

Overview of intravenous immune globulin (IVIG) therapy

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INTRODUCTION

[Immune globulin](#) derived from the plasma of paid and volunteer donors is used in the treatment of an array of disorders, including primary and secondary immune deficiency states and a variety of autoimmune and inflammatory disorders.

This topic will review the uses, proposed mechanisms of action, and administration of intravenous [immune globulin](#) (IVIG).

Additional topic reviews discuss the adverse effects of IVIG therapy and the administration of [immune globulin](#) by subcutaneous and intramuscular routes. (See "[Intravenous immune globulin: Adverse effects](#)" and "[Subcutaneous and intramuscular immune globulin therapy](#)".)

TERMINOLOGY

Several terms are used for [immune globulin](#) preparations according to the route of administration:

- **IVIG** – Intravenous [immune globulin](#) (immune globulin, intravenous [human]) will be referred to as "IVIG" in this review because this term is commonly used by clinicians, although the abbreviation used by industry and various regulatory agencies is "IGIV" (immune globulin intravenous).
- **SCIG** – Subcutaneous [immune globulin](#) (SCIG) is used for products administered subcutaneously, although immune globulin subcutaneous (IGSC) is the term preferred by regulatory agencies.
- **IMIG** – Intramuscular [immune globulin](#) (IGIM) is used for products administered intramuscularly.

Multiple products are available for each preparation, which vary in concentration of immunoglobulin G (IgG), additives and stabilizers, and IgA content. (See '[Production and composition](#)' below.)

- **Hyperimmune globulin** – Hyperimmune globulin refers to [immune globulin](#) prepared from plasma of individuals with high titers of specific antibodies to certain pathogens and/or individuals who are hyperimmunized to specific antigens. Some hyperimmune globulins for infectious diseases are of animal origin. (See "[Plasma derivatives and recombinant DNA-produced coagulation factors](#)", section on '[Hyperimmune globulins](#)'.)
- **Rho(D) immune globulin** – Rho(D) immune globulin (eg, HyperRHO, MICRhoGAM, RhoGAM, WinRho) is a type of hyperimmune globulin against the Rh(D) antigen on red blood cells (RBCs). It is used to prevent hemolytic disease of the fetus and newborn (HDFN) and in some cases to treat immune thrombocytopenia (ITP). (See "[Prevention of Rhesus \(D\) alloimmunization in pregnancy](#)" and "[Immune thrombocytopenia \(ITP\) in adults: Initial treatment and prognosis](#)", section on '[Anti-D](#)'.)

MECHANISMS OF ACTION

Protection against infection — When given in the setting of hypogammaglobulinemia, antibody deficiency disorders, and/or other immunodeficiency states, IVIG (and other [immune globulin](#) preparations) acts by providing adequate concentrations of antibodies against a broad range of pathogens. (See "[Immune globulin therapy in primary immunodeficiency](#)".)

Hyperimmune globulins provide specific passive immunity, typically in the setting of a known or expected exposure. These products are generated from individuals (or rarely animals) with high titer antibodies to the implicated organism (or toxin). They impart temporary, passive immunity to the target pathogen. It is theoretically possible to produce a hyperimmune globulin to any organism from convalescent plasma, which can safely be used as passive immunization. Intravenous hyperimmune globulins are available for treatment of infantile botulism (Baby BIG), prevention and treatment of vaccinia virus infection, prevention of hepatitis B virus infection in liver transplantation, and prevention and treatment of cytomegalovirus infections in patients undergoing organ transplantation. (See "[Plasma derivatives and recombinant DNA-produced coagulation factors](#)", section on '[Hyperimmune globulins](#)'.)

Alloimmunization — In the setting of pregnancy in an Rh(D)-negative woman with a fetus that is potentially Rh(D)-positive, the use of Rh(D) [immune globulin](#) works by a mechanism that is as yet unproven. Possibilities include rapid macrophage-mediated clearance of anti-D-coated red blood cells and/or downregulation of antigen-specific B cells before an immune response occurs [1,2]. (See "[Prevention of Rhesus \(D\) alloimmunization in pregnancy](#)".)

Suppression of inflammatory/autoimmune processes — [Immune globulin](#) has several potential anti-inflammatory and immunomodulatory effects [3-5]. The relative contribution of these in any individual patient is difficult to assess because different mechanisms may dominate in different diseases. Examples include the following:

- Interaction with/blocking of Fc receptors on phagocytic cells in the spleen and liver such as splenic macrophages [6-8]. In immune thrombocytopenia (ITP), this effect may prevent reticuloendothelial uptake of autoantibody-coated platelets [9,10].
- Inhibition of dendritic cell differentiation and maturation [11].
- Reduction of proinflammatory subsets of peripheral blood monocytes (CD14⁺CD16⁺⁺) and suppression of cytokine production by these cells [12].
- Suppression or neutralization of cytokines by specific antibodies in the IVIG.
- Blockade of leukocyte adhesion molecule binding to the vascular endothelium. In a murine model of sickle cell disease, IVIG reversed vaso-occlusive crises by inhibiting the binding of leukocytes to the vascular endothelium, in turn leading to improved blood flow [13]. This mechanism may also play a role in the effects of IVIG in Kawasaki disease.
- Blockade of Fas ligand-mediated apoptosis by anti-Fas antibodies in the IVIG. In a study of patients with toxic epidermal necrolysis (TEN), associated with keratinocyte death and epithelial desquamation, patient serum was found to contain lytically active FAS ligand, and IVIG was able to block Fas-mediated cell death in vitro [14]. In a companion study in 10 patients, IVIG rapidly reversed TEN disease progression [14].
- Induction of inhibitory Fc-gamma-RIIB receptors on effector macrophages. This effect on the Fc-gamma-RIIB receptor was linked to the sialylation of the glycan component in the CH2 domain of the immunoglobulin G (IgG) molecule [15]. In a mouse model, a C-type lectin receptor on dendritic cells and macrophages was required for the anti-inflammatory effects of IgG by binding IgG through the sialylated Fc domain [8,16]. The mediator involved in this process was interleukin (IL)-33 from dendritic cells, which in turn increased the production of IL-4 from basophils that lead to the upregulation of the Fc-gamma-RIIB receptor on effector macrophages and the inhibitory anti-inflammatory effects. Although the data in human autoimmune disease are limited, the peripheral blood monocytes in patients with chronic inflammatory demyelinating polyneuropathy (CIPD) treated with high-dose IVIG showed upregulation of the Fc-gamma-RIIB receptor [17].
- Supply of anti-idiotypic antibodies directed against idiotypes on circulating autoantibodies. Anti-idiotypic antibodies in the IVIG may bind either to circulating autoantibodies, resulting in increased clearance, or to B cell immunoglobulin receptors, leading to downregulation of antibody production. In individuals with acquired hemophilia due to autoantibodies against factor VIII (ie, acquired factor VIII inhibitors), this may account for the ability of IVIG to reduce the inhibitor titer. (See ["Acquired inhibitors of coagulation", section on 'Other options'](#).)
- Provision of neutralizing antibodies to microbial toxins.
 - In staphylococcal toxic shock syndrome, severe group A streptococcal infections, and Kawasaki disease, neutralizing antibodies directed against staphylococcal toxin and streptococcal "superantigens" (proteins that can bind simultaneously to MHC class II antigens and to the nonantigen-binding region of T cell receptors) and may in turn reduce cytokine production [18-20]. (See ["Invasive group A streptococcal infection and toxic shock syndrome: Treatment and prevention", section on 'Intravenous immune globulin'](#).)
 - In Shiga toxin-mediated hemolytic uremic syndrome (ST-HUS), for example, [immune globulin](#) may provide antibodies against the toxin; however, a role for IVIG in ST-HUS has not been established [21].
- Effects on the complement system, such as the following:
 - Solubilization and clearance of immune complex deposits and/or inhibition of the binding of active complement components such as C4b and membrane attack complex to target tissues [7]. This may be important in immune complex disorders such as membranous nephropathy and dermatomyositis [22]. (See ["Treatment of idiopathic membranous nephropathy"](#) and ["Treatment of recurrent and resistant dermatomyositis and polymyositis in adults"](#).)
 - Supply of an alternate binding site or "sink" for the complement component C3b, diverting it from binding to targets of complement activation [23]. The inflammatory actions of the complement fragments C3a and C5a may also be neutralized via a physical association between these anaphylatoxins and the constant region of F(ab)² [24].
- Alterations in regulatory T cells (Tregs). In a mouse model of multiple sclerosis, IVIG abrogated disease progression by expanding CD4⁺CD25⁺FoxP3⁺ Tregs and inhibiting the proinflammatory Th17 pathway [25]. This mechanism of IVIG was not dependent on the Fc domain and sialylation. Other models have demonstrated a requirement for IgG sialylation [26]. Many animal models have shown that IVIG promotes expansion of FoxP3⁺ Tregs and downregulates the Th17 pathway. The mechanism by which IVIG induces Tregs may be through the prostaglandin E2 pathway as demonstrated in human dendritic cells in vitro [27]. (See ["The adaptive cellular immune response: T cells and cytokines", section on 'Suppression'](#).)

Several studies in human disease support this mechanism:

- Patients with Kawasaki disease treated with IVIG show increased numbers of Tregs and increased expression of genes related to Treg activation [28,29].
- Patients with autoimmune disease treated with high-dose IVIG have increased activation of circulating Tregs [30].

- Accelerated clearance of pathogenic IgG. This may occur through increases in the total plasma concentration of IgG, which saturate the FcRn receptor on vascular endothelial cells of the IgG transport system [19,31,32]. Once this receptor becomes saturated, IgG is no longer protected and is degraded according to its relative serum level. The FcRn receptor accounts for the long half-life of serum IgG. This mechanism accounted for approximately 50 percent of the enhanced clearance of antiplatelet antibodies in a mouse model of ITP, and it may partially account for the long-term effects of IVIG in ITP. (See ["Immune thrombocytopenia \(ITP\) in adults: Initial treatment and prognosis"](#).)

Given the multiple anti-inflammatory effects of IVIG, probably more than one mechanism is responsible for its immune modulating effects in autoimmune disease. In any given disease state, it is not clear whether all the IgG molecules present in the polyclonal IgG preparation (or only a small sub-fraction of the IgG molecules) are responsible for the clinically beneficial effect. For example, when IVIG is used to neutralize certain autoantibodies or anti-HLA antibodies, only that small fraction of IgG molecules with specific anti-idiotypic activity are likely to be needed. In addition, laboratory evidence suggests that some IgG molecules with heavily sialylated Fc regions may preferentially exert anti-inflammatory effects. Nevertheless, available commercial products are not characterized for, nor differentiated by, their content of antibodies of different specificities or chemical compositions.

USES FOR IVIG

[Immune globulin](#) may be administered as a component of therapy for the following conditions [33]:

- Immunodeficiency states
 - Primary (congenital/hereditary) immunodeficiencies – (See ["Immune globulin therapy in primary immunodeficiency"](#).)
 - Severe protein loss (eg, through malnutrition or gastrointestinal or renal losses) – (See ["Malnutrition in children in resource-limited countries: Clinical assessment"](#).)
 - Post-hematopoietic cell transplantation (HCT) – (See ["Prevention of infections in hematopoietic cell transplant recipients", section on 'Intravenous immune globulin'](#).)
 - Chronic lymphocytic leukemia (CLL) – (See ["Overview of the complications of chronic lymphocytic leukemia", section on 'Infection'](#).)
 - Multiple myeloma – (See ["Treatment of the complications of multiple myeloma", section on 'Infection'](#).)
 - Therapies that suppress immunoglobulin production – (See ["Secondary immunodeficiency induced by biologic therapies"](#).)
- Infections
 - CLL with recurrent infections requiring intravenous antibiotics or hospitalization – (See ["Prevention of infections in patients with chronic lymphocytic leukemia", section on 'Immunoglobulin replacement'](#).)
 - Chronic parvovirus infection complicated by anemia – (See ["Treatment and prevention of parvovirus B19 infection", section on 'Chronic infection with anemia'](#) and ["Acquired pure red cell aplasia in the adult", section on 'Relapsed and resistant disease'](#).)
 - Relapsing or severe *Clostridioides* (formerly *Clostridium*) *difficile* infection – (See ["Clostridioides \(formerly Clostridium\) difficile infection in adults: Treatment and prevention", section on 'Alternative therapies'](#).)
 - Toxic shock syndrome – (See ["Invasive group A streptococcal infection and toxic shock syndrome: Treatment and prevention", section on 'Adjunctive therapy'](#) and ["Staphylococcal toxic shock syndrome", section on 'Adjunctive therapy'](#).)
 - Measles postexposure prophylaxis (if the patient is immunocompromised or nonimmune) – (See ["Measles, mumps, and rubella immunization in adults", section on 'Postexposure prophylaxis'](#).)
 - Some enteroviral infections – (See ["Enterovirus and parechovirus infections: Clinical features, laboratory diagnosis, treatment, and prevention", section on 'Treatment'](#).)
- Autoimmune/inflammatory conditions
 - Immune thrombocytopenia (ITP) – (See ["Immune thrombocytopenia \(ITP\) in adults: Initial treatment and prognosis", section on 'IVIg'](#).)
 - Neonatal alloimmune thrombocytopenia – (See ["Fetal and neonatal alloimmune thrombocytopenia: Parental evaluation and pregnancy management"](#).)
 - Acquired von Willebrand disease (VWD) in the setting of lymphoproliferative or other immunologic disorders – (See ["Acquired von Willebrand syndrome", section on 'Treatment of acute bleeding'](#).)
 - Autoimmune hemolytic anemia (AIHA) – (See ["Warm autoimmune hemolytic anemia: Treatment", section on 'Intravenous gamma globulin'](#) and ["Autoimmune complications following purine analog therapy", section on 'Intravenous immune globulin'](#).)
 - Autoimmune neutropenia – (See ["Immune neutropenia", section on 'Treatment and clinical course'](#).)

- Acquired factor VIII inhibitor – (See ["Acquired inhibitors of coagulation", section on 'Treatment of factor VIII inhibitors'.](#))
- Guillain-Barré syndrome – (See ["Guillain-Barré syndrome in adults: Treatment and prognosis".](#))
- Myasthenia gravis –
- Kawasaki disease – (See ["Kawasaki disease: Initial treatment and prognosis", section on 'Intravenous immune globulin'.](#))
- Chronic inflammatory demyelinating polyneuropathy (CIDP) – (See ["Chronic inflammatory demyelinating polyneuropathy: Treatment and prognosis", section on 'Intravenous immune globulin'.](#))
- Multifocal motor neuropathy – (See ["Multifocal motor neuropathy".](#))
- Some human immunodeficiency virus (HIV)-associated neuropathies – (See ["Epidemiology, clinical manifestations, diagnosis, and treatment of HIV-associated peripheral neuropathy".](#))
- Alloimmune processes
 - Hemolytic disease of the fetus and newborn (HDFN) – (See ["Postnatal diagnosis and management of hemolytic disease of the fetus and newborn", section on 'Immune globulin therapy'.](#))
 - Post-transfusion purpura – (See ["Immunologic transfusion reactions", section on 'Post-transfusion purpura'.](#))
 - Platelet alloimmunization with bleeding (as a temporizing measure) – (See ["Refractoriness to platelet transfusion therapy", section on 'Treatment of active bleeding'.](#))
 - Antibody-mediated organ transplant rejection – (See ["Prevention and treatment of antibody-mediated rejection of the renal allograft", section on 'Approach to initial therapy'.](#))
 - Hyperhemolytic crisis (a form of delayed hemolytic transfusion reaction) in individuals with sickle cell disease (SCD) – (See ["Overview of the clinical manifestations of sickle cell disease", section on 'Hyperhemolytic crisis'.](#))

One medical center reviewed the use of IVIG during a single calendar year. A total of 194 patients received 48,230 grams of IVIG [34]. The six most common conditions for which IVIG was used included:

- Chronic neuropathy (29 percent)
- Secondary hypogammaglobulinemia (18 percent)
- ITP (10 percent)
- Primary hypogammaglobulinemia (9 percent)
- Renal transplantation (6 percent)
- Myasthenia gravis (5 percent)

USES FOR HYPERIMMUNE GLOBULIN

Hyperimmune globulins are used in the setting of specific exposures. These products can be administered intravenously or intramuscularly.

Specific infection prophylaxis and therapy include the following:

- Various products (eg, [varicella-zoster immune globulin](#) [VarizIG]; [cytomegalovirus immune globulin](#) [CMVIG]) may be given to hematopoietic cell transplantation (HCT) recipients who have not yet been re-immunized against certain viral infections, as postexposure prophylaxis. (See ["Prevention of viral infections in hematopoietic cell transplant recipients".](#))
- [Hepatitis B immune globulin](#) (HBIG) may be given to an infant born to a hepatitis B virus (HBV)-infected mother, to an individual exposed to HBV who was not previously vaccinated, or to an HBV-infected individual undergoing liver transplantation. (See ["Prevention of hepatitis B virus and hepatitis C virus infection among health care providers"](#) and ["Hepatitis B virus immunization in infants, children, and adolescents", section on 'HBsAg-positive mother or mother with other evidence of HBV infection'](#) and ["Liver transplantation for chronic hepatitis B virus infection", section on 'Hepatitis B immune globulin'.](#))
- [Rabies immune globulin](#) (prepared from human or horse plasma) may be used in individuals exposed to rabies virus. (See ["Rabies immune globulin and vaccine".](#))
- [Botulism immune globulin](#) may be used for infants less than one year old diagnosed with botulism. (See ["Botulism", section on 'Botulinum immune globulin'.](#))
- [Tetanus immune globulin](#) is given to individuals with tetanus and may be used along with vaccination for certain individuals with puncture wounds. (See ["Infectious complications of puncture wounds", section on 'Tetanus immunization'](#) and ["Tetanus", section on 'Neutralization of unbound toxin'.](#))

- [Vaccinia immune globulin](#) may be available for selected cases of inadvertent inoculation or complications of vaccinia. (See ["Myopericarditis", section on 'Vaccinia-associated myopericarditis'.](#))

The use of Rho(D) immune globulin to prevent Rh(D) alloimmunization and reduce the risk of hemolytic disease of the fetus and newborn (HDFN) is discussed separately. (See ["Prevention of Rhesus \(D\) alloimmunization in pregnancy".](#))

PRETREATMENT TESTING

Pretreatment laboratory testing for evidence of viral infections and autoantibodies is performed according to the underlying indication for IVIG administration and the patient's overall health status.

For most patients, we obtain a complete blood count (CBC), hepatic transaminases, metabolic panel including glucose, serum creatinine, and urinalysis before initiating IVIG. This may identify pre-existing infection or risk for complications (see ["Intravenous immune globulin: Adverse effects"](#)) before the IVIG is administered and allows appropriate evaluation if required.

- For individuals with abnormal baseline testing, evaluation for bloodborne pathogens may be appropriate (eg, hepatitis, human immunodeficiency virus [HIV]). When indicated, testing for bloodborne pathogens should be done before starting IVIG therapy because serologic and nucleic acid tests (NAT) will become positive following IVIG administration due to the passively transferred antibodies in the IVIG, especially common viruses such as Epstein-Barr virus (EBV), cytomegalovirus (CMV), and hepatitis B virus (HBV). However, urgent therapy should not be delayed for this testing.

The overall risk of transmission of viruses or other pathogens from IVIG is extremely low (see ["Intravenous immune globulin: Adverse effects", section on 'Infectious risks'](#)). In most cases, this information is useful for identifying infections that require treatment rather than for "look back" purposes, in which attempts are made to identify a specific donor responsible for the transmission. Such lookback studies are extremely difficult, if not impossible, when dealing with a product in which plasma components from thousands of donors is pooled.

- Individuals with hypogammaglobulinemia (eg, primary immunodeficiencies) should be evaluated using NAT-based testing because they may have impaired production of specific antibodies, and serologic testing will be uninformative.
- Individuals without hypogammaglobulinemia can be evaluated using serologic or NAT-based testing.
- Some individuals with normal baseline testing may also benefit from information about pre-existing viral infections. As an example, it may be important to know whether a potential transplant recipient has been infected with CMV or viruses that might become reactivated during immunosuppressive therapy.

Direct antiglobulin (Coombs) testing (DAT) may be useful in some patients depending on their disease, especially certain types of autoimmune disorders, prior to IVIG therapy.

The intervention for positive Coombs testing depends on whether the finding was expected (eg, known autoimmune hemolytic anemia) or unexpected. (See ["Intravenous immune globulin: Adverse effects", section on 'Hemolysis'.](#))

PRODUCTION AND COMPOSITION

Production of IVIG begins with pooled human plasma from several thousand (2000 to 10,000) screened paid and volunteer donors. Products used in the United States are derived from the plasma of donors in the United States. Cold alcohol fractionation (by the Cohn or Kistler-Nitschmann procedures) is used to isolate the immunoglobulin-containing fraction. This is followed by further purification techniques, including additional precipitation steps to remove non-immunoglobulin G (IgG) proteins and ion exchange chromatography to further separate and purify the desired IgG. Most [immune globulin](#) preparations also undergo several specific treatments to inactivate or remove bloodborne pathogens that could be present. These include low pH treatment, fatty acid/alcohol treatment, solvent-detergent treatment, and/or heat treatment (pasteurization). All products undergo nanofiltration or depth filtration to remove potential prions from the donor plasma. These processes are reviewed in more detail elsewhere. (See ["Intravenous immune globulin: Adverse effects", section on 'Infectious risks'.](#))

The World Health Organization has published minimum standards for manufacturing IVIG preparations [\[35,36\]](#):

- IVIG should be extracted from a pool of at least 1000 individual donors
- It should contain as little IgA as possible
- It should be free from preservatives or stabilizers that might accumulate in vivo
- The IgG molecules should have as little biochemical modification as possible and possess opsonizing and complement-fixing activities

The preparations contain highly purified (generally >95 percent) polyvalent IgG. However, there are slight differences in the manufacturing procedures used by different producers, and different stabilizers (eg, sucrose, glucose, maltose) are used in the excipients ([table 1](#)). Many available products use amino acids such as glycine or proline to stabilize or prevent aggregation of the IgG molecules in IVIG. The sodium content of different products also varies. Products also differ in storage requirements and shelf life.

These refinements were made following the experience with earlier preparations used in the 1950s and 1960s, which were effective in the treatment of sepsis and viral infections but were associated with severe anaphylactic reactions thought to be due to highly vasoactive peptides and IgG aggregates [37-39].

Viral inactivation processes such as solvent/detergent treatment are effective in inactivating lipid-enveloped viruses (eg, HIV, HBV, HCV, EBV, CMV) but not non-lipid enveloped viruses such as hepatitis A virus and parvovirus B19; however, the IVIG product is likely to contain antibodies to these viruses that might reduce their pathogenicity. Viral inactivation processes and infectious risks of IVIG are discussed in more detail separately. (See "[Pathogen inactivation of blood products](#)", [section on 'Solvent/detergent treatment'](#)" and "[Intravenous immune globulin: Adverse effects](#)", [section on 'Infectious risks'](#)".)

SELECTING A PRODUCT

The majority of patients tolerate most IVIG products with a minimum of adverse events when an acceptable infusion rate is used. Thus, for many patients, selection of a product to conform to local dispensing or formulary preferences is appropriate, particularly when a limited duration of therapy is anticipated. However, there are some circumstances in which one product may be more suitable than another for a given patient. For example, patients with underlying renal disease should not get sugar-containing IVIG ([table 1](#)).

Selection of IVIG versus other routes — Most [immune globulin](#) products are labeled for a specific route of administration (eg, intravenous, subcutaneous, intramuscular). Several 10 percent IVIG solutions can be administered subcutaneously, and reports suggest that most intravenous products are well tolerated by the subcutaneous route [40]. By contrast, 20 percent subcutaneous and 16 percent intramuscular products are generally more concentrated than intravenous preparations and should not be given intravenously.

For individuals with immunodeficiencies, either subcutaneous or intravenous [immune globulin](#) are both effective. The subcutaneous route causes fewer systemic adverse effects and provides more stable serum immunoglobulin G (IgG) levels of immune globulin compared with the intravenous route, as discussed separately. Additionally, the subcutaneous route has been demonstrated to be cost effective and have better quality of life measures compared with the intravenous route in patients with primary immune deficiency disease [41-43]. (See "[Subcutaneous and intramuscular immune globulin therapy](#)", [section on 'Advantages of SCIG'](#)".)

Studies are emerging on the use of subcutaneous immune globulins in individuals with autoimmune/inflammatory disorders. Several studies in neuromuscular disease have shown promising results [44-47].

Selection among IVIG products — Available IVIG products generally are believed to be equally effective for the treatment of a variety of immunodeficiency and autoimmune/inflammatory states. However, products may differ from each other in ways that may be important in a particular patient. In the United States, IVIG products are supervised and licensed by the US Food and Drug Administration. Properties of products available in the United States are summarized in the table ([table 1](#)).

Examples of ways in which specific products may be tailored to specific patient groups include the following:

- Certain stabilizers may be associated with adverse effects in some patients:
 - **Sucrose** — Individuals with renal impairment should receive products that do not contain sucrose, due to an increased risk of osmotic renal injury with this particular sugar [48-50]. (See "[Intravenous immune globulin: Adverse effects](#)", [section on 'Renal complications'](#)".)
 - **Maltose or glucose** — Patients with diabetes should be careful with maltose-containing products, as certain types of glucose meters cannot discriminate between maltose and glucose. Diabetics should also be careful with glucose-containing products.
- Patients who have trouble tolerating increased intravascular volume may do better with preparations that are low in sodium and albumin. Some products may contain as much as 30 mg/mL (3 percent) albumin, in addition to the IgG itself, although most newer products contain lower sodium concentrations.
- Some products contain higher titers of antibodies to human blood group antigens than other products, particularly the ABO type "A" antigen. This may cause a positive direct antiglobulin (Coombs) test (DAT), although clinically significant hemolysis is extremely rare [51,52]. Certain chromatography steps may be used to reduce isohemagglutinins [53]. (See "[Intravenous immune globulin: Adverse effects](#)", [section on 'Hemolysis'](#)".)
- The variability in IgA levels may be important in individuals with absent IgA and anti-IgA antibodies, which have been implicated in causing anaphylaxis to IgA-containing blood products including IVIG in patients who are receiving IVIG for other conditions (eg, autoimmune/inflammatory disorders or severe antibody deficiency). The requirement for a product low in IgA is unpredictable, as most IgA-deficient patients tolerate products that contain IgA. Most clinicians choose a product with very low IgA content when treating an autoimmune process in a patient with undetectable levels of IgA. If anti-IgA antibodies in a patient are a concern, subcutaneous Ig (SCIG) is an alternative to IVIG in patients with primary immunodeficiency disease [54,55]. There is no indication to give IVIG to patients as therapy for selective IgA deficiency. (See "[Selective IgA deficiency: Management and prognosis](#)", [section on 'Immune globulin'](#)".)
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Products may have variable titers to less common infectious agents, such as strains of enterovirus, which may be important if the product is used to control enterovirus encephalitis. (See ["Enterovirus and parechovirus infections: Clinical features, laboratory diagnosis, treatment, and prevention", section on 'Treatment'.](#))

- Patients with hyperprolinemia should not be given proline-containing products, due to a theoretic risk of exacerbating their condition. However, adverse effects due to proline or other amino acid stabilizers have not been reported.
- It used to be thought that patients at risk for thrombotic complications (eg, patients who are bedridden or have cryoglobulinemia, monoclonal gammopathies, or elevated lipoprotein concentrations) should receive preparations with lower osmolality. However, it is thought that activated coagulation factor XI (FXIa) in the preparations were responsible for thromboembolic complications, and adequate hydration is the most important intervention to minimize this risk [56-60]. Manufacturers use manufacturing processes to remove thrombogenic coagulation factors and test products for procoagulant activity to minimize this risk [61]. (See ["Intravenous immune globulin: Adverse effects", section on 'Thromboembolic events'.](#))

Importantly, patients who require a specific type of hyperimmune globulin should receive a product intended for this purpose rather than IVIG.

Although most people tolerate most products, once a patient has found a product that is well tolerated, it is advisable not to change products unless there is a compelling reason to do so; administration of alternative products should only be done with the clinician's approval [62]. If an alternative product must be given to a patient on chronic therapy, it is usually prudent to use slow infusion rates and monitor the patient closely. (See ["Immune globulin therapy in primary immunodeficiency".](#))

DOSING AND ADMINISTRATION

Product handling and storage — Liquid products and reconstituted solutions of lyophilized products that have been stored in refrigerators should be allowed to come to room temperature before administration to minimize adverse events. However, IVIG solutions should not be microwaved or otherwise heated, because the immunoglobulin protein could become denatured, producing protein aggregates. Vigorous mixing causing excessive foaming should also be avoided. Reconstituted lyophilized products should be inspected before administration to assure that the product has been completely dissolved and that the solution is uniform. All products should be inspected for the presence of particulates and evidence of tampering before pooling or administration to the patient, and products with any evidence of particulates or broken seals should not be used.

Home versus healthcare facility administration — IVIG is usually administered in an infusion center or healthcare facility depending on the country. However, IVIG may be infused in the home setting, usually by an experienced infusion nurse. In some situations, this practice has been found to be more cost effective and result in improved quality of life measures [63,64]. The first few infusions should be administered with medical supervision, regardless of the longer term plan.

Premedications — Many patients receiving IVIG for immunoglobulin replacement therapy do not require premedication. However, some patients may receive [acetaminophen](#) or a nonsteroidal anti-inflammatory drug (NSAID; with the exception of [aspirin](#), which is not recommended for children) to relieve and/or prevent inflammatory and anaphylactoid symptoms. The occurrence of these adverse events depends on the product, route of administration, and patient status (eg, active infection) [65]. In contrast, premedication generally is not necessary prior to administration of subcutaneous [immune globulin](#) (SCIG). (See ["Subcutaneous and intramuscular immune globulin therapy", section on 'Administration and dosing of SCIG'.](#))

When used, these medications may be given 30 minutes prior to the infusion of IVIG. The following doses are commonly used:

Pediatric doses apply to infants through age 11 or weight up to 35 kg. Adult doses apply to children >age 11 and weight >35 kg.

- [Acetaminophen](#), 10 to 15 mg/kg (max 500 mg) orally for children or 650 to 1000 mg orally for adults, **or**
- [Ibuprofen](#), 10 mg/kg (max 400 mg) orally for children or 400 to 800 mg orally for adults

H1 antihistamines are also frequently given before or at the beginning of the infusion. [Diphenhydramine](#) can be given as 1 mg/kg (max 50 mg) orally, intravenously (IV), or intramuscularly (IM) for children; or 25 to 50 mg orally/IV/IM for adults.

Glucocorticoids can be given in selected patients who experience severe adverse reactions such as headaches, particularly if the first infusion was associated with a severe reaction. Changing IVIG products is also associated with more frequent and severe adverse reactions, particularly headaches [33,62]. Their mechanism of action suggests that they might be most effective if given one to two hours before the infusion is initiated. This may be done conveniently by dosing after the preceding meal or when the patient leaves home to come to the infusion site. Commonly used oral regimens include the following:

- [Prednisone](#) or [prednisolone](#) in children, 0.5 to 1 mg/kg (max 40 mg), **or**
- [Prednisone](#) or [methylprednisolone](#) in adults, 40 to 60 mg

Commonly, clinicians administer intravenous glucocorticoids (instead of oral) as soon as IV access is established and then wait 30 minutes before beginning the IVIG infusion. The following agents and doses can be used in this manner:

- [Methylprednisolone](#), 0.5 to 1 mg/kg (max 40 mg) IV in children or 40 to 60 mg IV in adults **or**
- [Hydrocortisone](#) sodium succinate (Solu-Cortef), 2 mg/kg IV in children or 100 mg IV in adults

Prehydration — Patients receiving IVIG should be well hydrated prior to the infusion. This is particularly important for patients with risk factors for thrombosis and/or renal complications of IVIG therapy, such as pre-existing renal insufficiency, diabetes mellitus, age greater than 65 years, paraproteinemia, heart disease, and concomitant use of nephrotoxic agents. Hydration should be given before IVIG preparations containing sucrose, as well.

Hydration can be accomplished by ample oral fluid intake or by administration of normal saline before giving the IVIG. Clinicians may administer intravenous fluids before starting high-dose IVIG, as therapy may be associated with adverse effects due to hyperviscosity, and preparations containing sucrose have been associated with osmotic renal damage. Normal saline 10 to 20 mL/kg is suggested for this purpose. (See "[Intravenous immune globulin: Adverse effects](#)", [section on 'Renal complications'](#)".)

Dosing in different disorders — Dosing varies depending upon whether the IVIG is administered for the purpose of preventing infections in immunodeficient patients or for suppression of an inflammatory or autoimmune process.

Immune deficiencies — IVIG doses in the range of 400 to 800 mg/kg/month are usually used for replacement therapy in patients with immune deficiencies. Bolus doses may be given every three to four weeks. Typical starting doses are in the range of 400 to 600 mg/kg. Lower weekly doses are used for subcutaneous immunoglobulin replacement therapy (eg, 100 to 150 mg/kg weekly) [33,66]. The use of subcutaneous [immune globulin](#) (SCIG), including hyaluronidase- and nonhyaluronidase-containing preparations, is reviewed in detail separately. (See "[Subcutaneous and intramuscular immune globulin therapy](#)", [section on 'Administration and dosing of SCIG'](#)".)

Dosing of IVIG can be adjusted depending on the patient's progress (eg, frequency of infections). Some patients may need higher or more frequent doses to remain free from acute infections; to control chronic infections, particularly of the sinopulmonary tract; and/or to maintain target serum immunoglobulin G (IgG) levels. As such, dosing is quite variable among patients in that each patient may have their own dosing requirements [63,67]. Compared with subcutaneous dosing given more frequently, bolus IV dosing yields lower serum levels of IgG at the end of each dosing interval as the time for the next dose nears. Some patients will become more susceptible to infections during this period or feel otherwise unwell; this is commonly called "wear-off." (See "[Immune globulin therapy in primary immunodeficiency](#)".)

Inflammatory/autoimmune disorders — In patients who require the anti-inflammatory or immunomodulatory properties of IVIG, intravenous administration of high doses are usually required. As an example, patients with Kawasaki disease are usually given 2 grams/kg as a single dose. In older patients and those with underlying conditions that may predispose to thrombosis and other complications, we give therapeutic doses of IVIG larger than 1 gram/kg in multiple increments divided over several consecutive days so that no more than 500 mg/kg is given in a 24-hour period. (See "[Kawasaki disease: Initial treatment and prognosis](#)" and "[Kawasaki disease: Initial treatment and prognosis](#)", [section on 'Intravenous immune globulin'](#)".)

Dosing for specific diseases is discussed in the appropriate topic reviews:

- Immune thrombocytopenia – (See "[Immune thrombocytopenia \(ITP\) in adults: Initial treatment and prognosis](#)", [section on 'IVIG'](#)".)
- Guillain-Barré syndrome (children) – (See "[Guillain-Barré syndrome in children: Treatment and prognosis](#)", [section on 'Intravenous immune globulin'](#)".)
- Guillain-Barré syndrome (adults) – (See "[Guillain-Barré syndrome in adults: Treatment and prognosis](#)", [section on 'Intravenous immune globulin'](#)".)
- Chronic inflammatory demyelinating polyneuropathy – (See "[Chronic inflammatory demyelinating polyneuropathy: Treatment and prognosis](#)", [section on 'Intravenous immune globulin'](#)".)
- Kawasaki disease – (See "[Kawasaki disease: Initial treatment and prognosis](#)", [section on 'Intravenous immune globulin'](#)".)
- Chronic parvovirus infection with anemia – (See "[Treatment and prevention of parvovirus B19 infection](#)", [section on 'Chronic infection with anemia'](#)".)

Interval between doses — Serum trough levels of IgG or steady state serum IgG levels are often used as one criterion of the adequacy of treatment in patients with antibody deficiency diseases receiving IVIG. Other approaches include measuring specific antibodies to pneumococcal polysaccharides or the IgG3 subclass, since this IgG subclass has the shortest half-life. (See "[Immune globulin therapy in primary immunodeficiency](#)", [section on 'Trough levels'](#)".)

The rationale for measuring trough levels (or steady state IgG levels) is that the rate of [immune globulin](#) metabolism may vary with the clinical state. One study, for example, evaluated 15 patients with chronic lymphocytic leukemia who were given 400 mg/kg of IVIG every three weeks; the mean half-life was 39.1 days (standard deviation = 9.6 days) [68]. This is longer than the half-life of approximately three to four weeks observed in patients with primary immunodeficiencies or in healthy volunteers given IVIG. The rate of metabolism does not appear to increase with chronic administration. However, detailed pharmacokinetic studies are not available in patients with autoimmune diseases given repeated high dosages of IVIG.

In contrast, it is not established that measurement of IgG levels is relevant in patients with autoimmune disorders, where the endpoint is clinical improvement.

Infusion rates — Many infusion-related adverse effects seem related to the rate of administration. Therefore, it is customary to start each IVIG infusion at a slow rate, such as 0.01 mL/kg per minute, which would provide 0.5 or 1 mg/kg of [immune globulin](#) per minute depending upon whether a 5 or 10 percent solution is being infused, respectively. The infusion rate may then be increased at 20- to 30-minute intervals, while monitoring the patient closely for alterations in vital signs or subjective symptoms.

If the patient continues to do well, the rate of infusion may be increased. The specific increments and infusion rates should conform to the product information for the product being administered. We commonly increase the rate to 0.02 mL/kg per minute, then 0.04 mL/kg per minute, and in one or two

additional increments until a maximum rate of 0.08 mL/kg per minute (4 or 8 mg/kg per minute if 5 percent or 10 percent solutions are used, respectively) is achieved.

Higher rates may be tolerated in selected patients and with preparations that are low in sodium and/or free of high concentrations of sugar as stabilizers. After it has been established that a given patient tolerates a certain product at a specific rate, fewer steps and/or shorter intervals may be used during the "ramp up," but patients should always be monitored closely because lot-to-lot and patient-to-patient variation in tolerability may occur.

Dosing in obese patients — There is insufficient evidence upon which to base recommendations for dosing in obese or morbidly obese patients, and there is no clearly defined standard approach. A reasonable approach would be to start with a dose based on ideal body weight (IBW) ([calculator 1](#)) or adjusted body weight (also called dosing weight) and then modify the dose further based upon the patient's clinical response ([69](#)).

Monitoring — IVIG products are virally inactivated, and monitoring for bloodborne infections is not routinely performed.

Routine monitoring may include the following:

- As described above, pretreatment testing is done to evaluate hematologic parameters, renal function, metabolic status, glucose, and possible infections such as hepatitis (eg, by testing hepatic transaminases). These can be repeated at six-month or yearly intervals ([70](#)). (See '[Pretreatment testing](#)' above.)
- Several IVIG products have been associated with positive Coombs (direct antiglobulin) tests (DAT) and/or frank hemolysis. Thus, when high-dose IVIG is to be given over two or more days for treating autoimmune disorders, it is prudent to check for a drop in hemoglobin and/or Coombs positivity before proceeding with the second or subsequent doses ([71](#)).
- If a previously negative Coombs test becomes positive, one or both of the following may be done:
 - Switch the patient to a different IVIG preparation in which isohemagglutinins have been reduced ([53](#)).
 - Delay or fractionate the remaining dose.

The patient should be well hydrated and monitored closely for hemolysis.

VACCINATION OF PATIENTS RECEIVING IVIG

Administration of IVIG may interfere with the efficacy of vaccinations because the antibodies in the [immune globulin](#) may bind to the antigenic substance in the vaccine and interfere with the normal immune response to the vaccination. This is particularly problematic in patients who received live virus vaccines such as measles, mumps, and rubella (MMR) or varicella vaccines while on or within months after receiving IVIG, since the passively transferred immunoglobulin G (IgG) may prevent the viral replication that is necessary for inducing the desired immune response. In addition, individuals with underlying immune deficiency may have an immunologic defect that blunts the immune response to vaccination independent of IVIG administration. The American Academy of Pediatrics has made specific recommendations for administration of live vaccines against measles and varicella in individuals receiving IVIG. (See '[Measles, mumps, and rubella immunization in infants, children, and adolescents](#)', section on '[Recent receipt of blood or immune globulin](#)'.)

In selected cases (eg, vaccination during a period of IVIG administration for an autoimmune disorder), it may make sense to check titers following vaccination six months after IVIG has been discontinued to determine whether the patient has protective immunity and to re-immunize if the titers are not protective. However, we would not discontinue IVIG in a patient with immunodeficiency solely to assess vaccine efficacy.

Firm recommendations regarding influenza virus immunization are challenging because of a lack of comprehensive data and antigenic variability of the viruses from year to year. To the extent that new antigens arise each year, immunization with inactivated vaccine may induce some protective antibody that is not present in the donor plasma pool. Data correlating the response to inactivated influenza vaccines with the timing after IVIG administration are lacking, but if the antigens in any given vaccine are unique, exogenous IVIG should not interfere with the host's ability to respond, if that is intact. IVIG is unlikely to interfere with local replication of attenuated live (nasal) vaccines, however, these are not usually recommended for immunodeficient patients. Many clinicians give [inactivated influenza vaccine](#) to patients receiving IVIG therapy to stimulate T cell immunity to the virus, which may help in recovery from influenza.

CONSENT AND RECORD KEEPING

Some institutions require signed consent before any blood product or blood derivative is administered. Documentation in the records that potential risks (see '[Intravenous immune globulin: Adverse effects](#)') have been explained and that the patient/parent has received this information, has been given the opportunity to ask questions, and has given consent to receiving IVIG before initiating therapy is often only necessary. Appropriate institutional protocols should be followed.

The dose, brand, lot number, expiration date, and manufacturer of any [immune globulin](#) product infused into any patient should be recorded in the medical record. In addition, patients should be encouraged to keep their own logs of this information, in case a "look back" is ordered. Most vials of IVIG have a

perforated sticker that can be removed and kept in the patient's personal log book, or the lot number can be requested from the hospital pharmacy or other provider.

ADVERSE EFFECTS

Adverse effects of IVIG are discussed in detail separately. (See ["Intravenous immune globulin: Adverse effects"](#).)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See ["Society guideline links: Immune thrombocytopenia \(ITP\) and other platelet disorders"](#) and ["Society guideline links: Primary immunodeficiencies"](#).)

SUMMARY AND RECOMMENDATIONS

- The mechanism of intravenous [immune globulin](#) (IVIG) action depends on the indication for which it is given (see ["Mechanisms of action"](#) above):
 - IVIG provides adequate concentrations of antibodies against a broad range of pathogens for patients with hypogammaglobulinemia, antibody deficiency disorders, other immunodeficiency states, and certain infections.
 - Hyperimmune globulins provide specific passive immunity, typically in the setting of a known or expected exposure.
 - IVIG has a number of immunosuppressive and anti-inflammatory properties that include modulation of immunoglobulin G (IgG) levels, lymphocyte and reticuloendothelium function, cytokine production, complement regulation, and clearance of pathogenic IgG.
- Uses of IVIG and hyperimmune globulin are discussed in detail in separate disease-specific topic reviews listed in the sections above. (See ["Uses for IVIG"](#) above and ["Uses for hyperimmune globulin"](#) above.)
- For most patients, we obtain pretreatment laboratory testing that includes a complete blood count (CBC), hepatic transaminases, metabolic panel including glucose, serum creatinine, and urinalysis before initiating IVIG. Patients with abnormalities in this testing may require additional evaluation. (See ["Pretreatment testing"](#) above.)
- IVIG is produced from pooled plasma donated by several thousand screened donors. Numerous quality control procedures and manufacturing standards are in place to ensure highly purified and stable solutions, although slight differences exist in different products ([table 1](#)). Choices among products depend on patient and disease factors as well as clinical judgment. Importantly, patients who require a specific type of hyperimmune globulin should receive a product intended for this purpose rather than IVIG. Once a patient has found an IVIG product that is well tolerated, it is advisable not to change products unless there is a compelling reason to do so; administration of alternative products should only be done with the clinician's approval. (See ["Production and composition"](#) above and ["Selecting a product"](#) above.)
- Dosing in different disorders, interval between doses, use of premedication, and infusion rates depend on patient and/or disease factors. (See ["Dosing and administration"](#) above.)
- The dose, brand, lot number, expiration date, and manufacturer of any [immune globulin](#) product infused into any patient should be recorded in the medical record, as done for blood products. Some institutions also require informed consent for IVIG. (See ["Consent and record keeping"](#) above.)
- Adverse effects of IVIG are discussed in detail separately. (See ["Intravenous immune globulin: Adverse effects"](#).)

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GRAPHICS

Available immunoglobulin products and their properties

Route	Product	Dosage form	Diluent	Refrigeration required?	Filtration required?	Osmolality (mOsm/L)	Sodium	pH	IgA (mcg/mL)	Stabilizer or regulator	Pathogen inactivation/removal
IV	Bivigam	10% liquid	NA	Yes	No	Not available	0.100 to 0.140 mol/L	4.0 to 4.6	≤200	Glycine	FP, S/D, NF
	Carimune NF	Lyophilized	0.9% sodium chloride, sterile water, 5% dextrose	No	No	498 (3%), 690 (6%), 882 (9%), 1074 (12%)	0.01 mEq/mL (3%), 0.02 (6%), 0.03 (9%), 0.041 (12%)	6.6	720	Sucrose	DF, pH 4, pH 4/pepsin, NF
						192 (3%), 384 (6%), 576 (9%), 768 (12%)	None				
						444 (3%), 636 (6%), 828 (9%), 1020 (12%)	None				
	Flebogamma DIF 5%	5% liquid	NA	No [¶]	Optional	240 to 370	Trace	5.0 to 6.0	<50	D-sorbitol	Past, S/D, NF, FP, PEG, pH
	Flebogamma DIF 10%	10% liquid	NA	No [¶]		240 to 370	Trace		<100	D-sorbitol	
	Gammagard 5% S/D	Lyophilized	Sterile water	No	Yes	636	8.5 mg/mL NaCl	6.8	<1	2% glucose and glycine	CEF, pH 4.2, DF, CAP, CHR
	Gammalex	5% liquid	NA	No	15 to 20 micron filter preferred	420 to 500	30 to 50 mmol/L	4.8 to 5.0	<10	Sorbitol and glycine and polysorbate 80	S/D, VF, low pH
	Octagam 5%	5% liquid	NA	No [¶]	No	310 to 380	0.03 mEq/mL	5.1 to 6.0	<100	Maltose	CEF, S/D, pH 4, UF, CHROI
	Octagam 10%	10% liquid	NA	No [¶]	No	310 to 380	<30 mmol/L	4.5 to 5.0	106 mcg/mL	Maltose	CEF, S/D, pH 4, UF, CHROI
IV or SC	Privigen	10% liquid	NA	No	No	240 to 440	Trace	4.6 to 5.0	<25	L-proline	pH4, NF, DF
	Gammagard liquid	10% liquid	NA	No	No	240 to 300	None added	4.6 to 5.1	37	Glycine	S/D, low pH, NF
	Gammaked	10% liquid	NA, incompatible with saline	No ^Δ	No	258	None added	4.0 to 4.5	46	Glycine	CEF, pH 4.2, DF, CAP, CHR
SC	Gamunex-C	10% liquid	NA, incompatible with saline	No ^Δ	No	258	None added	4.0 to 4.5	46	Glycine	CEF, pH 4.2, DF, CAP, CHR
	Cuvitru	20% solution	NA	No [◊]	No	208 to 290	None	4.6 to 5.1	80	Glycine	CEF, CHROM, NF, S/D
	Hizentra	20% liquid	NA	No	No	380	Trace, <10 mmol/L	4.6 to 5.2	≤50	Proline	pH 4, DF, VF, OAF
Intramuscular	Hyqvia	10% liquid + hyaluronidase	NA	No	No	240 to 300	None added	4.6 to 5.1	37	Glycine	S/D, low pH, NF
	Gammastan	15 to 18% liquid	NA	2 to 8°C	No	Not available	0.4 to 0.5%	6.4 to 7.2	Not measured	Glycine	CEF, S/D, UF

Refer to UpToDate topics on IVIG, SCIG, and IMIG and the product information for the indications and use of these products.

IgA: immunoglobulin A; IV: intravenous; NA: not applicable; FP: fraction precipitation; S/D: solvent detergent; Nano, NF: nanofiltration; DF: depth filtration; DIF: dual inactivation and filtration; Past: pasteurization; PEG: polyethylene glycol precipitation; CEF: cold ethanol fractionation; CAP: caprylate; CHROM: chromatography; VF: virus filtration; UF: ultrafiltration; SC: subcutaneous; OAF: octanoic acid fractionation.

* Pathogen inactivation/removal using CEF, DF, UF, CAP, CHROM, Nano, double sequential nanofiltration, VF, S/D, Past, FP, or OAF.

[¶] Not required (+2 to 25°C).

^Δ Storage is 2 to 8°C for 36 m or 25°C for 6 m.

[◊] Storage is 2 to 8°C × 36 m or room temperature 25°C × 12 m.

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Contributor Disclosures

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