Immunoglobulin Use in Immune Deficiency and Autoimmune Disease States

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ABSTRACT

Although immunoglobulin (Ig) has been available since the 1950s for replacement therapy in primary immune deficiency, many other effective uses of this class of biologics have been investigated and evolved over recent decades. Ig administration has become common practice in the treatment of the immunocompromised patient and has recently expanded into the treatment of those patients with an inflammatory disease and autoimmune neuropathies per established clinical guidelines. As research into the genetic basis of disease advances, clinicians should better assess complex data surrounding safe and effective uses of Ig to treat patients who present with B-cell and T-cell deficiencies, along with those harboring gene deletions or genetic anomalies who may potentially benefit from Ig therapy. Evidence-based clinical indications for the use of Ig include idiopathic thrombocytopenic purpura, B-cell chronic lymphocytic leukemia, Kawasaki disease, chronic idiopathic demyelinating polyneuropathy, multifocal motor neuropathy, bone marrow transplantation, and pediatric HIV infection, among others, and have evolved over time. Ig is also often tried in refractory cases that might benefit from its anti-inflammatory effects or empirically in off-label situations. Due to its anti-inflammatory effects, high-dose Ig has been used for numerous off-label indications with varying levels of effectiveness and evidence to support its use. A review of all autoimmune conditions for which Ig has been used is beyond the scope of this article and newer treatments are available for many of these disorders. Here the focus will be on selected conditions in which Ig has clear benefit. Because there is a limited supply of Ig and a need for further research into optimal use, it is important for healthcare professionals to better understand current and developing indications and data/levels of evidence to support Ig therapy as its role continues to evolve.

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For author information and disclosures, see end of text.

Overview of the History of the Use of Immunoglobulin

The history of treating disease with antibodies began in the 1800s after tetanus and diphtheria toxins were discovered, leading to the realization that immunity to the infections caused by these organisms could be transferred through immune serum. Results of research determined that antibody proteins could be isolated and used as a defense against infectious disease. The arrival of scientific methods to separate antibodies from plasma for safe human injection was the starting point for development of human gamma globulin for individuals with inherited antibody deficiencies.[1]

However, these early immunoglobulin (Ig) treatments were limited by an intramuscular or subcutaneous (SC) route of administration due to low product purity. Ig was shown to be effective for prophylaxis for those exposed to measles or hepatitis A infections. The standard dose at the time was approximately 100 to 150 mg/kg; however, intravenous (IV) administration of these doses to children with measles resulted in severe adverse effects (AEs), including convulsions, fever, restlessness, chills, and even vasomotor collapse. These reactions limited Ig use to administration via intramuscular or SC routes at that time.[1,2] The desire to deliver larger Ig doses led to changes in manufacturing to produce safe IV injectable formulations. This administration route allowed for Ig to be used for a wider variety of clinical conditions. Treatment with Ig was expanded to allow for larger doses for disease suppression in inflammatory and autoimmune disorders. Further research led to more concentrated Ig formulations that can be injected SC for therapy. In addition, home-based SC infusion methods entered the treatment landscape, allowing for improved and more convenient access for patients who needed Ig therapy.[1]

Immunoglobulins are antibodies produced by differentiated B cells called plasma cells. The Ig molecule has a distinctive structure that has the ability to recognize specific antigenic determinants. Ig formulations are produced from the pooled human plasma of thousands of healthy donors, which allows the Ig formulations to contain a large and diverse antibody repertoire.[3] It is important to understand that the supply of Ig is finite because it depends

on donated plasma. Appropriate administration of Ig can be life-saving, and clinicians must be familiar with how to manage any associated AEs. Clinicians prescribing Ig need to better recognize current clinical indications for Ig therapy and the levels of evidence to support its use in immune disorders.[4]

Disease State Overviews, Place of Immunoglobulin in Therapy, and Evidence for Use

Primary Immunodeficiency Diseases

Primary immunodeficiency diseases comprise a heterogenous collection of genetic disorders that impact distinct elements within the innate and adaptive immune system; these may include macrophages, natural killer cells, dendritic cells, neutrophils, complement proteins, B lymphocytes, and T lymphocytes.[3] Primary immunodeficiencies are relatively uncommon. They are inherited genetic disorders that may occur alone or as part of a syndrome, and heterogeneity may be substantial within each disorder. Primary immunodeficiencies tend to become apparent during infancy or childhood, but many primary immunodeficiencies present in adulthood. The estimated overall incidence of primary immunodeficiencies is 1 per 1200 individuals.[5,6] Originally, a male-to-female ratio ranging from 2:1 to 1.4:1 was reported; however, this ratio was found to be closer to 1:1 in more recent data from a US cohort.[7,8] Recent advances in molecular and cellular characterizations of these disorders have delineated their genetic complexity with an estimated 354 inborn errors of immunity defined as of February 2017.[9]

Agammaglobulinemia

Agammaglobulinemia comprises a class of primary immunodeficiency diseases characterized by absent or very low serum antibodies caused by the absence of B lymphocytes in both blood and bone marrow.[4,10] Although the exact incidence of agammaglobulinemia has yet to be elucidated, it has been estimated overall to affect approximately 1 in 300,000 individuals, with X-linked agammaglobulinemia (XLA), having an estimated prevalence ranging between 1 in 350,000 to 1 in 700,000.[11,12] This disorder is further classified into 3 subclasses: XLA, XLA with growth hormone deficiency, and autosomal recessive agammaglobulinemia.[10] The XLA form of the disorder is caused by a defect in the Bruton tyrosine kinase gene, which is vital to B-cell maturation and development. Because this gene is located on the X chromosome, only males are affected, whereas females are carriers. This form of the disorder comprises approximately 85% of agammaglobulinemia cases.[11]

The major symptoms associated with agammaglobulinemia are frequent and severe bacterial infections due to failures in immune response related to the B-cell defects.[10] They usually manifest as recurrent upper and lower respiratory tract infections and begin within the first few years of life in patients with XLA.[13] The respiratory infections related to agammaglobulinemia are most often caused by bacteria such as *Streptococcus pneumoniae*, *Haemophilus influenzae* type B, *Streptococcus pyogenes*, and *Pseudomonas*. Antibody binding is critical for the clearance of these microorganisms. The recurrence of respiratory infections in young patients creates substantial morbidity during the active illness and may also increase the patient's risk for developing chronic lung disease. Repeated episodes of pneumonia can result in chronic airway inflammation, such as bronchiectasis and scarring.[11,13,14]

Agammaglobulinemia caused by a lack of B cells is the clearest indication for the replacement of Ig.[4] Historical retrospective data of children with agammaglobulinemia have demonstrated that both the number and severity of complications related to infection are inversely correlated with intravenous immunoglobulin (IVIG) dose administrations.[4,15,16] In fact, serious bacterial illness was prevented when immunoglobulin G (IgG) trough levels were maintained above 500 mg/dL.[4,16]

More recently, a study by Orange et al centered on the question of the effect of trough level on the incidence of pneumonia. The investigators performed a meta-analysis of clinical trial studies evaluating trough IgG and pneumonia incidence in patients with hypogammaglobulinemia primary immunodeficiencies. This encompassed 17 studies with 676 total patients and 2127 patient-years of follow-up. Results demonstrated that the incidence of pneumonia declined by 27% with each 100 mg/dL increment in trough IgG level. The pneumonia risk for patients at trough levels of 1000 mg/dL was one-fifth of those whose trough levels were 500 mg/dL. Overall, the findings suggest that pneumonia risk can be progressively reduced by higher trough IgG levels.[4,17,18]

Hypogammaglobulinemia

Hypogammaglobulinemia occurs when Ig levels in the serum decrease or there is a significant lack of IgG antibody response to an antigen vaccine challenge. In these patients, deficient antibody production leads to decreased Ig concentrations and a considerable inability of a patient to have an IgG antibody response to challenge with an antigen. Notable diagnostic factors associated with hypogammaglobulinemia include recurrent infections (*S pneumoniae* or *H influenzae*), infections caused by atypical pathogens, and repeated use of antibiotics for treatment. Primary hypogammaglobulinemia affects young children and adults. Examples of primary immunodeficiencies that fall into this category include combined immunodeficiency disorders, combined immunodeficiency with syndromic features, such as Wiskott-Aldrich syndrome (WAS), hyper-immunoglobulin M (IgM) syndromes, and diseases of immune dysregulation with autoimmunity.[4]

Ig replacement is indicated for patients with recurrent bacterial infections and reduced serum Ig levels who also fail to respond to a protein or polysaccharide vaccine challenge. For example, a patient may be unable to make IgG antibodies against the tetanus

toxoid and/or pneumococcal polysaccharide vaccines. A patient with common variable immunodeficiency (CVID) is a typical example, as CVID is the most frequently diagnosed heterogenous disorder related to antibody deficiency.[4] An international consensus definition of CVID was recently published and includes the following criteria for diagnosis: a low IgG level measured on at least 2 occasions 3 weeks apart (repeated measurement may be eliminated if the IgG level is 100-300 mg/dL), low IgM and/or IgA, impaired antibody response (vaccine responses) to at least 1 type of T dependent or independent antigen, and exclusion of other types of hypogammaglobulinemia.[19] CVIDs are the most common culprit identified in symptomatic primary antibody failure in both children and adults.[20]

Data from a cohort of patients with confirmed CVIDs in a medical center over a 22-year period assessed Ig doses for IVIG therapy, finding that the doses had been adjusted in accordance to infection severity versus treated to any trough IgG level. Trough IgG levels ranging from 5 g/L to 17 g/L were found to prevent breakthrough infection. Doses of replacement Ig used for preventive purposes ranged from 0.2 g/kg/month to 1.2 g/kg/month. There was a strong correlation between baseline serum IgG levels and the increases to IgG levels, at which point patients were free of infection. Complications also played a significant role. Patients with bronchiectasis received higher Ig doses than those without bronchiectasis. In addition, the clinical phenotype of each CVID was an important factor. Patients who had enteropathy, cytopenias, and polyclonal lymphoproliferation needed substantially higher Ig doses to prevent infection than patients with lymphoid malignancies. Results overall hallmarked the importance of Ig therapy in these patients; replacement doses required to keep a patient bacterial infection-free have to be individualized for each patient. This highlights the heterogeneity of the patient population, CVID phenotypes, and the need for individualized management of each patient with CVID and hypogammaglobulinemia who requires Ig replacement.[4,18,20]

Specific Antibody Deficiency

Specific antibody deficiency (SAD), also termed selective antibody deficiency, is a primary immunodeficiency characterized by normal levels of Igs but that is impaired by specific antibody production.[4,6] Patients with SAD have normal IgA, IgM, total IgG, and IgG subclass levels; however, they also have recurrent infections and poor antibody responses to polysaccharide antigens after vaccination. SAD presents complex diagnostic and therapeutic challenges because there is a lack of consensus over both areas. The overall clinical significance of SAD disorders is not well understood.[21] Four phenotypes of SAD have been defined: memory, mild, moderate, and severe. Any of the phenotypes may require antibiotic prophylaxis, Ig replacement, or both depending on the individual patient and actual clinical illness. Patients who can initially mount adequate antibody concentrations against polysaccharide antigens but have a waning response to an antigen challenge over a 6-month period have the memory phenotype.[4,22]

Ig replacement for patients with SAD should be provided if severe polysaccharide nonresponsiveness (against the 23-valent pneumococcal polysaccharide vaccine) has been firmly established along with evidence for recurrent bacterial infections requiring antibiotic therapy for the individual patient.[4,21] Antibiotics are the first-line therapy for infections; however, infection severity and antibiotic prophylactic efficacy are critical to any decision surrounding Ig replacement in patients. Further evidence of infection should be documented, including abnormalities of sinus or pulmonary imaging, elevations in C-reactive protein, and erythrocyte sedimentation rates, which may provide additional evidence to support Ig replacement therapy. In addition, although patients with SAD may receive benefit from conjugate vaccine immunization, Ig replacement is indicated if there is poor antibody response to vaccination.[23,24] Ig replacement is considered appropriate in patients with recurrent and treatment-refractory otitis media who are at risk for permanent hearing loss, bronchiectasis, recurrent infections requiring IV antibiotics, failed antibiotic prophylaxis, and diminished quality of life because of recurrent infections, in addition to any hypersensitivities to antibiotic prophylaxis that may inhibit optimal therapy.[4]

Recurrent Infections Due to Unknown Immune Mechanism

Ig therapy may be the only feasible option for treatment in patients with primary immunodeficiency diseases where the actual mechanism surrounding the individual's inability to prevent recurrent infection has no obvious etiology. In these cases, the patient presents with recurrent episodes of an infection but has normal or near-normal immune function upon assessment. Culprit disorders include hyper-immunoglobulin E (IgE) syndrome with normal IgG, IgM, and IgA but defects in antibody response; WAS with normal total IgG but impaired protein and polysaccharide antigen response; or ataxia telangiectasia (AT) with IgA and IgG2 deficiencies and a documented history of infection susceptibility.[4]

The consensus is that Ig therapy in these disorders is a useful adjunct to therapy. Data have demonstrated that some patients with hyper-IgE syndrome and recurrent respiratory infections have benefited from Ig replacement.[4,25] Use of Ig replacement with prophylactic antibiotics in patients with WAS was supported in a study of 73 centers and 507 patients.[4,26] It has also been estimated that 12% to 15% of patients with AT require Ig therapy.[4]

Secondary Immunodeficiency

A secondary immunodeficiency results from immune system compromise due to a nongenetic factor.[27] Ig replacement therapy

has been utilized in a variety of diseases that lead to a secondary humoral deficiency, including hematologic malignancies, pediatric HIV infections, prematurity, geriatrics, hypogammaglobulinemia associated with solid organ or bone marrow transplantation, and patients who have received B-cell–depleting agents for therapy.[4]

Chronic Lymphocytic Leukemia

The most common complication and cause of mortality in chronic lymphocytic leukemia (CLL), a hematologic malignancy, is infection that occurs in patients with hypogammaglobulinemia, advanced disease, or both.[4] Recurrent infections create substantial morbidity and mortality in patients with CLL, causing 30% to 50% of deaths from the disease.[28-31] Hypogammaglobulinemia is a frequent complication of hematologic malignancies, most commonly seen in CLL and multiple myeloma (MM).[31]

Data from studies of patients with CLL have demonstrated the benefit of Ig replacement therapy to prevent infection. Raanani et al assessed multiple trials of patients with CLL and MM and found that there was a significant decrease in the occurrence of major infections in patients treated with Ig (relative risk, 0.45). Although there was no survival benefit noted in this trial, the investigators concluded that Ig replacement therapy should be considered on an individual basis for patients with CLL and hypogammaglobulinemia.[32]

Clinicians may consider replacement Ig therapy for patients with CLL and recurrent serious bacterial infections whose antibody levels fall below the protective level following the receipt of diphtheria, tetanus, or pneumococcal vaccine.[4] It is important to emphasize that patient selection for Ig treatment should be based on proven antibody production deficit rather than hypogammaglobulinemia alone.[31] In fact, current guidelines for therapy specifically state that hypogammaglobulinemia by itself does not constitute a basis for even initiating CLL treatment.[33]

Multiple Myeloma

Infections are a major factor for increased morbidity and mortality in patients with MM.[34] Early data surrounding approximately 3100 patients with MM demonstrated that 45% of early deaths (within 6 months) in patients with MM were caused by infections.[34,35] A more recent study of 9253 patients found that patients with MM had a 7-fold higher risk of developing any infection versus matched controls.[34]

As noted above with CLL, data from studies of patients with MM have demonstrated the benefit of Ig replacement therapy to prevent infection. Results from multiple trials have shown a significant decrease in the occurrence of major infections in patients with MM treated with Ig.[32] A recent analysis of 47 patients with MM who had a history of recurrent moderate to severe bacterial infections demonstrated that treatment with IVIG resulted in a significant decline in the infection rate following therapy. The rate declined from 17% to 0% in patients with severe infection, 55% to 34% in patients with a moderate degree of infection, and 28% to 21% in patients who were considered to have mild infection.[36] Ig replacement therapy should be considered on an individual basis for patients with MM, hypogammaglobulinemia, and proven antibody deficit.[31,32]

Autoimmune Diseases

Immunoglobulin has been used for therapy in a number of autoimmune disorders, although efficacy in this area varies. Complicating factors exist because this category includes several different autoimmune diseases (eg, hematologic, neurologic, organ-specific) and the treatment approach to these diseases has markedly changed and advanced with the introduction of biologic and immunomodulating drugs for therapy.[4]

Guillain-Barré Syndrome

Guillain-Barré syndrome (GBS) is a demyelinating peripheral neuropathy, specifically a polyradiculopathy, characterized by acute progressive motor weakness that involves the extremities, bulbar and facial muscles, and sensory or autonomic dysfunction in some patients. The disorder is thought to be caused by the immunologic destruction of either myelin or the Schwann cells of the peripheral nervous system.[4] It is a syndrome that occurs post infection, most commonly with *Campylobacter jejuni*, although the Epstein-Barr virus, *Mycoplasma pneumoniae*, and *H influenzae* have also been implicated in the development of GBS. Rapid and progressive weakness is a key feature of GBS and is usually reached within 4 weeks, followed by a plateau phase that can last from several weeks to months.[37]

GBS can be treated with a combination of IVIG, corticosteroids, and plasma exchange.[4] IVIG is administered at 2 g/kg body weight, usually in 0.4 g/kg doses for 5 consecutive days.[37] Data from randomized trials have suggested that IVIG started within 14 days from the onset of GBS symptoms accelerates recovery as much as plasma exchange (plasma exchange is considered superior to supportive care alone). IVIG therapy has been found to be more likely to be completed versus plasma exchange because of its enhanced convenience and greater availability, in addition to fewer AEs.[37,38]

Kawasaki Disease

Kawasaki disease (KD), also termed Kawasaki syndrome or mucocutaneous lymph node syndrome, occurs in children. It is hallmarked by fever, rash, hand and foot swelling, red and irritated eyes, mouth and throat inflammation, and swollen lymph nodes in the neck. Acute disease tends to be self-limiting and not serious, although long-term cardiac complications can occur in some patients if not diagnosed and treated early.[39]

The administration of IVIG and aspirin in the acute phase is considered the standard of care in children with KD to prevent

the development of cardiac complications, specifically coronary aneurysms.[4,40] Standard first-line therapy for KD centers around a recommended dose of 2 g/kg of IVIG in combination with 80 mg/kg to 100 mg/kg oral aspirin administered within the first 10 days when the illness is evident. This regimen has shown significant efficacy in preventing coronary aneurysm development. However, approximately 15% to 20% of patients treated with this regimen will require a second IVIG treatment to control inflammation. The addition of corticosteroids to therapy is undergoing continued investigation, with some Japanese studies demonstrating additional therapeutic benefit.[41]

Immune Thrombocytopenic Purpura

Immune thrombocytopenic purpura (ITP) is a hematologic disorder characterized by isolated thrombocytopenia caused by low levels of platelets. The disorder affects both adults and children, with pediatric patients accounting for half of the diagnoses of ITP.[42,43] Although ITP can occur without signs or symptoms, typical symptoms include easy and excessive bruising, superficial bleeding into the skin that appears as petechiae and nosebleeds, and gum bleeding.[43,44]

Treatment of ITP is usually indicated in children who are at the highest risk of complication from bleeding and patients with chronic refractory disease.[4] Current standards of care outline that corticosteroids are the cornerstone of treatment for ITP. IVIG and anti-D Ig (for patients with Rh-positive blood type) have also been recommended for first-line therapy. IVIG can rapidly increase the platelet count and is the preferred therapy for those patients with active bleeding. IVIG is usually administered as a single dose that can be repeated as needed based on platelet increase response that is expected within 24 to 48 hours in up to 85% of those who are treated, although further use of IVIG after the initial dose is dependent on clinical response to the initial dose.[45-48]

Chronic Inflammatory Demyelinating Polyneuropathy

Chronic inflammatory demyelinating polyneuropathy (CIDP) is a neurologic disease that manifests as progressive weakness in the arms and legs along with an impaired sensory function in the extremities. The disorder occurs from damage to the myelin sheath over the peripheral nerves. Most common in young adults and in men, CIDP often begins with symptoms of tingling or numbness that initiates in the fingers and toes, extremity weakness, areflexia, and feelings of abnormal sensations. This disorder is closely related to GBS and is often referred to as a clinical counterpart of that neurologic disorder.[49] However, the progression of CIDP is less acute and often takes weeks or months.[4]

Immunoglobulin has become part of the therapy regimen for CIDP over the past 2 decades along with corticosteroids and plasma exchange. Approximately 50% to 70% of patients with CIDP will respond to IVIG therapy.[50] The IVIG in CIDP Efficacy Trial (ICE) studied 117 patients with CIDP who received either IVIG or placebo using the Inflammatory Neuropathy Cause and Treatment (INCAT) criteria and assessed improvement in the INCAT disability score for the analysis over 24 weeks. Those who showed improvement could then be reassigned in a 24-week extension trial. Results demonstrated that 54% of patients treated with IVIG had an improvement in an adjusted disability score versus 21% of those who received placebo, and that was maintained to week 24. This was a crossover trial, and results were similar during the crossover period. The investigators concluded that this trial demonstrated the short- and long-term efficacy of IVIG to treat patients with CIDP.[50,51] With the evolving treatment landscape, home-based SC infusion for immunoglobulin agents have proved to be another option as well, allowing for improved and more convenient access for patients. It should also be a consideration for patients with poor venous access, cardiovascular risks, and systemic IVIG-related AEs.

Conclusions

Ig therapy is now essential and standard for the treatment of many different immune and inflammatory diseases and has also been determined to be useful in other disorders, not limited to the diseases discussed here. As noted earlier, appropriate use of Ig can reduce disease morbidity and even save lives. With the growing list of indications for Ig administration, it is imperative for healthcare professionals to fully comprehend the optimal use of this therapy. Ig therapy needs to be applied where it is supported by well-researched evidence and where it will provide the most clinical benefit. Data surrounding best practices in Ig use will continue to evolve, providing more treatment options for patients that may improve outcomes and quality of life for those affected by a variety of both common and rare diseases. ■

Please note that information on the use of Ig in disorders other than the ones covered here can be found in the following review article: 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. doi: 10.1016/j.jaci.2016.09.023.

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REFERENCES

1. Hooper JA. The history and evolution of immunoglobulin products and their clinical indications. *LymphoSign J.* 2015;2(4):181-194. doi: 10.14785/lpsn-2014-0025.
2. Schiff RI. Intravenous gammaglobulin: pharmacology, clinical uses and mechanisms of action. *Pediatr Allergy Immunol.* 1994;5(2):63-87.
3. Fernández-Cruz E, Alecsandru D, Ramón SS. Mechanisms of action of immune globulin. *Clin Exp Immunol.* 2009;157(suppl 1):1-2. doi: 10.1111/j.1365-2249.2009.03955.x.
4. 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. doi: 10.1016/j.jaci.2016.09.023.
5. Boyle JM, Buckley RH. Population prevalence of diagnosed primary immunodeficiency diseases in the United States. *J Clin Immunol.* 2007;27(5):497-502. doi: 10.1007/s10875-007-9103-1.
6. Bonilla FA, Khan DA, Ballas ZK, et al; American Academy of Allergy, Asthma and Immunology; American College of Allergy, Asthma and Immunology; Joint Council of Allergy, Asthma and Immunology. Practice parameter for the diagnosis and management of primary immunodeficiency. *J Allergy Clin Immunol.* 2015;136(5):1186-1205. doi: 10.1016/j.jaci.2015.04.049.
7. Joshi AY, Iyer VN, Hagan JB, et al. Incidence and trends of primary immunodeficiency: a population-based cohort study. *Mayo Clin Proc.* 2009;84(1):16-22. doi: 10.1016/S0025-6196(11)60802-1.
8. Rezaei N, de Vries E, Gambineri E, Haddad E. Common presentations and diagnostic approaches. In: Sullivan KE, Stiehm ER, eds. *Stiehm's Immune Deficiencies*. London, UK: Elsevier; 2014:9.
9. 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(1):96-128. doi: 10.1007/s10875-017-0464-9.
10. Agammaglobulinemia. National Organization for Rare Disorders website. rarediseases.org/rare-diseases/agammaglobulinemia. Published 2018. Accessed January 22, 2019.
11. Geng B. Understanding agammaglobulinemia. IG Living website. igliving.com/magazine/articles/IGL_2017-04_AR_Understanding-Agammaglobulinemia.pdf#search=%22agammaglobulinemia%22. Published April-May 2017. Accessed April 30, 2019.
12. Orphanet. X-lined agammaglobulinemia. December 2013. Orphanet website. orpha.net/consor/cgi-bin/OC_Exp.php?Lng=GB&Expert=47. Accessed March 5, 2019.
13. Winkelstein JA, Marino MC, Lederman HM, et al. X-linked agammaglobulinemia: report on a United States registry of 201 patients. *Medicine (Baltimore).* 2006;85(4):193-202. doi: 10.1097/01.md.0000229482.27398.ad.
14. Tarzi MD, Grigoriadou S, Carr SB, et al. Clinical immunology review series: an approach to the management of pulmonary disease in primary antibody deficiency. *Clin Exp Immunol.* 2009;155(2):147-155. doi: 10.1111/j.1365-2249.2008.03851.x.
15. Liese JG, Wintergerst U, Tympner KD, Belohradsky BH. High- vs low-dose immunoglobulin therapy in the long-term treatment of X-linked agammaglobulinemia. *Am J Dis Child.* 1992;146:335-339.
16. Quartier P, Debre 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(5):589-596.
17. Orange JS, Grossman WJ, Navickis RJ, Wilkes MM. Impact of trough IgG on pneumonia incidence in primary immunodeficiency: a meta-analysis of clinical studies. *Clin Immunol.* 2010;137(5):21-30. doi: 10.1016/j.clim.2010.06.012.
18. Immunoglobulin therapy standards of practice. 2nd ed. 2018. Immunoglobulin National Society website. ig-ns.org/product/ig-therapy-standards-of-practice. Accessed February 13, 2019.
19. Bonilla FA, Balan I, Chapel H, et al. International Consensus Document (ICON): Common Variable Immunodeficiency Disorders. *J Allergy Clin Immunol Pract.* 2016;4(1):38-59. doi: 10.1016/j.jaip.2015.07.025.
20. Lucas M, Lee M, Lortan J, Lopez-Granados E, Misbah S, Chapel H. Infection outcomes in patients with common variable immunodeficiency disorders: relationship to immunoglobulin therapy over 22 years. *J Allergy Clin Immunol.* 2010;125(6):1354-1360. doi: 10.1016/j.jaci.2010.02.040.
21. Perez E, Bonilla FA, Orange JS, Ballow M. Specific antibody deficiency: controversies in diagnosis and management. *Front Immunol.* 2017;8:586. doi: 10.3389/fimmu.2017.00586.
22. Orange JS, Ballow M, Stiehm E, et al. Use and interpretation of diagnostic vaccination in primary immunodeficiency: a working group report of the Basic and Clinical Immunology Interest Section of the American Academy of Allergy, Asthma & Immunology. *J Allergy Clin Immunol.* 2012;130(3 suppl):S1-S24. doi: 10.1016/j.jaci.2012.07.002.
23. Bonilla FA, Bernstein IL, Khan DA, et al; American Academy of Allergy, Asthma and Immunology; American College of Allergy, Asthma and Immunology; Joint Council of Allergy, Asthma and Immunology. Practice parameter for the diagnosis and management of primary immunodeficiency. *Ann Allergy Asthma Immunol.* 2005;94(5 suppl 1):S1-S63 [erratum in *Ann Allergy Asthma Immunol.* 2006;96(3):504]. doi: 10.1016/j.jaci.2015.04.049.
24. Albin S, Cunningham-Rundles C. An update on the use of immunoglobulin for the treatment of immunodeficiency disorders. *Immunotherapy.* 2014;6(10):1113-1126. doi: 10.2217/imt.14.67.
25. Bilora F, Petrobelli F, Boccioletti V, Pomerri F. Moderate-dose intravenous immunoglobulin treatment of Job's syndrome. Case report. *Minerva Med.* 2000;91(5-6):113-116.
26. Conley ME, Saragoussi D, Notarangelo L, Etzioni A, Casanova JL; PAGID; ESID. An international study examining therapeutic options used in treatment of Wiskott-Aldrich syndrome. *Clin Immunol.* 2003;109(3):272-277.
27. Secondary immune deficiency disease definition. American Academy of Allergy, Asthma and Immunology website. aaaai.org/conditions-and-treatments/conditions-dictionary/secondary-immune-deficiency-disease. Published 2019. Accessed January 22, 2019.
28. Hamblin AD, Hamblin TJ. The immunodeficiency of chronic lymphocytic leukaemia. *Br Med Bull.* 2008;87:49-62. doi: 10.1093/bmb/ldn034.
29. Morrison VA. Infectious complications in patients with chronic lymphocytic leukemia: pathogenesis, spectrum of infection, and approaches to prophylaxis. *Clin Lymphoma Myeloma.* 2009;9(5):365-370. doi: 10.3816/ CLM.2009.n.071.
30. Dhalla F, Lucas M, Schuh A, et al. Antibody deficiency secondary to chronic lymphocytic leukemia: should patients be treated with prophylactic replacement immunoglobulin? *J Clin Immunol.* 2014;34(3):277-282. doi: 10.1007/s10875-014-9995-5.
31. Sánchez-Ramón S, Dhalla F, Chapel H. Challenges in the role of gammaglobulin replacement therapy and vaccination strategies for hematological malignancy. *Front Immunol.* 2016;7:317. doi: 10.3389/fimmu.2016.00317.
32. Raanani P, Gafter-Gvili A, Paul M, Ben-Bassat I, Leibovici L, Shpilberg O. Immunoglobulin prophylaxis in chronic lymphocytic leukemia and multiple myeloma: systematic review and meta-analysis. *Leuk Lymphoma.* 2009;50(5):764-772. doi: 10.1080/10428190902856824.
33. Hallek M, Cheson BD, Catovsky D, et al. iwCLL guidelines for diagnosis, indications for treatment, response assessment, and supportive management of CLL. *Blood.* 2018;131(25):2745-2760. doi: 10.1182/blood-2017-09-806398.
34. Bilmark C, Holmberg E, Mellqvist UH, et al. Multiple myeloma and infections: a population-based study on 9253 multiple myeloma patients. *Haematologica.* 2015;100(1):107-113. doi: 10.3324/haematol.2014.107714.
35. Augustson BM, Begum G, Dunn JA, et al. Early mortality after diagnosis of multiple myeloma: analysis of patients entered onto the United Kingdom Medical Research Council trials between 1980 and 2002--Medical Research Council Adult Leukaemia Working Party. *J Clin Oncol.* 2005;23(36):9219-9226. doi: 10.1200/JCO.2005.03.2086.
36. Khalafallah A, Maiwald M, Cox A, et al. Effect of immunoglobulin therapy on the rate of infections in multiple myeloma patients undergoing autologous stem cell transplantation or treated with immunomodulatory agents. *Mediterr J Hematol Infect Dis.* 2010;2(1):e2010005. doi: 10.4084/MJHID.2010.005.
37. van Doorn PA, Kuitwaard K, Walgaard C, van Koningsveld R, Ruts L, Jacobs BC. IVIG treatment and prognosis in Guillain-Barré syndrome. *J Clin Immunol.* 2010;30(suppl 1):S74-S78. doi: 10.1007/s10875-010-9407-4.
38. Hughes RA, Raphael JC, Swan AV, Doorn PA. Intravenous immunoglobulin for Guillain-Barré syndrome. *Cochrane Database Syst Rev.* 2004(1):CD002063. doi: 10.1002/14651858.CD002063.pub2.
39. Kawasaki disease. American Heart Association website. heart.org/en/health-topics/kawasaki-disease. Published 2018. Accessed January 22, 2019.
40. Sundel RP. Update on the treatment of Kawasaki disease in childhood. *Curr Rheumatol Rep.* 2002;4(6):474-482.
41. Shulman ST. Intravenous immunoglobulin for the treatment of Kawasaki disease. *Pediatr Ann.* 2017;46(1):e25-e28. doi: 10.3928/19382359-20161212-01.
42. Cines DB, Bussel JB. How I treat idiopathic thrombocytopenic purpura (ITP). *Blood.* 2005;106(7):2244-2251. doi: 10.1182/blood-2004-12-4598.
43. Kayal L, Jayachandran S, Singh K. Idiopathic thrombocytopenic purpura. *Contemp Clin Dent.* 2014;5(3):410-414. doi: 10.4103/0976-237X.137976.
44. Cines DB, McMillan R. Management of adult idiopathic thrombocytopenic purpura. *Annu Rev Med.* 2005;56:425-442. doi: 10.1146/annurev.med.56.082103.104644.
45. Stasi R, Provan D. Management of immune thrombocytopenic purpura in adult patients. *Mayo Clin Proc.* 2004;79(4):504-522. doi: 10.4065/79.4.504.
46. Neunert C, Lim W, Crowther M, Cohen A, Solberg N Jr, Crowther MA; American Society of Hematology. The American Society of Hematology 2011 evidence-based practice guideline for immune thrombocytopenia. *Blood.* 2011;117(16):4190-4207. doi: 10.1182/blood-2010-08-302984.
47. Khan AM, Mydra H, Nevarez A. Clinical practice updates in the management of immune thrombocytopenia. *PT.* 2017;42(12):756-763.
48. Podjasek JC, Abraham RS. Autoimmune cytopenias in common variable immunodeficiency. *Front Immunol.* 2012;3:189. doi: 10.3389/fimmu.2012.00189.
49. Chronic inflammatory demyelinating polyneuropathy (CIDP). National Institute of Neurological Disorders and Stroke website. ninds.nih.gov/Disorders/All-Disorders/Chronic-Inflammatory-Demyelinating-Polyneuropathy-CIDP-Information-Page. Updated June 15, 2018. Accessed January 22, 2019.
50. Gorson KC. An update on the management of chronic inflammatory demyelinating polyneuropathy. *Ther Adv Neuro Disord.* 2012;5(6):359-373. doi: 10.1177/1756285612457215.
51. Hughes R, Donofrio P, Bril V, et al; ICE Study Group. Intravenous immune globulin (10% caprylate-chromatography purified) for the treatment of chronic inflammatory demyelinating polyradiculoneuropathy (ICE study): a randomised placebo-controlled trial. *Lancet Neurol.* 2008;7(2):136-144. doi: 10.1016/S1474-4422(07)70329-0.