Immunotherapy

An update on the use of immunoglobulin for the treatment of immunodeficiency disorders

For patients with significant antibody deficiencies, immunoglobulin therapy is the mainstay of treatment as it significantly reduces both the frequency and severity of infections. The formulations and delivery methods of immunoglobulin have evolved over time, and continued improvements have allowed for increased access to this effective medication. This review is an update on the current status of immunoglobulin therapy in immunodeficiency disorders, and discusses the mechanisms, forms and dosing, and indications for immunoglobulin replacement.

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Immunoglobulin therapy

Therapeutic immunoglobulin is a blood product derived from thousands of healthy, pooled donors [1,2], and preparations are made up of almost exclusively IgG (although commercially available products also contain trace amounts of IgA and IgM) [3,4]. Routine administration of immunoglobulin is required as replacement therapy in immunodeficient patients who do not naturally produce robust, protective antibodies. Replacement doses usually start between 400 and 600 mg/kg every 3–4 weeks intravenously (or the equivalent given in divided doses once or twice a week subcutaneously). Since its inception, the goal of therapy is to provide levels of functional serum IgG expected in normal subjects, and sufficient amounts of passive antibodies capable of neutralization and opsonization of broad categories of infectious pathogens, including bacteria, viruses and parasites [5]. These levels of Ig are called replacement doses, but it should also be appreciated that immunoglobulin therapy likely has an active role in the development and function of various immune cells including dendritic cells, monocytes/macrophages, granulocytes, NK cells, and T and B cells.

In contrast to replacement doses, sometimes much higher, immunomodulating doses of immunoglobulin are indicated for autoimmune and inflammatory conditions. Some of the mechanisms contributing to these immunomodulating processes have been elucidated, but much of the complex role immunoglobulin plays in shaping the immunologic environment is still poorly understood [1,6]. While these varied functions have provided a basis for the use of this therapy in a large number of autoimmune and inflammatory disorders [7–10], this aspect of immunoglobulin therapy is beyond the scope of this review.

Immunoglobulin therapy in immune deficiencies

While there are well over 150 different forms of primary immunodeficiency diseases, about 70% of all patients have defects of antibody production, and thus immunoglobulin replacement therapy provides the first line of treatment for these subjects [11]. Antibody deficiencies can result from errors in B-cell differentiation at different stages of development, dysfunctional immunoglobulin development through B- and T-cell inter-

Table 1. Primary immunodeficiency diseases and indications for immunoglobulin replacement.

Disease	Clinical findings	Immunologic findings	Immunoglobulin replacement	Comments
XLA	Recurrent bacterial infections Absent/reduced tonsils and lymph nodes	<1% normal B cells Agammaglobulinemia Poor specific antibodies	Start replacement at the time of diagnosis	Patients require lifelong Ig replacement
CVID	Recurrent bacterial infections Inflammatory and autoimmune disease Lymphoid malignancies	Hypogammaglobulinemia Poor specific antibodies Variable T-cell abnormalities	Start replacement at the time of diagnosis	Ig replacement does not treat noninfectious complications
IgG subclass deficiency	Recurrent bacterial infections	Normal total IgG Low levels of IgG subclasses (one or more) Poor specific antibodies	Consider replacement if patient meets criteria and has clinically significant infections	There is no consensus on whether or not these patients require Ig replacement
Specific antibody deficiency	Recurrent bacterial infections	Normal IgG, IgA, IgM Abnormal IgG antibody responses to protein and/or unconjugated polysaccharide vaccines	Consider replacement if patient has vaccine nonresponsiveness and clinically significant infections	After several years on Ig replacement, patients can be taken off to attempt vaccine re-challenge (particularly in young patients)
Selective IgA deficiency	Recurrent bacterial infections Allergic disorders Enteropathy Autoimmune disease Lymphoid malignancies	Low IgA (<0.07 g/l) Normal IgG and IgM	Consider replacement only in rare cases in which IgG antibody deficiency, with or without IgG2 deficiency, is also identified	Most patients are asymptomatic and do not require any treatment
HIGM	Recurrent infections Opportunistic infections Cytopenias Lymph node hyperplasia (AR forms) Inflammatory and autoimmune disease (AR forms)	Normal or elevated IgM Low or absent IgG, IgA and IgE Poor specific antibodies Variable T-cell abnormalities	Start replacement at the time of diagnosis	
WAS	Recurrent infections Microthrombocytopenia with or without bleeding Atopic dermatitis Autoimmune disease Lymphoid malignancies	Decreased lymphocytes Variable defects in T-, B- and NK-cell function Variable IgM Normal or elevated IgA Elevated IgG and IgE Often abnormal IgG antibody responses to unconjugated polysaccharide vaccines	Consider replacement at the time of diagnosis	Bone marrow transplantation is the only curative treatment; Ig replacement is supportive

CVID: Common variable immunodeficiency; HIES: Hyper IgE syndrome; HIGM: Hyper IgM syndromes; SCID: Severe combined immunodeficiency; WAS: Wiskott-Aldrich syndrome; XLA: X-linked agammaglobulinemia

Table 1. Primary immunodeficiency diseases and indications for immunoglobulin replacement (cont.).			
Disease	**Clinical findings**	**Immunologic findings**	**Immunoglobulin replacement**	**Comments**
SCID	Recurrent infections Opportunistic infections Chronic diarrhea Failure to thrive Graft versus host disease	T-cell deficiency Variable B- and NK-cell function	Start replacement at the time of diagnosis	Bone marrow transplantation is the only curative treatment; Ig replacement is supportive (but may still be required after transplant)
Others				
Transient hypogammaglobulinemia	Physiologic delay in maturation	Low serum IgG and IgA Poor specific antibodies	Some are given replacement for a period	Treatment stopped after some months to ascertain recovery
DiGeorge syndrome	Constellation of findings associated with embryologic defects including cardiac anomalies, parathyroid gland hypoplasia and thymus hypoplasia or aplasia	Often low circulating T cells Variable degrees of hypogammaglobulinemia Variable specific antibodies	Consider replacement if patients have low serum IgG	A recent survey reported that overall, between 2 and 3% of patients were receiving Ig replacement therapy
HIES	Loss of IL-21 B-cell signals	Poor specific antibodies	Some are on replacement	

CVID: Common variable immunodeficiency; HIES: Hyper IgE syndrome; HIGM: Hyper IgM syndrome; SCID: Severe combined immunodeficiency; WAS: Wiskott-Aldrich syndrome; XLA: X-linked agammaglobulinemia

actions, loss of cytokine signals, or underlying defects in immunoglobulin class switching. While these diseases differ in their epidemiology, pathophysiology and clinical phenotype, they all share an increased susceptibility to infection due to a deficiency of antibody and are treated with immunoglobulin therapy. The main categories of these diseases are outlined here and summarized in Table 1.

X-linked agammaglobulinemia

X-linked agammaglobulinemia (XLA) is an antibody deficiency caused by a mutation in the gene for Bruton's tyrosine kinase, which leads to a marked (<1% of normal) reduction in B cells and agammaglobulinemia [12]. The estimated birth rate for XLA in the US is around 1/379,000 births [13], and the age of onset of symptoms for most patients is between 3 months and 3 years [14]. Patients are protected by maternally transmitted IgG antibodies in the first few months of life, and often remain clinically well for those first months of life. The clinical manifestations of XLA include recurrent bacterial infections such as otitis, sinusitis and pneumonia, with physical exam findings of absent or barely detectable tonsillar and lymph node tissue [15]. Infections are typically from encapsulated bacteria, mainly *Streptococcus pneumoniae* and *Haemophilus influenzea* [16]. In addition, patients with XLA are subject to infections at other sites (urinary, joint and brain) by pathogens such as *Ureaplasma* and enterovirus [17,18].

Subjects with XLA have severe infectious morbidity without appropriate therapy, but immunoglobulin replacement has proven successful in preventing infections and allowing patients to lead healthy and productive lives [19,20]. Formal guidelines recommend the initiation of immunoglobulin at the time of diagnosis, although there are no additional specifics regarding timing of this therapy in the earliest months [21]. In an unusual report of a prenatally diagnosed patient, quantitative and specific immunoglobulin levels were tracked from birth. All levels were initially normal, but immunoglobulin replacement was started at 2 months of age with the first evidence of waning, nonprotective specific antibodies [22]. Regardless of the timing of initiation, all patients require replacement immunoglobulin as a life-long treatment.

Larger amounts of immunoglobulin may be considered in special circumstances of XLA, including those with persistent bacterial infections, bronchiectasis and nonbacterial infections [23]. In general, if infections are not controlled on immunoglobulin monotherapy, routine antibiotic prophylaxis may be required [21]. However, it should be appreciated that some expert clinicians prescribe daily, therapeutic doses of antibiotics along with immunoglobulin for all XLA patients as their standard of care [16]. Of the nonbacterial infections, enterovirus is of particular concern and can cause a chronic course marked by encephalitis, meningitis, pneumonia, hepatitis or dermatomyositis [13]. Case reports have shown that treatment with more IVIG may lead to significant clinical improvement in patients with chronic enteroviral infection [24]. The antiviral pleconaril has been used with benefit in some cases, but is not approved for use in the USA [21].

Common variable immunodeficiency

Common variable immunodeficiency (CVID) is a heterogeneous group of disorders, but all patients by definition have hypogammaglobulinemia (low levels of two out of three major isotypes) with evidence of nonprotective antibody responses against pathogens. Patients can also have a variety of T-cell abnormalities [25]. This immune defect often occurs without an identified genetic cause, although cohorts of CVID patients have been found to have mutations in CD81, CD19, CD20, CD21, inducible costimulator, transmembrane activator and calcium-modulating and cyclophilin ligand interactor, and B-cell activating factor among others [26]. CVID affects approximately 1/20,000 to 1/50,000 individuals, and it is most frequently diagnosed between the age of 20 and 40 [27]. The clinical manifestations of CVID include infections (particularly respiratory, sinus and gastrointestinal), inflammatory disease, autoimmune phenomenon, and an increased incidence of cancer and lymphoma [28]. Infections are typically from encapsulated bacteria, mainly *S. pneumoniae* and *H. influenzea*, but can also be caused by atypical bacteria such as *Mycoplasma* and parasites such as *Giardia* [28].

The evidence for effectiveness of immunoglobulin for reducing serious infections, particularly pneumonia, has been well established for CVID [29,30]. As with XLA, immunoglobulin replacement may be used in conjunction with prophylactic antibiotics. Immunoglobulin therapy often starts at the time of diagnosis, as recurrent infections can lead to bronchiectasis and worsening of pre-existing disease [31]. As for XLA, larger doses of immunoglobulin can be considered in special circumstances of CVID, including in the setting of persistent bacterial infections, bronchiectasis and pregnancy [32,33]. Immunoglobulin does not primarily treat the noninfectious manifestations of CVID however, and additional immunosuppressive, anti-inflammatory, cytotoxic and anti-proliferative medications may be required in the appropriate context of autoimmune and malignant conditions [21].

IgG subclass deficiency

IgG has four subclasses: IgG1, IgG2, IgG3 and IgG4, with somewhat different structural and biological properties. A deficiency of one or more of these subclasses with a normal total IgG level is termed IgG subclass deficiency, and for the most part, the causes and prevalence of this deficiency are not known. One study estimated that approximately 1–3% of the Caucasian population may be heterozygotes for heavy-chain gene deletions that could lead to a laboratory finding of a decreased IgG subclass [34]. However, clinically symptomatic patients are rare and may not be due to gene mutations. In these cases, IgG2 and IgG3 deficiencies are the most common subclass defects, in children and adults, respectively [35,36]. IgG subclass deficiency remains a controversial diagnosis, and most experts agree that the loss of one or more IgG isotype may not be clinically relevant if there is sufficient antibody production.

When patients are symptomatic, they usually have a history of recurrent sinopulmonary infections, although more serious and invasive infections may also occur [37]. Antibody to polysaccharide capsular antigens are somewhat more concentrated in the IgG2 fraction, thus subjects lacking IgG2 may be at risk for infections with *S. pneumoniae*, *Haemophilus influenzae* type b and *Neisseria meningitides* [38]. IgG3 deficiency is more prevalent in the adult population and as for IgG1, contains higher concentrations of antibody to protein antigens (toxoids and viruses), as well as to *Moraxella catarrhalis* and the M component of *Streptococcus pyogenes* [39].

Examination of serum of patients and demonstrating low levels of one or more IgG subclasses cannot be used to determine biological relevance, as compensating antibody to various microbes can be contained in any of the isotypes. For this reason, immunoglobulin replacement is indicated only if significant antibody dysfunction (i.e., nonprotective antibody response after vaccine or disease exposure) can be established. However, there are suggestions of consensus but no firm guidelines on the laboratory assessment and the definition of a 'normal antibody response' in this disease [40]. A clear exception is the case of IgA deficiency with IgG2 subclass deficiency, as the loss of anti-carbohydrate antibody in such cases can lead to devastating bacterial illnesses and chronic lung disease [41,42]. Aside from these cases, there are few reports on the efficacy of IVIG in IgG subclass deficiency, although an open-label study evaluating efficacy of monthly replacement (albeit in a very small group of patients) showed deceased number of infections, decreased antibiotics, decreased hospitalizations and improved quality of life [43].

Specific antibody deficiency

Specific antibody deficiency is an antibody deficiency of unknown origin, but is characterized by normal concentrations of IgG, IgA, IgM and IgG subclasses with abnormal IgG antibody responses to protein and/or unconjugated polysaccharide vaccines (i.e., PPV23) [44,45]. Patients may have normal responses to protein antigens, such as tetanus and diphtheria toxoids, and conjugate vaccines, such as *Haemophilus influnzae* type B, PCV7 and PCV 13. Diagnosis is established by evaluating vaccine titers after 2 years of age, particularly examining the production of antibodies specific for panels of proteins and pneumococcal capsular antigens. The interpretation of anti-pneumococcal antibodies is based on pre- and postimmunization concentrations, and adequate responses are defined as postimmunization antibody concentrations equal to or greater than 1.3 µg/ml or at least fourfold over baseline (as long as the preimmunization titer is less than 4 µg/ml) [21,46]. The disease prevalence for impaired anti-carbohydrate responses is reportedly 7–19% among children with recurrent sinopulmonary infections, including sinusitis, otitis media, bronchitis and pneumonia [47]. Infections in these cases are caused by bacteria such as *S. pneumoniae, Haemophilus influenzae, M. catarrhalis* and *Staphylococcus aureus* [48].

Patients with specific antibody deficiency may benefit from immunization with conjugate vaccines [21], although some may not respond to these additional vaccination efforts. In these cases, immunoglobulin replacement should be provided in the setting of severe polysaccharide nonresponsiveness with recurrent infections requiring antibiotic therapy. However, clinicians should be thoughtful about the duration of immunoglobulin treatment in very young children, as the ability to mount responses to unconjugated polysaccharide vaccines improves with age [49]. After several years, patients may be tried off immunoglobulin and re-challenged with pneumococcal or other vaccines after a period ranging from 2 to 6 months [21]. However, the decision to take a patient off of replacement therapy is best determined by individual physicians on a case-by-case basis, particularly as adults may not have significant improvement with time.

Selective IgA deficiency

Selective IgA deficiency is defined as decreased (<0.07 g/l) serum IgA levels in the presence of normal levels of serum IgG and IgM [50]. Although there is no well-defined genetic susceptibility in IgA deficiency, familial clustering has been found in some cases, with a common finding of maturation defects in B cells that produce IgA [51]. Selective IgA deficiency is considered the most common primary immunodeficiency,

although the incidence varies depending on ethnic background. It is most common among Caucasian populations, and frequency in the US ranges from 1:500 to 1:3000 among healthy blood donors [50]. The vast majority of patients with IgA deficiency are clinically asymptomatic, but a significant number develop recurrent infections, allergic disorders, enteropathy, autoimmune phenomenon or possibly, lymphoid malignancies. The sinopulmonary and gastrointestinal tracts are particularly vulnerable as their protective barrier is compromised in the absence of secretory IgA, and infections at these sites are often from *S. pneumoniae*, *Haemophilus influenza* and *Giardia lamblia* [51].

Asymptomatic patients with selective IgA deficiency do not need immunoglobulin treatment as most are quite healthy and are often identified through incidental observation. Recurrent infections should be treated as needed with prophylactic antibiotics, and immunoglobulin replacement may be considered only in rare cases when concomitant findings (such as a specific antibody defect) are present [21]. It should be reinforced that despite isolated cases, in general selective IgA deficiency is not an indication for immunoglobulin, and administration may lead to anaphylaxis or similarly severe reactions for IgA-deficient patients who have IgG or IgE anti-IgA antibodies [52], although this appears to be a very uncommon event [53].

Hyper IgM syndromes

Hyper IgM syndromes (HIGM) are a group of antibody deficiencies characterized by defective CD40/CD40L interactions, leading to impaired immunoglobulin isotype switching. Patients have normal or elevated IgM levels with low or absent IgA, IgG and IgE levels in the serum, and they can also have defective T-cell function [54]. HIGM is genetically characterized by X-linked and autosomal recessive patterns of inheritance; X-linked forms of the disease are caused by mutations in CD40 ligand or (rarely) NF-κB essential modulator, and autosomal recessive forms are caused by mutations in CD40 or downstream signaling molecules including AID and UNG [55]. HIGM is very rare, with one national registry in the US estimating a minimal incidence of approximately 1/1,030,000 live births [56]. The clinical manifestations of HIGM depend on the molecular defect, with phenotypes ranging from that of a primary antibody deficiency to a combined immunodeficiency with susceptibility to opportunistic infections. Patients may develop cytopenias, especially neutropenia. X-linked HIGM often presents within the first 2 years of life with lower respiratory tract infections, frequently caused by *Pneumocystis jiroveci*. These patients also develop chronic diarrhea and liver disease, from pathogens such as *Cryptosporidium* [57]. Autosomal recessive

HIGM also presents with sinopulmonary infections, but these patients do not typically develop opportunistic infections. Unlike the X-linked form, patients with autosomal recessive disease develop lymph node hyperplasia (caused by the presence of giant germinal centers) as well as more predominant autoimmune and inflammatory disorders [58].

Immunoglobulin therapy is indicated for all forms of HIGM to decrease frequency and severity of infections, and studies have shown that patients treated with immunoglobulin have reduced incidence of pneumonia and protection against meningitis [56–58]. Additional treatments include prophylactic antibiotics (which cover *Pneumocystis*) and GCSF for neutropenia. Bone marrow transplant has been successful in reconstitution of X-linked CD40L deficiency, although there has been significant mortality with this intervention when *Cryptosporidium* infection is reactivated [59].

Wiskott-Aldrich syndrome

Wiskott-Aldrich syndrome is a disease commonly described as a triad of recurrent infections, microthrombocytopenia and eczema, although the characteristics of immunodeficiency and expression of clinical features vary from patient to patient [60]. Patients also are predisposed to autoimmune disorders and malignancies, particularly EBV-related lymphomas [21]. It is an X-linked disease caused by mutations in the *WASP* gene, which in turn affects production of the WAS protein found exclusively in hematopoietic cells. WAS protein is involved in the transduction of signals from receptors on the cell surface to the actin cytoskeleton, and mutations can lead to both absent and decreased protein expression with variable clinical phenotypes [61]. Absent protein expression results in a more severe Wiskott-Aldrich syndrome with defects in the function of multiple hematopoietic cell lineages, while decreased protein expression can result in a milder disease of X-linked thrombocytopenia, characterized mainly by isolated thrombocytopenia [62]. The immunologic profile of patients with Wiskott-Aldrich syndrome includes decreased lymphocyte counts, defects in T-, B- and NK-cell function, variable levels of serum IgM, normal to high levels of IgA and high levels of IgG and IgE. Patients can produce a normal antibody response to protein antigens, but often cannot mount a normal antibody response to polysaccharide antigens [61]. This combined immunodeficiency puts patients at risk for bacterial, viral and fungal infections. The incidence of Wiskott-Aldrich syndrome is estimated at less than 1/100,000 live births, making it a rare disease [63].

Bone marrow transplant is the only curative treatment for Wiskott-Aldrich syndrome, although supportive treatment includes immunoglobulin therapy,

antibiotics and antivirals, splenectomy, measures to control bleeding, judicious use of platelet transfusions when there is active bleeding, and disease-specific agents for autoimmune and malignant conditions [64]. About half of the centers treating patients reported using immunoglobulin replacement routinely to reduce the incidence of infections. In addition, there are no well-controlled studies documenting that immunoglobulin therapy is beneficial in this manner for patients with Wiskott-Aldrich syndrome [65]. There is some published data however, that immunoglobulin therapy can result in increased platelet numbers in patients with thrombocytopenia as a central feature [66]. As such, high-dose immunoglobulin therapy has been used for thrombocytopenia in Wiskott-Aldrich syndrome, but the response is variable [21]. In general, the use of immunoglobulin would be preferred for thrombocytopenia in Wiskott-Aldrich syndrome as splenectomy has an associated lifelong risk of infections.

Severe combined immunodeficiency

Severe combined immunodeficiency (SCID) is a heterogeneous group of genetic disorders characterized by significant T-cell deficiency, with variable production and function of B and NK cells [67]. It affects both cellular and humoral immunity, as antibody response is defective due to either direct deficiencies in B cells or indirect deficiency in B-cell activation from a lack of functional CD4 helper T cells. There are a number of genetic mutations leading to SCID, including mutations in *IL2RG*, *JAK3*, *IL7RA*, *RAG1* and *RAG2*, *DCLRE1C* and *ADA* among others [68–70]. The incidence of SCID is estimated to be around 1/50,000 live births, with a higher prevalence in males, as the most commonly identified mutation (IL2RG) is inherited in an X-linked fashion [71].

Infants born with SCID often appear normal at birth, but the risk of developing clinical manifestations with life-threatening infections, chronic diarrhea and failure to thrive increases as passively transferred maternal antibodies begin to wane after the first few months of life [72]. Infants can also develop symptoms of graft-versus-host disease from transplacental passage and engraftment of alloreactive maternal T cells. Infections are severe and originate from virtually any pathogen, including bacteria, viruses, fungi, protozoa, mycobacteria and opportunistic organisms. In a recent report of 50 infants with SCID from the Primary Immune Deficiency Treatment Consortium, the most common opportunistic infections at the time of diagnosis were viral (25%) including respiratory syncytial virus, rotavirus and enterovirus, also *P. jiroveci* (25%); bacterial infections (16%) including *Pseudomonas*, *Streptococcus* and *Staphylococcus*, and nontuberculous *Mycobacteria* (2%); and also *Candida* (16%) [67]. It should be noted however, that some patients with hypomorphic mutations of SCID-associated genes may have a later onset and milder immunodeficiency, which may however, include autoimmune complications [73].

SCID is considered a pediatric emergency, and it is uniformly fatal without hematopoietic stem cell transplantation. Early diagnosis and transplantation within the first three and half months of life has been found to have superior outcomes, which has been aided by the inclusion of T-cell receptor excision DNA circle (TREC) assays in various state-mandated newborn screens [74,75]. While awaiting transplant, patients with SCID are given prophylactic antibiotics and immunoglobulin replacement [21]. Immunoglobulin replacement should be started as early as possible, so as to prevent infections in the pretransplantation period, and it should be continued consistently until sufficient immune reconstitution has occurred. Immune reconstitution should be evaluated based on vaccine responses in the post-transplantation period, as a significant number of transplanted SCID patients continue to require immunoglobulin replacement secondary to failure of B-cell engraftment. In a publication reviewing a large cohort of SCID patients treated at one medical center from 1981 to 2000, only 6/12 survivors of HLA-identical and 22/77 survivors of haploidentical transplants had evidence of donor B cells, and 50/89 were on immunoglobulin replacement after transplantation [76].

Others

The production of immune globulin and functional antibodies relies on the interplay between many cells of the immune system. Thus, aside from the traditional categories of immune defects for which immunoglobulin is prescribed, a number of other immune defects lead to B-cell dysfunction. Some of the best known are the humoral defects that stem from insufficient T-cell development, such as in DiGeorge syndrome. For some years, it has been clear that moderate to more severe levels of immune globulin deficiency can be identified in these subjects, and a recent survey reported that overall, between 2 and 3% of patients with DiGeorge syndrome were receiving immunoglobulin replacement therapy [77]. This survey offered a potential strategy for determining the need for immunoglobulin replacement in DiGeorge syndrome; consider therapy for patients with recurrent sinopulmonary infections, deficits in serum immunoglobulin levels, and insufficient diphtheria and tetanus titers in the setting of prior immunization [77].

Table 2. Characteristics of immunoglobulin products available in the USA.

	Gammagard S/D	Gammagard liquid	Gammaplex	Bivigam	Carimune NF	Hizentra	Privigen	Flebogamma DIF	Gamunex-C	Gammaked	Octagam
Manufacturer	Baxter	Baxter	Bio Products Laboratory	Biotest Pharmaceuticals Corporation	CSL Behring	CSL Behring	CSL Behring	Grifols	Grifols	Kedrion	Octapharma
Available concentrations	5%, 10%	10%	5%	10%	3–12%	20%	5%, 10%	5%, 10%	10%	10%	5%
Sugar content	20 mg/ml glucose (5%), 40 mg/ml glucose (10%)	No added sugars	5% D-sorbitol	No added sugars	1.67 g sucrose/1 g of protein	None	None	None	None	None	100 mg/ml maltose
Sodium content	8.5 mg/ml sodium chloride (5%), 17 mg/ml sodium chloride (10%)	No added sodium	30–50 mmol/l	0.100–0.140 M sodium chloride	<20 mg sodium chloride/1 g of protein	Trace amount	Trace amount	Trace amount	Trace amount	Trace amount	≤30 mmol/l
Osmolarity/osmolality	636 mOsm/kg (5%), 1250 mOsm/kg (10%)	240–300 mOsm/kg	460–500 mOsm/kg	≤510 mOsm/kg	192–1074 mOsm/kg	380 mOsm/kg	Isotonic (320 mOsm/kg)	240–370 mOsm/kg	258 mOsm/kg	258 mOsm/kg	310–380 mOsm/kg
pH	6.8 ± 0.4	4.6–5.1	4.6–5.1	4.0–4.6	6.4–6.8	4.6–5.2	4.8	5.0–6.0	4.0–4.5	4.0–4.5	5.1–6.0
Stabilizer	Glucose	Glycine	D-sorbitol	Polysorbate	Sucrose	Proline	Proline	Sorbitol	Glycine	Glycine	Maltose
IgA content	≤1 µg/ml (5%), N/A for 10%	37 µg/ml	Average <4 mcg/ml	≤200 µg/ml	720 µg/ml	≤50 mcg/ml	≤25 mcg/ml	average <3 mcg/ml	46 µg/ml	46 µg/ml	<100 µg/ml
Approved methods of administration	iv.	iv., sc.	iv.	iv.	iv.	sc.	iv.	iv.	iv., sc.	iv., sc.	iv.

iv.: Intravenously; sc.: Subcutaneously.
Adapted from the Immune Deficiency Foundation's chart, characteristics of immune globulin products used to treat primary immunodeficiency diseases licensed for use in the US [81].

Another circumstance in which immunoglobulin therapy has occasionally been prescribed is infants with transient hypogammaglobulinemia. Here, delayed B-cell maturation appears to lead to a temporary B-cell defect. Antibiotic prophylaxis is often the initial method of preventative therapy. However, guidelines recommend that if antibiotic prophylaxis is not tolerated or effective, some patients could benefit from immunoglobulin therapy, particularly during seasons of pervasive respiratory infections [21]. The numbers of such patients treated is not clear, but in each case, careful follow-up with cessation of therapy after a year or two to retest is important. While some authors had suggested that immunoglobulin therapy might retard normal B-cell development in this context, a recent study showed that this was not the case [78].

A third example of a congenital defect in which antibody deficiency may be important is the Hyper IgE syndrome. While mutations in the *STAT3* gene lead to multiple outcomes, one includes signaling via the IL-21 receptor, important for B-cell function [79]. For some years, loss of antibody production had been noted in some subjects with Hyper IgE syndrome, although the molecular cause was not immediately identified. In some cases, immunoglobulin therapy has been used in these patients to help protect against bacterial infections.

Forms & dosing of immunoglobulin therapy

In the past, immunoglobulin was commonly administered by the intramuscular route, but this did not allow sufficient doses of immune globulin to raise serum IgG levels into the normal zone. Manufacturing advances led to the production of additional formulations. There currently are two routes of administration for immunoglobulin replacement in the US: intravenous (IVIG), first approved for use in 1979 and subcutaneous

(SCIG), first approved for use in 2006 [80]. There are eight commercial products readily available for intravenous use and three available for subcutaneous use. The products are not identical (although often treated as interchangeable in the hospital environment), and they vary in their concentration, osmolality, sugar, sodium, amino acid and IgA content [81] (Table 2). These biochemical properties should be considered in the context of unique patient profiles. For example, patients with cardiac impairment should avoid immunoglobulin with higher volumes, patients with renal dysfunction should avoid immunoglobulin with higher osmolality, and patients with anti-IgA antibodies can be treated with the IgA depleted product.

Early studies demonstrated no significant differences in efficacy between IVIG and SCIG [82] and no difference in quality of life when either treatment was done at home. However, SCIG may be preferable in some cases as it provides a comparatively more consistent IgG level [83]. Many patients also prefer weekly subcutaneous infusions, reporting independence from hospital-based infusion settings, flexibility and ease in dosing and decreased side effects [84,85]. As the SCIG formulations can be given in any location and generally do not require refrigeration, they simplify the needs of the traveler, or a student who does not live at home. On the other hand, for most adults, weekly administration is required due to volume considerations, in contrast to infusions every 3 or 4 weeks as needed for the intravenous route. Contrasts in aspects of these therapies are provided in (Table 3).

Strict evidence-based data on starting doses, infusion intervals and titration schedules for immunoglobulin replacement do not exist. Most consensus guidelines recommend starting in doses between 400 and 600 mg/kg every 3–4 weeks intravenously (or the equivalent given in divided doses once or twice a

Table 3. Contrasting intravenous and subcutaneous immunoglobulin therapy.		
	Intravenous	**Subcutaneous**
Route and timing	Every 3–4 weeks Faster increase of trough level at initiation Need for venous access	Weekly or biweekly Given by self administration Portable for use during travel Advantageous when venous access is poor
Compliance	Closer monitoring	Looser monitoring
Tolerance of drug	Systemic reactions are possible, especially on first infusions Usually no local reactions (i.e., redness and swelling)	No systemic reactions Local reactions include redness and itching, but these diminish Possibly better in patients with renal or cardiac insufficiency
Time needed	2–4 h	60–90 min with conventional infusions 5–20 min with push method
Others	High dose therapy possible	More stable IgG levels

week subcutaneously) to achieve trough IgG serum levels around 6–8 g/l [21,86,87]. However, starting doses may be higher depending on the clinical scenario. For example, immunodeficient patients with bronchiectasis may require higher replacement doses than those without lung disease [88]. Similarly, goal troughs may vary depending on baseline IgG levels, as patients with higher starting IgG levels and yet documented antibody deficiency should likely have higher trough levels as much of the IgG level is not functional. Most clinicians accept that higher IgG troughs are likely to diminish rates of infections, but there are mixed results in research looking at frequency and severity of infections as related to immunoglobulin dosing and trough levels [89–91]. Moreover, as clinical improvement is the gold standard, immunoglobulin therapy should be titrated up (either by increasing the dose or shortening the timing between infusions) based on the unique infectious patterns of an individual [88]. As a general rule however, levels 20% or more above the upper limit of normal should not be required.

Conclusion & future perspective

Immunoglobulin therapy is an important agent in the therapeutics armamentarium for primary immunodeficiency disorders affecting antibody production. It is accepted as a critical treatment for patients at risk of recurrent infection due to deficiency of antibody. While global antibody deficiency mandates immunoglobulin replacement, standardized and practical guidelines for immunoglobulin replacement in patients with more modest humoral immunodeficiency have not been defined. As practice currently stands, the antibody deficiencies listed above are the most common diagnoses to be treated with immunoglobulin, but physicians have a broad spectrum of discretion with regard to the therapy provided to individual patients.

In terms of a future direction for immunoglobulin therapy, first and foremost the hope remains that there will be improved education regarding appropriate patient workup before initiation of therapy. Baseline immunoglobulin levels, as well as specific antibodies to prior vaccinations should always be documented before beginning treatment with immunoglobulin replacement. If this is not accomplished, the practitioner cannot fully understand or appreciate the functional status of a patient's natural antibodies.

Outside of improved practices around pretreatment investigation, the future of immunoglobulin therapy hopefully also holds more convenient and specialized products. Commercially available formulations are moving toward more concentrated solutions, more

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Executive summary

Mechanism of immunoglobulin therapy
- Immunoglobulin is a blood product sourced from thousands of healthy, pooled donors.
- Preparations of immunoglobulin are made up of almost exclusively IgG, although commercial preparations also contain trace amounts of IgA.
- Patients with antibody deficiencies receive replacement immunoglobulin, which works by passive transfer of antibodies capable of neutralization and opsonization of a broad category of infectious pathogens.
- Patients with inflammatory disorders receive high-dose immunoglobulin, which works by unclear mechanisms of anti-inflammatory immune modulation.

Indications for use of immunoglobulin therapy
- Indications for immunoglobulin therapy in the setting of primary immunodeficiency include XLA, CVID, HIGM and SCID among others.

Forms & dosing of immunoglobulin therapy
- Immunoglobulin preparations vary in their concentration, osmolality, sugar content, sodium content and IgA content.
- Immunoglobulin replacement can be delivered intravenously or subcutaneously.
- Strict evidence-based data on starting doses, infusion intervals and titration schedules for immunoglobulin therapy do not exist, but most guidelines recommend starting between 400 and 600 mg/kg every 3–4 weeks intravenously (or equivalent dose divided weekly subcutaneously) to achieve trough IgG around 6–8 g/l.
- Therapy should be titrated up according to unique infectious patterns of an individual.

Conclusion & future perspective
- Immunoglobulin replacement is critical in many primary immunodeficiency disorders affecting antibody production.
- Patients should always have immunoglobulin levels and specific antibodies to prior vaccination checked before initiating therapy.
- Subcutaneous immunoglobulin paired with recombinant human hyaluronidase is an example of a new formulation aiming to improve absorption and availability of the drug, and other improved formulations are in development.

subcutaneous solutions and more integration with home care companies. Many of these efforts are aimed at improving patient quality of life, focusing on products that have less volume and can be infused in the home setting. In addition, specialized immunoglobulin preparations are already in the works; for example, recombinant human hyaluronidase (rHuPH20) has been combined with subcutaneous immunoglobulin to increase tissue permeability and facilitate absorption of drug. One open-label, multicenter study investigated the efficacy and tolerability of rHuPH20-facilitated SCIG (IGHy) in patients with primary immunodeficiency, and it found IGHy to be effective, safe and pharmacokinetically equivalent to IVIG with fewer systemic reactions [92]. Other specialized preparations are also in the works, including immunoglobulin enhanced with the neonatal Fc receptor. The neonatal Fc receptor regulates pH-dependent intracellular trafficking of IgG (resulting in a prolonged half-life in the serum), and groups have begun to explore this receptor as a means of enhancing absorption, distribution, metabolism and excretion of IgG-based therapeutics [93]. With inevitable advances in basic immunology and protein engineering, the future looks bright for immunoglobulin therapy.

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