TABLE 374-1 CLASSIFICATION OF PRIMARY IMMUNE DEFICIENCY DISEASES

Deficiencies of the Innate Immune System	
• Phagocytic cells:	
- Impaired production: severe congenital neutropenia (SCN)	
- Asplenia	
- Impaired adhesion: leukocyte adhesion deficiency (LAD)	
- Impaired killing: chronic granulomatous disease (CGD)	
• Innate immunity receptors and signal transduction:	
- Defects in Toll-like receptor signaling	
- Mendelian susceptibility to mycobacterial disease	
• Complement deficiencies:	
- Classical, alternative, and lectin pathways	
- Lytic phase	
Deficiencies of the Adaptive Immune System	
• T lymphocytes:	
- Impaired development	Severe combined immune deficiencies (SCIDs)
	DiGeorge syndrome
- Impaired survival, migration, function	Combined immunodeficiencies
	Hyper-IgE syndrome (autosomal dominant)
	DOCK8 deficiency
	CD40 ligand deficiency
	Wiskott-Aldrich syndrome
	Ataxia-telangiectasia and other DNA repair deficiencies
• B lymphocytes:	
- Impaired development	XL and AR agammaglobulinemia
- Impaired function	Hyper-IgM syndrome
	Common variable immunodeficiency (CVID)
	IgA deficiency
Regulatory Defects	
• Innate immunity	Autoinflammatory syndromes (outside the scope of this chapter)
	Severe colitis
• Adaptive immunity	Hemophagocytic lymphohistiocytosis (HLH)
	Autoimmune lymphoproliferation syndrome (ALPS)
	Autoimmunity and inflammatory diseases (IPEX, APECED)

Abbreviations: APECED, autoimmune polyendocrinopathy candidiasis ectodermal dysplasia; AR, autosomal recessive; IPEX, immunodysregulation polyendocrinopathy enteropathy X-linked syndrome; XL, X-linked.

of recurrent infections, inflammation, and autoimmunity can be observed in a number of PIDs, thus creating obvious therapeutic challenges. Finally, some PIDs increase the risk of cancer, notably but not exclusively lymphocytic cancers, e.g., lymphoma.

DIAGNOSIS OF PRIMARY IMMUNODEFICIENCIES

The most frequent symptom prompting the diagnosis of a PID is the presence of recurrent or unusually severe infections. As mentioned above, recurrent allergic or autoimmune manifestations may also alert the physician to a possible diagnosis of PID. In such cases, a detailed account of the subject's personal and family medical history should be obtained. It is of the utmost importance to gather as much medical information as possible on relatives and up to several generations of ancestors. In addition to the obvious focus on primary symptoms, the clinical examination should evaluate the size of lymphoid organs and, when appropriate, look for the characteristic signs of a number of complex syndromes that may be associated with a PID.

The performance of laboratory tests should be guided to some extent by the clinical findings. Infections of the respiratory tract (bronchi, sinuses) mostly suggest a defective antibody response. In general, invasive bacterial infections can result from complement deficiencies, signaling defects of innate immune responses, asplenia, or defective antibody responses. Viral infections, recurrent *Candida* infections, and opportunistic infections are generally suggestive of impaired T cell immunity. Skin infections and deep-seated abscesses primarily reflect innate immune defects (such as chronic granulomatous disease); however, they may also appear in the autosomal dominant hyper-IgE syndrome. Table 374-2 summarizes the laboratory tests that are most frequently used to diagnose a PID. More specific tests (notably genetic tests) are then used to make a definitive diagnosis.

The PIDs discussed below have been grouped together according to the affected cells and the mechanisms involved (Table 374-1, Fig. 374-1).

PRIMARY IMMUNODEFICIENCIES OF THE INNATE IMMUNE SYSTEM

PIDs of the innate immune system are relatively rare and account for approximately 10% of all PIDs.

SEVERE CONGENITAL NEUTROPENIA

Severe congenital neutropenia (SCN) consists of a group of inherited diseases that are characterized by severely impaired neutrophil counts (<500 polymorphonuclear leukocytes [PMN]/μL of blood). The condition is usually manifested from birth. SCN may also be cyclic (with a 3-week periodicity), and other neutropenia syndromes can also be intermittent. Although the most frequent inheritance pattern for SCN is autosomal dominant, autosomal recessive and X-linked recessive conditions also exist. Bacterial infections at the interface between the body and the external milieu (e.g., the orifices, wounds, and the respiratory tract) are common manifestations. Bacterial infections can rapidly progress through soft tissue and are followed by dissemination in the bloodstream. Severe visceral fungal infections can also ensue. The absence of pus is a hallmark of this condition.

Diagnosis of SCN requires examination of the bone marrow. Most SCNs are associated with a block in granulopoiesis at the promyelocytic stage (Fig. 374-1). SCN has multiple etiologies, and to date, mutations in 11 different genes have been identified. Most of these mutations result in isolated SCN, whereas others are syndromic (Chap. 80). The most frequent forms of SCN are caused by the premature cell death of granulocyte precursors, as observed in deficiencies of GFI1, HAX1, and elastase 2 (*ELANE*), with the latter accounting for 50% of SCN sufferers. Certain *ELANE* mutations cause cyclic neutropenia syndrome. A gain-of-function mutation in the *WASP* gene (see the section on "Wiskott-Aldrich syndrome" below) causes X-linked SCN, which is also associated with monocytopenia.

As mentioned above, SCN exposes the patient to life-threatening, disseminated bacterial and fungal infections. Treatment requires careful hygiene measures, notably in infants. Later in life, special oral and dental care is essential, along with the prevention of bacterial infection by prophylactic administration of trimethoprim/sulfamethoxazole. Subcutaneous injection of the cytokine granulocyte colony-stimulating factor (G-CSF) usually improves neutrophil development and thus prevents infection in most SCN diseases. However, there are two caveats: (1) a few cases of SCN with *ELANE* mutation are refractory to G-CSF and may require curative treatment via allogeneic hematopoietic stem cell transplantation (HSCT); and (2) a subset of G-CSF-treated patients carrying *ELANE* mutations are at a greater risk of developing acute myelogenous leukemia associated (in most cases) with somatic gain-of-function mutations of the G-CSF receptor gene.

ASPLENIA

Primary failure of the development of a spleen is an extremely rare disease that can be either syndromic (in Ivemark syndrome) or isolated with an autosomal dominant expression; in the latter case, mutations in the ribosomal protein SA gene were recently found. Due to the