Humoral immunodeficiencies: conferred risk of infections and benefits of immunoglobulin replacement therapy

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Primary immunodeficiency (PID) diseases result from genetic defects of the immune system that increase a patient's susceptibility to infections. The types of infections that occur in patients with PID diseases are dictated largely by the nature of the immunodeficiency, which can be defined by dysfunction of cellular or humoral defenses. An increasing number of PID diseases, including those with both cellular and humoral defects, have antibody deficiency as a major feature, and as a result can benefit from immunoglobulin replacement therapy. In fact, the most common PID diseases worldwide are antibody deficiencies and include common variable immunodeficiency, congenital agammaglobulinemia, hyper-IgM syndrome, specific antibody deficiency, and Good syndrome. Although immunoglobulin replacement therapy is the cornerstone of treatment for the majority of these conditions, a thorough understanding of the specific infections for which these patients are at increased risk can hasten diagnosis and guide additional therapies. Moreover, the infection trends in some patients with PID disease who have profound defects of cellular immunity, such as autosomal-dominant hyper-IgE syndrome (Job/Buckley syndrome) or dedicator of cytokinesis 8 (DOCK8) deficiency, suggest that select patients might benefit from immunoglobulin replacement therapy even if their immunodeficiency is not limited to antibody defects. In this review, we provide an overview of the predisposition to infections seen in PID disease that may benefit from immunoglobulin replacement therapy.

With the ever-increasing sophistication of diagnostic tools, more than 300 distinct primary immunodeficiency (PID) diseases are now recognized.[1] Along with this expansive recognition of distinct PID disease etiologies are associations with

ABBREVIATIONS: AD-HIES = autosomal-dominant hyper-IgE syndrome; AID = activation-induced cytidine deaminase; BTK = Burton tyrosine kinase; CMV = cytomegalovirus; CVID = common variable immunodeficiency; DOCK8 = dedicator of cytokinesis 8; EBV = Epstein-Barr virus; HIGM = hyper-IgM syndrome; HSCT = hematopoietic stem cell transplantation; ICOS = inducible costimulator gene; Ig = immunoglobulin; IL2RG = common gamma chain deficiency; JAK3 = Janus kinase 3; NEMO = NF-κB essential modulator; NF-κB = nuclear factor kappa-light-chain-enhancer of activated B cells; PI3K = delta 110 phosphatidylinositol-3 kinase; PID = primary immunodeficiency; PJP = *Pneumocystis jiroveci* pneumonia; RAG1 = recombination activating gene 1; RAG2 = recombination activating gene 2; SCID = severe combined immunodeficiency; STAT3 = signal transducer and activator of transcription 3; TACI = calcium-modulating cyclophilin ligand interactor; TMP-SMX = trimethoprim-sulfamethoxazole; UNG = uracil *N*-glycosylase; XLA = X-linked agammaglobulinemia

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clinical and immunologic characteristics that confer susceptibility to specific infectious processes. The most common PID diseases worldwide are predominately those that involve antibody deficiencies,[2] which include common variable immunodeficiency (CVID), congenital agammaglobulinemia, hyper-IgM syndrome (HIGM), specific antibody deficiency, and Good syndrome. Many patients with these conditions require immunoglobulin (Ig) replacement therapy to prevent life-threatening infections and related chronic complications. This is also true of patients with immune defects that extend beyond the humoral compartment, such as many with severe combined immunodeficiency (SCID), even after hematopoietic stem cell transplantation (HSCT), or those with autosomal-dominant hyper-IgE syndrome (AD-HIES) and dedicator of cytokinesis 8 (DOCK8) deficiency. Thus, many more patients than those with selective antibody deficiencies may benefit from Ig replacement therapy. In this review, we characterize the predisposition to specific infections conferred by PID diseases in which antibody deficiency is a prominent component, with the goal of hastening diagnosis and guiding the use of Ig replacement therapy for these highly vulnerable patients (Table 1).

Common variable immunodeficiency

Common variable immunodeficiency (or CVID) is the most common symptomatic primary immunodeficiency and is characterized by profound antibody dysfunction.[3] This diagnosis represents a heterogeneous group of genetic etiologies all characterized by the shared phenotype of reduced serum levels of IgG, low IgA and/or IgM, and impaired antibody response to vaccination. B-cell numbers are typically present at low or normal levels, whereas CD4 T-cell numbers may be decreased in some patients.[4] CVID is believed to result from the absence of B-cell maturation into long-lived isotype-switched memory B cells and plasma cells due to a variety of potential mechanisms that are poorly understood. Many patients with CVID experience heightened susceptibility to both infections and autoimmune and inflammatory complications (e.g., autoimmune cytopenia, enteropathy, and lung disease).[5] Notably, patients with CVID with the lowest levels of isotype-switched memory B cells (CD27 + IgD− IgM−) have been reported to have the greatest risk of these complications.[6] Because antibody deficiency is the prominent feature of CVID, Ig replacement therapy is the standard of care, although this treatment does not seem to alter the course of autoimmune and inflammatory complications in many patients.[5]

The most common infections in patients with CVID involve the respiratory tract, reported in 84% in one large study, with bronchitis and sinusitis the most frequent manifestations and pneumonia also occurring in more than half of patients.[7] Recurrent sinopulmonary infections in patients with CVID are typically caused by encapsulated organisms (*Streptococcus pneumoniae* and *Haemophilus influenzae*)[8] or viral pathogens such as rhinovirus, coronavirus, adenovirus, and influenza virus.[9] When pulmonary infections are severe and recurrent, patients may develop irreversible lung damage such as bronchiectasis, which occurs in one-third or more of patients.[7,10,11] *Mycoplasma* and *Ureaplasma* are under recognized causes of infections in these patients and may involve atypical locations such as the joints. Notably, Ig replacement therapy has been shown to reduce the incidence of pneumonia, the onset of bronchiectasis, and other severe respiratory tract infections in CVID, although its role in limiting sinusitis is less clear.[12–14] In CVID patients with bronchiectasis, chronic pulmonary symptoms and recurrent infections may persist despite standard Ig replacement.[15,16] In these patients, there may be benefit in aiming for higher IgG troughs or steady-state levels, and a decrease in pneumonia has been observed for every 100 mg/dL increment increase in IgG trough level up to 1000 mg/dL.[14,17] Higher IgG trough levels can be achieved through either more frequent Ig replacement dosing or administration of higher doses per treatment. In addition, prophylactic antibiotics can be considered for patients who continue to have infections despite Ig replacement therapy (generally azithromycin or amoxicillin) (Table 2).

Acute or chronic diarrhea remains the most common gastrointestinal (GI) symptom in patients with CVID.[18–20] *Giardia lamblia* is a common cause of infectious diarrhea in patients with CVID, and its eradication may be difficult, leading to chronic diarrhea and metabolic complications of malabsorption. More recently, infection with norovirus has been reported as an important enteric infection in patients with CVID, and it has also been associated with chronic infection that causes malabsorption and severe enteropathy.[21–23] Some patients may benefit from antiviral therapy to clear norovirus infection.[22] Patients are also predisposed to GI infections with *Campylobacter jejuni*, *Salmonella* species, and cytomegalovirus (CMV). Surprisingly, despite frequent courses of antibiotics, patients with CVID appear to be at no greater risk than the general population of infection due to *Clostridium difficile*.[7] Thus, in addition to infections of the sinopulmonary tract, GI pathogens are a major concern in CVID. However, the impact of Ig replacement therapy for GI complications is not clear and may be overshadowed by the role of IgA at mucosal surfaces, which is not replenished by this treatment.

Agammaglobulinemia

X-linked agammaglobulinemia (XLA) is a primary immunodeficiency caused by mutations in the gene for Bruton tyrosine kinase (BTK), resulting in profound B-cell lymphopenia and agammaglobulinemia in most instances.[24] XLA can also be associated with severe transient neutropenia and impairment of toll-like receptor (TLR) signaling.[24,25] Ig replacement therapy is the standard of care for XLA, and many providers also include prophylactic antibiotics in the

TABLE 1. Summary of the PID diseases, their underlying immune defects, their specific infections, and the effect of immunoglobulin replacement therapy

Condition	Immune defect	Clinical infections	Culprit organisms	Effects of immunoglobulins
CVID	Genetic cause often unknown In a minority of patients monogenic cause has been identified (TACI, ICOS, CD19 deficiency)	URIs/LRIs Sinusitis Diarrhea	Encapsulated bacteria Enterovirus *Helicobacter*, *Campylobacter*, and *Flexispira*	Reduced frequency of pneumonia and onset of bronchiectasis[13,14]
Bruton Agammaglobulinemia (XLA)	85% Familial Mutation in *BTK*, 15% de novo mutation in *BTK*	URIs/LRIs Sinusitis Diarrhea	Encapsulated bacteria (*H. influenzae* *S. pneumoniae)* *Enterovirus,* *Helicobacter,* *Campylobacter,* and *Flexispira*	Reduced frequency of pneumonia and onset of bronchiectasis[13–15,27]
Hyper-IgM	CD40 ligand CD40 AID UNG NEMO PIK3CD	URIs/LRIs Otitis Skin/soft tissue GI	Bacteria *Pneumocystis* *Cryptosporidium*	Although data are limited, some benefit has been shown in reducing meningitis and pneumonias[13,83]
Selective antibody deficiency	Unknown etiology	Recurrent bacterial sinopulmonary infections (otitis media, sinusitis, and pneumonia).	Encapsulated bacteria (*H. influenzae* *S. pneumoniae*)	Unknown
Good syndrome	Unknown etiology	Recurrent sinopulmonary infections GI infections Bacteremia Opportunistic infections	Encapsulated bacteria *(H. influenzae,* *S. pneumoniae*) *Campylobacter* CMV *Candida* *Pneumocystis*	One-third to two-thirds of patients experience a reduction in infections/ need for antibiotics[52,53]
AD-HIES	STAT3 deleterious mutation	Pneumonia Cold skin abscess CMC	*S. aureus* *H. influenzae* *P. aeruginosa* *Aspergillus fumigatus* *C. albicans*	Might reduce the number of pneumonias[68]
DOCK8 deficiency	DOCK8 variant	Viral infections Pneumonia Atopy Malignancy	*S. aureus* EBV	Reduced risk of skin infections and pneumonia
SCID	Multiple genetic diseases	Severe viral and fungal infections	CMV, adenovirus, parainfluenza, *Pneumocystis*, *Candida, Salmonella,* and *Pseudomonas* species	Reduced risk of infections pre- and post-HSCT

CVID = common variable immunodeficiency; TACI = transmembrane activator and CAML interactor; ICOS = inducible T cell costimulator; URI = upper respiratory tract infection; LRI = lower respiratory tract infection; XLA = X-linked agammaglobulinemia; BTK = Bruton's tyrosine kinase; AID = activation induced cytosine deaminase; UNG = uracil DNA glycosylase; NEMO = NFκB essential modulator; PIK3CD = phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit delta; GI = gastrointestinal; AD-HIES = autosomal dominant hyper IgE syndrome; STAT3 = signal transducer and activator of transcription 3; DOCK8 = dedicator of cytokinesis 8; CMV = cytomegalovirus; EBV = Epstein-Barr virus; SCID = severe combined immunodeficiency; HSCT = h hematopoietic stem cell transplantation.

management of these patients (Table 2).[26] As with CVID, Ig replacement may be dosed to achieve higher trough IgG levels if there is concern for bronchiectasis, chronic sinusitis, or nonbacterial infections.[27]

Similar to patients with CVID, patients with XLA typically have recurrent bacterial infections of the upper and lower respiratory tract. *Mycoplasma* and *Ureaplasma* infections can cause pneumonia as well as destructive septic arthritis.[28] Patients with XLA are also susceptible to infections with *Campylobacter* and *Helicobacter*, which can be responsible for cellulitis, ulcers of the lower extremities, bacteremia, osteomyelitis, and septic arthritis in addition to GI infections.[29,30] In the setting of transient neutropenia, patients with XLA can present with *Pseudomonas* or *Staphylococcus* sepsis.[31] Prophylactic antibiotics, such as trimethoprim-sulfamethoxazole (TMP-SMX), may be particularly useful in preventing infections during bouts of neutropenia. Finally, like patients with CVID, patients with XLA can present with enteropathy secondary to *Giardia*, *Campylobacter*, and *Salmonella*.[30,32,33]

TABLE 2. Prophylaxis regimens used in PID diseases[79,84,85]

Condition	Antibiotic prophylaxis	Antifungal prophylaxis
CVID	Amoxicillin 20 mg/kg divided twice daily (maximum of 500 mg twice daily) or azithromycin 10 mg/kg once weekly (maximum of 1 g once weekly) or azithromycin 5 mg/kg 3 times weekly (maximum 250 mg 3 times weekly)	None
Bruton Agammaglobulinemia (XLA)	Amoxicillin or azithromycin (refer to CVID for dosage)	None
Hyper IgM	TMP-SMX 5 mg/kg TMP component 3 times weekly; azithromycin (may have a role in CD40L or CD40 deficiency) NEMO: azithromycin 20 mg/kg divided twice daily or azithromycin 10 mg/kg once weekly	
Selective antibody deficiency	Amoxicillin or azithromycin (refer to CVID for dosage)	None
Good syndrome	Amoxicillin or a fluoroquinolone can be considered for patients with recurrent bacterial infections[57] TMP-SMX has been used for PJP and toxoplasmosis prophylaxis in patients with CD4 lymphopenia; this may also be adequate for prophylaxis against respiratory pathogens[52,57]	Fluconazole for patients with recurrent candidiasis
AD-HIES	TMP-SMX; cloxacillin (typically for TMP-SMX failures)	Posaconazole, itraconazole, voriconazole
DOCK8 deficiency	Daily TMP-SMX (2.5 mg/kg of TMP component twice daily) is useful to decrease skin and lung infections	
SCID	PJP prophylaxis: TMP-SMX dosed as 4-6 mg/kg/day of TMP component divided twice daily 3 days per week (after 30 days of life)	Fungal prophylaxis: fluconazole 6 mg/kg/d daily

In addition to bacterial pathogens and parasites, patients with XLA can have an increased susceptibility to enterovirus infections (poliovirus, coxsackievirus, and echovirus), which can become chronic. Enterovirus infections can progress to meningoencephalitis and fatal disseminated disease.[21,34,35] Fortunately, these complications have decreased since Ig replacement therapy has become routine.[27]

Hyper-IgM syndrome

Hyper-IgM syndrome is a collective name for a heterogeneous group of disorders united by defects in antibody isotype class switching and somatic hypermutation.[36,37] The most common cause is X-linked mutation of the gene encoding CD40 ligand and thus is often called X-linked hyper-IgM syndrome (XHIGM). The most common autosomal recessive form of this condition results from genetic deficiency of activation-induced cytidine deaminase (AID), whereas mutations in the genes encoding CD40 and uracil *N*-glycosylase (UNG) are other rare autosomal-recessive etiologies.[37] Other immunodeficiency syndromes can have elevation of serum IgM without complete impairment of antibody isotype switching, including hypohidrotic ectodermal dysplasia with immunodeficiency, which is due to X-linked mutations in the NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) essential modulator (NEMO), gain-of-function mutations in the delta 110 subunit of phosphatidylinositol-3 kinase (PIK3CD), and some patients with CVID that do not otherwise have genetic etiologies consistent with hyper-IgM syndrome.

Infections of the upper and lower respiratory tract, ears, skin and soft tissue, and GI tract are the most commonly reported infectious manifestations in patients with HIGM.[38] It should be noted that in addition to common bacterial pathogens including *S. pneumoniae* and *Pseudomonas aeruginosa*, *Pneumocystis jiroveci* (PJP) pneumonia is common in patients with XHIGM. In fact, PJP pneumonia is the presenting manifestation of hyper-IgM syndrome in almost half of diagnosed patients.[39] This association with PJP pneumonia is likely due to the role of CD40L in T-cell effector function, including activation of macrophages and other immune cells to kill intracellular pathogens, and thus such patients effectively have a combined (B- and T-cell) immunodeficiency. In fact, mutations in CD40 ligand, CD40, and NEMO appear to be the most highly associated with severe infections and opportunistic infections, likely due to impairment of macrophage activation and T-cell effector function.[38,40] *Cryptosporidium* is also frequently reported in patients with HIGM, and infection can contribute to high rates of sclerosing cholangitis and hepatobiliary disease.[36] Patients appear to be at increased risk for parvovirus B19 and *Candida* infections as well.[38] Patients with NEMO defects may be especially prone to invasive bacterial infections (abscesses, meningitis, arthritis, osteomyelitis, and sepsis) as well as chronic infections including *Mycobacterium avium*[36,37,40]

Patients with HIGM demonstrate higher mortality compared to patients with other PID diseases due to infectious complications and end-organ complications such as

hepatobiliary disease.[38,39] Patients should be treated with a combination of Ig replacement, PJP prophylaxis, and lifestyle modification, such as clean drinking practices to minimize the risk of exposure to *Cryptosporidium*. Patients with NEMO defects are generally prescribed broad-spectrum antibiotic prophylaxis[37] (Table 2), and hematopoietic stem cell transplantation (or HSCT) can be considered for definitive treatment.[38,39,41] HSCT appears to have superior outcomes when performed at an earlier age before the onset of severe infection and resultant end-organ damage.

Specific antibody deficiency

Specific antibody deficiency (or SAD) is characterized by normal serum concentrations of IgG but poor IgG antibody responses to specific pathogens, most commonly polysaccharide antigens. Per diagnostic guidelines, patients must be older than 2 years of age;[42] however, it is clear that antibody responses to carbohydrate antigens can be delayed well into adolescence, causing this to be a difficult diagnosis to establish in children.[43,44] Patients with SAD usually present with recurrent bacterial sinopulmonary infections (otitis media, sinusitis, and pneumonia) due to encapsulated bacteria such as *S. pneumoniae*.[45,46] Systemic, invasive, or opportunistic infections are uncommon.[47] If warranted by the frequency and severity of infections, patients with SAD may be managed with prophylactic antibiotics or Ig replacement therapy.

Good syndrome

Good syndrome was first described by Dr. Robert Good in the 1950s as a rare adult-onset immunodeficiency characterized by a finding of thymoma associated with hypogammaglobulinemia.[48,49] It is estimated that 2%-6% of patients with thymoma are affected.[50,51] In just under half of cases, the finding of thymoma predates the finding of hypogammaglobulinemia, and patients may be identified as having Good syndrome after a delay of months to years.[52] In the other 50% of cases, both the thymoma and hypogammaglobulinemia are diagnosed concurrently. The average age at first presentation is 56-59 years, and there does not appear to be any sex predilection.[52–55]

In addition to hypogammaglobulinemia, key laboratory findings include profound B-cell lymphopenia, impaired cell-mediated immunity with CD4+ lymphopenia, an inverted CD4:CD8+ T-cell ratio, neutropenia, and eosinopenia.[52,53] The clinical course is marked by frequent and severe infections.[52,53,55] Invasive bacterial, viral, fungal, and opportunistic infections have been described. It should be noted that this pattern of infections is not seen in patients with CVID, who may have more profound hypogammaglobulinemia, or in patients with HIV, who demonstrate more severe CD4+ lymphopenia.

Regarding bacterial infections, the most highly reported are pneumonia, upper respiratory infections, and GI infections. Pathogens most frequently associated in patients with upper and lower respiratory infections include *H. influenzae* type B, *P. aeruginosa*, *S. pneumoniae*, and *Klebsiella pneumoniae*.[52] The most common GI pathogens include *Salmonella* and *C. jejuni*. Patients with Good syndrome appear to be at significant risk for bacteremia as a consequence of both pulmonary and gastrointestinal infections.[52,53,55] With respect to viral infections, it is most notable that patients with Good syndrome have high rates of CMV infection.[52] These infections have been noted to be quite severe and include a fatal case of CMV colitis.[53] There have been multiple reports of infection with the parasite *Giardia*, and the most common fungal infection is candidal. In addition to those previously mentioned (CMV, *Candida*), other opportunistic infections that may be encountered in patients with Good syndrome include PJP, recurrence of herpes simplex virus (HSV), and human herpesvirus 8 (HHV-8) resulting in Kaposi's sarcoma.[52,53,55,56]

As in other patients with thymomas, patients with Good syndrome have high rates of autoimmunity, with pure RBC aplasia, myasthenia gravis, oral lichen planus, and inflammatory colitis.[52,55] Inflammatory colitis has been reported in about one-third of cases, although the mechanism underlying its development in these patients remains very poorly understood.[55] Dysregulation of T-cell function, such as impairment of the regulatory T-cell subset in particular, may predispose to autoimmune and inflammatory complications in these patients, but this remains to be demonstrated.

The cornerstone of management of Good syndrome includes thymectomy and Ig replacement.[53] Although thymectomy has been associated with resolution of some autoimmunity, no benefit has been observed with regard to patients' immune function. There may be a role for prophylactic antibiotics in select patients, but there are no guidelines for such treatment and this decision is typically made on an individual basis.[52,55] For patients with recurrent bacterial infections, amoxicillin-clavulanic acid or a fluoroquinolone may be reasonable choices for prophylaxis (Table 2).[57] Acyclovir can be used for patients with recurrent HSV or VZV, with valganciclovir used in cases of CMV. Patients with recurrent candidiasis may benefit from prophylactic fluconazole or an alternative in the setting of fluconazole resistance. PJP prophylaxis with TMP-SMX is indicated for patients with CD4 lymphopenia or toxoplasma seropositivity.

Hyper-IgE syndrome

Autosomal-dominant hyper-IgE syndrome (or AD-HIES) is characterized by eczematoid dermatitis, recurrent pulmonary and skin infections, and elevated total IgE level.[58] The major underlying mechanism responsible for this multisystem disease is loss-of-function mutations in signal transducer and activator of transcription 3 (STAT3).[59–61] Patients present in infancy with an eczematoid and pustular rash on

their face.[62] Wound cultures will often grow *Staphylococcus aureus*. Patients with AD-HIES often develop recurrent pneumonia secondary to *S. aureus* or *H. influenzae*. In fact, 95% of patients with AD-HIES had a history of recurrent pneumonia in a 100-patient multicenter cohort.[63] When pneumatoceles and bronchiectasis develop, the spectrum of pulmonary infections may change and may include *P. aeruginosa*, nontuberculous mycobacteria, or filamentous molds such as *Aspergillus fumigatus*.[64]

Patients with AD-HIES must be treated with prophylactic antibiotics against *P. aeruginosa* and *S. aureus* (TMP-SMX) as well as prophylactic antifungal therapy for life (the choice of the antifungal therapy depends on the specific fungal pathogen and presence of cystic lung disease) (Table 2). STAT3 plays an important role in B-cell function, both intrinsically[65,66] and via follicular helper T cells,[67] providing a rationale for the use of Ig replacement in patients with HIES. In fact, patients with AD-HIES on Ig replacement therapy have been shown to have a possible reduced incidence of pneumonia.[68–71]

Before the identification of the molecular defect, many patients with variants in the dedicator of cytokinesis 8 gene (or DOCK8) were categorized as having autosomal-recessive HIES.[72] It should be noted that many of the DOCK8-related family members activate Ras-related C3 botulinum toxin substrate (RAC) family members and CDC42 to initiate actin reorganization, which plays a crucial role in many immune processes, such as phagocytosis.[73] Patients with DOCK8 deficiency present with severe viral skin infections (warts, *Molluscum contagiosum*), severe atopic disease (food allergy, eczema), recurrent *S. aureus* skin infections, and pneumonias.[72,74,75] These patients may also have an increased risk of malignancy, in particular, lymphoma and squamous cell carcinoma.[72] The key laboratory findings include a decrease in numbers of T and B cells, elevated IgE levels, and eosinophilia. The main treatment for patients with DOCK8 deficiency is HSCT.[76] Before undergoing stem cell transplantation, patients with DOCK8 deficiency should be treated with Ig replacement therapy as well as prophylactic TMP-SMX to decrease the risk of lung and skin infections.

Severe combined immunodeficiency

The primary immunodeficiency treatment consortium has proposed formal diagnostic criteria for SCID. "Typical" or "classic" SCID is characterized by profound T-cell lymphopenia (CD3 T-cell count <300 cells/μL) together with a < 10% phytohemagglutinin (PHA) response compared to control values or identification of maternal T cells in the infant circulation.[42,77,78] Partial or "leaky" SCID, including Omenn syndrome, is diagnosed based on T-cell lymphopenia adjusted for age (age <2 years, <1000 cells/mm^3; age 2-4 years, <800 cells/mm^3; age >4 years, <600 cells/mm^3) and PHA response <30% of the control value.[79] Although B cells are present in many types of SCID (common gamma chain deficiency [IL2RG], JAK3 deficiency), antibody production is greatly impaired in the absence of adequate costimulation by CD4+ T cells. Patients with SCID often present with chronic respiratory infections, protracted diarrhea, and chronic candidiasis. Common pathogens include bacteria such as *Salmonella* and *Pseudomonas*; viruses such as parainfluenza, respiratory syncytial virus, adenovirus, and CMV; protozoa; and fungi such as PJP and *Candida albicans*.[80]

All patients with SCID must be treated with prophylaxis for PJP as well as Ig replacement. Both of these therapies have been shown to reduce the risk of infection before definitive treatment with HSCT.[81] Even following successful HSCT, many patients do not have B-cell engraftment. Indeed, half of the survivors have been shown to require Ig replacement therapy. This includes 62% of patients with IL2RG deficiency[82] and 80% of patients with recombination activating gene 1 and 2 (RAG1 and RAG2) deficiency.

CONCLUSION

PID diseases, and specifically primary antibody deficiencies, represent a heterogeneous group of disorders. Patients with these immune disorders are vulnerable to a wide variety of infections, although specific PID diseases do appear to have their own signature with regard to conferred risk of certain infections. Thorough understanding of the predisposition observed for each of these diagnoses allows clinicians to anticipate infectious complications and make full use of our armamentarium including Ig replacement therapy, prophylactic antibiotics, and even HSCT in certain instances to reduce morbidity and mortality in these highly vulnerable patients.

CONFLICTS OF INTEREST

The authors have disclosed no conflicts of interest.

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