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.
clinical and immunologic characteristics that confer susceptibility to specific infectious processes. The most common PID diseases worldwide are predominately those that involve antibody deficiencies, 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. 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. 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). 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. 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.

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. Recurrent sinopulmonary infections in patients with CVID are typically caused by encapsulated organisms (*Streptococcus pneumoniae* and *Haemophilus influenzae*) or viral pathogens such as rhinovirus, coronavirus, adenovirus, and influenza virus. 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. 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. In CVID patients with bronchiectasis, chronic pulmonary symptoms and recurrent infections may persist despite standard Ig replacement. 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. 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. *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. Some patients may benefit from antiviral therapy to clear norovirus infection. Patients are also predisposed to GI infections with *Campylobacter jejuni*, *Salmonella* species, and cytomegalovirus (CMV). Surprisingly, despite frequent courses of antibodies, patients with CVID appear to be at no greater risk than the general population of infection due to *Clostridium difficile*. 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. XLA can also be associated with severe transient neutropenia and impairment of toll-like receptor (TLR) signaling. Ig replacement therapy is the standard of care for XLA, and many providers also include prophylactic antibiotics in the
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

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

| 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, Flexispira | Reduced frequency of pneumonia and onset of bronchiectasis<sup>13,14</sup> |
| Bruton Agammaglobulinemia (XLA)    | 85% Familial Mutation in BTK, 15% de novo mutation in BTK | URIs/LRIs, Sinusitis | Encapsulated bacteria (H. influenzae, S. pneumoniae), Enterovirus, Helicobacter, Campylobacter, Flexispira | Reduced frequency of pneumonia and onset of bronchiectasis<sup>13–15,27</sup> |
| Hyper-IgM                          | CD40 ligand AID UNG NEMO PIK3CD         | URIs/LRIs, Otis, Skin/soft tissue, GI                  | Bacteria, Pneumocystis, Cryptosporidium | Although data are limited, some benefit has been shown in reducing meningitis and pneumonias<sup>13,83</sup> |
| Selective antibody deficiency      | Unknown etiology                        | Recurrent bacterial sinopulmonary infections (otitis media, sinusitis, and pneumonia), GI infections, Bacteremia, Opportunistic infections | Encapsulated bacteria (H. influenzae, S. pneumoniae), Campylobacter, CMV, Candida, Pneumocystis | 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<sup>52,53</sup> |
| 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<sup>48</sup> |
| 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, 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 cytokine 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 = dicator of cytokinesis 3; DOCK8 deficiency = DOCK8 variant; SCID = severe combined immunodeficiency; HSCT = hematopoietic stem cell transplantation.
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.\textsuperscript{21,34,35} Fortunately, these complications have decreased since Ig replacement therapy has become routine.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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 manifestations in patients with HIGM.\textsuperscript{38} It should be noted that in addition to common bacterial pathogens including \textit{S. pneumoniae} and \textit{Pseudomonas aeruginosa}, \textit{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.\textsuperscript{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.\textsuperscript{38,40} \textit{Cryptosporidium} is also frequently reported in patients with HIGM, and infection can contribute to high rates of sclerosing cholangitis and hepatobiliary disease.\textsuperscript{36} Patients with NEMO defects may be especially prone to invasive bacterial infections (abscesses, meningitis, arthritis, osteomyelitis, and sepsis) as well as chronic infections including \textit{Mycobacterium avium}\textsuperscript{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

| 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                            | Amoxicillin or azithromycin (refer to CVID for dosage)       | None                            |
| 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) | None                            |
| Hyper IgM                        | NEMO: azithromycin 20 mg/kg divided twice daily or azithromycin 10 mg/kg once weekly | None                            |
| 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\textsuperscript{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 | None                            |
| 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 |
antibiotic prophylaxis and hematopoietic stem cell transplantation (or HSCT) can be considered for definitive treatment. 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; 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. Patients with SAD usually present with recurrent bacterial sinopulmonary infections (otitis media, sinusitis, and pneumonia) due to encapsulated bacteria such as S. pneumoniae. Systemic, invasive, or opportunistic infections are uncommon. 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. It is estimated that 2%-6% of patients with thymoma are affected. In just under half of cases, the finding of thymoma predicts the finding of hypogammaglobulinemia, and patients may be identified as having Good syndrome after a delay of months to years. 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.

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. The clinical course is marked by frequent and severe infections. 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. 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. With respect to viral infections, it is most notable that patients with Good syndrome have high rates of CMV infection. These infections have been noted to be quite severe and include a fatal case of CMV colitis. 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. As in other patients with thymomas, patients with Good syndrome have high rates of autoimmune, with pure RBC aplasia, myasthenia gravis, oral lichen planus, and inflammatory colitis. Inflammatory colitis has been reported in about one-third of cases, although the mechanism underlying its development in these patients remains very poorly understood. 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. 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. For patients with recurrent bacterial infections, amoxicillin-clavulanic acid or a fluoroquinolone may be reasonable choices for prophylaxis. 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. The major underlying mechanism responsible for this multisystem disease is loss-of-function mutations in signal transducer and activator of transcription 3 (STAT3). Patients present in infancy with an eczematoid and pustular rash on
INFECTIONS IN HUMORAL IMMUNODEFICIENCIES

their face. 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.

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.

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 and via follicular helper T cells, 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.

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. 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.

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. These patients may also have an increased risk of malignancy, in particular, lymphoma and squamous cell carcinoma. 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. Before undergoing stem cell transplantation, patients with DOCK8 deficiency should be treated with Ig replacement therapy in addition to 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. Partial or “leaky” SCID, including Omenn syndrome, is diagnosed based on T-cell lymphopenia adjusted for age (age <2 years, <1000 cells/mm³; age 2-4 years, <800 cells/mm³; age >4 years, <600 cells/mm³) and PHA response <30% of the control value. 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.

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. 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 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.

REFERENCES

1. Picard C, Bobby Gaspar H, Al-Herz W, et al. International union of immunological societies: 2017 primary immunodeficiency diseases committee report on inborn errors of immunity. J Clin Immunol 2018;38:96-128.
2. Modell V, Gee B, Lewis DB, et al. Global study of primary immunodeficiency diseases (PI)—diagnosis, treatment, and economic impact: an updated report from the Jeffrey Modell Foundation. Immunol Res 2011;51:61-70.
3. Cunningham-Rundles C, Maglione PJ. Common variable immunodeficiency. J Allergy Clin Immunol 2012;129:1425-6.
4. Azi G, Rezaei N, Kiae F, et al. T-cell abnormalities in common variable immunodeficiency. J Investig Allergol Clin Immunol 2016;26:33-43.
5. Maglione PJ. Autoimmune and lymphoproliferative complications of common variable immunodeficiency. Curr Allergy Asthma Rep 2016;16:19.
6. Wehr C, Kivioja T, Schmitt C, et al. The EUROclass trial: defining subgroups in common variable immunodeficiency. Blood 2008;111:77-85.
7. Oksenhendler E, Gerard L, Fieschi C, et al. Infections in 25 patients with common variable immunodeficiency. Clin Infect Dis 2008;46:1547-54.
8. Verma N, Grimbacher B, Hurst JR. Lung disease in primary antibody deficiency. Lancet Respir Med 2015;3:651-60.
9. Sperlich JM, Grimbacher B, Workman S, et al. Respiratory infections and antibiotic usage in common variable immunodeficiency. J Allergy Clin Immunol Pract 2017;6:159-168.
10. Schussler E, Beasley MB, Maglione PJ. Lung disease in primary antibody deficiencies. J Allergy Clin Immunol Pract 2016;4:1039-52.
11. Maglione PJ, Overbey JR, Radigan L, et al. Pulmonary radiologic findings in common variable immunodeficiency: clinical and immunological correlations. Ann Allergy Asthma Immunol 2014;113:452-9.
12. Cunningham-Rundles C. Intravenous immune serum globulin in immunodeficiency. Vox Sang 1985;49(Suppl 1):8-14.
13. Busse PJ, Razvi S, Cunningham-Rundles C. Efficacy of intravenous immunoglobulin in the prevention of pneumonia in patients with common variable immunodeficiency. J Allergy Clin Immunol 2002;109:1001-4.
14. Orange JS, Grossman WJ, Navickis RJ, et al. Impact of trough IgG on pneumonia incidence in primary immunodeficiency: a meta-analysis of clinical studies. Clin Immunol 2010;137:21-30.
15. Quinti I, Soresina A, Guerra A, et al. Effectiveness of immunoglobulin replacement therapy on clinical outcome in patients with primary antibody deficiencies: results from a multicenter prospective cohort study. J Clin Immunol 2011;31:315-22.
16. Ballow M. Optimizing immunoglobulin treatment for patients with primary immunodeficiency disease to prevent pneumonia and infection incidence: review of the current data. Ann Allergy Asthma Immunol 2013;111(Suppl 6):S2-5.
17. Orange JS, Belohradsky BH, Berger M, et al. Evaluation of correlation between dose and clinical outcomes in subcutaneous immunoglobulin replacement therapy. Clin Exp Immunol 2012;169:172-81.
18. Uzzan M, Ko HM, Mehandru S, et al. Gastrointestinal disorders associated with common variable immune deficiency (CVID) and chronic granulomatous disease (CGD). Curr Gastroenterol Rep 2016;18:17.
19. Washington K, Stenzel TT, Buckley RH, et al. Gastrointestinal pathology in patients with common variable immunodeficiency and X-linked agammaglobulinemia. Am J Surg Path 1996;20:1240-52.
20. Agarwal S, Mayer L. Pathogenesis and treatment of gastrointestinal disease in antibody deficiency syndromes. J Allergy Clin Immunol 2009;124:658-64.
21. Brown JK, Clark I, Brown JR, et al. Norovirus infection in primary immune deficiency. Rev Med Virol 2017;Mar 8. http://doi.org/10.1002/rmv.1926.
22. Woodward J, Gkrania-Klotsas E, Kumararatne D. Chronic norovirus infection and common variable immunodeficiency. Clin Exp Immunol 2017;188:363-70.
23. Woodward JM, Gkrania-Klotsas E, Cordero-Ng AY, et al. The role of chronic norovirus infection in the enteropathy associated with common variable immunodeficiency. Am J Gastroenterol 2015;110:320-7.
24. Loughar V, Baronio M, Vitali M, et al. Bruton tyrosine kinase mediates TLR9-dependent human dendritic cell activation. J Allergy Clin Immunol 2014;133:1644-50.
25. Farrar JE, Rohrer J, Conley ME. Neutropenia in X-linked agammaglobulinemia. Clin Immunol Immunopathol 1996;81:271-6.
26. Hendriks RW, Bredius RG, Pike-Overzet K, et al. Biology and novel treatment options for XLA, the most common monogenetic immunodeficiency in man. Expert Opin Ther Targets 2011;15:1003-21.
27. Quartier P, Debré M, De Blic J, et al. Early and prolonged intravenous immunoglobulin replacement therapy in childhood agammaglobulinemia: a retrospective survey of 31 patients. J Pediatr 1999;134:589-96.
28. Webster AD, Taylor-Robinson D, Furr PM, et al. Mycoplasma (ureaplasma) septic arthritis in hypogammaglobulinaemia. Br Med J 1978;1:478-9.
29. Sugimoto M, Takeuchi T, Muramatsu H, et al. Recurrent cellulitis caused by Helicobacter cinaedi in a patient with X-linked agammaglobulinemia. Acta Derm Venereol 2017;97:277-8.
30. Degand N, Dautremer J, Plinis B, et al. Helicobacter bilis-associated suppurative cholangitis in a patient with X-linked agammaglobulinemia. J Clin Immunol 2017;37:727-31.
31. Munoz-Miguelsanz MA, Alvarez Morales T, Martin Garcia JA, et al. Pseudomonas aeruginosa liver abscess as the first manifestation of X-linked agammaglobulinemia with a novel mutation. J Invest Allergol Clin Immunol 2017;27:129-31.
32. Arai A, Kitano A, Sawabe E, et al. Relapsing Campylobacter coli bacteremia with reactive arthritis in a patient with X-linked agammaglobulinemia. Intern Med 2007;46:605-9.
33. Gerrard J, Alfredson D, Smith I. Recurrent bacteremia and multifocal lower limb cellulitis due to Helicobacter-like organisms in a patient with X-linked agammaglobulinemia. Clin Infect Dis 2001;33:E116-8.
34. Gofshtein J, Cardenas AM, Bearden D. Treatment of chronic enterovirus encephalitis with fluoxetine in a patient with X-linked agammaglobulinemia. Pediatr Neurol 2016;64:94-8.
35. Bearden D, Collett M, Quan PL, et al. Enteroviruses in X-linked agammaglobulinemia: update on epidemiology and therapy. J Allergy Clin Immunol Pract 2016;4:1059-65.
36. Qamar N, Fuleihan RL. The hyper IgM syndromes. Clin Rev Allergy Immunol 2014;46:120-30.
37. de la Morena MT. Clinical phenotypes of hyper-IgM syndromes. J Allergy Clin Immunol Pract 2016;4:1023-36.
38. Leven EA, Maizzi U, Ochs HD, et al. Hyper IgM syndrome: a report from the USIDNET registry. J Clin Immunol 2016;36:490-501.
39. de la Morena MT, Leonard D, Torgerson TR, et al. Long-term outcomes of 176 patients with X-linked hyper-IgM syndrome treated with or without hematopoietic cell transplantation. J Allergy Clin Immunol 2017;139:1282-92.
40. Picard C, Casanova JL, Puel A. Infectious diseases in patients with Irak-4, MyD88, NEMO, or IkappaBalpha deficiency. Clin Microbiol Rev 2011;24:490-7.

41. Mitsui-Sekinaka K, Imai K, Sato H, et al. Clinical features and hematopoietic stem cell transplantations for CD40 ligand deficiency in Japan. J Allergy Clin Immunol 2015;136:1018-24.

42. Bonilla FA, Khan DA, Ballas ZK, et al. Practice parameter for the diagnosis and management of primary immunodeficiency. J Allergy Clin Immunol 2015;136:1186-205.e1–78.

43. Aucouturier P, Berthier M, Bonneau D, et al. Serum levels of IgG subclasses in the normal child. Evaluation by an immunoenzymatic method using monoclonal antibodies. Arch Fr Pediatr 1988;45:255-8.

44. Douglas RM, Paton JC, Duncan SJ, et al. Antibody response to pneumococcal vaccination in children younger than five years of age. J Infect Dis 1983;148:131-7.

45. Abrahamian F, Agrawal S, Gupta S. Immunological and clinical profile of adult patients with selective immunoglobulin subclass deficiency: response to intravenous immunoglobulin therapy. Clin Exp Immunol 2010;159:344-50.

46. Fried AJ, Bonilla FA. Pathogenesis, diagnosis, and management of primary antibody deficiencies and infections. Clin Microbiol Rev 2009;22:396-414.

47. Perez E, Bonilla FA, Orange JS, et al. Specific antibody deficiency: controversies in diagnosis and management. Front Immunol 2017;8:586.

48. Good R. Agammaglobulinemia- a provocative experiment of nature. Bull Univ Minn 1954;26:1-19.

49. Good RA, Varco RL. A clinical and experimental study of agammaglobulinemia. J Lancet 1955;75:245-71.

50. Gray GF, Gutowski WT 3rd. Thymoma. A clinicopathologic study of 54 cases. Am J Surg Path 1979;3:235-49.

51. Souadjian JV, Enriquez P, Silverstein MN, et al. The spectrum of diseases associated with thymoma. Coincidence or syn-drome? Arch Intern Med 1974;134:374-9.

52. Kelesidis T, Yang O. Good syndrome: an evidence. Clin Immunol 2016;4:1054-8.

53. Tarr PE, Sneller MC, Mechanic LJ, et al. Infections in patients with immunodeficiency with thymoma (Good syndrome). Report of 5 cases and review of the literature. Medicine (Baltimore) 2001;80:123-33.

54. Jansen A, van Deuren M, Miller J, et al. Prognosis of good syndrome: mortality and morbidity of thymoma associated immunodeficiency in perspective. Clin Immunol 2016;171:12-7.

55. Malphettes M, Gerard L, Galicier L, et al. Good syndrome: an adult-onset immunodeficiency remarkable for its high incidence of invasive infections and autoimmune complications. Clin Infect Dis 2015;61:e13-9.

56. Agarwal S, Cunningham-Rundles C. Thymoma and immunodeficiency (Good syndrome): a report of 2 unusual cases and review of the literature. Ann Allergy Asthma Immunol 2007;98:185-90.

57. Multani A, Gomez CA, Montoya JG. Prevention of infectious diseases in patients with Good syndrome. Curr Opin Infect Dis 2018;31:267-77.

58. Buckley RH, Wray BB, Belmaker EZ. Extreme hyperimmunoglobulinemia E and undue susceptibility to infection. Pediatrics 1972;49:59-70.

59. Holland SM, DeLeo FR, Elloumi HZ, et al. STAT3 mutations in the hyper-IgE syndrome. N Engl J Med 2007;357:1608-19.

60. Minegishi Y, Karasuyama H. Hyperimmunoglobulin E syndrome and tyrosine kinase 2 deficiency. Curr Opin Allergy Clin Immunol 2007;7:506-9.

61. Renner ED, Torgerson TR, Rylaarsdam S, et al. STAT3 mutation in the original patient with Job’s syndrome. N Engl J Med 2007;357:1667-8.

62. Chamlin SL, McElmont TH, Cunningham BB, et al. Cutaneous manifestations of hyper-IgE syndrome in infants and children. J Pediatr 2002;141:572-5.

63. Woellner C, Gertz EM, Schaffer AA, et al. Mutations in STAT3 and diagnostic guidelines for hyper-IgE syndrome. J Allergy Clin Immunol 2010;125:424-32 e8.

64. Almyroudis NG, Holland SM, Segal BH. Invasive aspergillosis in primary immunodeficiencies. Med Mycol 2005;43(Suppl 1):S247-59.

65. Meyer-Bahlburg A, Renner ED, Rylaarsdam S, et al. Heterozygous signal transducer and activator of transcription 3 mutations in hyper-IgE syndrome result in altered B-cell maturation. J Allergy Clin Immunol 2012;129:559-62, 562.e1-2.

66. Speckmann C, Enders A, Woellner C, et al. Reduced memory B cells in patients with hyper IgE syndrome. Clin Immunol 2008;129:448-54.

67. Ma CS, Avery DT, Chan A, et al. Functional STAT3 deficiency compromises the generation of human T follicular helper cells. Blood 2012;119:3997-4008.

68. Chandesris MO, Melki I, Natividad A, et al. Autosomal dominant STAT3 deficiency and hyper-IgE syndrome: molecular, cellular, and clinical features from a French national survey. Medicine (Baltimore) 2012;91:e1-19.

69. Gernez Y, Tsuang A, Smith TD, et al. Hemoptysis in a patient with elevated immunoglobulin E. J Allergy Clin Immunol Pract 2016;4:1054-8.

70. Bilora F, Petrobelli F, Boccioletti V, et al. Moderate-dose intravenous immunoglobulin treatment of Job’s syndrome. Case report. Minerva Med 2000;91:113-6.

71. Kimata H. High-dose intravenous gamma-globulin treatment for hyperimmunoglobulinemia E syndrome. J Allergy Clin Immunol 1995;95:771-4.

72. Zhang Q, Davis JC, Lamborn IT, et al. Combined immunodeficiency associated with DOCK8 mutations. N Engl J Med 2009;361:2046-55.

73. Mizesko MC, Banerjee PP, Monaco-Shawver L, et al. Defective actin accumulation impairs human natural killer cell function in patients with dedicator of cytokinesis 8 deficiency. J Allergy Clin Immunol 2013;131:840-8.

74. Aydin SE, Kilic SS, Aytekin C, et al. DOCK8 deficiency: clinical and immunological phenotype and treatment options - a review of 136 patients. J Clin Immunol 2015;35:189-98.

75. Chu EY, Freeman AF, Jing H, et al. Cutaneous manifestations of DOCK8 deficiency syndrome. Arch Dermatol 2012;148:79-84.
76. Freeman AF, Shah NN, Parta M, et al. Haploidentical related donor hematopoietic stem cell transplantation with post-transplantation cyclophosphamide for DOCK8 deficiency. J Allergy Clin Immunol Pract 2016;4:1239-42.e1.Epub 2016 Sep 15.
77. Griffith LM, Cowan MJ, Notarangelo LD, et al. Primary Immune Deficiency Treatment Consortium (PIDTC) report. J Allergy Clin Immunol 2014;133:335-47.
78. Shearer WT, Dunn E, Notarangelo LD, et al. Establishing diagnostic criteria for severe combined immunodeficiency disease (SCID), leaky SCID, and Omenn syndrome: the primary immune deficiency treatment consortium experience. J Allergy Clin Immunol 2014;133:1092-8.
79. Dorsey MJ, Dvorak CC, Cowan MJ, et al. Treatment of infants identified as having severe combined immunodeficiency by means of newborn screening. J Allergy Clin Immunol 2017;139:733-42.
80. Kalman L, Lindegren ML, Kobrynski L, et al. Mutations in genes required for T-cell development: IL7R, CD45, IL2RG, JAK3, RAG1, RAG2, ARTEMIS, and ADA and severe combined immunodeficiency: HuGE review. Genet Med 2004;6:16-26.
81. Pachlopnik Schmid J, Gungor T, Seger R. Modern management of primary T-cell immunodeficiencies. Pediatr Allergy Immunol 2014;25:300-13.
82. White H, Thrasher A, Veys P, et al. Intrinsic defects of B cell function in X-linked severe combined immunodeficiency. Eur J Immunol 2000;30:732-7.
83. 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:S1-S46.
84. Kuruvilla M, de la Morena MT. Antibiotic prophylaxis in primary immune deficiency disorders. J Allergy Clin Immunol Pract 2013;1:573-82.
85. Mikoluc B, Pietrucha B, Motkowski R, et al. Prevention of infections in primary and secondary antibody deficiency. Przegl Epidemiol 2009;63:55-60.