Plasma-derived immunoglobulin (Ig) is used for an astonishingly wide range of autoimmune and inflammatory diseases, in addition to its traditional uses for prevention of infection and as antibody replacement and augmentation therapy in immune deficiency diseases. Increased recognition and treatment of immune deficiencies in the developing world have added to the global demand for IgG. However, the major reason for the continued strong growth in demand for IgG products is the increased use of "high-dose" therapy, particularly in autoimmune neurologic diseases. Long-term treatment of adults with doses in the range of 1–2 gr/kg or even more per month is the major contributor to the continuously growing global utilization of Ig products, which exceeded 143 metric tons in 2014. Indeed, the demand for Ig is the major driver of the increased demand for plasma and growth in fractionation capacity.

**Structure and origin of Ig molecules**

In order to understand the many uses for serum immunoglobulin preparations, it is necessary to understand the major difference between immunoglobulins and most other plasma proteins: diversity. The prototypic immunoglobulin molecule is a tetramer composed of two identical heavy chains, each with a molecular mass of approximately 55 kD and two identical light chains of 22 kD, giving an overall molecular mass of 155 kD. There are four major classes, or *isotypes*, of immunoglobulins in plasma: IgA, IgE, IgG, and IgM, with IgG accounting for 75% of all of the immunoglobulin in plasma. These classes are defined by the heavy chains α, ε, γ, and μ, respectively. Gamma heavy chains are actually a family of four types, γ1–γ4, which are grossly related but contain differences that result in different effector functions (Table 31.1). Depending on which chain a particular IgG molecule contains, it is assigned to "subclass" 1–4. Besides IgA, IgE, IgG, and IgM, there is a fifth class, IgD, composed of molecules with δ heavy chains. These play an important role in B-cell differentiation, but are only a minor component of the total plasma Ig pool. There are two types of light chains, κ and λ, and only one type is used in any individual Ig molecule. In addition, there are loci in the γ and κ chain genes at which different individuals may have different alleles or markers called *allotypes* in genetic studies, but their clinical significance is not known.

The four chains are arranged into a pair of dimers linked together with varying numbers of interchain disulfide bonds and sugar chains at characteristic positions in each class or subclass. Immunoglobulin molecules are generally depicted as having a Y-like structure (Figure 31.3). Each light chain contains a single variable region and a single constant region, whereas each heavy chain also has a single variable region, but three to four constant regions. The junction between the first and second constant regions of the heavy chain is considered a "hinge" that gives some flexibility to the arms. The variable regions of the light and heavy chains are aligned together to form the antigen-binding sites, whereas the heavy chain constant domains align to form a "handle," which binds receptors and other proteins that facilitate the effector functions and determine the metabolic fate of each class of molecules. IgA and IgM may contain an extra *joining (J) chain*, which binds to the heavy chains and holds together two of the four-chain units in the former, and five in the latter.

Ig molecules are cleaved into characteristic fragments by proteolytic enzymes such as papain or pepsin (Figure 31.3): The dimer containing the second and third constant domains of each of the heavy chains from all members of a class is crystallizable, and it has therefore been termed *Fc*. In contrast, because of the diversity of the variable regions, the fragments containing the antigen-binding sites are not crystallizable. With papain, the cleavage occurs toward the amino terminus side of the "hinge," and two separate but identical antigen-binding fragments (Fab) are released. With pepsin, cleavage occurs toward the carboxyl side of the hinge, and a single fragment with two identical antigen-binding sites ([F(ab′)]2) is produced. The antigen-binding specificity of each immunoglobulin molecule is determined by the sequences of several short stretches of amino acids in the N-terminal domain of each heavy and light chain, which are called *hypervariable* or *complementarity-determining* regions.

Each person’s immune system can make approximately 1012 different antibody specificities. This remarkable diversity initially arises by *rearranging* or splicing together multiple DNA segments for different variable and constant region domains at slightly different junctions, to make a single antibody gene unique to that particular immature B cell. Upon exposure to an antigen, a naïve B-lymphocyte with a complementary binding site is selected and stimulated to proliferate, forming a germinal center in a lymph node or the spleen. Among the progeny of that B cell, in the appropriate milieu of antigen, helper T cells, and cytokines, some cells undergo further cutting and splicing of their heavy chain genes, resulting in isotype switching. Somatic hypermutation can also occur in their variable region genes, resulting in *affinity maturation*. At any point, some cells may stop differentiating and become...
Figure 31.1 Global demand for IgG products (IVIG and SCIG). Source: Data from Bult (2014). Reproduced with permission of Medical Data Services and Solutions (www.mdsas.com).

Figure 31.2 Use of IgG for diseases in different specialities. Source: O’Shaughnessy et al. (2012). Reproduced with permission of Medical Data Services and Solutions (www.mdsas.com).

Table 31.1 Mechanisms of action of IgG

- Dependent on Antigen-Binding (Fab) Region
  - Precipitation, agglutination, and neutralization of toxins and antigens
  - Sensitizing targets for phagocytosis, complement, and cell-mediated cytolysis
  - Neutralize viral adhesion
  - Neutralizing superantigens
  - Elimination of complement-activating circulating immune complexes
  - Neutralizing autoantibodies (anti-id)

- Dependent on Fc Interactions with Effectors/Receptors
  - Binding to cellular receptors and activating phagocytosis and cell-mediated cytolysis
  - Binding C1q and activating complement
  - Increasing catabolism of autoantibodies by saturating FcγR
  - Inhibiting C3 deposition or further activation
  - Downregulation of B- and T-cell function
  - Cytokine regulation
  - Fc receptor blockage, altering phagocyte function
plasma cells, which are totally devoted to producing antibodies of a single isotype and specificity. Other cells may become quiescent “memory” cells, which can be rapidly stimulated on re-exposure to antigen. Upon initial exposure to an antigen or vaccine, the “primary” antibody response usually consists of IgM and relatively low-affinity IgG. Upon re-exposure, however, or during progression of an infection, class switching and affinity maturation will result in an increase of the ratio of IgG to IgM and an increase in the avidity: a product of the affinity, specificity, and quantity or “iter” of the overall antibody response. High-avidity IgG production is characteristic of “secondary” responses to vaccines and convalescent sera following infections.

The unique combination of light and heavy chain hypervariable regions that form the antigen-binding sites of any given antibody molecule may, in turn, seem “new” to the body and can serve as an antigen itself. Each unique antigen-binding site is called an “idiotype” because it belongs only to that specificity. An antibody that recognizes or blocks the antigen-binding site of another antibody is therefore called an “anti-idiotype” (anti-id). Therefore, the circulating pool of IgG contains thousands or even millions of different antibody and anti-id specificities (Figure 31.4). Anti-ids are believed to be important in regulating B- and T-cell responses, forming a major component of the “network” hypothesis for which Jerne received a Nobel Prize in 1984. Anti-idiotypic neutralization of autoantibodies may be a major mechanism by which therapeutic IgG ameliorates autoimmune diseases (discussed further in this chapter).

A short history of commercial IgG production

Although sera from vaccinated animals had been used for passive immunity since the late 1800s, and convalescent human sera and placental extracts were used in the 1920s and 1930s, large-scale purification of immunoglobulins from plasma did not begin until the 1940s. With a grant from the US Navy, Edwin Cohn, a physical biochemist at Harvard University, developed a process for fractionating plasma using sequential precipitations with increasing concentrations of cold ethanol to produce large amounts of purified, stable albumin (fraction V) for treatment of shock on the battlefield during World War II. The globulins containing most of the antibody activity were found in fractions II and III, which also contained clotting factors and lipoproteins. Onley modified the procedure by manipulating the pH, ionic strength, and ethanol concentration, and succeeded in recovering most of the 7 s gamma globulins (now recognized as IgG) in fraction II, with the clotting factors and faster sedimenting globulins in fraction III. During the 1940s, intramuscular injections of fraction II immune serum globulin (ISG) were studied for prevention of hepatitis and measles. Janeaway et al. in Boston and Barandun in Switzerland attempted to give ISG intravenously, but their efforts were abandoned because of severe immediate reactions, including hypotension, chills, and fever. IM injections of 16% plasma-derived ISG were routinely used for antibody replacement in immune deficiency patients and for prophylaxis against infectious disease until the 1980s, but the doses that
could be tolerated by this route were limited, and efficacy in immune deficiencies was far from ideal.

Studies through the 1960s and 1970s suggested that the majority of vasomotor reactions and other immediate adverse effects that accompanied the early trials of intravenous (IV) administration of ISG were attributable to complement activation by aggregates of the 7 s globulins. Barandun et al. showed that these could be removed by ultracentrifugation or dissociated by treatment with low concentrations of pepsin, incubation at pH 4, and/or reduction and alkylation of disulfide bonds.9 Other protein modifications such as S-sulfonylation and treatment with β-propiolactone were also studied. The first commercial IVIGs were pepsin- or plasmin-treated preparations that contained fragmented IgG molecules that sedimented slower than intact IgG (i.e., at 5–6.5 s) and had shortened half-lives and decreased effector function compared to the IgG in the IM preparations.

By the late 1970s, combined treatments including mild reduction and alkylation, reconstitution in 0.3 M glycine, and/or treatment at pH 4 with low concentrations of pepsin were introduced to prevent aggregate formation while leaving the IgG molecules intact. These processes eventually led to the first preparations that could safely be given by the IV route, Gamimune® and Sandoglobulin®, respectively. The most important contribution to the tolerability of these preparations, however, was arguably the use of high concentrations of sugars as stabilizers: maltose in Gamimune and sucrose in Sandoglobulin.

Despite minimization of complement-binding aggregates, early IVIG preparations still frequently caused hypotension and/or other signs associated with vasodilatation and increased capillary permeability, which were shown to be associated with the presence of contaminating amounts of proteins such as pre-kallikrein activator and kallikrein itself.10 Contamination with factor XIa was also found to be responsible for procoagulant activity in many ISG and early IVIG preparations.10 In addition, other studies showed that isolated Fc fragments, IgG aggregates, and antigen–antibody complexes induced secretion of prostaglandin E2 from monocytes, suggesting that this mediator might also be contributing to pain and other adverse effects of early IVIG preparations.11

In 1981, the World Health Organization published a set of “Desirable Characteristics of IVIG Preparations”:12

- IVIG should be extracted from a pool of at least 1000 individual donors.
- IVIG should contain as little IgA as possible.

![Figure 31.4](image_url)
The IgG should be modified biochemically as little as possible and possess opsonizing and complement-fixing activities.

IVIG should be free from preservatives or stabilizers that might accumulate in vivo.

These characteristics were not fully achieved until the most recent generation of IVIG products were developed in the new millennium. Because there is no suitable alternative to polyclonal human IgG for antibody replacement therapy in immunodeficient patients, and because of the critical role of IVIG in treating a number of other diseases, the WHO includes IgG in its "Model List of Essential Medicines."

Current IgG products

Additional methods to increase the yield of IgG per liter of plasma, improve the convenience of administration, and minimize AEs resulted in liquid IVIG preparations that are >95% pure IgG are readily available in most countries. Many manufacturers now utilize modified purification procedures which employ only a single ethanol precipitation step and substitute precipitation with fatty acids such as caprylate, or medium-chain alcohols, together with depth filtration for the serial Cohn–Onley ethanol steps. Anion exchange column chromatography is used to improve the purity by decreasing the concentrations of IgA and potentially vasoactive and/or thrombogenic protein contaminants, and some manufacturers also add cation exchange chromatography to further purify the IgG.

To improve the convenience of preparing and administering IVIG, most manufacturers have developed IVIG preparations that are available as 10% liquids and can be kept at room temperature for at least part of their shelf life. Currently, three products—Gammagard (Baxter), Gamunex (Grifols), and Privigen (CSL Behring)—dominate the US market. Gammagard and Gamunex are stabilized with glycine, and Privigen is stabilized with L-proline. All are available as 10% liquids, none contain any sugars, and none contain more than 50 mcg/ml IgA. IM ISG is rarely used in the United States, but Gammagard, Gammunex, and Gammaked are utilized for subcutaneous administration, and CSL Behring markets a 20% protein-stabilized product, Hizentra, specifically for subcutaneous use.

Prevention of pathogen transmission

Although clotting factor concentrates prepared by Cohn fractionation were known to have transmitted what is now known as hepatitis B, fraction II ISG had been given to hundreds of children for measles prophylaxis with only one case of apparent transmission of that virus. The subsequent widespread use of fraction II ISG provided confidence that this product carried little risk of transmission of blood-borne infectious agents. Unfortunately, that turned out to be false confidence. Even after the recognition of AIDS, complacency persisted because HIV (then termed HTLV III) was inactivated and/or partitioned out by the ethanol precipitation procedure. In the late 1980s, reports of "non-A, non-B" hepatitis, (now termed hepatitis C, caused by hepatitis C virus [HCV]) began to appear among recipients of IVIG and other plasma products, and further, dedicated steps were added to assure safety of these products (see Chapter 56). To date, there have been no reports of virus or prion transmission by current IgG products, but we must continue to be vigilant because of the threat of emerging pathogens.

Pharmacokinetics and metabolism of IgG

Conventional-dose IVIG therapy (for immune deficiencies)

As recognition of primary immune deficiencies increased in the 1950s, a study by the British Medical Research Council resulted in the recommendation that most patients with hypogammaglobulinemia could be successfully treated with 25 mg/kg/week of IM ISG. Within a few years after IVIG became available in the early 1980s, this was increased to 400–500 mg/kg at intervals of 3–4 weeks, which kept the serum IgG levels in most recipients at or above the lower limit of normal, approximately 500 mg/dl, at the "trough" just before the next dose was given. An intravenous bolus of 400 mg/kg of IgG given intravenously immediately raises the serum IgG level by about 1000–1200 mg/dl. The levels then drop by 40–50% over 48–72 hours, because IgG is distributed into the total extracellular fluid volume, of which only about 50% is intravascular. After this equilibration phase, the IgG is catabolized with first-order kinetics and a half-life of 21–30 days, which differs in different individuals, so it is usually repeated every 3–4 weeks. A major reason for this relatively long half-life of IgG, compared to IgA, IgM, and other plasma proteins, is due to a specific, saturable receptor on the surface of endothelial cells termed FcRn because it is also found in the placenta and is responsible for facilitated transport of IgG into the fetus. IgG, which binds to FcRn, is internalized into recycling endosomes in which it is protected from lysosomal degradation, returned to the apical surface, and exocytosed back into the circulation. Because IgG is not sequestered into other compartments such as intracellular or lipid-bound pools, two compartment models are traditionally used to describe its kinetics, although single-compartment models are sometimes used as an alternative. Early studies with radioactively labeled IgG showed that after equilibration, 45–50% of the IgG remained intravascular. Because the ratio of total extracellular fluid volume to body mass index shows excellent linearity (r = 0.97, p < 0.001) across a range of BMIs from 15 to 40, there seems little justification for limiting the dose of IVIG according to the "ideal body weight" in obese individuals, as some pharmacies and committees have recommended.

Subcutaneous IgG therapy

Although first introduced in the late 1970s as an alternative to IM injections of ISG, the use of small portable pumps to deliver concentrated IgG solutions subcutaneously has increased in popularity in the past decade and is now employed by more than half of the PID patients in several countries. There are two fundamental differences between the subcutaneous route of administration of IgG (SCIG) and the intravenous route (IVIG), which lead to most of the practical differences between the two routes. The first of these is the lack of a requirement for venous access with SCIG; the second is the relatively slow adsorption of SCIG into the intravascular compartment, which was described in detail more than a hundred years ago. In contrast, a trained professional is usually required to administer IVIG, and rapid infusion may contribute to systemic adverse events (AEs). The doses of IgG that are practical to give by the subcutaneous (SC) route are smaller than those by the IV route, so SCIG is usually given weekly or even more frequently. These differences result in a number of other effects that may lead to a preference for one route versus the other in a variety of different individual situations. With SCIG, the initial direction of the movement of IgG is opposite that of IVIG: The IgG must first diffuse from a subcutaneous depot into lymphatics, from which it reaches the bloodstream indirectly via the thoracic duct. Equilibration of the IgG from the subcutaneous sites into the total intravascular and extracellular fluid space requires about the same amount of time as equilibration of IVIG out of the intravascular compartment. Thus, with SCIG, the intravascular IgG concentration increases more gradually, peaking at 36–72 hours after the end of an infusion. Most other features of SCIG are consequences of this difference in
kinetics. For example, many of the systemic AEs of IVIG are related to the rate of the infusion and resolve when the infusion is slowed. The C_max achieved with SCIG is, on average, only 61% of the peak achieved with IV infusions. In recent studies comparing IVIG and SCIG in PID patients, the mean peak serum C_max immediately after IV infusions was 2303 mg/dL, and the interval (t_max) between beginning an SCIG infusion and the peak IgG concentration was 62.6 h (2.61 days). In contrast, the mean peak with SCIG was 1410 mg/dL, and the interval (t_max) between beginning an SCIG infusion and the peak IgG concentration was 32.3 h (1.38 days). This slower rate of rise toward the peak and the truncation of its height are believed to be responsible for the much lower incidence of systemic AEs with SCIG. This is consistent with observations that many AEs of IVIG infusions are rate related, and it has been repeatedly confirmed. No differences have been reported in the half-life (t_1/2) of IgG given by the subcutaneous versus IV routes, which is about 30–35 days. With weekly SCIG, there are only about four days between the t_max of one dose and the administration of the next dose, suggesting that only about 10–20% of the administered IgG is metabolized before the serum level starts to rise again. In contrast, with IVIG dosing intervals of 3–4 weeks, approximately 36–48% of the IgG may be metabolized by the time the next dose is due. These differences in the dosing intervals used in most SCIG-versus-IVIG regimens result in increased trough (C_min) serum IgG levels with SCIG. Pooled data from seven studies in which equivalent monthly IgG doses were given as weekly SCIG infusions versus IVIG infusions every 21–28 days showed that trough serum IgG levels were 10–20% (mean, 12.7%) higher with weekly SCIG. After 6–12 weekly infusions, SCIG results in steady-state IgG levels, with differences between C_min and C_max ≤5–10% of the overall mean. (This steady state can also be achieved by "loading" the patient with five or six consecutive daily infusions of what will then be the weekly SCIG dose.) In contrast, with IVIG, the trough-to-peak difference is often ≥100% of the overall mean.

Another approach to subcutaneous IgG therapy involves the use of recombinant human hyaluronidase to temporarily depolymerize the hyaluronan chains that cross-link the subcutaneous tissue. This increases the dispersion and absorption of medications delivered into the subcutaneous space and allows full monthly doses of 30% IVIG (in the range of 200–500 ml) to be given as a single SC infusion into a subcutaneous site. The C_max is between that of standard SCIG and an IV bolus, but the C_min (trough) is not changed from that experienced with conventional 3–4 weekly IVIG dosing. The combination product, containing one vial of recombinant hyaluronidase and one of 10% Gammagard, is marketed as HyQvia by Baxter. In clinical studies in immune-deficient patients, HyQvia was well-tolerated and efficacious, but because experience with this form of therapy is limited, its label includes cautions and restrictions about use in children and during pregnancy.

The area under the curve (AUC) of serum concentration versus time of a drug after a single intravenous infusion is defined as 100% bioavailability. The bioavailability of the drug when given by any other route is generally lower, so this is not unexpected with subcutaneous versus IV administration of IgG, and it is also found with therapeutic fusion proteins containing its Fc domains.

In licensing studies of SCIG, the US Food and Drug Administration (FDA) mandated determination of the bioavailability of SCIG as compared to IVIG and calculation of the dose adjustment which would be necessary to achieve an AUC with SCIG equal to that previously measured with IVIG in the same patients. Multiple studies and different lines of evidence demonstrated that the bioavailability of SCIG is about two-thirds of that of IVIG, regardless of the preparations being compared. Interestingly, and in close agreement with the results of the SCIG licensing trials, the results of pooled analyses including 500 subjects and 20 different IgG preparations show that the slopes of regression lines for IgG level versus monthly dose indicate an increment of 87 mg/dL for every 100 mg/kg increase in monthly SCIG dose compared to an increment of 121 mg/dL in the trough level of IgG for every 100 mg/kg increase in monthly IVIG dose, suggesting a bioavailability of 71.9%. The decreased bioavailability may involve degradation in the tissues and/or local binding in the intercellular matrix, but seems to be a general property of IgG. The European Medicines Agency does not require dose adjustment for SCIG as compared to IVIG, and analyses of large payor databases in the United States suggest that equivalent or even slightly lower total monthly doses of SCIG versus IVIG are given to PID patients.

High-dose IVIG therapy for autoimmune and inflammatory diseases

The initial dose of IVIG used for most autoimmune/inflammatory diseases is 2 g/kg given over 2–5 days, followed by maintenance doses of 1–2 g/kg every 3–4 weeks. This regimen is based on the serendipitous 1981 observation that five consecutive daily repetitions of the monthly dose of IVIG for immune deficiencies at that time (400 mg/kg) normalized the platelet counts in immune-deficient patients who also had immune thrombocytopenia. Infusion of 2 g/kg of IVIG increases the serum IgG level greater than fourfold, from pretreatment means of 700–1060 mg/dL to peaks well above 3000 mg/dL. and IgG levels as high as 5000–7000 mg/dL have been reported. These extremely high levels may contribute to vaso-occlusive AEs due to hyperviscosity in some patients. The distribution phase of the IVIG is not expected to be altered by the IgG level, but if serum levels are sufficient to saturate FcRn, the catabolic rate may be increased.

Drug interactions

Standard polyclonal IVIG is not known to bind or influence the distribution or metabolism of small molecules; neither does conventional drug therapy alter the levels or metabolism of IgG. Although not formally studied, high-dose IVIG might be expected to increase the catabolism of IgG monoclonal antibodies and fusion proteins containing the Fc of IgG, due to saturation of FcRn, as explained further in this chapter. IVIG therapy, whether given by the IV or SC route, may decrease the antigenicity of live virus vaccines such as measles, mumps, and rubella (MMR); varicella; and Zostavax, so it is recommended that a period of six months be allowed to elapse between the last IgG therapy and administration of any of these vaccines. If a patient has not been immunized and has received IgG therapy more than one month before potential exposure to MMR or varicella, passive immunization with IgG would be recommended.

Adverse reactions to IVIG and SCIG

Immediate reactions

Mild reactions to IVIG infusions are common, occurring in 15–20% of infusions and in 50% of patients at one time or another. These AEs are mostly uncomfortable and/or unpleasant but rarely serious. Symptoms may include headache, nausea, musculoskeletal
pain, and flushing and tachycardia. When severe, IVIG infusion reactions may resemble anaphylaxis, but they usually do not involve IgE and should be termed anaphylactoid. A key difference between these anaphylactoid reactions that accompany IVIG infusions and true IgE-mediated anaphylaxis is that the former are usually associated with hypertension, rather than hypotension. Furthermore, anaphylactoid IVIG reactions often are less severe with subsequent infusions rather than more severe as would be expected with true allergy. In most cases, symptoms during IVIG infusions can be easily managed by slowing or temporarily stopping the infusion until the symptoms subside and/or by treatment with acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), and/or antihistamines. Some patients may require corticosteroids; and many patients are given NSAIDs or steroids prophylactically. Most AEs are related to the rate of infusion and can be avoided by beginning the infusion slowly (0.01 ml/kg/min) and gradually increasing the rate stepwise as tolerated.

Patients who are naïve to IVIG replacement, have had interruptions in their therapy, and/or who are actively or chronically infected have an increased risk of infusion-related AEs. This may be related, in part, to formation of antigen–antibody complexes as the IgG is being given, and/or the rapid release of lipopolysaccharide or other components of pathogens already present in the recipient. The risk of these reactions can be reduced by making sure patients are afebrile and that those with active infections are on antibiotics before giving an IVIG dose. The incidence of reactions may increase when patients already on therapy are given a different brand of IVIG, so whenever this occurs, it is prudent to begin the infusion slowly and/or by premedicating the IgG subcutaneously.

Systemic reactions to SCIG infusions are rare. Gardulf et al. reported only 30 systemic reactions in 25 immunodeficient patients given 3232 infusions (0.93%). A subsequent review, which included additional studies totaling over 40,000 infusions, showed that only one study reported a rate of systemic AEs >1%. Although nearly 75% of patients may have some local discomfort associated with the swelling and redness at the site of the infusions, the swelling and local symptoms usually subside within 24–48 hours, and do not usually deter patients from continuing with their SCIG regimen. Because of the infrequency of systemic side effects with SCIG, premedication is rarely necessary, nor is close monitoring required during the infusion. SCIG has thus emerged as an ideal route for home use in many patients.

The increasing use of IVIG, particularly with large doses for inflammatory and autoimmune diseases, has resulted in other serious adverse events, including transmission of hepatitis C, aseptic meningitis, renal failure, thromboembolism, and hemolytic anemia. This has led to the requirement (in the United States) that all IVIG products contain a “Black Box” warning about acute renal dysfunction/failure, and “Warnings and Precautions” about the risk of thromboembolic events, hemolytic anemia, aseptic meningitis syndrome, and transfusion-associated acute lung injury (TRALI). Most reports of acute renal failure or dysfunction were due to osmotic nephrosis related to the use of sucrose as a stabilizer in certain products. The risk of aseptic meningitis seems to be highest in patients receiving high-dose IVIG for neurologic diseases, and TRALI seems very rare.

**Thromboembolic events (TEEs)**

Determining the true rates of TEEs and hemolytic incidents are difficult because the FDA and manufacturers’ pharmacovigilance efforts rely on voluntary efforts of patients/providers and because there are little data with which to calculate a denominator such as the numbers of doses given or patients treated. Hyperviscosity due to high-dose IVIG and slow blood flow in critical vascular beds may contribute to TEEs in some patients; and endothelial cell and/or platelet activation also likely play a role. There are multiple reports of myocardial infarction, transient cerebral ischemic attacks, and strokes related to high-dose IVIG therapy. Best estimates suggest a baseline incidence of 0.16–0.6 TEEs for every one million grams of IVIG sold. Considering 50 grams as a median adult dose, these rates represent roughly 0.8–3 cases per 100,000 doses. In a recent well-investigated episode, TEEs were reported in nine patients involving seven different lots of a single product.

Subtle changes in the procedure used to fractionate the plasma and produce that product, including the use of resins to isolate certain clotting system proteins, apparently increased contact activation of factor XI, which had co-purified with the IgG during the initial ethanol precipitation. Because the total factor XI plus Xla was still within acceptable limits by the assays in use at that time, the affected product was within specifications. Only recently developed thrombin-generation assays have sufficient sensitivity to detect activated FXla. Factor XI and kallikrein are difficult to separate from IgG because their isoelectric points are similar to IgG’s, and they co-precipitate during ethanol precipitation. On one hand, the results suggest that contamination of one or two individual lots was not responsible for the increase in factor Xla, because many lots were affected. On the other hand, even with the affected lots, TEEs were extremely rare, suggesting that multiple risk factors in the individual affected patients also contributed.

Better chromatographic purification methods, and the use of specific immunoadsorbents to remove FXI/FXla from products that are made by multiple precipitations without ion exchange chromatography, should decrease the risk of factor Xla-related AEs. Furthermore, the use of the new thrombin generation assays should insulate the absence of procoagulant activity in current and future IgG products.

**Hemolytic reactions**

An analogous problem is the presence of antibodies to erythrocytes (isoagglutinins), resulting in positive Coombs’ tests, occasional cases of clinically significant hemolytic anemia, and extremely rare episodes of acute severe intravascular hemolysis. In the original Cohn–Oncley fractionation scheme, isoagglutinins, which have higher isoelectric points than other IgGs, were greatly reduced by removing fraction III and continuing with fraction II alone. Several recent production schemes combine the fraction II and III precipitates as the starting material for IgG purification, and many manufacturers have substituted caprylic acid or fatty alcohols for the ethanol steps that removed more of the isoagglutinins, resulting in 2–4-fold increases in isoagglutinin titers in the final products.

As with thromboembolic events, true rates of Coombs’ positivity, hemolytic anemia, and acute severe hemolysis in relation to IVIG therapy are difficult to estimate. However, risk factors that have been identified include non-O blood group, underlying associated
inflammatory state, and high cumulative doses of IVIG over several days. Some studies of high-dose IVIG therapy report that as many as 20% of patients may convert to Coombs’ positivity shortly after infusions, but the incidence of clinically significant anemia or acute severe hemolysis is significantly lower than that. Analysis of recent US and Canadian series reported clinically significant hemolysis after IVIG in a combined total of 37 patients, including 23 patients with blood type A, nine with type B, four with type AB, and only one with type O. Prescreening of donors to avoid using plasma units with high isoagglutinin titers in the pools from which the IVIG is prepared, and the use of specific immunoadsorbents to lower the titers of Anti-A and Anti-B, are steps now being introduced to decrease this problem.

Mechanisms of action of IVIG
IgG has both Fc-dependent and Fc-independent mechanisms that contribute to defense against infection. (Table 31.1). Fc-independent functions include neutralization of toxins, which are important virulence factors in several types of bacterial infection, agglutination, and precipitation of infectious particles, and neutralization of adhesion and attachment molecules. Fc-dependent functions include activating complement, facilitating phagocytosis (both locally at sites of tissue invasion and in bloodstream clearance by macrophages in the reticuloendothelial organs), and enhancing direct cell-mediated cytotoxicity. In general, all of these mechanisms involve stoichiometric interactions between the IgG and antigens and/or effector molecules such as C1q and Fcγ receptors. Therefore, it is not surprising that most studies comparing the efficacy of different doses of IgG replacement therapy in immune-deficient patients show fewer infections in groups that received higher doses. Pooled analyses of recent licensing studies of IVIG and SCIG clearly show that the incidence of pneumonia and other infections decreases as serum IgG levels increase.

A broad array of mechanisms of action of IVIG of potential relevance to the use of high-dose therapy have been demonstrated in vitro and in animal models. However, it is rarely clear which effects are most important in any given disease in vivo, because the pathogeneses of most autoimmune or inflammatory diseases are incompletely understood. Therefore, it is difficult to know whether any given effect demonstrated in vitro or in a model is really relevant in the diseased patient in vivo. One useful way to categorize mechanisms of action in these diseases is by considering whether they are likely to involve direct competition between normal molecules in therapeutic IgG and pathogenic autoantibodies. Clues suggesting situations in which competitive effects are likely include strong dependency on the dose of therapeutic IgG or the amount of therapeutic IgG in the circulation at any point in time, “wearing off” of the IVIG effect as its concentration wanes, and efficacy of plasmapheresis or immunoadsorption to remove pathologic antibodies. Several mechanisms of this type are detailed below.

Complement scavenging
Complement components C4 and C3 contain a unique internal thioester bond that can transfer to the target during complement activation, forming a covalent bond. Covalent binding of C4b and/or C3b provides increases the stability of convertases and the likelihood that the initial activation will be amplified. The CH1 domain in IgG has particularly good acceptors for this reaction, and high concentrations of soluble IgG can compete with surface-bound IgG for newly activated C3b. Inhibition of complement deposition by IVIG at concentrations readily achieved during high-dose therapy has been demonstrated in vitro and in animal models.

Anti-idiotypic binding
Because each individual’s immune repertoire arises randomly, it is readily understandable that some individuals respond to a given pathogen with antibodies that cross-react with self-antigens (e.g., Campylobacter jejuni and myelin gangliosides in Guillain–Barré syndrome [GBS]), whereas other individuals recognize different epitopes. Furthermore, it is easy to speculate that individuals who mount rigorous anti-id responses will rapidly bring a self-reactive response under control, whereas those whose anti-id response is weak or ineffective may continue to produce clinically significant amounts of autoantibodies. Because IVIG contains the antibodies from tens of thousands of healthy donors, it follows that it likely contains many different anti-ids.

 Shortly after its introduction, IVIG was found to neutralize “inhibitors” of the clotting protein factor VIII in hemophilia patients receiving replacement therapy. These “inhibitors” are in fact antibodies against factor VIII (FVIII). Furthermore, F(ab’)2 fragments of the IVIG neutralized the inhibitors, suggesting anti-id binding. Subsequent studies have shown that IVIG contains a wide variety of anti-ids, consistent with Jerne’s network theory of anti-id suppression of potential autoimmunity, and suggesting that this is actually quite common in normal physiology. The most important support for an anti-id mechanism of IVIG in vivo would be the observations that F(ab’2) or F(ab’)2 fragments from IVIG neutralize the autoantibody in vitro and/or can remove it by affinity chromatography, that removal of the autoantibodies by plasmapheresis has a similar effect, and that autoantibodies recovered from patients reproduce the disease physiology in vitro or in animals.

FcRn saturation increases catabolism of endogenous antibodies
As noted above, FcRn on endothelial cells maintains the relatively high normal concentration and long half-life of IgG in the circulation. In FcRn knockout mice and in patients with FcRn mutations, the half-life of IgG is very short, and its plasma concentration is quite low. Furthermore, it is difficult to passively transfer IgG-mediated pathology in FcRn knockout mice, because the half-life of the pathologic IgG is so short. By analogy, if FcRn is saturated by high doses of exogenous IVIG, the catabolism of endogenous pathologic IgG is greatly increased. In wild-type mice, high-dose IgG dramatically increases the catabolism of pathogenic IgG; whereas, in FcRn knockout mice, high-dose IgG does not further enhance the already rapid catabolism of the exogenous pathologic IgG. Thus, by saturating FcRn with normal anti-ids, IVIG increases degradation of pathogenic IgG. This therapeutic effect of IVIG therefore requires that the total IgG concentration exceeds the binding capacity of FcRn and depends on the ratio of the serum concentration of normal IgG to the concentration of pathogenic autoantibodies.
and in humans being treated for dermatomyositis.71 Clinical improvement following IVIG treatment in that condition is accompanied by decreased activation of C3 and decreased deposition of C3b and C5-9 on endomyosal capillaries.71 Basta et al. (2003) also showed that IgG could bind C3a and C5a noncovalently, thereby diminishing pro-inflammatory effects of complement activation.72

Indirect actions of IVIG that do not involve competition per se

Most recent reviews of “the” mechanism of action of IVIG focus on putative immunomodulatory effects involving networks of T cells, B cells, and cytokines.61,62 Modulation of activities of macrophages or self-reactive T cells are more likely to be important when these cells, rather than autoantibodies, are directly responsible for the end-organ pathology. Furthermore, many of these immunomodulatory effects of IVIG have prolonged time courses, and are therefore not likely to be responsible for therapeutic effects that “wear off” before a dose of IVIG has reached its half-life.61–63 Analysis of the pharmacodynamics of IgG therapy in any given disease may thus shed light on the mechanism by which the therapeutic IgG is acting, and also on the immunopathogenesis of the disease.63

IVIG can interfere with maturation of dendritic cells in vitro, and can inhibit expression of HLA–antigen complexes and the costimulatory molecules CD80 and CD86.61,74,75 It certainly seems possible that decreasing or altering dendritic cell activity would decrease antigen presentation and alter the pattern of cytokine production, modulating the role of the dendritic cells in stimulating different types of T cells. IVIG can decrease the production of pro-inflammatory cytokines like interleukin-1 (IL1), IL12, and interferon-γ and increase production of regulatory molecules like IL10 and IL1 RA.61,76 In this way, IVIG could alter the balance between regulatory (CD25+) and effector (CD4+ or CD8+) T cells,76 and could also decrease the inflammatory activity of macrophages. However, when the pathology involves direct effects of antibodies and/or complement on target tissues, it is not clear how modulating T cells or macrophages could produce dramatic beneficial effects. One report showed that IVIG decreased a B-cell activating cytokine that was elevated in sera from chronic idiopathic demyelinating polyneuropathy (CIDP) patients; but the clinical correlation was poor, the time course of changes in cytokine levels was not reported, and the role of that cytokine (and autoantibodies, for that matter) in CIDP is not clear.77 A recent report that IVIG decreases the number of circulating “natural killer” (NK) cells; their expression of the low affinity Fc receptor, CD16; and their cytokotic activity more likely represent in vitro blockade of CD16 than a genuine physiologic downregulation,78 and the role(s) played by NK or other cells that can mediate antibody-dependent cellular cytotoxicity has not been established in the diverse autoimmune diseases for which IVIG is used.

Putative effects of IVIG in ameliorating autoimmune disease by modulating programmed cell death have been proposed, but this remains a very controversial area. Some studies suggest that anti-Fas antibodies in IVIG can induce apoptosis in B cells.79 However, other results suggesting that IVIG has limited or only transient effects on autoantibody production (or alloantibody, in the case of transplant rejection) would not be consistent with induction of apoptosis as a major mechanism by which IVIG acts in autoimmune disease. Because the level of Fas expression and the sensitivity of cells to pro-apoptotic signals vary with the degree of activation and physiologic state of the cells in question, however, it is not difficult to see how different results could be obtained in different experimental systems. Further compounding the issues are observations suggesting not only that IVIG preparations may contain antibodies against Fas and another important family of proteins that regulate cell death called Siglecs, but also that dimers in IVIG preparations may contain anti-idiotypic antibodies that can complex with and neutralize these autoantibodies.80 Thus, a number of factors such as low-pH treatment during preparation and storage (which tends to dissociate dimers), stabilizers, and the percentage of dimers in any IgG preparation may also influence the results of laboratory studies, and perhaps the results with different preparations in vivo.

In the past decade, there has been intense focus on increased expression of the inhibitory receptor FcRiIB, as a mechanism of action of a small subset of molecules in IVIG that have fully sialylated carbohydrate side chains.81,82 These heavily sialylated IgG molecules are proposed to bind to a distinct receptor termed DC-SIGN, inducing the cytokine IL32, which increases FcRiIB expression and inhibits activity of inflammatory macrophages.81 This putative mechanism would explain why high doses of IVIG are necessary for anti-inflammatory effects, because only a small percentage of the IgG molecules are sialylated. Although a mouse model showed that merely 33 mg/kg of a highly sialylated Fc analog could replicate the effects of 1 g/kg of standard IVIG,83 these effects appear to depend on the mouse strain and model used.83,84 Thus, their relevance to specific human diseases is not clear.

Dosing and scheduling IgG treatment regimens

Immune deficiencies

Antibody replacement therapy in immune deficiencies is typically initiated at doses of 400–600 mg/kg of IVIG every 3–4 weeks, or 100–200 mg/kg/week subcutaneously. Doses in this range usually yield trough (in the case of IVIG) or steady-state (in the case of SCIG) serum IgG levels toward the low end of the normal range, and are quite effective in preventing sepsis or other serious bacterial infections.40,41 However, based on results of clinical observations and a few controlled studies,95,96 patients with chronic lung and/or sinus disease, and those suffering frequent breakthrough infections, are usually given higher doses. Several lines of evidence suggest that the resistance to acute infections is directly related to the serum (and tissue) IgG level at any point in time.90,91 Analyses of large pooled datasets suggest that patients receiving IVIG every four weeks are more likely to experience infections and hospitalizations in the last week of their dosing cycle, before their next dose is due. In a survey performed by the US immune deficiency foundation before the use of SCIG was common, two-thirds of respondents on IVIG answered positively to a question about whether they could feel their IVIG “wearing off” before the next dose was due.89 A small case series illustrated that different patients require different “biologic IgG trough levels” to remain infection free,90 and results from a cohort of 90 patients with X-linked agammaglobulinemia or common variable immunodeficiency followed at a single center for over 20 years showed that the range of IgG doses needed to keep the patients free from breakthrough infections varied widely: from 0.2 to 1.2 g/kg/mo, resulting in trough serum IgG levels varying from 500 to 1700 mg/dl (5–17 g/l).91 Thus, although guidelines can be used to recommend starting doses in previously untreated patients, dose, dosing interval, and route of administration should be individualized based on the clinical results for each patient.90,91
Acute autoimmune or inflammatory diseases
In contrast to immune deficiencies, in which the frequency of infection can be used to monitor and individualize IgG treatment, there are few such metrics available for guiding therapy in most acute inflammatory or autoimmune diseases treated with IVIG, so the regimen of 2 grams of IVIG per kg is usually used.

Kawasaki syndrome is an acute, severe inflammatory vasculitis syndrome of uncertain etiology that is most common in young children. IVIG is the major treatment used, and a meta-analysis of studies in which different doses of IVIG were co-administered with aspirin showed a correlation between the dose of IVIG and its efficacy in terms of preventing coronary artery aneurysms, which were present at the convalescent phase in only 3.8% of patients who received the highest dose studied: 2 g/kg. Furthermore, a randomized trial in 549 subjects and the meta-analysis cited above both reported that administering the IVIG as a single infusion over 8–12 hours led to more rapid resolution of symptoms and was more effective than giving it as five consecutive daily doses of 400 mg each. Thus, the commonly used first-line treatment for Kawasaki syndrome is 2 g/kg of IVIG given as a single large bolus over 8–12 hours. The observation that more rapid administration of the large infusion increases its efficacy suggests that the peak IgG level achieved—rather than the total dose, AUC, or trough level—is the most important determinant of efficacy in this particular situation. This conclusion, in turn, may be most consistent with the hypothesis that the target of IVIG in Kawasaki syndrome is intravascular, perhaps involving endothelial cells per se and/or circulating leukocytes.

Guillain–Barré syndrome is acute autoimmune polyneuropathy causing flaccid paralysis that frequently follows resolution of an infectious disease, most notably gastroenteritis due to C. jejuni. The leading hypothesis for the pathogenesis of GBS is that the antibodies produced by the host’s immune system in response to the lipo-oligosaccharide of the infectious agent cross-react with ganglioside antigens on myelin, activating complement and causing dysfunction and demyelination of peripheral nerves. As such, GBS is frequently cited as a leading example of the molecular mimicry theory of autoimmune disease. Although GBS is generally considered an acute, monophasic disease, as many as 3% of patients succumb during the acute episode, and up to 20% may have slow recovery and/or prolonged disability. First-line treatments for GBS include high-dose IVIG and/or plasma exchange. Laboratory evidence supports hypotheses that IVIG acts predominantly by blocking the binding of autoantibodies to the nerves, presumably due to the presence of anti-idiotypes and/or by blocking complement deposition.

It is likely that plasmapheresis also acts primarily by removing autoantibodies. However, different autoantibodies targeting different epitopes may be involved in different patients and different clinical variants, and neither measurements of autoantibodies nor in vitro determinations of the ability of IVIG to neutralize them are used to select or adjust the dose or schedule of IVIG treatment. Practice parameters of the American Academy of Neurology consider plasma exchange and IVIG as equally effective first-line treatments. A recent Cochrane Review reached the same conclusion but noted that the full course of IVIG treatments was more likely to be completed than the series of plasma exchanges, and that there was little additional benefit of combining the two modalities. The most common dose of IVIG is 2 g/kg, usually given over 2–5 days. One study of 39 subjects suggested that six days of 0.4 g/kg (total dose = 2.4 g/kg) was preferable to three days of 0.4 g/kg (total dose = 1.2 g/kg) in terms of the number of days until subjects could walk with assistance, but the difference did not reach significance except in a smaller subgroup. A more recent study showed that the serum IgG levels achieved by patients receiving 0.4 g/kg/day for five days were quite variable, and that patients with the highest increments in IgG level from baseline to day 14 showed the best response in terms of the percentage able to walk unaided six months after the acute episode, and vice versa. These results suggest that caution should be used in institutions in which the maximum dose of IVIG is restricted to a preset total number of grams, or in which dosing is based on lean or ideal body mass rather than actual body mass, because such rules may result in underdosing GBS patients, and their efficacy in this situation has not been established. Some investigators have suggested that high-risk patients may benefit from a “second dose” (or course) of IVIG, but this has not yet been formally studied. The International GBS Outcomes Study (IGOS) is being carried out to determine how to identify patients at high risk of death or long-term disability and who might benefit from more rigorous treatment.

Immune thrombocytopenic purpura (ITP), as noted in this chapter, was the first condition in which beneficial effects of IVIG in an autoimmune disease were reported (in ITP, autoantibodies mediate destruction of the patient’s own platelets). ITP patients may suffer or be at risk for clinically important bleeding episodes, including acute severe blood loss and intracerebral hemorrhage. Corticosteroid therapy is frequently sufficient to increase the platelet count enough to control symptoms such as nosebleeds and menorrhagia. However, when more severe and/or acute bleeding requires a faster increase in the platelet count, IVIG is often used at a dose of 1–2 g/kg given over several consecutive days. In general, this will increase the platelet count to >50,000 within seven days of beginning a course of therapy in >80% of patients. IVIG may also be used preoperatively to raise the platelet count and decrease the risk of bleeding in ITP patients. In patients with Rh+ red cells, anti-Rh(D) immune globulin (Rhophylac®, WinRho®, and RhoGAM®) may be used as an alternative to IVIG, obviating many of the potential adverse effects of high-dose IVIG. The Rh(D) immune globulin is believed to act by creating immune complexes with the recipient’s red cells that then saturate phagocytic receptors in the reticuloendothelial organs, sparing the platelets. This, in turn, is associated with some destruction of the antibody-coated red cells, but the resulting hemolysis is rarely clinically significant. IVIG is repeated at monthly intervals in some patients, but many individuals with chronic ITP are managed with corticosteroids, splenectomy, rituximab, and/or thrombopoietin receptor agonists.

IVIG may be expected to have effects in autoimmune neuropsychiatric, autoimmune hemolytic anemia, and alloimmune thrombocytopenia (sensitization of baby’s platelets with maternal IgG transferred across the placenta) similar to those in ITP, but these disorders are less common than ITP. Furthermore, if IVIG is used, it would frequently be given together with corticosteroids, with which it should have synergistic effects. High-dose IVIG is used as a treatment for pure red cell aplasia secondary to parvovirus B19 infection. In that situation, the IVIG likely helps the host control the infection.

Chronic autoimmune or inflammatory diseases
Chronic idiopathic demyelinating polyneuropathy: In many ways, CIDP resembles a chronic form of GBS. CIDP differs in that few patients recall preceding infections or other triggering events. CIDP is considered by many to be an autoantibody-mediated disease, and plasma exchange is very effective.
However, unlike the putative role of antiganglioside antibodies in GBS, no single major target antigen(s) has been identified in CIDP. Based upon results of a randomized, placebo-controlled trial of IVIG in 117 CIDP patients (the ICE study), the FDA approved IVIG for CIDP using a loading dose of 2 g/kg followed by maintenance dosing of 1 g/kg every three weeks. In many patients, the effects of IVIG in CIDP are transient, suggesting a mechanism of action involving competition with autoantibodies rather than inhibition of their production, and “wear-off” effects are common. Guidelines call for individualization of therapy, and prescribing regimens other than those used in the ICE trial are prevalent. A recent prospective study found that 60% of CIDP patients required IVIG more often than once every two weeks to stably maintain optimal strength. Anecdotal reports and small series suggest that continuously maintaining high serum IgG levels by the use of SCIG may result in more stable maintenance of strength, and a large, randomized, controlled multicenter study of SCIG therapy is now underway. Multifocal motor neuropathy (MMN): MMN is characterized by multiple motor nerve conduction blocks with sparing of sensory nerves. The electrophysiology is consistent with segmental demyelination, but recent studies suggest immunologic target(s) on axons rather than, or in addition to, Schwann cells or myelin. Unlike GBS and CIDP, corticosteroids and PLEX are usually not effective in MMN, raising questions about its immunopathogenesis. About half of MMN patients have IgM antibodies against the ganglioside GM1, and these seropositive patients tend to have more severe weakness, disability, and eventual axon loss than seronegative patients. Efficacy of IVIG was demonstrated in multiple anecdotal and case series reports in the mid-1990s. Small controlled studies soon followed, and the results of a 44-subject, randomized, double-blind, placebo-controlled crossover trial were reported by Hahn et al. in 2013. Mean maximal grip strength declined 31% during placebo treatment and increased 3.75% during IVIG treatment (p = 0.005). IVIG was recommended as first-line treatment by a European Federation of Neurological Sciences/Peripheral Nerve Society task force in 2006 and 2010, and it is usually given in doses of 1–2 g/kg every 3–4 weeks. Interestingly, early reports noted that improvement in strength and conduction began within a few days after the IVIG, but lasted only 1–2 months, at best. As with CIDP, many patients complain that their strength deteriorates in the third or fourth week after an IVIG dose. Small case series suggest that SCIG may help to ameliorate these “wear-off effects” and promote more constant activity, but long-term follow-up studies of SCIG are needed to determine if this will prevent the slow deterioration that now characterizes most MMN patients.

Autoimmune mucocutaneous bullous (blistering) diseases: Autoimmune mucocutaneous bullous (blistering) diseases are a family of conditions including multiple subtypes of pemphigus and pemphigoid in which separation of intraepidermal or subepidermal layers of skin occurs because of antibodies against intercellular adhesion molecules such as desmoglein. Most of these disorders have relapsing-remitting courses, and subtypes are characterized by differences in the locations and depth of the blisters, which in turn are probably related to differences in the specific targets of the autoantibodies. In general, corticosteroids are first-line therapies, and most patients are also given cytotoxic drugs such as cyclophosphamide or azathioprine. “High-dose” IVIG is often added as an alternative or addition to steroids in patients who develop complications of steroid treatment, and is regarded as a “steroid-sparing” therapy. IVIG may also be preferentially used in patients with poor tolerance of cytotoxic agents. A major effect of IVIG seems to be reduction of autoantibody titer, although this has been reported to take several months, so it is not clear whether the mechanism is competitive or mediated by other pathways. In cases of severe mucosal and/or ocular involvement, high-dose IVIG may be used to achieve a more rapid remission of acute attacks or exacerbations.

IgG in transplantation

IgG therapy has three main uses in solid organ transplantation. High-dose IVIG is employed along with plasmapheresis and rituximab in regimens designed to “desensitize” or remove preformed anti-HLA antibodies (“panel reactive antibodies” [PRA]) before transplantation in patients who have developed these antibodies in response to alloantigens in their fetuses, in the case of multiparous women, or in a previous transplant. In this situation, the IVIG is likely acting by anti-idiotypic blocking, exchanging with endogenous IgG in the extravascular spaces, so the latter can be removed by plasmapheresis, and saturating FC receptors to increase the catabolism of the endogenous anti-HLA antibodies. Particularly with kidney transplant patients, caution must be used in selecting the IVIG product and scheduling the infusions to avoid adverse effects due to isoagglutinins or sucrose. The newer IVIG preparations with reduced isoagglutinin content and nonsugar stabilizers should ameliorate these concerns. The second major use also involves high-dose IVIG, which is used to treat acute antibody mediated rejection. In this situation, part of the effect of the IVIG is undoubtedly to neutralize and/or accelerate the catabolism of the antibodies against the graft that are causing the rejection. However, immunomodulatory and inflammatory activities, including inhibiting complement, blocking Fc receptors, and altering the cytokine milieu, are also likely important. Many recipients of solid organ transplants become at least transiently hypogammaglobulinemic as a result of their immunosuppressive regimen, because of GI losses in visceral transplants and/or because of preexisting hypogammaglobulinemia or specific antibody deficiency that may have been undiagnosed before the transplant (particularly in lung transplant recipients). Such patients may benefit from antibody replacement, which may be given by the IV or subcutaneous routes, using regimens like those used for patients with primary antibody deficiency. Formerly, cytomegalovirus (CMV) hyperimmune globulin was used prophylactically after transplants, especially in antibody-negative recipients of organs from CMV+ donors (so-called D+/R− transplants). This has become much less common in the current era in which antiviral chemotherapy with Gancyclovir and Valgancyclovir is available, but it may still be used in patients who do not tolerate those agents and/or who develop active CMV disease.

In recipients of hematopoietic stem cell transplantations (HSCTs) for severe combined immune deficiency (SCID), particularly the X-linked form due to mutations in the cytokine receptor common γ chain, B-cell reconstitution frequently occurs much slower than hematopoietic and T-cell reconstitution. Most SCID patients are given IgG replacement for at least a year after transplantation, and some require it for life.

Based on the results of a large, randomized, double-blind, placebo controlled study in France, an independent meta-analysis in Canada, and a Cochrane Database Review, IVIG is not recommended for routine prophylaxis of infection after allogeneic...
HSCT. However, in some lymphoproliferative diseases, especially when rituximab is used in combination with conventional chemotherapy (e.g., CHOP [cyclophosphamide, hydroxydaunorubicin, oncovin, and prednisone or prednisolone], and in some cases in which rituximab is used (with or without cytotoxic agents) for nonmalignant antibody-mediated disorders, prolonged depletion of circulating B cells and significant hypogammaglobulinemia may occur, resulting in severe and/or recurrent infections. Such patients should be evaluated for IgG and/or specific antibody deficiency, and IgG replacement therapy using regimens similar to those used for primary immune deficiency should be considered.

Hyperimmune globulins

Hyperimmune globulins are made from plasma obtained from normal subjects with high titers of antibodies to the desired microbe or antigen detected by screening, or because they have been immunized or are convalescing. Plasma is processed as for regular (IM) ISG or IVIG, and the final product is tested to assure an adequate antibody titer to the microbe or other antigen. In general, hyperimmunes contain about fivefold higher titers of specific antibodies to the microbe or antigen for which they are labeled than standard IVIG preparations (on the basis of a unit of specific antibody per gram of IgG). Thus, to get the same amount of specific antibody, fivefold higher doses of standard IVIG would have to be given, constituting an extremely high dose of the latter. For example, to get the recommended amount of specific IgG for protection against respiratory syncytial virus required 750 mg/kg of the hyperimmune RespiGam® but would require 3750 mg/kg of “standard” IVIG. To put this in a current perspective, the same amount of specific IgG is contained in 15 mg/kg of the monoclonal anti-RSV antibody palivizumab (Synagis®), which can be given as a simple IM injection.

Other hyperimmunes target the Rh(D) red cell antigen (RhoGAM, PhoPhylac, etc.) to prevent sensitization of Rh(D)-negative women to Rh(D)+ fetal erythrocytes, and also for ITP in Rh(D)+ individuals, CMV (CytoGam® and Cytotect®), botulism toxins (BIG-IV® and Baby-BIG®), hepatitis B virus (HepaGamB, HyperHepB S/D), rabies virus (BayRab, Imogam-Rabies HT), tetanus (HyperTet), and varicella–zoster virus (VarizIG®). The same adverse effects may occur with the hyperimmunes as with standard IgG preparations. However, the doses of IV hyperimmunes are generally lower than the high doses of IVIG used for immunomodulatory effects, and so are less likely to produce serious adverse effects unless they are administered too rapidly.

Antivenoms used for spider and snake bites and anti-thymocyte globulin used for immunosuppression (i.e., in transplant recipients) are usually animal antisera and may be associated with anaphylaxis and/or serum sickness.

Summary

Given the diversity of the immune repertoire and the multiple interactions of its Fc domains with receptors and other effector systems, it is not really surprising that polyclonal IgG, pooled from tens of thousands of individuals, has a broad multiplicity of uses. Modern preparations are highly purified and contain stabilizers designed to prevent aggregate formation, and thus can be given intravenously or subcutaneously with relative freedom from severe systemic adverse reactions. Caution and monitoring are still necessary as occasional serious and/or life-threatening AEs still occur, especially individuals with identifiable risk factors. Doses in the range of 600–1000 mg/kg/month are generally used for replacement therapy for immune-deficient patients. This may be given in IV boluses every 3–4 weeks, or fractionated into smaller increments given by the subcutaneous route weekly or even more often. Although the former require venous access and are frequently monitored by trained medical personnel, the latter are frequently self-administered in the home, greatly facilitating the convenience of long-term IgG therapy and the quality of life for patients and their families. High-dose IVIG therapy (1–2 g/kg, usually every 2–4 weeks) is used for a growing number of autoimmune/inflammatory diseases, generally in clinical settings, and accounts for a continuously increasing global demand for IgG products.

Key references
