scheduled, the vaccine should be delayed for the suggested interval. If a dose of MMR or VZV vaccine is administered after an antibody-containing product but at an interval shorter than the suggested interval, the vaccine dose should be repeated at the suggested interval unless an antibody response to the vaccine is documented.
- If the antibody-containing product is necessary within 14 days *after* administration of MMR or VZV vaccine, the vaccine dose should be repeated after the suggested interval, unless an antibody response to the vaccine is documented.

Caution is advised when checking and interpreting IgG-based serologies while on IgRT. Stopping IgRT to assess vaccine efficacy in immunodeficient patients is generally not recommended. Neoantigen vaccines such as *Salmonella typhi Vi* can be used to assess a patient's ability to make specific antibodies while on IgRT, but this is not widely available.

Annual inactivated influenza vaccine is generally recommended for immunodeficient patients, including those on IgRT, presumably to stimulate T-cell immunity, although data are lacking that demonstrate induction of protective antibodies. The influenza vaccine may be given simultaneously or at any time interval before or after IgRT infusion.

Clinical trials using gene therapy with retroviral vectors have been conducted for several inborn errors of immunity including ADA-SCID, X-linked SCID, X-linked CGD, and WAS in which immunity was restored but with leukoproliferative complications due to insertion of the vector into oncogenes, in all except for ADA-SCID. The use of lentiviral vectors represented a breakthrough in the field with clinical recovery and immune reconstitution while minimizing vector-related complications. For further details on HSCT and gene therapy/editing, see Chapters 177 and 178.

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Section 6

Hematopoietic Stem Cell Transplantation

Chapter 177

Principles and Clinical Indications of Hematopoietic Stem Cell Transplantation

Rachel A. Phelan and David Margolis

Allogeneic (from a donor) or autologous (from the same individual) hematopoietic stem cells have been used to cure both malignant and nonmalignant disorders. **Autologous** transplantation is employed as a rescue strategy after delivering otherwise lethal doses of chemotherapy with or without radiotherapy 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 hemoglobinopathies, primary immunodeficiency diseases, various inherited metabolic diseases, and bone marrow failure. Allogeneic transplant is also used as treatment for hematologic malignancies, such as leukemia and myelodysplastic syndromes. Bone marrow had originally represented the only source of hematopoietic progenitor cells. Growth factor (granulocyte colony-stimulating factor)–mobilized peripheral blood hematopoietic stem cells and umbilical cord blood hematopoietic progenitors have also been regularly used in clinical practice to perform hematopoietic stem cell transplantation **(HSCT)**.

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

Protocols for allogeneic HSCT consist of two parts: the preparative regimen and transplantation itself. During the **preparative conditioning regimen**, chemotherapy, at times in conjunction with irradiation, is administered to eliminate 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 immunosuppressive and aim at inducing a state of reduced immune competence of the recipient 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 histocompatibility antigens displayed on recipient leukemia cells. However, because some of these histocompatibility antigens are also displayed on tissues, unwanted T-cell–mediated alloreactions may ensue. Specifically, donor alloreactive immune cells may attack recipient tissues, particularly the skin, gastrointestinal (GI) tract, and liver, causing acute or chronic **graft-versus-host disease (GVHD)**, a condition of varying severity that in some cases can be life-threatening or even fatal (see Chapter 179).

The success of allogeneic HSCT is undermined by diversity between donors and recipients in major and minor histocompatibility antigens. **HLA**, including HLA-A, HLA-B, and HLA-C major histocompatibility complex (MHC) class I molecules, present peptides to $CD8^+$ T cells, whereas 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, HLA-B, HLA-C, or HLA-DRB1 alleles in the donor-recipient pair are independent risk factors for both acute and chronic GVHD. There is also increasing evidence that HLA-DQ and HLA-DP may play a role, prompting some transplant centers to also explore matching at these alleles.

Minor histocompatibility antigens derive from differences between the HLA-matched recipient and donor in peptides that are presented by the same HLA allotype. These antigens result from polymorphisms of non-HLA proteins, differences in the level of expression of proteins, or 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, GVHD may occur even when the donor and recipient are HLA identical.

The preferred donor for any patient undergoing HSCT has traditionally been 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, <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 because affected siblings will not be considered donor candidates.

HSCT FROM AN HLA–IDENTICAL SIBLING DONOR

Allogeneic HSCT from an HLA-compatible sibling is the treatment of choice for children with hematologic malignancies and various congenital or acquired diseases (Table 177.1). Best results are achieved in patients with congenital or acquired nonmalignant 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 at *high risk* of leukemia recurrence (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 probabilities of 3-year overall survival (OS) for US patients <18 years of age with ALL transplanted in the first or second complete remission is 70–80% and 60–70%, respectively. Inferior results are obtained in patients receiving transplants in more advanced disease phases (50–60%; Fig. 177.1). The use of total body irradiation (TBI) during the preparative regimen offers an advantage in terms of better event-free survival (EFS) compared to a regimen consisting of cytotoxic drugs alone, but it can induce more long-term side effects. This has prompted more investigation into TBI-sparing alternatives. Less intensive GVHD prophylaxis is also associated with a better outcome. Bone marrow is generally the preferred source of stem cells to be employed for transplantation, although this differs among transplant centers.

Although the main benefit for allogeneic HSCT recipients with leukemia derives from the GVL effect displayed by immunocompetent cells, disease recurrence remains the main cause of treatment

Table 177.1 Indications for Allogeneic Hematopoietic Stem Cell Transplantation for Pediatric Diseases

MALIGNANCY
- ALL
  - First complete remission for patients at very high risk of relapse
  - T-cell immunophenotype and poor response to corticosteroid therapy
  - Not in remission at the end of the induction phase
  - Marked hypodiploidy (<43 chromosomes)
  - Minimal residual disease at the end of consolidation therapy
- High-risk infant ALL
  - Second complete remission
  - Third or later complete remission
- Acute myeloid leukemia in first 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
  - High-risk CNS tumors

ANEMIAS
- Severe acquired aplastic anemia
- Fanconi anemia
- Paroxysmal nocturnal hemoglobinemia
- Congenital dyskeratosis
- Diamond-Blackfan anemia
- Thalassemia major
- Sickle cell disease
- Shwachman-Diamond syndrome

IMMUNOLOGIC DISORDERS
- Variants of severe combined immunodeficiency
- Hyper-IgM syndrome
- Leukocyte adhesion deficiency
- Omenn syndrome
- Zap-70 kinase deficiency
- Cartilage-hair hypoplasia
- PNP deficiency
- CD40 ligand deficiency
- MHC class II deficiency
- Wiskott-Aldrich syndrome
- Chédiak-Higashi syndrome
- Kostmann syndrome (infantile malignant agranulocytosis)
- Chronic granulomatous disease
- Autoimmune lymphoproliferative syndrome
- X-linked lymphoproliferative disease (Duncan syndrome)
- IPEX syndrome
- Interleukin-10 receptor deficiency
- Hemophagocytic lymphohistiocytosis
- Interferon-γ receptor deficiency
- Griscelli disease
- Granule deficiency

OTHER DISORDERS
- Selected severe variants of platelet function disorders (e.g., Glanzmann thrombasthenia, congenital amegakaryocytic thrombocytopenia)
- Selected types of mucopolysaccharidosis (e.g., Hurler disease) or other liposomal/peroxisomal disorders (e.g., Krabbe disease, adrenoleukodystrophy)
- Infantile malignant osteopetrosis
- Life-threatening cytopenia unresponsive to conventional treatments

ALL, Acute lymphoblastic leukemia; CNS, central nervous system; IPEX, immune dysregulation, polyendocrinopathy, enteropathy, X-linked; MHC, major histocompatibility complex; PNP, purine nucleoside phosphorylase.

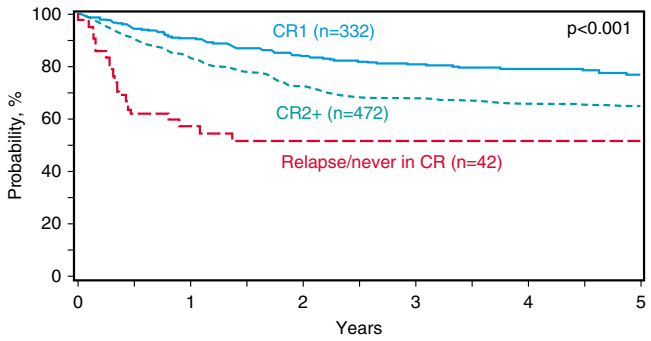

Fig. 177.1 Survival after matched related donor hematopoietic stem cell transplantation for acute lymphoblastic leukemia (ALL), age <18 years, 2008-2018. CR1, first complete remission; CR2+, second or greater remission. *(From Phelan R, Arora M, Chen M. Current use and outcome of hematopoietic stem cell transplantation: CIBMTR US summary slides 2020.* http://www.cibmtr.org.*)*

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. 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 also been used. 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 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 downregulation 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 (TCR)-CD3 complex. The addition to the *CAR* gene construct of co-stimulation signals and cytokines promoting T-cell expansion and 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.

ACUTE MYELOID LEUKEMIA

Allogeneic HSCT is largely employed as postremission treatment of pediatric patients with acute myeloid leukemia (AML) who meet certain high-risk disease criteria. This subset of children with AML in first complete remission who are given allogeneic HSCT as consolidation therapy have a better probability of EFS than those treated with either chemotherapy alone or autologous transplantation. Results obtained in patients given HSCT after either a TBI-containing or a chemotherapy-based preparative regimen are similar. Therefore, for AML, conditioning regimens generally omit the use of TBI because of associated long-term side effects. Children with acute promyelocytic leukemia in

molecular remission at the end of treatment with chemotherapy and all-*trans*-retinoic acid, or with AML and translocation t(8;21) inversion of chromosome 16 (inv16), translocation t(16;16), or normal cytogenetics and presence of *NPM1* or *CEPBα* pathogenic variants are no longer considered eligible for allogeneic HSCT in first complete remission in view of their improved 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 the end of induction therapy. Approximately 40–60% of pediatric patients with AML in the second complete remission can be rescued by HSCT. The probabilities of 3-year OS for US patients <18 years of age with AML transplanted in the first or second complete remission is 60–70%. Similar to ALL, inferior results are obtained in patients receiving transplants in more advanced disease phases (30–40%).

CHRONIC MYELOGENOUS LEUKEMIA

For many years, allogeneic HSCT has been considered 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 (related or unrelated), and time between diagnosis and HSCT are 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. Unlike other forms of pediatric leukemia, infusion of donor leukocytes can reinduce a state of complete remission in a large proportion of patients experiencing leukemia relapse.

Treatment with the specific BCR-ABL tyrosine protein kinase inhibitors (imatinib mesylate, dasatinib, nilotinib), targeting the enzymatic activity of the BCR-ABL fusion protein, has modified the natural history of the disease and thus the indications for transplantation. The indication for HSCT in this population is generally reserved for patients with a poor response to tyrosine kinase inhibitors or those who do not tolerate their side effects.

JUVENILE MYELOMONOCYTIC LEUKEMIA

Juvenile myelomonocytic leukemia (JMML) is a rare hematopoietic malignancy of early childhood, representing 2–3% of all pediatric leukemias. 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 (GM-CSF) 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 months from diagnosis. Rare patients with *CBL1* or *N-RAS* mutations can survive for years without an allograft.

HSCT can 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. Leukemia recurrence is the main cause of treatment failure in children with JMML after HSCT, with the relapse rate 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 posttransplantation outcome. Donor leukocyte infusion is not useful to rescue patients experiencing disease recurrence; a second allograft can induce sustained remission in approximately 30% of children with JMML relapsing after a first 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 65–70%. 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 is also considered in children with refractory cytopenia associated with monosomy 7, GATA 2 deficiency, complex karyotype, life-threatening infections, profound neutropenia, or transfusion dependency. For children with **refractory cytopenia**, the probability of EFS after HSCT may be as high as 80%, and disease recurrence is 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 very responsive to conventional chemoradiotherapy; some patients have refractory disease or 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-matched donor is available, allogeneic transplantation can 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 EFS rates of 50–60%. Patients with relapsed or refractory HD do well after autologous HSCT, with EFS of 50–60%. HD patients may also benefit from a GVL effect when given an allograft.

ACQUIRED APLASTIC ANEMIA

Because the probability of long-term survival for a matched-sibling bone marrow transplant (BMT) is reproducibly >80% for children and young adults, BMT is the treatment of choice for children and young adults with acquired severe aplastic anemia. Historically, the treatment of choice for children and young adults without an HLA-matched sibling has been intensive immunosuppression. Because the outcomes of matched unrelated donor transplant for children with acquired aplastic anemia have improved substantially over the years, the use of unrelated donor HSCT upfront *without* prior immunosuppressive therapy is being considered more frequently.

For patients who do not have a matched-sibling donor or well-matched unrelated donor, historically the transplant options were very disappointing. Fortunately, there is hope in using haploidentical transplant for this disease. The use of a reduced intensity conditioning regimen combined with GVHD prophylaxis, including posttransplant cyclophosphamide, have shown significant improvement over prior experiences with survival approaching transplants using well matched unrelated donors.

INHERITED BONE MARROW FAILURE SYNDROMES

Fanconi anemia (FA) and dyskeratosis congenita are genetic disorders associated with a high risk of developing pancytopenia. FA 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 FA, along with being at risk for 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, FA patients have an exquisite sensitivity to alkylating agents and radiation therapy. Thus they must be prepared for the allograft with reduced doses of cyclophosphamide and only judicious use of radiation. Many FA 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 posttransplantation head and neck cancers. Low-dose cyclophosphamide combined with fludarabine has been very well tolerated in patients with FA who have a matched-related donor. The addition of low-dose TBI and antithymocyte globulin (ATG) for those with an unrelated donor has shown similar success. Currently, the 5-year OS is >90% in patients with FA who receive HSCT before the transformation to hematologic malignancy. Because of their underlying disorder, however, patients with FA must be monitored closely in

the years after transplant to assess for late effects, including secondary malignancies and endocrinopathies.

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, with a 10-year survival of 20–30%, because 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 the 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 these patients the risk of dying from transplant-related complications depends primarily on patient age, iron overload, and concomitant hepatic viral infections. Adults, especially with chronic active hepatitis, have a poorer outcome than children. Among children, three classes of risk have been identified on the basis of three parameters: 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 has been 60%.

With improvements in supportive care and conditioning regimens, even patients with more advanced liver disease have had excellent outcomes (Fig. 177.2). The most effective pharmacologic combinations (e.g., including cyclosporine and methotrexate) should be employed to prevent GVHD. The outcome of patients transplanted from an unrelated donor has been reported similar to that of HLA-identical sibling recipients. The increased use of umbilical cord blood and haploidentical donors in this population is being explored to expand the number of patients eligible for HSCT. Also, advancements in gene therapy are being made in thalassemia in clinical trials, which may eventually change the approach to this disease.

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. 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; however, allogeneic HSCT is the only curative treatment for this disease currently. Although HSCT can cure homozygous hemoglobin S, hemoglobin Sβ0, or hemoglobin sickle cell 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 (CNS) infarcts. The main indications for performing HSCT in patients with sickle cell disease are history of strokes or abnormal transcranial Doppler ultrasound, recurrent acute chest syndrome, and/or recurrent vasoocclusive crises. The results of HSCT are best when performed in children with an HLA-identical sibling, with a probability of cure of 80–90%. However, the use of alternative donor transplants in this population, including matched unrelated donors and haploidentical donors, is being investigated through a number of clinical trials and may increase the number of patients eligible to undergo potentially curative HSCT. Reduced-intensity and reduced-toxicity regimens are also being explored to further decrease transplant-related morbidity and mortality, although graft failure remains an important issue in this patient population. Gene therapy for sickle cell disease is currently being investigated in clinical trials.

IMMUNODEFICIENCY DISORDERS

HSCT is the treatment of choice for children affected by severe combined immunodeficiency (SCID), as well as for other inherited immunodeficiencies, including Wiskott-Aldrich syndrome, leukocyte adhesion deficiency (LAD), and chronic granulomatous disease (see Table 177.1). 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 SCID, mainly those without residual natural killer activity or maternal T-cell engraftment, may be transplanted without receiving any preparative regimen; the donor lymphoid cells are usually the only elements that engraft. Sustained donor engraftment is more difficult to achieve in children with Omenn syndrome, hemophagocytic lymphohistiocytosis (HLD), or LAD. Life-threatening opportunistic fungal and viral infections occurring before the allograft adversely affect the patient's outcome after HSCT. Because of this, patients with the most severe immunodeficiencies must be transplanted as early as possible to prevent infectious complications.

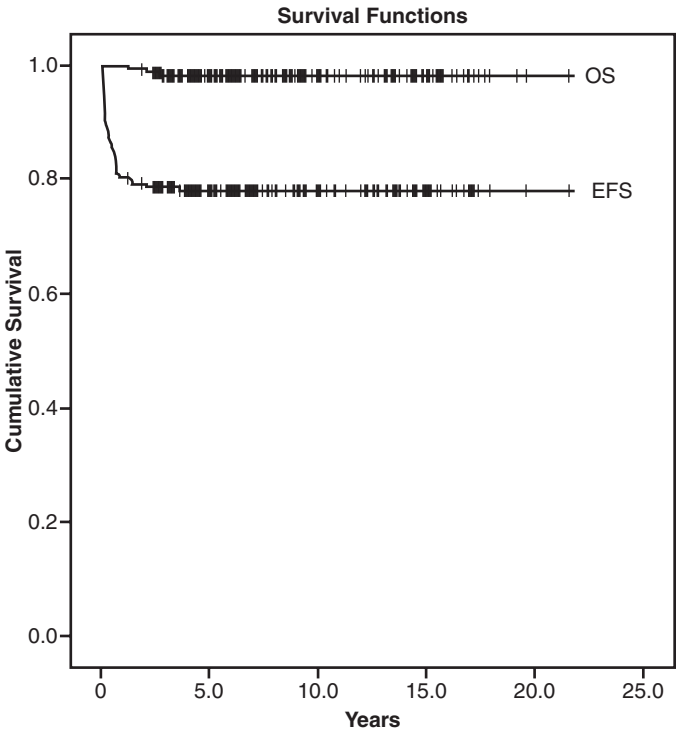

Fig. 177.2 Overall survival (OS) and event-free (graft failure) survival (EFS) after hematopoietic stem cell transplantation in children ≥1 year from transplant for β-thalassemia major. *(From Chaudhury S, Ayas M, Rosen C, et al. A Multicenter Retrospective Analysis Stressing the Importance of Long-Term Follow-Up after Hematopoietic Cell Transplantation for β-Thalassemia. Biol Blood Marrow Transplant. 2017;23(10):1695–1700.)*

INHERITED METABOLIC DISEASES

Inherited metabolic diseases are a broad group of diseases that result from the accumulation of substrate within tissues caused by dysfunction of the lysosome or peroxisome. The use of HSCT has been established for a variety of inherited metabolic diseases, including mucopolysaccharidosis type 1 (Hurler syndrome) and adrenoleukodystrophy (ALD). Although some of these diseases are treatable with exogenous enzyme replacement therapy, the clinical manifestations of disease tend to progress over time, especially disease in the CNS, where enzyme is unable to be reliably delivered. It is thought that undergoing HSCT results in the engraftment of microglial cells that are able to provide new enzyme to the areas where enzyme replacement therapy, if available, cannot have a substantial impact. Multiple studies have shown significantly improved outcomes for patients who are diagnosed with their underlying conditions relatively early and are able to undergo HSCT expeditiously, before significant damage from accumulated substrate that may be irreversible.

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Chapter 178

Hematopoietic Stem Cell Transplantation from Alternative Sources and Donors

Rachel A. Phelan and David Margolis

Two thirds of patients who need allogeneic hematopoietic stem cell transplantation (HSCT) do not have an available HLA-identical sibling. Alternative sources of hematopoietic stem cells (HSCs) are being increasingly used and include **matched unrelated donors, unrelated umbilical cord blood**, and **HLA-haploidentical relatives**. Each of these three 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-, and transplant-related factors; center experience; and physician preference.

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. Worldwide international registries include almost 27 million HLA-typed volunteer donors. HLA-A, HLA-B, HLA-C class I loci, and the DRB1 class II locus are the HLA loci that most influence outcome after HSCT from an unrelated volunteer. Other class II loci (namely, DQB1 and DP1 loci), as well as **killer cell immunoglobulin-like receptor (KIR)** haplotypes, are also increasingly considered when choosing a donor, although their impact on outcome is less well elucidated.

Although in the past serologic (low-resolution) typing was used for HLA-A and HLA-B loci, currently the unrelated donors are selected using high-resolution (allelic) molecular typing of loci HLA-A, HLA-B, HLA-C, and -DRB1. The chance of finding an HLA-matched unrelated donor depends on the frequency of the HLA phenotype, which is closely linked to the ethnic origin of the registry donors. Data from the National Marrow Donor Program (NMDP) donor registry and banked cord blood units estimated that essentially every patient in need of a transplant would be able to find a donor in a timely fashion, despite the recipient's race/ethnic group, donor availability, and cell dose. However, many of those patients may not have access to an "ideal" graft, defined as HLA matching of a minimum of 8/8 for bone marrow and 6/6 for cord blood.

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). 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 in outcome. Indeed, outcomes from a fully matched unrelated volunteer donor are now similar to those of HSCT from an HLA-identical sibling. The outcomes of haploidentical transplantation are similarly reaching that of matched unrelated donors as well as matched sibling donors.

Although a single locus disparity in patients with leukemia may be seen as beneficial by a reduction in the relapse rate caused by the graft-versus-leukemia (GVL) effect, in patients with nonmalignant disorders in whom GVL is not beneficial, 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, with variable efficacy. Studies are looking at selectively depleting donor α/β T cells, which are the T cells that drive GVHD, while preserving the T cells and natural killer (NK) cells, which may be responsible for GVL and protection from infection.

Although the majority of patients who have required a matched unrelated donor transplant have received a bone marrow or peripheral stem cell graft, 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 this subset of patients who urgently need a transplant, attention has focused on unrelated cord blood and HLA-haploidentical, mismatched family donors.

UMBILICAL CORD BLOOD TRANSPLANTS

Umbilical cord blood transplantation (UCBT) is a viable option for children who need allogeneic HSCT. 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, with the median time from start of search to transplantation of only 3-4 weeks. Compared with bone marrow transplantation (BMT), the advantages of UCBT are also represented by lower incidence of chronic GVHD 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 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 (risk of infection), and lack of adoptive transfer of pathogen-specific memory T cells. 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 demonstrated that an inverse correlation exists between the number of nucleated cord blood cells infused per kilogram recipient body weight and the risk of dying for transplantation-related causes. In particular, engraftment is a major concern when the nucleated cells are $<2.5 \times 10^7$/kg of recipient body weight. Because a cord blood unit usually contains between 1×10^9 and 1.8×10^9 cells, it is not surprising that UCBT 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. Efforts have focused on approaches capable of increasing the number of UCB cells to be transplanted. Selection of the richest cord blood units or infusion of 2 units in the same recipient (i.e., double UCBT) have been explored to improve the results of UCBT. The results of these studies have been mixed, with one large study demonstrating no survival advantage for children and adolescents that receive double UCBT. Preliminary studies of ex vivo expansion of a single umbilical cord sample with UM171, an HSC self-renewal agonist, have suggested improved engraftment, reduced infection, and low rates of severe acute GVHD.

The long-term results of UCB transplants are similar to those after transplantation from other sources of HSCs for pediatric hematologic malignancies. In patients with hematologic malignancies, recipients of UCBT may be transplanted from donors with greater HLA disparities, receive 1-log fewer nucleated cells, have delayed neutrophil and platelet recovery, and show reduced incidence of GVHD compared with children given BMT from unrelated donors. In one study, there were similar rates of acute GVHD, but significantly less chronic GVHD in patients who received UCBT. Nevertheless, both the relapse rate and the overall survival probability did not differ in unrelated UCBT or BMT pediatric recipients. Thus, 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 certain nonmalignant disorders to proceed to transplant quickly and prevent further progression of disease.

HAPLOIDENTICAL TRANSPLANTS

HSCT from an HLA-haploidentical **(haplo-HSCT)** donor offers an immediate source of HSCs to almost all 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 one haploidentical–3 loci mismatched family member who is promptly available as donor. The few patients who reject the haploidentical transplant also have the advantage of another immediately available donor within the family. Moreover, this may represent an approach that would be attractive in the global health setting, where more sophisticated donor registries and cell-processing techniques are less unavailable.

Efficient T-cell depletion of the graft has been demonstrated to prevent acute and chronic GVHD even when using haploidentical parental grafts. This can be done ex vivo or in vivo with the use of chemotherapeutic agents before and after cell infusion. The use of post-transplant cyclophosphamide is one such in vivo technique now being widely incorporated into haploidentical transplant regimens. The benefits of T-cell depletion were first demonstrated in transplantation of children with severe combined immunodeficiency (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.

The elimination of mature T cells from the graft, necessary for preventing GVHD in a context of great immune genetic disparity, results in recipients being unable to benefit from the adoptive transfer of donor memory T lymphocytes, through their peripheral expansion, are the main factor responsible for protection from infections in the first few months after transplantation. A state of profound immunodeficiency lasts for at least 4-6 months 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 (Epstein-Barr virus [EBV], human cytomegalovirus, *Aspergillus*, adenovirus) have been successfully tested in trials to protect the recipients in the early posttransplant period.

For many years the absence of the T-cell–mediated GVL effect has been considered as 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.

Selective approaches of graft manipulation in haploidentical and unrelated donor transplant 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, which are believed to be the mediators of GVHD. B lymphocytes are also depleted to prevent EBV-related lymphoproliferative disease. Through this approach the patient can benefit from the adoptive transfer of committed hematopoietic progenitors, mature NK cells and γ/δ^+ T cells, which can confer a protection against life-threatening infections as well as provide a GVL effect.

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, most importantly the state of remission at transplantation, with poorer outcomes in children with myeloid leukemias than in those with lymphoid leukemia. In haplotype-mismatched parent-to-child HSCT, patients with acute leukemia grafted from the mother had reduced relapse rates compared with recipients of paternal grafts, translating into better event-free survival.

DONOR VERSUS RECIPIENT NK CELL ALLOREACTIVITY

NK cells are the first lymphocytes derived from the donor to recover after allogeneic HCT. Donor versus recipient NK cell alloreactivity 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 **KIRs,** which are clonally distributed with each cell in the repertoire bearing at least one receptor that is specific for self-MHC class I molecules. Because NK cells co-express 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. The potential for donor versus recipient NK cell alloreactivity, which can be predicted by standard HLA typing, is increasingly being examined when selecting the donor of choice. The importance of KIR haplotype in transplants other than haploidentical transplantation in preventing GVHD as well as relapse has been shown to be increasingly beneficial.

Table 178.1 Indications for Autologous Hematopoietic Stem Cell Transplantation for Pediatric Diseases

- 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 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. Bone marrow was once the only source of stem cells employed in patients given an autograft. The 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 can be extremely effective in mobilizing hematopoietic progenitors in the periphery. Compared with bone marrow, the use of peripheral blood progenitors is associated with a faster hematopoietic recovery and a comparable outcome.

Autologous HSCT is employed primarily for selected children with relapsed lymphomas and select solid tumors (Table 178.1).

Patients with sensitive lymphomas and minimal 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 poor outcome, with survival rates of 10–20%.

Autologous HSCT in patients with high-risk neuroblastoma is associated with a better outcome than conventional chemotherapy. A Children's Oncology Group (COG) study demonstrated further survival advantage by performing two sequential, or tandem, transplants that use different chemotherapeutic agents. Because of these improved outcomes, tandem autologous transplants are now considered the standard recommended treatment. 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 179

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

Rachel A. Phelan and David Margolis

A 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 who shows 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 (MHC) antigens or minor histocompatibility antigens. GVHD is usually subdivided in two forms: **acute GVHD**, which occurs within 3 months 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 (e.g., systemic sclerosis, Sjögren syndrome).

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 3-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 (IL)-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 (TNF)-α, IL-2, and interferon (IFN)-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, kill recipient cells and further disrupt tissues.

Acute GVHD usually develops 2-8 weeks after transplantation. The primary manifestations depend on the sites of involvement and may include an erythematous maculopapular rash (Figs. 179.1 and 179.2), persistent anorexia, vomiting and/or diarrhea, and liver disease with increased serum levels of bilirubin, alanine transaminase (ALT), aspartate transaminase (AST), and alkaline phosphatase (ALP). Diagnosis may benefit from skin, liver, or gastrointestinal (GI) 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 GI tract. Grade I acute GVHD (skin rash alone) has a favorable prognosis and often requires no treatment, or topical treatment alone. 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 (Table 179.1).

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 (MMF), and other immunosuppressive agents. Infusion of cyclophosphamide on days +3 and +4 after transplantation has been used as a strategy to deplete alloreactive donor T lymphocytes that become activated after exposure to recipient antigens. This approach has been successful in patients undergoing haploidentical transplantation. Pretransplantation infusion of either antithymocyte globulin (ATG) or monoclonal antibodies (mAbs) 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 is the removal of T lymphocytes from the graft **(T-cell depletion)**. Other approaches are being used to selectively remove the α/β T cells, which are thought to be responsible for the development of GVHD, while preserving the γ/δ T cells in order to sustain graft-versus-leukemia (GVL) and the ability to fight infection. Any form of GVHD prophylaxis may impair posttransplantation immunologic reconstitution, increasing the risk of infection-related deaths. Traditional T-cell depletion of the graft is also associated with an increased risk of leukemia recurrence in patients transplanted from an HLA-identical sibling or an unrelated volunteer.

Despite prophylaxis, significant acute GVHD develops in approximately 30% of recipients of HSCT from matched siblings and in as many as 60% of HSCT recipients from unrelated donors. These numbers are estimates, and the actual risk of acute GVHD is highly variable depending on several factors. Risk for development of GVHD is increased by diagnosis of malignant disease, older donor and recipient age, and in patients given an unmanipulated allograft. The most important risk factor for acute GVHD is the presence 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

Fig. 179.1 Acute graft-versus-host disease. Involvement of the scalp, ears, palms, and soles is common. (*From Paller AS, Mancini AJ, eds.* Hurwitz Clinical Pediatric Dermatology. *5th ed. Philadelphia: Elsevier, 2016. p 577.*)

Fig. 179.2 Acute graft-versus-host disease. Almost confluent eruption of erythematous macules and papules in an immunodeficient neonate treated with extracorporeal membrane oxygenation (ECMO) and transfusion of nonirradiated blood. (*From Paller AS, Mancini AJ, eds.* Hurwitz Clinical Pediatric Dermatology. *5th ed. Philadelphia: Elsevier; 2016. p 577.*)

Table 179.1 Clinical Staging and Grading* of Acute Graft-Versus-Host Disease

STAGE	SKIN (ACTIVE ERYTHEMA ONLY)	LIVER (BILIRUBIN)	UPPER GI	LOWER GI (STOOL OUTPUT/DAY)
0	No active (erythematous) GVHD rash	<2 mg/dL	No or intermittent nausea, vomiting, or anorexia	*Adult:* <500 mL/day or <3 episodes/day *Child:* <10 mL/kg/day or <4 episodes/day
1	Maculopapular rash <25% BSA	2-3 mg/dL	Persistent nausea, vomiting or anorexia	*Adult:* 500-999 mL/day or 3-4 episodes/day *Child:* 10-19.9 mL/kg/day or 4-6 episodes/day
2	Maculopapular rash 25–50% BSA	3.1-6 mg/dL		*Adult:* 1,000-1,500 mL/day or 5-7 episodes/day *Child:* 20-30 mL/kg/day or 7-10 episodes/day
3	Maculopapular rash >50% BSA	6.1-15 mg/dL		*Adult:* >1,500 mL/day or >7 episodes/day *Child:* >30 mL/kg/day or >10 episodes/day
4	Generalized erythroderma (>50% BSA) plus bullous formation and desquamation >5% BSA	>15 mg/dL		Severe abdominal pain with or without ileus or grossly bloody stool (regardless of stool volume)

*Overall clinical grade (based on most severe target organ involvement):
Grade 0: no stage 1-4 of any organ.
Grade I: stage 1-2 skin without liver, upper GI, or lower GI involvement.
Grade II: stage 3 rash and/or stage 1 liver and/or stage 1 upper GI and/or stage 1 lower GI.
Grade III: stage 2-3 liver and/or stage 2-3 lower GI, with stage 0-3 skin and/or stage 0-1 upper GI.
Grade IV: stage 4 skin, liver, or lower GI involvement, with stage 0-1 upper GI.
GI, Gastrointestinal; GVH, graft-versus-host; BSA, body surface area.
From Harris AC, Young R, Devine S, et al. International, Multicenter Standardization of Acute Graft-versus-Host Disease Clinical Data Collection: A Report from the Mount Sinai Acute GVHD International Consortium. *Biol Blood Marrow Transplant.* 2016;22(1):4–10.

corticosteroids. The risk of transplantation-related mortality is much higher in patients who do not respond to corticosteroids than in those showing a complete response. Ruxolitinib, targeting the JAK signaling pathway, or other drugs targeting molecules expressed on T cells or cytokines released during the inflammatory cascade (including infliximab and etanercept targeting TNF, vedolizumab targeting $\alpha_4\beta_7$-integrin, and tocilizumab targeting IL-6), which underlies the pathophysiology of GVHD, have been used in patients with steroid-resistant acute GVHD. Extracorporeal photopheresis is another second-line treatment for GVHD and is most efficacious for skin GVHD. A patient's peripheral blood is exposed to a photosensitive compound and then exposed to ultraviolet light. The cells are then reinfused into the patient. It is thought that this process results in an increase in apoptosis of lymphocytes responsible for GVHD as well as the upregulation of anti-inflammatory cytokines and regulatory T cells. Promising results in children with steroid-resistant acute GVHD have also 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 months after transplantation and is the most frequent late complication of allogeneic HSCT with an incidence of approximately 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 use of unmanipulated peripheral blood as the stem cell source have 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 (TBI) 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 (Table 179.2). The predominant cytokines involved in the pathophysiology of chronic GVHD are usually

Table 179.2 Clinical Findings in Chronic Graft-Versus-Host Disease

ORGAN SYSTEM	SYMPTOMS AND SIGNS
Systemic	Immunodeficiency and recurrent infections
Skin	Lichen planus, scleroderma, hyperpigmentation or hypopigmentation, erythema, freckling, ichthyosis, ulcerations Flexion contractures Vaginal scars Onycholysis Nail loss
Hair	Alopecia; scarring or nonscarring
Mouth	Sicca syndrome, lichen planus, depapillation of tongue with variegations, scalloping of lateral margins, xerostomia, mucocele
Joints	Diffuse myositis/tendonitis, arthritis, contractures
Eyes	Decreased tearing, injected sclerae, scarring conjunctivitis, keratopathy
Liver	Increased enzymes, cholestasis, hepatomegaly, cirrhosis
Gastrointestinal	Failure to thrive, malabsorption, chronic diarrhea Esophageal strictures
Lung	Cough, dyspnea, wheezing Bronchiolitis obliterans, chronic rales, pneumothorax, fibrosis
Hematology	Thrombocytopenia, eosinophilia, Howell-Jolly bodies (splenic dysfunction)

type II cytokines such as IL-4, IL-5, and IL-13. IL-4 and IL-5 contribute to eosinophilia and B-cell hyperactivity with elevated IgM, 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, bronchiolitis obliterans, and bile duct degeneration with cholestasis.

Patients with chronic GVHD involving only the skin and liver have a favorable course (Figs. 179.3 and 179.4). 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 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. Chronic GVHD can be classified as mild, moderate, or severe depending on extent of involvement. Single-agent prednisone is the standard treatment, although other agents have been employed with variable success. Ruxolitinib, a Janus kinase inhibitor, has been a beneficial treatment for steroid-dependent or refractory chronic GVHD. In addition, ibrutinib, a Bruton tyrosine kinase inhibitor, has been approved by the FDA for the treatment of chronic GVHD. Treatment with imatinib mesylate, which inhibits the synthesis of collagen, has been effective in some 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 (TMP/SMX). Chronic GVHD resolves in most pediatric patients but may require 1-3 years of immunosuppressive therapy before the drugs can be withdrawn without the disease recurring. Chronic GVHD promotes the development of secondary neoplasms, in particular in patients with Fanconi anemia, and has a significant impact on quality of life.

Fig. 179.3 Chronic graft-versus-host disease (GVHD), lichenoid. After bone marrow transplantation, this patient had acute GVHD and subsequently developed cutaneous scaling papules and plaques typical of lichen planus. (*From Paller AS, Mancini AJ, eds.* Hurwitz Clinical Pediatric Dermatology. *5th ed. Philadelphia: Elsevier; 2016. p 577.*)

Fig. 179.4 Chronic graft-versus-host disease. Note the extensive alopecia of the scalp with dyschromia and numerous sclerodermatous plaques of the scalp and back. (*From Paller AS, Mancini AJ, eds.* Hurwitz Clinical Pediatric Dermatology. *5th ed. Philadelphia: Elsevier; 2016. p 579.*)

GRAFT FAILURE

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 0.5×10^9/L after transplantation. **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 major 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 TMP/SMX 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

Table 179.3 Severity Grading Thresholds of Sinusoidal Obstructive Syndrome Among Children, Adolescents, and Young Adults

	MILD	MODERATE	SEVERE	VERY SEVERE
ALT, AST, GLDH (mg/dL)	<2× normal	2-5× normal	2-5× normal	>5× normal
Bilirubin (mg/dL)	<2	<2	≥2	Bilirubin doubles in 48 hr
Coagulopathy (not responsive to vitamin K administration; INR)	<1.5	1.5-1.9	>2	Need for replacement of coagulation factors
Ascites	Mild (minimal fluid by liver, spleen or pelvis)	Moderate (<1 cm fluid)	Severe (fluid in all 3 regions with >1 cm fluid in at least 2 regions)	Requires paracentesis
Weight gain (from baseline)	2.5%	5–10% despite diuretic use	>10%	Persistent rise
Renal function score	KDIGO 1: serum creatinine 1.5-1.9× baseline or ≥0.3 mg/dL (≥26.5 mmol/L) increase or urine output <0.5 mL/kg/hr for 6-12 hr	KDIGO 2: serum creatinine 2.0-2.9× baseline or urine output <0.5 mL/kg/hr for ≥12 hr	KDIGO 3: serum creatinine 3.0× baseline or increase in serum creatinine ≥4.0-mg/dL (≥353.6 mmol/L) or initiation of renal replacement therapy or decrease in eGFR to <35 mL/min per 1.73 m^2 (patients <18 years) or urine output <0.3 mL/kg/hr for ≥24 hr or anuria for ≥12 hr (patients <18 years)	Persistent need for renal replacement therapy
Encephalopathy	CAPD <9	CAPD <9	CAPD ≥9	CAPD ≥9
Persistent RT	<3 days	3-7 days	—	>7 days
Pulmonary function	<2 L	<2 L	NIV/IMV	IMV

ALT, Alanine aminotransferase; AST, aspartate aminotransferase; GLDH, glutamate dehydrogenase; INR, international normalized ratio; KDIGO, Kidney Disease: Improving Global Outcomes score; eGFR, estimated glomerular infiltration rate; CAPD, Cornell Assessment of Pediatric Delirium; RT, refractory thrombocytopenia; NIV, noninvasive ventilation; IMV, invasive mechanical ventilation.

From Mahadeo KM, Bajwa R, Abdel-Azim H, et al. Diagnosis, grading, and treatment recommendations for children, adolescents, and young adults with sinusoidal obstructive syndrome: An international expert position statement. *Lancet Haematol*. 2020;7(1):e61–e72.

by a highly immunosuppressive regimen, is frequently employed to rescue patients experiencing graft failure. High-intensity regimens are generally tolerated poorly if administered within 100 days from a first transplant because of cumulative toxicities, but this risk must be balanced with the risk of infection from prolonged neutropenia and lymphocytopenia.

VENOOCCLUSIVE DISEASE

Hepatic venoocclusive disease (VOD), also known as sinusoidal obstruction syndrome, presents with hepatomegaly, right upper quadrant tenderness, jaundice, coagulopathy, thrombocytopenia, and weight gain from fluid retention and ascites (Table 179.3). It results from endothelial damage within the liver, which can then progress to multiorgan dysfunction. 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 VOD has a high mortality rate (>80%) without treatment.

Prophylaxis has traditionally used ursodeoxycholic acid and occasionally heparin; only **defibrotide** has demonstrated efficacy in treating VOD. A phase 3 study demonstrated improvement in survival and response rate to VOD in patients treated with defibrotide. Defibrotide is a combination of porcine oligodeoxyribonucleotides that reduces procoagulant activity and enhances fibrinolytic properties of endothelial cells. Defibrotide is FDA approved for the treatment of VOD in adult and pediatric patients with renal or pulmonary dysfunction after HSCT. Defibrotide is often used as prophylaxis in Europe, with data showing efficacy, but this use is not yet approved in the United States.

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Chapter 180

Infectious Complications of Hematopoietic Stem Cell Transplantation

Anna R. Huppler

Hematopoietic stem cell transplantation (HSCT) recipients experience a transient but profound state of immune deficiency. The risk of infection depends on the stage after transplantation (pre- vs postengraftment), ongoing immunosuppression, disruption in barrier functions (indwelling catheters, graft-versus-host disease [GVHD], mucositis, and preexisting infections (Fig. 180.1). Management approaches may include the use of prophylactic antimicrobials, preemptive antimicrobials for infection prior to symptomatic disease, or antimicrobial treatment of documented or suspected infection.

Immediately after transplantation, the absence or paucity of neutrophils **(neutropenia)** renders patients susceptible to bacterial and fungal infections. Consequently, consideration is given to the use of antipseudomonal and antifungal prophylaxis during the conditioning regimen. Evidence is moderate quality against systemic antibacterial prophylaxis and for systemic antifungal prophylaxis, which is reflected in published society guidelines. Even with the use of prophylactic measures, the majority of patients will develop fever and signs of infection in the early posttransplantation period. The common pathogens include enteric gram-negative bacteria and fungi. An indwelling central venous line, routinely employed in all children given HSCT, is a significant risk factor for infection. Staphylococcal species and *Candida* species are the most frequent pathogens in catheter-related infections (see Chapter 224). Multidrug-resistant strains of *Pseudomonas aeruginosa* and *Klebsiella pneumoniae* can cause infection, with prevalence highly variable among centers. Severe lower respiratory tract disease caused by seasonal respiratory viruses, such as influenza, respiratory syncytial virus (RSV), parainfluenza virus, and human metapneumovirus, can occur during the pre- or postengraftment phase. Emerging infections, such as SARS-CoV-2, can also cause severe or persistent infection in immunocompromised individuals. Published guidelines from the International Pediatric Fever and Neutropenia Guideline Panel address the management of fever and neutropenia after HSCT (Table 180.1).

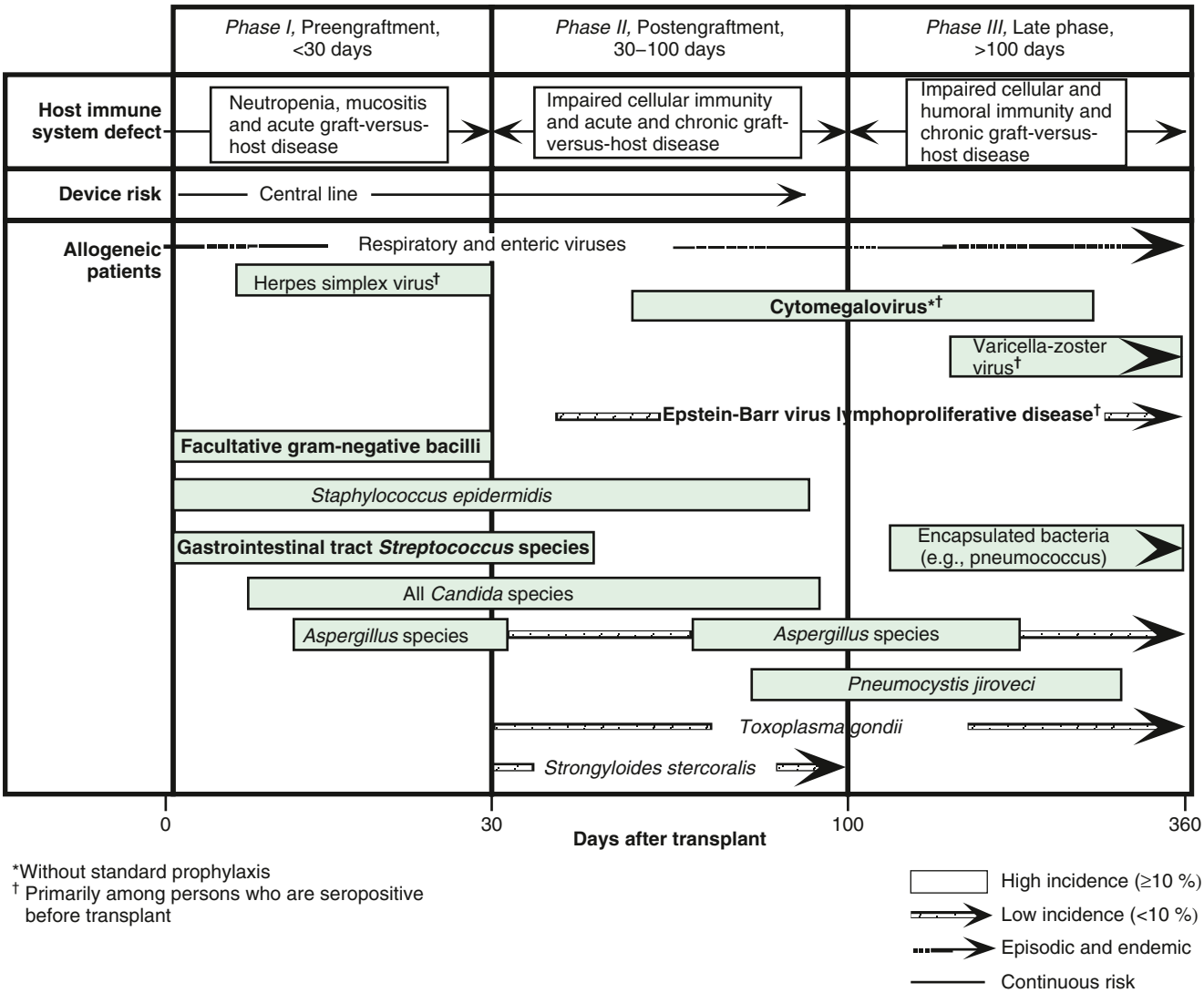

Fig. 180.1 Phases of opportunistic infections among allogeneic HSCT recipients. (*From Centers for Disease Control and Prevention; Infectious Disease Society of America; American Society of Blood and Marrow Transplantation. Guidelines for preventing opportunistic infections among hematopoietic stem cell transplant recipients [published correction appears in MMWR Recomm Rep. 2004 May 14;53(19):396]. MMWR Recomm Rep. 2000;49(RR-10):1–CE7.*)

Table 180.1 Overall Summary of Recommendations for Management of Fever and Neutropenia

INITIAL MANAGEMENT

Risk Stratification

A1. Adopt a validated risk stratification strategy and incorporate it into routine clinical management (strong recommendation, low-quality evidence).

Evaluation

A2. Obtain blood cultures at the onset of FN from all lumens of central venous catheters (strong recommendation, low-quality evidence).

A3. Consider obtaining peripheral blood cultures concurrent with central venous catheter cultures (weak recommendation, moderate-quality evidence).

A4. Consider urinalysis and urine culture in patients in whom a clean-catch, midstream specimen is readily available (weak recommendation, low-quality evidence).

A5. Obtain chest radiography only in patients with respiratory signs or symptoms (strong recommendation, moderate-quality evidence).

Treatment

A6. In high-risk FN:

A6a. Use monotherapy with an antipseudomonal β-lactam, a fourth-generation cephalosporin, or a carbapenem as empirical therapy in pediatric high-risk FN (strong recommendation, high-quality evidence).

A6b. Reserve addition of a second gram-negative agent or a glycopeptide for patients who are clinically unstable, when a resistant infection is suspected, or for centers with a high rate of resistant pathogens (strong recommendation, moderate-quality evidence).

A7. In low-risk FN:

A7a. Consider initial or step-down outpatient management if the infrastructure is in place to ensure careful monitoring and follow-up (weak recommendation, moderate-quality evidence).

A7b. Consider oral antibiotic administration if the child is able to tolerate this route of administration reliably (weak recommendation, moderate-quality evidence).

ONGOING MANAGEMENT

Modification of Treatment

B1. In patients who are responding to initial empirical antibiotic therapy, discontinue double coverage for gram-negative infection or empirical glycopeptide (if initiated) after 24 to 72 hours if there is no specific microbiologic indication to continue combination therapy (strong recommendation, moderate-quality evidence).

B2. Do not modify the initial empirical antibacterial regimen based solely on persistent fever in children who are clinically stable (strong recommendation, low-quality evidence).

B3. In children with persistent fever who become clinically unstable, escalate the initial empirical antibacterial regimen to include coverage for resistant gram-negative, gram-positive, and anaerobic bacteria (strong recommendation, very low-quality evidence).

Cessation of Treatment

B4. In all patients, discontinue empirical antibiotics in patients who have negative blood cultures at 48 hours, who have been afebrile for at least 24 hours, and who have evidence of marrow recovery (strong recommendation, low-quality evidence).

B5. In patients with low-risk FN, consider discontinuation of empirical antibiotics at 72 hours in patients who have negative blood cultures and who have been afebrile for at least 24 hours, irrespective of marrow recovery status, as long as careful follow-up is ensured (weak recommendation, moderate-quality evidence).

EMPIRICAL ANTIFUNGAL THERAPY

Risk Stratification

C1. Patients at high risk of IFD are those with AML, high-risk ALL, or relapsed acute leukemia, and children undergoing allogeneic HSCT. Children with prolonged neutropenia and children receiving high-dose corticosteroids are also at high risk of IFD. All others should be categorized as IFD low risk (strong recommendation, low-quality evidence).

Evaluation

C2. In terms of biomarkers to guide empirical antifungal management for prolonged (≥96 hours) FN in IFD high-risk patients:

C2a. Consider not using serum GM (weak recommendation, moderate-quality evidence).

C2b. Do not use β-d-glucan (strong recommendation, low-quality evidence).

C2c. Do not use fungal PCR testing in blood (strong recommendation, moderate-quality evidence).

C3. In terms of imaging for the evaluation of prolonged (≥96 hours) FN in IFD high-risk patients:

C3a. Perform CT of the lungs (strong recommendation, low-quality evidence).

C3b. Consider imaging of abdomen in patients without localizing signs or symptoms (weak recommendation, low-quality evidence).

C3c. Consider not routinely performing CT of sinuses in patients without localizing signs or symptoms (weak recommendation, low-quality evidence).

Table 180.1 Overall Summary of Recommendations for Management of Fever and Neutropenia—cont'd

Treatment

C4. In IFD high-risk patients with prolonged (≥96 hours) FN unresponsive to broad-spectrum antibacterial agents, initiate caspofungin or liposomal amphotericin B for empirical antifungal therapy (strong recommendation, high-quality evidence).

C5. In IFD low-risk patients with prolonged (≥96 hours) FN, consider withholding empirical antifungal therapy (weak recommendation, low-quality evidence).

ALL, Acute lymphoblastic leukemia; AML, acute myeloid leukemia; FN, fever and neutropenia; GM, galactomannan; HSCT, hematopoietic stem cell transplantation; IFD, invasive fungal disease; PCR, polymerase chain reaction.

Modified from Lehrnbecher T, Robinson P, Fisher B, et al. Guideline for the management of fever and neutropenia in children with cancer and hematopoietic stem-cell transplantation recipients: 2017 Update. *J Clin Oncol.* 2017;35(18):2082–2094. Table 1, p. 2084–2086.

HSCT recipients remain at increased risk of developing severe infections even after the neutrophil count has normalized because of prolonged depression in T-cell number and function. The manifestations of GVHD, as well as the associated immunosuppressive therapy, are additional risk factors for fungal and viral opportunistic infections. After umbilical cord blood transplant (UCBT), infections are the consequence of both slow neutrophil engraftment and donor T-cell naïveté. In haploidentical transplantation, T-cell depletion results in an increased risk of infection in the first 4-6 months. Recipients of this type of transplantation, as well as those receiving UCBT, do not have the benefit of adoptive transfer of donor-derived, antigen-experienced T cells. For HSCT recipients after engraftment, **invasive fungal disease (IFD),** herpesviruses, and adenovirus infections represent life-threatening complications that significantly affect outcomes. Additional pathogens to consider include nontuberculous mycobacteria, BK virus, *Clostridium difficile,* and norovirus.

IFD remains a significant cause of infectious morbidity and mortality in allogeneic HSCT recipients. Empirical treatment for IFD is considered for HSCT patients with persistent fever despite 96 hours of broad-spectrum antibiotic treatment. The most common organisms are *Aspergillus* and *Candida* species. Infections also occur with non-*Aspergillus* molds, including *Mucor* and *Rhizopus* species (among other agents of mucormycosis), *Fusarium,* and *Scedosporium* species. *Pneumocystis jiroveci* is a unique, noncultivatable cause of fungal pneumonia in immunocompromised patients. Despite prompt and aggressive administration of potent antifungal agents, proven cases of IFD carry case fatality rates of 20–70%. IFD can present early after transplant, although there is a shift toward presentation of infection in the postengraftment period in the presence of GVHD. The risk of developing IFD is mainly influenced by history of previous fungal infection, duration of neutropenia, use of corticosteroid therapy, mucosal tissue damage (GVHD, posttransplant cytomegalovirus [CMV] infection, viral respiratory tract infections), and for candidiasis, presence of central venous catheters.

Disseminated candidiasis presents frequently as a central venous catheter–associated infection. However, up to 50% of patients with disseminated candidiasis do not present with positive blood cultures. Patients with and without candidemia can have infection of normally sterile organs, including liver, spleen, kidney, brain, heart, and eye. Mortality rates in pediatric series range from 10–25%. Echinocandins (micafungin, caspofungin) are the initial drugs of choice for candidiasis in immunocompromised patients with pediatric data supporting reduced 14-day failure rates compared to initial triazole or amphotericin B therapy.

Pulmonary disease is the common presentation of invasive **aspergillosis**. The upper airway mucosa (nose and sinuses) can also be a site of initial infection. Infection progresses from lung or sinus sites by direct extension across tissue or angioinvasion resulting in hematogenous dissemination to brain and other organs. The earliest imaging finding is classically one or more small pulmonary nodules (Figs. 180.2 and 180.3). As a nodule enlarges, the dense central core of infarcted tissue may become surrounded by edema or hemorrhage, forming a hazy rim known as the *halo sign.* When bone marrow function recovers, the infarcted central core may cavitate, creating the *crescent sign.* Unfortunately, radiographic signs, including the halo sign, crescent sign, and cavitation, have low sensitivity in pediatric patients. Clinical criteria are used to diagnose proven or probable IFD, requiring direct or indirect microbiologic data. Direct, culture-based diagnosis requires invasive

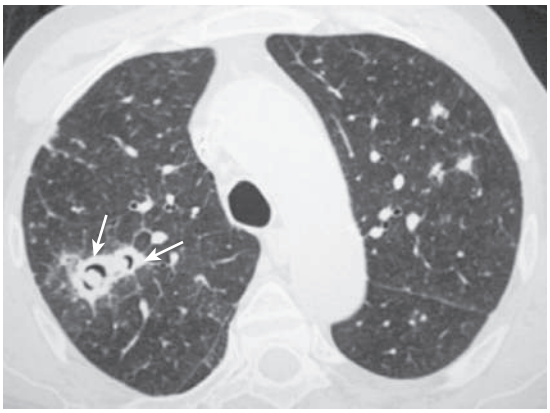

Fig. 180.3 Angioinvasive aspergillosis. CT section at the level of the lower trachea shows a consolidation with an eccentric cavitation and air crescent sign *(arrows).* This finding in this neutropenic patient is highly diagnostic of angioinvasive aspergillosis. (*From Franquet T. Nonneoplastic parenchymal lung disease. In Haaga JR, Boll DT, eds.* CT and MRI of the Whole Body, *6th ed. Philadelphia: Elsevier; 2017. Fig 36.14.*)

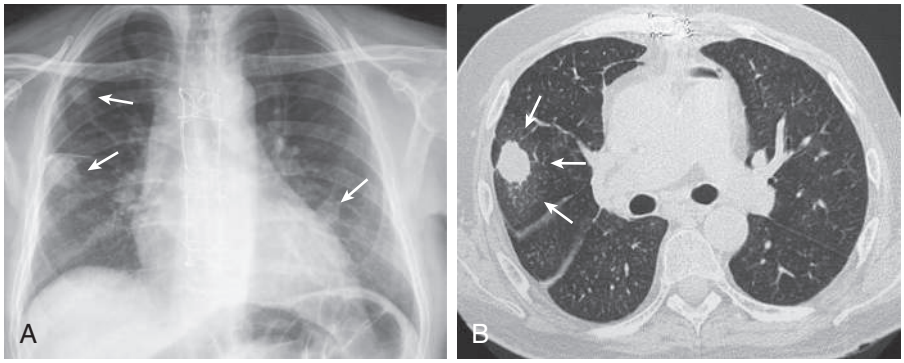

Fig. 180.2 Angioinvasive aspergillosis. **A,** Posteroanterior radiograph shows multiple nodules in the lungs *(arrows).* **B,** CT section at the level of the intermediary bronchus shows a nodule surrounded by a halo of ground-glass attenuation *(arrows).* (*From Franquet T. Nonneoplastic parenchymal lung disease. In Haaga JR, Boll DT, eds.* CT and MRI of the Whole Body, *6th ed. Philadelphia: Elsevier; 2017. Fig 36.13.*)

procedures, such as sinus endoscopy or lung biopsy. Indirect measures, including *fungal biomarkers,* are used in HSCT patients to screen for or diagnose probable aspergillosis. Galactomannan from serum or bronchoalveolar lavage fluid is an adjunct to diagnostic strategies because of a high negative predictive value for aspergillosis; however, lack of detection of mucormycosis limits its utility as a single diagnostic test. Other limitations include poor positive predictive values due to false-positive test results and lack of validation in patients without neutropenia. Another widely available biomarker, (1→3)-β-D-glucan, is insufficiently studied for routine use in pediatric patients.

Fungal infection prevention includes isolation of the patient in a laminar airflow or positive pressure room. Universal prophylaxis to prevent *Pneumocystis* pneumonia is advocated until the return of T-cell function in HSCT patients; the primary agent for prophylaxis is trimethoprim/sulfamethoxazole. Alternative agents are pentamidine, dapsone, and atovaquone. For prevention and treatment of other IFDs, liposomal amphotericin B, azole compounds (itraconazole, voriconazole, posaconazole, isavuconazole), and echinocandins (caspofungin, micafungin) are used. Voriconazole represents the treatment of choice for adult patients with invasive aspergillosis, but achieving adequate trough levels can be challenging in young children. The agents of mucormycosis are resistant to most azole and echinocandin medications, which makes liposomal amphotericin B the initial drug of choice. IFD often does not respond satisfactorily to antifungal agents alone, and infection may persist until adequate source control is achieved with surgical debridement and immune function recovers.

Herpesviruses, including CMV, Epstein-Barr virus (EBV), human herpesvirus 6 (HHV-6), herpes simplex virus (HSV-1 and HSV-2), and varicella-zoster virus (VZV) are pathogens that can cause significant disease after HSCT. Because herpesviruses can establish latency in the human host, symptomatic infection can occur from viral reactivation as well as acquisition from the donor or de novo infection. Baseline susceptibility to disease and viremia before symptom development can be established with laboratory monitoring (pretransplant donor-recipient serology, posttransplant viral load monitoring) and can inform decisions on prophylactic and preemptive antiviral treatment.

CMV infection remains the most common and potentially severe viral complication in patients receiving allogeneic HSCT. Risk factors for CMV viremia include recipient seropositivity, UCBT, and acute GVHD. The period of maximal risk for CMV disease is 1-4 months after transplantation. Late presentation of CMV disease is associated with GVHD. 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 has been reported to occur in up to 15–20% of bone marrow transplant recipients, with a case fatality rate of 85% in the absence of early treatment. Tachypnea, hypoxia, and nonproductive cough signal respiratory involvement. Chest radiography often reveals bilateral interstitial or reticulonodular infiltrates, which begin in the periphery of the lower lobes and spread centrally and superiorly. Gastrointestinal CMV involvement may lead to ulcers of the esophagus, stomach, small intestine, and colon with complications of bleeding or perforation. Fatal CMV infections are often associated with persistent viremia and multiorgan involvement.

CMV disease has largely been prevented through prophylaxis or preemptive approaches. Prophylaxis is based on administration of antiviral drugs to at-risk transplanted patients for a median duration of 3 months after transplantation. The major drawbacks of this approach are drug toxicity, late CMV disease after withdrawal of prophylaxis, potential unnecessary treatment of patients who would not have reactivated CMV infection, and low cost-effectiveness. Preemptive therapy aims at treating only patients who experience CMV reactivation and thus are at risk of developing overt disease; it starts on detection of CMV in blood but before symptom development. The major drawback of this strategy is the need of serial monitoring of CMV by polymerase chain reaction (PCR) in blood. First-line therapy is usually ganciclovir, with foscarnet as an alternative for resistant strains or ganciclovir intolerance.

EBV-related posttransplant lymphoproliferative disease (PTLD) is a major complication in HSCT and solid-organ transplantation. In patients receiving HSCT, selective procedures of T-cell depletion–sparing B lymphocytes and use of HLA–partially matched family and unrelated donors are risk factors for the development of PTLD. PTLD usually presents in the first 4-6 months after transplantation as high-grade, diffuse, large-cell B-cell lymphomas that are oligoclonal or monoclonal. High EBV viral loads in blood by PCR predict development of PTLD. Standard treatment of PTLD includes the reduction of immunosuppression, monoclonal antibodies directed against CD20 on B cells (rituximab), or cytotoxic chemotherapy. Prophylactic strategies with rituximab for EBV-positive recipients during conditioning for HSCT have also been employed. Histologic diagnosis of PTLD is required to assess for the emergence of neoplasms in which cells are $CD19^+$ but $CD20^-$, thus eliminating susceptibility to rituximab.

Disseminated adenovirus infection is a life-threatening complication of HSCT recipients. Clinical manifestations include fever, hepatitis, enteritis, meningoencephalitis, and pneumonia. Young children or recipients of donor cells naïve to adenovirus (T-cell–depleted grafts or UCBT) are at particular risk of developing this complication. Diagnosis is based on the demonstration of high viral loads by PCR in blood or recovery of virus in tissue biopsies. Pharmacologic treatment of adenovirus infections is with the antiviral **cidofovir**, which has significant renal toxicity and limited potency at controlling viral replication. The enterally available prodrug brincidofovir showed initial promise in allogeneic pediatric HSCT recipients with refractory adenovirus infection but is not available clinically for this indication. Recovery of immune system function is associated with improved survival with disseminated adenovirus infection.

In immunocompromised hosts, severe viral infections, including PTLD and adenovirus infection, originate from a deficiency of virus-specific **cytotoxic T lymphocytes** (CTLs). This finding provides the rationale for developing strategies of adoptive cell therapy to restore virus-specific immune competence. Multiple protocols are in clinical trials and available at some centers for the rapid generation of specific CTL lines of donor or third-party origin.

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Chapter 181

Late Effects of Hematopoietic Stem Cell Transplantation

Rachel A. Phelan and David Margolis

Pediatric hematopoietic stem cell transplantation (HSCT) is considered standard-of-care treatment for several malignant and nonmalignant conditions. Treatment generally involves exposure to chemotherapy and occasionally radiation to encourage engraftment of donor stem cells and prevent donor and recipient rejection. The period immediately after transplant is associated with the risk for a number of serious acute complications, including profound immunosuppression and subsequent risk for infection, graft-versus-host disease (GVHD), and organ toxicities (see Chapters 179 and 180). Fortunately, significant progress has been made in supportive care strategies to reduce the risk of acute complications and treat them more effectively if they do arise. This has resulted in a growing number of pediatric patients who are now long-term survivors following HSCT. The estimated total number of HSCT survivors in 2009 was 108,900, and this is expected to increase 5 times by 2030 to over 500,000. Of these survivors, approximately 14% (64,000) in 2030 will have received a transplant in childhood (<18 years of age).

Exposure to chemotherapy, radiation, or a combination of both, places patients at similar long-term risks as the pediatric cancer population; the high doses and types of chemotherapy and radiation often amplify the risk for issues such as ovarian failure/infertility and neurocognitive difficulties. Total body irradiation (TBI) has been shown to increase dramatically the risk for late complications after transplant. In addition, late effects may be additive if the patient received therapy before HSCT for their underlying malignancy. Moreover, the indication for transplant in pediatric patients is not always related to malignancy, but rather an underlying immunodeficiency, bone marrow failure syndrome, or metabolic disorder. These patients are potentially at risk for late effects related to this underlying disease and require different types of monitoring.

Essentially, every organ system can be impacted by the long-term effects of therapy, and each must be considered when undergoing late effects surveillance (Table 181.1). As a result of growing evidence of the importance of lifelong care for HSCT survivors, multiple groups have published consensus guidelines to help in caring for this patient population. As the field of survivorship continues to expand, *we recommend the following reference for real-time evidence-based recommendations from the* ***Children's Oncology Group*** (see http://survivorshipguidelines.org).

ENDOCRINE EFFECTS

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 TBI as part of the preparative regimen. Chronic GVHD and its treatment with corticosteroids may also contribute to growth impairment.

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.

The use of TBI during the preparative regimen involves the thyroid gland in the irradiation field and may result in **hypothyroidism**. Younger children 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. 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 as well as high doses of alkylating agents 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 sexual maturity rating (Tanner) scores and endocrine function. Supplementation of gonadal hormones is useful for primary gonadal failure and is administered with GH to promote pubertal growth. **Infertility** during adulthood remains a significant risk for these patients, especially those undergoing traditional myeloablative conditioning for HSCT. The use of reduced-intensity regimens may result in sparing fertility in a large proportion of patients, although conditioning regimens vary and studies are limited.

Bone health of HSCT survivors can also be impacted by hormonal changes as well as lifestyle practices, such as inadequate exercise and/or dietary intake of vitamin D. Prior exposures, including corticosteroid use, can result in changes to bone density as well as predispose to the development of avascular necrosis. Dual-energy x-ray absorptiometry (DXA) scans are routinely incorporated into the care of those patients at risk for low bone mineral density.

CARDIOVASCULAR EFFECTS

Survivors of childhood HSCT are at risk for the future development of cardiovascular complications. This population can be prone to developing **metabolic syndrome** (dyslipidemia, hypertension, diabetes mellitus, obesity), especially those with a history of TBI exposure and subsequent hormonal derangements. Prior exposures such as anthracycline chemotherapy and chest radiation further increase the risk for **cardiomyopathy** as well as **atherosclerosis**. As a result, routine anthropometric, imaging, and laboratory screening should be performed in survivors of childhood HSCT to assess and monitor their cardiovascular health.

SECONDARY MALIGNANCY

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. The development of myelodysplastic syndrome as well as secondary leukemias must be considered in survivors of HSCT. Several other 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. Routine physical exams, including yearly skin in exams, in those that received TBI are important in the care of these patients.

GRAFT-VERSUS-HOST DISEASE

In the posttransplant period, multiple studies have shown that quality of life is severely impacted by the presence of GVHD, which is an issue that is also unique to HSCT (see Chapter 179).

OTHER EFFECTS

HSCT patients can also experience complications related to their pulmonary function, renal function, dental health, and gastrointestinal system, often related to prior exposures as well as their conditioning regimen. It is also important to note that long-term survivors must be monitored for psychologic issues because of their prior and current underlying health conditions. They may need extra assistance

Table 181.1 Summary of Late Effects After Hematopoietic Stem Cell Transplantation in Childhood

EXPOSURE	LATE EFFECT*
HSCT experience in general	Dental abnormalities Renal toxicity Hepatic toxicity Low BMD Avascular necrosis Increased risk of second cancers Adverse psychosocial/quality-of-life effects Mental health disorders, risk behaviors Psychosocial disability caused by pain or fatigue
TRANSPLANTATION CONDITIONING	
Alkylating agent	Cataract (busulfan) Pulmonary fibrosis (busulfan) Renal toxicity Urinary tract toxicity Gonadal dysfunction Therapy-related AML/MDS Bladder cancer
Epipodophyllotoxin[†] DNA intersecting and cross linking agents (i.e., platinum, heavy metal)	Therapy-related AML/MDS Ototoxicity Renal toxicity Gonadal toxicity
TBI[‡]	Neurocognitive deficits Leukoencephalopathy Cataract Dental abnormalities GH deficiency Hypothyroidism, thyroid nodule Pulmonary toxicity Breast tissue hypoplasia Cardiac toxicity Renal toxicity Gonadal dysfunction Uterine vascular insufficiency Diabetes Dyslipidemia Musculoskeletal growth problems Second cancers
PRETRANSPLANTATION EXPOSURES (NOT LISTED ABOVE)	
Anthracycline/anthraquinone	Cardiac toxicity Therapy-related AML/MDS
Bleomycin	Pulmonary toxicity
Cytarabine	Neurocognitive deficits Leukoencephalopathy
Methotrexate	Neurocognitive deficits Leukoencephalopathy Renal toxicity Low BMD
Corticosteroid	Cataract Low BMD Avascular necrosis
Cranial radiation[§]	Neurocognitive deficits Leukoencephalopathy Cerebrovascular disease Cataract Craniofacial abnormalities Dental abnormalities, xerostomia GH deficiency Hypothyroidism thyroid nodule Increased obesity Precocious puberty Brain tumor
Spinal radiation (in addition to cranial dose)	Cardiac toxicity Scoliosis/kyphosis, musculoskeletal problems
AFTER TRANSPLANTATION (NOT LISTED ABOVE)	
Chronic GVHD	Xerophthalmia Xerostomia, dental abnormalities Pulmonary toxicity Gastrointestinal strictures Genitourinary strictures Skin and joint changes Immunodeficiency Second cancers, especially skin, oral, cervical, lymphoma
Tyrosine kinase inhibitor	Acute cardiac toxicity reported, but not known to cause late cardiotoxicity
OTHER EXPOSURES	
Blood transfusions	Hepatitis C, HIV

*Focused on those late effects that can develop or persist even after cessation of therapy.
[†]Includes etoposide, teniposide.
[‡]At given total dose, risks greater for single-fraction vs fractionated total body irradiation (TBI); single-fraction myeloablative TBI (>500 cGy) now rarely used.
[§]Effects listed are those more likely to be associated with doses used in HSCT survivors (e.g., those given for leukemia treatment, <25 Gy); late effects are more likely if TBI also given.
AML/MDS, Acute myeloid leukemia/myelodysplastic syndrome; BMD, bone mineral density; GH, growth hormone; GVHD, graft-versus-host disease; HSCT, hematopoietic stem cell transplantation.
From Chow EJ, Anderson L, Baker KS, et al. Late Effects Surveillance Recommendations among Survivors of Childhood Hematopoietic Cell Transplantation: A Children's Oncology Group Report. *Biol Blood Marrow Transplant.* 2016;22(5):782–795.

with school and vocational attainment. These patients are also often at higher risk for depression and anxiety; yearly psychosocial assessments can identify survivors who need additional therapy or psychotropic medication. Parents may also have posttraumatic stress from the experience.

SPECIAL CONSIDERATIONS

Certain patient populations who undergo HSCT are at increased risk for late effects. Young children appear to be at a heightened risk for late complications related to TBI, especially those related to growth, thyroid function, and neurocognition. Patients with an *underlying genetic condition* must also be monitored more closely for specific consequences of therapy, such as specific secondary malignancies in the Fanconi anemia population caused by an underlying DNA repair defect and patients with sickle cell anemia and thalassemia who are predisposed to iron overload.

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