with increased numbers of acute and chronic respiratory infections that may lead to bronchiectasis. In addition, over their lifetime, these patients experience an increased susceptibility to drug allergies, atopic disorders, and autoimmune diseases. Symptomatic IgA deficiency is probably related to CVID, since it can be found in relatives of patients with CVID. Furthermore, IgA deficiency may progress to CVID. It is thus important to assess serum Ig levels in IgA-deficient patients (especially when infections occur frequently) in order to detect changes that should prompt the initiation of immunoglobulin replacement. Selective IgG2 (+G4) deficiency (which in some cases may be associated with IgA deficiency) can also result in recurrent sinopulmonary infections and should thus be specifically sought in this clinical setting. These conditions are ill-defined and often transient during childhood. A pathophysiologic explanation has not been found.

Selective Antibody Deficiency to Polysaccharide Antigens Some patients with normal serum Ig levels are prone to *S. pneumoniae* and *H. influenzae* infections of the respiratory tract. Defective production of antibodies against polysaccharide antigens (such as those in the *S. pneumoniae* cell wall) can be observed and is probably causative. This condition may correspond to a defect in marginal zone B cells, a B cell subpopulation involved in T-independent antibody responses.

Immunoglobulin Replacement IgG antibodies have a half-life of 21–28 days. Thus, injection of plasma-derived polyclonal IgG containing a myriad of high-affinity antibodies can provide protection against disease-causing microorganisms in patients with defective IgG antibody production. This form of therapy should not be based on laboratory data alone (i.e., IgG and/or antibody deficiency) but should be guided by the occurrence or not of infections; otherwise, patients might be subjected to unjustified IgG infusions. Immunoglobulin replacement can be performed by IV or subcutaneous routes. In the former case, injections have to be repeated every 3–4 weeks, with a residual target level of 800 mg/mL in patients who had very low IgG levels prior to therapy. Subcutaneous injections are typically performed once a week, although the frequency can be adjusted on a case-by-case basis. A trough level of 800 mg/mL is desirable. Whatever the mode of administration, the main goal is to reduce the frequency of the respiratory tract infections and prevent chronic lung and sinus disease. The two routes appear to be equally safe and efficacious, and so the choice should be left to the preference of the patient.

In patients with chronic lung disease, chest physical therapy with good pulmonary toilet and the cyclic use of antibiotics are also needed. Immunoglobulin replacement is well tolerated by most patients, although the selection of the best-tolerated Ig preparation may be necessary in certain cases. Since IgG preparations contain a small proportion of IgAs, caution should be taken in patients with residual antibody production capacity and a complete IgA deficiency, as these subjects may develop anti-IgA antibodies that can trigger anaphylactic shock. These patients should be treated with IgA-free IgG preparations. Immunoglobulin replacement is a lifelong therapy; its rationale and procedures have to be fully understood and mastered by the patient and his or her family in order to guarantee the strict observance required for efficacy.

PRIMARY IMMUNODEFICIENCIES AFFECTING REGULATORY PATHWAYS (TABLE 374-1)

An increasing number of PIDs have been found to cause homeostatic dysregulation of the immune system, either alone or in association with increased vulnerability to infections. Defects of this type affecting the innate immune system and autoinflammatory syndromes will not be covered in this chapter. However, three specific entities (hemophagocytic lymphohistiocytosis, lymphoproliferation, and autoimmunity) will be described below.

HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS

Hemophagocytic lymphohistiocytosis (HLH) is characterized by an unremitting activation of CD8+ T lymphocytes and macrophages that leads to organ damage (notably in the liver, bone marrow, and central nervous system). This syndrome results from a broad set of inherited diseases, all of which impair T and NK lymphocyte cytotoxicity. The manifestations of HLH are often induced by a viral infection. EBV is the most frequent trigger. In severe forms of HLH, disease onset may start during the first year of life or even (in rare cases) at birth.

Diagnosis relies on the identification of the characteristic symptoms of HLH (fever, hepatosplenomegaly, edema, neurologic diseases, blood cytopenia, increased liver enzymes, hypofibrinogenemia, high triglyceride levels, elevated markers of T cell activation, and hemophagocytic features in the bone marrow or cerebrospinal fluid). Functional assays of postactivation cytotoxic granule exocytosis (CD107 fluorescence at the cell membrane) can suggest genetically determined HLH. The conditions can be classified into three subsets:

1. Familial HLH with autosomal recessive inheritance, including perforin deficiency (30% of cases) that can be recognized by assessing intracellular perforin expression; Munc13-4 deficiency (30% of cases); syntaxin 11 deficiency (10% of cases); Munc18-2 deficiency (20% of cases); and a few residual cases that lack a known molecular defect.
2. HLH with partial albinism. Three conditions combine HLH and abnormal pigmentation, where hair examination can help in the diagnosis: Chédiak-Higashi syndrome, Griscelli syndrome, and Hermansky Pudlak syndrome type II. Chédiak-Higashi syndrome is also characterized by the presence of giant lysosomes within leukocytes (Chap. 80), in addition to a primary neurologic disorder with slow progression of symptoms over time.
3. X-linked proliferative syndrome (XLP) is characterized in most patients by the induction of HLH following EBV infection, while other patients develop progressive hypogammaglobulinemia similar to what is observed in CVID and/or certain lymphomas. XLP is caused by a mutation in the *SH2DIA* gene that encodes the adaptor protein SAP (associated with a SLAM family receptor). Several immunologic abnormalities have been described, including low 2B4-mediated NK cell cytotoxicity, impaired differentiation of NKT cells, defective antigen-induced T cell death, and defective T cell helper activity for B cells. A related disorder (XLP2) has recently been described. It is also X-linked and induces HLH (frequently after EBV infection), although the clinical manifestation may be less pronounced. The condition is associated with a deficiency of the antiapoptotic molecule XIAP. The pathophysiology of XLP2 and its relationship to XLP1 remain unclear.

HLH is a life-threatening complication. The treatment of this condition requires aggressive immunosuppression with either the cytotoxic agent etoposide or anti–T cell antibodies. Once remission has been achieved, HSCT should be performed, since it provides the only curative form of therapy.

AUTOIMMUNE LYMPHOPROLIFERATIVE SYNDROME

Autoimmune lymphoproliferative syndrome (ALPS) is characterized by nonmalignant T and B lymphoproliferation causing splenomegaly and enlarged lymph nodes; 70% of patients also display autoimmune manifestations such as autoimmune cytopenias, Guillain-Barré syndrome, uveitis, and hepatitis (Chaps. 79 and 372e). A hallmark of ALPS is the presence of CD4–CD8– TCRαβ+ T cells (2–50%) in the blood of affected individuals. Hypergammaglobulinemia involving IgG and IgA is also frequently observed. The syndrome is caused by a defect in Fas-mediated apoptosis of lymphocytes, which can thus accumulate and mediate autoimmunity. Furthermore, ALPS can lead to malignancies.

Most patients carry a heterozygous mutation in the gene encoding Fas that is characterized by dominant inheritance and variable penetrance, depending on the nature of the mutation. A rare and severe form of the disease with early onset can be observed in patients carrying a biallelic mutation of Fas, which profoundly impairs the protein's expression and/or function. Fas-ligand, caspase 10, caspase 8, and neuroblastoma RAS viral oncogene homologue (NRAS) mutations have also been reported in a few cases of ALPS. Many cases of ALPS have not been precisely delineated at the molecular level. A B cell–predominant ALPS has recently been found associated with a protein kinase Cδ gene mutation. Treatment of ALPS is essentially based on the use of proapoptotic drugs, which need to be carefully administered in order to avoid toxicity.