Subject: Intravenous Immune Globulin (IVIg) Therapy for Solid Organ Transplant	Original Effective Date: 02/02/15
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DISCLAIMER

This Medical Policy is intended to facilitate the Utilization Management process. It expresses Molina's determination as to whether certain services or supplies are medically necessary, experimental, investigational, or cosmetic for purposes of determining appropriateness of payment. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that this service or supply is covered (i.e., will be paid for by Molina) for a particular member. The member's benefit plan determines coverage. Each benefit plan defines which services are covered, which are excluded, and which are subject to dollar caps or other limits. Members and their providers will need to consult the member's benefit plan to determine if there are any exclusion(s) or other benefit limitations applicable to this service or supply. If there is a discrepancy between this policy and a member's plan of benefits, the benefits plan will govern. In addition, coverage may be mandated by applicable legal requirements of a State, the Federal government or CMS for Medicare and Medicaid members. CMS's Coverage Database can be found on the CMS website. The coverage directive(s) and criteria from an existing National Coverage Determination (NCD) or Local Coverage Determination (LCD) will supersede the contents of this Molina medical coverage policy (MCP) document and provide the directive for all Medicare members.

SUMMARY

This policy addresses the coverage of **Intravenous Immune Globulin (IVIg) for Solid Organ Transplantation** when appropriate criteria are met.

Solid Organ Transplantation

Acute rejection after transplant can be broadly divided into two categories, the more common acute cellular rejection (ACR) related to activation of T cells and the less common antibody-mediated rejection reaction (AMR) related to the presence of anti-donor antibodies. While ACR typically responds to immunologic therapy directed at T cells, AMR does not, and, as such, has also been referred to as "steroid-resistant rejection." The risk of AMR is related to the presence of preformed allo-antibodies in the recipient due to prior blood transfusions, transplants, or pregnancies. The presence of allo-antibodies is assessed by using a panel reactive antibody (PRA) screen, which combines the recipient's serum with samples of antigen containing cells taken from 60 individuals representative of the potential donor pool. The percentage of PRA is the percentage of positive reactions. Those with a PRA greater than 20% are referred to as "sensitized," and these patients often have prolonged waiting times to identify a compatible donor. Living donor kidney transplants have also been performed using ABO mismatched donor organs. These recipients are also at risk of AMR. As an immunomodulatory agent, IVIg has been widely used in the prevention and management of AMR, often in conjunction with plasma exchange. For instance, in patients at high risk for AMR, IVIg may be given prior to transplant to reduce the numbers of allo-antibodies and the risk of AMR, thus reducing the wait time for a compatible organ. IVIg may be one component of therapy after transplant if AMR develops.

Treatment Goals

The aim of immunosuppression in clinical practice is to control an undesirable immune response while avoiding, if possible, the complications of immunodeficiency. The effect can be achieved by ablation (i.e., irreversibly damaging immune tissue); by altering lymphocyte location and traffic; by altering lymphocyte or dendritic cell function; or by affecting lymphokines. These interventions may be physical (i.e., by irradiation, plasmapheresis, photopheresis) or pharmacological (i.e., IVIg).

Patients with high levels of "anti-donor" antibodies often have very high rejection rates after transplant, especially in kidney transplant. Rejection risks are very high for a patient whose immune system has been exposed to "non-self" human leukocyte antigens (HLA). Exposure to HLAs may occur in a number of ways, including prior organ transplant or blood transfusions.

IVIg increases a highly sensitized patient's chance of successful transplant. IVIg is a new immune-modulating therapy that can reduce high antibody levels and improve transplant rates. IVIg helps by modifying the immune system rather than suppressing it.

IVIg is given while a highly sensitized patient waits for transplant, with the goal of decreasing their overall level of sensitization and therefore increasing the possibility that a donor kidney would be acceptable to their immune system.

Pharmacologic Agents/Conventional Therapy

Intravenous immune globulin is prepared from plasma pooled from thousands of healthy donors. This pooling provides a diversity of antibody repertoires and antibody specificities. Currently, immune globulin is used in the treatment of a wide variety of diseases, with more than 75% of the intravenous immune globulin in the United States administered to patients with autoimmune or inflammatory conditions.[a-j] The donors in a typical pool of plasma have a wide range of antibodies against infectious agents.[l] These products have IgG subclasses similar to that found in normal humans. Immunoglobulins are administered intravenously to provide immediate antibody levels. The dosage and administration schedule varies by diagnosis.

The precise mechanism of action of IVIg is unclear. For individuals who are unable to produce their own antibodies, IVIg is used to temporarily provide these patients with the antibodies required to defend against infection. In patients with autoimmune diseases, or other conditions where the body's immune system is not functioning as it should, IVIg may support the regulation of an overactive immune system by signaling it to slow down or stop inflammatory processes.[a-j] It has also been hypothesized that IVIg might redirect the out-of-control immune system from the body's tissues by serving as a target for the auto-antibodies.

Three formulations of human IgG are available for delivery by intravenous infusion (IVIg) by subcutaneous infusion (SCIg), or by intramuscular (IMIg) depot injections.

- SCIg is administered as a subcutaneous infusion to be started one week after the patient's last Immune Globulin Intravenous (Human) infusion (IVIg). SCIg should be administered on a weekly basis.
- IMIg formulations are not available in the United States due to volume constraints and pain preclude delivery of sufficient product weekly into each buttock to yield therapeutic serum levels of IgG, leaving recipients susceptible to infections.

Product Comparisons

- Several brands of IVIg products are FDA approved. While they are generally considered equally effective, they are not identical and are not rated as bioequivalent by the FDA. There are differences in production method, virus elimination, and composition which may result in differences in safety and tolerability in individual patients. Product characteristics such as content (e.g., IgA concentration, stabilizer), volume, and osmolarity may be important considerations for some patients. However, comparative data are lacking and it is not known whether one specific product is superior for a particular disease or clinical setting.

- Presently, there is no evidence of efficacy differences among the different IVIg products, although there may be potential differences in adverse effects among the different products. Patients with renal dysfunction, diabetes, sepsis, or age >65 years are at increased risk of developing kidney problems if a sucrose-containing product is used. In general, products with higher IgA content are associated with increased adverse effects. There is a higher chance of adverse effects if the IVIg product is switched after establishing therapy with a particular product.

❖ **POSITION:** IVIG products are similar in efficacy and should be prescribed based on the risk of adverse events with each formulation, cost-effectiveness, and history of IVIG use. Therefore, all IVIG preparations are generally considered therapeutically interchangeable unless otherwise documented by prescribing physician as applicable to individual patient, or Molina member.

❖ **Immune globulin subcutaneous [human] (SCIg)** products are currently labeled for the treatment of primary immunodeficiency syndromes (PID) only.

- At present, four immune globulin products are FDA-approved for subcutaneous administration in patients with PID. Clinical experience with subcutaneous administration of immune globulin for treating conditions other than PID is limited at this time and is generally not recommended. **Therefore, SCIg will <u>not</u> be addressed in this policy.**
- The SCIg formulation may be attractive to patients due to a lack of requirement of venous access, a perceived sense of independence associated with self-administration, and more consistent serum IgG levels. However, limitations of SCIg include increased dosing frequency, requirement of multiple dosing sites, and the need for competent and adherent patients. Additionally, since other diagnoses usually require larger doses (based on grams per kilogram) with a high volume per dose, subcutaneous administration is generally not practical.
- There is no strong evidence that indicates a preferential route of administration of IgG. Systematic reviews and cross-trial comparisons indicate that there is no difference in efficacy between IVIG and SCIg products. Products with low IgA counts may be preferable to those who experience infusion reactions.
- There is no strong evidence that shows that the differences in the pharmacokinetic profiles of IVIg and SCIg translate to meaningful improvements in patient outcomes. While some studies showed a lower incidence of adverse events in SCIg versus IVIg, the 20% SCIG formulation has not been directly compared to IVIg.

***Refer to 'Appendix 1' for further specific product information.**

CLASSIFICATION: Biologic Response Modifiers; Immunoglobulins

FDA INDICATIONS

INTRAVENOUS IMMUNE GLOBULIN (IVIg)
Several IVIg products are available for clinical use in the United States. The labeled indications approved by the U.S. Food and Drug Administration (FDA) for IVIg are listed in the Policy section. Several off-label indications have been investigated; some of the most common are inflammatory myopathies, neuropathies (e.g., Guillain-Barré syndrome), myasthenia gravis, multiple sclerosis, and solid organ transplantation.

This policy only addresses the coverage of Intravenous Immune Globulin (IVIg) for SOLID ORGAN TRANSPLANTATION when appropriate criteria are met.

Clinical indications for which IVIg has been FDA-approved are as follows:[k]

1) Treatment of **primary immunodeficiency diseases (PID)** [such as common variable immunodeficiency (CVID), X-linked agammaglobulinemia, Wiskott-Aldrich syndrome, and severe combined immunodeficiencies]
2) Prevention of bacterial infections in patients with hypogammaglobulinemia and recurrent bacterial infection caused by **B-cell chronic lymphocytic leukemia**
3) Prevention of coronary artery aneurysms in **Kawasaki disease (KD)**
4) Prevention of infections, pneumonitis, and acute graft-versus-host disease (GVHD) after **bone marrow transplantation**
5) Reduction of serious bacterial infection in **children with human immunodeficiency virus (HIV)**
6) Increase of platelet counts in idiopathic thrombocytopenic purpura (ITP) to prevent or control bleeding
7) To improve neuromuscular disability and impairment and for maintenance therapy to prevent relapse in **chronic inflammatory demyelinating polyneuropathy (CIDP)**
8) As a maintenance therapy to improve muscle strength and disability in adult patients with **multifocal motor neuropathy (MMN).**

Available as: *Refer to Appendix 1*. **NOTE:** In absence of a product listed and in addition to applicable criteria outlined within the drug policy, prescribing and dosing information from the package insert is the clinical information used to determine benefit coverage.

FDA Approved:

- Immune globulin products from human plasma were first used in 1952 to treat immune deficiency.
- Immune globulin subcutaneous [human] (SCIg): The first immune globulin for subcutaneous use was FDA approved in 2006.

Black Box Warnings from the product information labels for the intravenous Ig formulations include the following:

- Thrombosis may occur with immune globulin products. Risk factors may include: advanced age, prolonged immobilization, hypercoagulable conditions, history of venous or arterial thrombosis, use of estrogens, indwelling vascular catheters, hyperviscosity, and cardiovascular risk factors. For patients at risk of thrombosis, administer the immune globulin at the minimum dose and infusion rate practicable. Ensure adequate hydration in patients before administration. Monitor for signs and symptoms of thrombosis and assess blood viscosity in patients at risk for hyperviscosity.
- IVIg products have been associated with renal dysfunction, acute renal failure, osmotic nephrosis, and death. For patients at risk of renal dysfunction or failure, administer immune globulin at the minimum concentration available and the minimum infusion rate practicable. Renal dysfunction and acute renal failure occur more commonly in patients receiving IVIg products containing sucrose. Cariumune NF contains sucrose, the other products included in this review do not. Hizentra does not carry this warning.
  NOTE: Although all IVIg products carry a black box warning regarding the increased risk of renal dysfunction, they are not contraindicated in patients with renal insufficiency.[a-j] IVIG is used in the treatment of certain complications of renal transplantation.[D] IVIg has been studied to decrease anti–human leukocyte antigen (HLA) alloantibody titers before transplantation, to prevent rejection of organs after transplantation, as immunomodulatory medication after retransplantation, and as an alternative immunosuppressant option.[3,4]

RECOMMENDATIONS/COVERAGE CRITERIA

Solid Organ Transplantation

Intravenous Immune Globulin (IVIg) may be authorized for members who meet **ALL** of the following criteria **[ALL]**

1. Prescriber specialty [ONE]

- ❒ Prescribed by, or in consultation with, a board-certified physician affiliated with a transplant center. Submit consultation notes if applicable.

- ❒ Cytomegalovirus infection prophylaxis associated with organ transplantation: Prescribed by or in consultation with an oncologist, hematologist, or an infectious diseases physician.

2. Diagnosis/Indication [ONE]

Prescribed for ONE of the following (*includes clinical notes from the member's medical records including any applicable labs and/or tests, supporting the diagnosis*) and medication usage must be supported by documentation from the member's medical records:

- ❒ Prescribed for Solid Organ Transplantation for ONE (1) of the following conditions: [ONE]

  - ❍ **PRIOR** to solid organ transplant for prevention of acute rejection (pre- and peri-operative): Prevention of antibody-mediated rejection prior to solid organ transplant, or in the peri-operative period, for patients at **high-risk** for antibody-mediated rejection [including highly sensitized patients, and those receiving an ABO-incompatible organ]

❍ **POST** solid-organ transplant: [ONE]

- Treatment of antibody-mediated (humoral) rejection following solid organ transplant: Confirmation by either biopsy or presence of panel reactive antibodies (PRAs), if used in combination with plasmapheresis

- Transplant recipients at high-risk for cytomegalovirus infections (CMV), OR for treatment of CMV pneumonitis in combination with antiviral therapy[n,q,D]
  - ➢ *Prophylaxis with intravenous Cytomegalovirus Intravenous Immune Globulin (CMV-IG; Cytogam®) has been demonstrated to reduce the morbidity associated with CMV disease in CMV-seronegative kidney, liver, pancreas, lung, and heart transplant recipients who receive organs from seropositive donors. Prophylaxis with the globulin should be considered for all CMV-seronegative transplant patients scheduled to receive kidneys, liver, pancreas, lung and heart from cytomegalovirus-seropositive donors. This recommendation should apply to recipients of cadaveric transplants as well as recipients of transplants from living related donors [Micromedex; Cytomegalovirus Immune Globulin, Human].*

3. Age/Gender/Other restrictions [ALL APPLICABLE]

❑ Requests for treatment 100 days or greater post-transplant ONLY (not applicable to CMV infection prophylaxis requests): [ONE]

❍ IgG less than 400mg/dL, OR

❍ Documented CMV, EBV or RSV infection

❑ Requests **PRIOR** to kidney transplant ONLY:

Documentation that treatment is prescribed for member with high levels of "anti-donor" antibodies [i.e., patients highly sensitized to the tissue of the majority of living or cadaveric donors because of "non-self" human leukocyte antigen [HLA] or ABO incompatibility][A]

- ➢ *To reduce the risk of acute antibody-mediated rejection, IVIg is recommended for kidney transplant patients who have donor-specific antibodies preoperatively. IVIg is not recommended for kidney transplant patients who do not have donor-specific antibodies.[A] (The National Advisory Committee on Blood and Blood Products and Canadian Blood Services, 2010)*

4. Step/Conservative Therapy/Other condition Requirements [ALL: A, B]

❑ Requests for CMV infection prophylaxis associated with organ transplantation ONLY: Seronegative recipients of seropositive organs may receive prophylaxis with CMV-IG: Trial of antiviral prophylaxis required

- ➢ *Prophylaxis with intravenous CMV Immune Globulin has been demonstrated to reduce the morbidity associated with CMV disease in cytomegalovirus-seronegative kidney, liver, pancreas, lung, and heart transplant recipients who receive organs from seropositive donors. Toxicity has been minimal; one case of hypotension was observed during 1039 infusions in clinical trials. Prophylaxis with the globulin should be considered for all cytomegalovirus-seronegative transplant patients scheduled to receive kidneys, liver, pancreas, lung and heart from cytomegalovirus-seropositive donors. (Micromedex 2015)*
- ➢ *Antiviral therapy is currently used.[7,8] Antiviral agents (ganciclovir, Valcyte™ [valganciclovir oral tablets or solution]) and Cytogam are effective in preventing and treating CMV in solid organ transplant recipients.*
- ➢ *Refer to Summary of Evidence section, under 'Evidence-Based Guideline' and 'International Consensus Guidelines: Solid Organ Transplantation[B]' for additional information.*

5. Contraindications/Exclusions/Discontinuations

Authorization will not be granted if ANY of the following conditions apply [ANY]

- ❒ Non-FDA approved indications
- ❒ Anaphylactic or severe systemic reaction to human immune globulin or components of the product
- ❒ IgA deficiency with antibodies against IgA and a history of hypersensitivity; IG products contain trace amounts of IgA
- ❒ Hereditary intolerance to fructose, including infants and neonates for whom sucrose or fructose tolerance has not been established
- ❒ Severe thrombocytopenia or any coagulation disorder which would contraindicate IM injections (IM)

Specific product indication [ANY]

- ❒ Octagam: Contraindicated in patients with acute hypersensitivity reaction to corn.
- ❒ Gammaplex and Flebogamma: Contraindicated in those with intolerance to any component of the product (i.e. intolerance to fructose). Gammaplex is also contraindicated in infants and neonates for whom sucrose or fructose tolerance has not been established.
- ❒ Flebogamma: Contraindicated or intolerance to any component of Flebogamma, such as sorbitol (i.e., intolerance to fructose)
- ❒ Privigen and Hizentra: Contraindicated in patients with hyperprolinemia (type I or II); Hizentra® and Privigen® contain the stabilizer L-proline.

6. Labs/Reports/Documentation required [ALL]

All documentation for determination of medical necessity must be submitted for review. Prescriber to submit medical records and specific labs, chart notes, and documentation as indicated in the criteria above. Letters of support and/or explanation are often useful, but are not sufficient documentation unless ALL specific information required by this MCP is included.

- ❒ Date of transplant and IVIG treatment period requested
- ❒ Medical record documentation confirms the member has been definitively diagnosed (by an appropriate specialist) with one of the listed diagnosis above (#2)

CONTINUATION OF THERAPY

Intravenous Immune Globulin (IVIg) may be authorized for continuation of therapy if meet **ALL** of the following criteria are met: **[ALL]**

1. Initial Coverage Criteria

- ❑ Member currently meets ALL initial coverage criteria

2. Compliance

- ❒ No persistent or uncorrectable problems with adherence to IVIG treatment

3. Labs/Reports/Documentation required [ALL APPLICABLE]

- ❒ Documentation of **stabilization or clinical improvement** as evidenced by physical findings and /or clinical symptoms following the initial IVIG treatment period
- ❒ Member is closely followed by the prescribing specialist, and treatment response has clearly defined endpoints to measure effectiveness

4. Discontinuation of Treatment [ANY]

Authorization will not be granted if ANY of the following conditions apply [ANY]

- ❒ Non-FDA approved indications
- ❒ Anaphylaxis or severe systemic reaction to human immunoglobulins, or to any component of the product, including polysorbate 80
- ❒ Hereditary intolerance to fructose, including infants and neonates for whom sucrose or fructose tolerance has not been established
- ❒ Hyperprolinemia (type I or II); Hizentra® and Privigen® contain the stabilizer L-proline
- ❒ IgA deficiency with antibodies against IgA, and a history of hypersensitivity; IG products contain trace amounts of IgA
- ❒ Severe thrombocytopenia or any coagulation disorder which would contraindicate IM injections (IM)

1. Recommended Dosage [ALL]

- ❒ IVIg: 2 gm/kg IV monthly, or 100mg/kg IV when used after plasmapheresis session

- ❒ Cytomegalovirus Immune Globulin Intravenous (Cytogam): 150 milligrams/kilogram/dose should not be exceeded.[q]
  NOTE: Refer to Appendix 2 for additional dosing information on CMV-IG
  - *No standardized dose used for CMV-Ig in the literature*
  - *No trials comparing efficacy of IVIg and CMV-Ig for treatment. There is no clear evidence that CMV-Ig provides advantage over IVIg for treatment of CMV disease, and IVIg has also shown in some trials to be effective for adjunctive treatment of CMV pneumonia.*

2. Authorization Limit [ALL]

- ❒ Quantity limit: [ONE]

  - ❍ **PRIOR** to Transplant:

    - Prevention of acute rejection (pre- and peri-operative): Up to FOUR (4) doses pre-transplant, then 1 dose weekly for 4 weeks post-transplant. Maximum of 8 doses. Authorization duration: 3 months

  - ❍ **POST** Transplant:

    - Treatment of antibody-mediated (humoral) rejection: ONE (1) dose, once per rejection episode. Authorization duration: 2 weeks

    - Transplant recipients at high risk for cytomegalovirus infections (CMV) or for treatment of CMV pneumonitis in combination with antiviral therapy: Maximum recommended total dosage per infusion is 150 mg IG/kg; max rate: 60mg/kg/hr

- ❒ Dispensing limit: N/A

- ❒ Duration of initial authorization: Dependent on individual diagnosis

  - ❍ **PRIOR** to Transplant: 3 months

  - ❍ **POST** Transplant

    - Treatment of antibody-mediated (humoral) rejection: 2 weeks

    - Transplant recipients at high risk for cytomegalovirus infections (CMV) or for treatment of CMV pneumonitis in combination with antiviral therapy: 3 months

- ❒ Continuation of treatment: Re-authorization for continuation of treatment is dependent on individual diagnosis as follows: [ONE]

  - ❍ Prevention of acute rejection (pre- and peri-operative): Further authorization will be reviewed as Post-Transplant "Treatment of antibody-mediated (humoral) rejection"

- ❍ Treatment of antibody-mediated (humoral) rejection: Documented improvement from previous course and confirmation of another episode of rejection; one dose.

- ❍ Transplant recipients at high risk for cytomegalovirus infections (CMV) or for treatment of CMV pneumonitis in combination with antiviral therapy: Continued treatment may be considered if the member demonstrates a need for continued prophylaxis. Prescriber submit documentation for Medical Director Review.

❒ Duration of continuation of treatment: May be authorized up to **THREE (3) months** at a time.

3. Route of Administration [ALL]

❒ Intravenous Immune Globulin (IVIg) is considered a **provider-administered** medication

❒ Site of administration: The decision regarding place of administration of a patient's IgG therapy (in a hospital, hospital outpatient, community office or home-based setting) must be based upon clinical and patient characteristics and circumstance in order to minimize risk to the patient such as co-morbid conditions, individual patient's ability to administer IgG at home, compliance, and availability and ease of IV access

❒ IVIg products are not interchangeable. Any changes of IVIg product brand should be provided under physician supervision in a facility equipped to handle the most severe acute medical complications whenever feasible.

COVERAGE EXCLUSIONS

Intravenous Immune Globulin (IVIg) is considered **experimental and investigational** for all other indications not addressed in the 'Recommendations/Coverage Criteria." Diagnoses which are unproven and/or do not support a conclusion concerning the health outcomes or benefits associated with this procedure. Therefore, all other uses of Intravenous Immune Globulin (IVIg) that are not an FDA-approved indication or included in 'Coverage Criteria' section above are considered experimental/investigational and is not a covered benefit.

❒ Organ Transplant Rejection: refer to page

❒ IVIg and Rituxan (Rituximab) for desensitization **prior** to renal transplantation
- ➢ *The combination of IVIg and Rituxan (Rituximab) for desensitization prior to renal transplantation is investigational at this time. Larger, prospective, randomized controlled trials are required to evaluate the long-term efficacy and safety of this treatment and to compare this protocol with the current treatment of IVIg alone.*

❒ Desensitization Therapy Prior to and Immediately after Solid Organ (Kidney, Heart, Lung, Liver, Intestinal) Transplantationp. *Refer to 'Summary of Evidence' section for additional information.*
EXCEPTION: Medical Director may consider authorization if prescribed by, or in consultation with, a physician affiliated with a transplant center. Additional documentation and discussion with Prescriber, as deemed necessary by Molina Medical Director, may be required.
- ➢ *There is insufficient evidence to recommend for, or against, the use of IVIg for desensitization for patients undergoing heart, lung, or liver transplantation.*[A]

- Immune globulin (IVIg) derived from human plasma, is a collection of antibodies pooled together from multiple human donors. It is a mixture of various normal human antibodies, and, when administered by intravenous infusion, provides immediate antibody levels.

- IVIG products are similar in efficacy and should be prescribed based on the risk of adverse events with each formulation, cost-effectiveness, and history of IVIG use. Therefore, all IVIG preparations are generally considered therapeutically interchangeable unless otherwise documented by prescribing physician as applicable to individual patient, or Molina member.

- Antibody-mediated rejection
  - Acute allograft (organ) rejection may be cellular (T-cell mediated) or humoral (antibody-mediated) (AHR, AMR).
  - Pre-treatment with IVIg (desensitization) may reduce the risk of AMR antibody-mediated rejection (AMR) in highly sensitized renal transplant patients.[1]
  - A randomized, double-blind trial comparing IVIg to placebo in 101 highly sensitized renal transplant candidates concluded that IVIG is better than placebo in improving transplantation rates.[2]
  - Acute humoral rejection (AHR) is also an AMR and can occur outside of the peri-operative period, but most commonly within 6 months after transplant. The diagnosis is confirmed by a renal biopsy. The goal of therapy is early antibody elimination with IVIG, pheresis or a combination of modalities.
  - A variety of protocols have been developed for the use of IVIg in treating AMR after solid organ transplant.[1]

Reference:

1. *Kälble T, Alcaraz A, et al. Guidelines on renal transplantation. Arnhem, The Netherlands: European Association of Urology (EAU); 2009 Mar. [cited March 21, 2013]; Available from: http://www.uroweb.org/fileadmin/tx_eauguidelines/2009/Full/Renal_Transplant.pdf*
2. *Jordan SC, et al. Evaluation of intravenous immunoglobulin as an agent to lower allosensitization and improve transplantation in highly sensitized adult patients with end-stage renal disease: report of the NIH IG02 trial. J Am Soc Nephrol 2004 15:3256-62.*

- There are no consensus statements available for the use of IVIG in solid organ transplantation.[AMR Review 2015]

- Antibody-mediated rejection (AMR) consensus criteria have been defined in kidney and heart transplantation by histological changes, circulating donor-specific antibody (DSA), and C4d deposition in affected tissue. But the actual treatment of antibody mediated rejection with IVIG comes mainly from large single-center retrospective and prospective studies. [AMR Review 2015]

KIDNEY TRANSPLANT

- Jordan et al. (2004) reported outcomes of a randomized, double-blind, placebo-controlled clinical trial for the reduction of anti-HLA antibody levels and improvement of transplant rates with IVIg.[7]
  - A total of 101 participants with end stage renal disease (ESRD) and highly sensitized to HLA antigens (panel reactive antibody [PRA] greater than or equal to 50% monthly for 3 months) were enrolled in a National Institutes of Health (NIH) sponsored trial (IG02).[2]
  - Participants received either IVIg 2 gm/kg monthly for 4 months or an equivalent volume of placebo with additional infusions at 12 and 24 months after entry, if not transplanted.
  - If transplanted, additional infusions were given monthly for 4 months.
  - Baseline PRA levels were similar in both groups. However, IVIg significantly reduced PRA levels in the IVIg group compared with placebo. Sixteen IVIg participants (35%) and 8 placebo participants (17%) were transplanted.
  - Result: Rejection episodes occurred in 9 of 17 IVIg and 1 of 10 placebo subjects. Seven graft failures occurred (4 IVIg; 3placebo) among adherent participants with similar 2-year graft survival rates (80% IVIg;

75% placebo). With a median follow-up of 2 years after transplant, the viable transplants functioned normally.

- It was concluded that IVIg is better than placebo in reducing anti-HLA antibody levels and improving transplantation rates in highly sensitized individuals with ESRD. Transplant rates for highly sensitized patients with ESRD awaiting kidney transplants are improved with IVIG therapy.

Reference: Jordan SC, Tyan D, Stablein D, et al. Evaluation of intravenous immunoglobulin as an agent to lower allosensitization and improve transplantation in highly sensitized adult patients with end-stage renal disease: report of the NIH IG02 trial. J Am Soc Nephrol. 2004; 15(12):3256-3262.

HEART TRANSPLANT

No randomized trial has compared CMVIG with or without antiviral therapy in heart transplantation,[12] however a retrospective study in 207 D+/R− transplants reported significantly lower rates of CMV disease and CMV-related disease with the addition of IV ganciclovir.[13] Randomized comparisons of CMVIG plus IV ganciclovir versus IV ganciclovir alone are lacking.[12]

❖ Kobashigawa et al. (2009) reported recommendations from an international consensus conference addressing those who are sensitized and awaiting heart transplant. The 71-member panel examined diagnostic and treatment regimens from transplant centers and reached consensus for anti-HLA antibody screening and testing methodology. The desensitization recommendations pre-transplant included IVIg, plasmapheresis, and possibly rituximab.
Reference: Kobashigawa J, Mehra M, West L, et al. Report from a consensus conference on the sensitized patient awaiting heart transplantation. J Heart Lung Transplant. 2009; 28(3):213-225.

❖ Kobashigawa and colleagues (2011) reported recommendations from an international consensus conference addressing antibody mediated rejection (AMR) in heart transplantation. The conference participants noted that the problem of AMR is due to the many different features of AMR making the current methods for diagnosis and treatment difficult. The panel examined diagnostic and treatment regimens from transplant centers and the published literature. Regarding the use of IVIg, initial treatment for AMR may include high dose corticosteroids, plasmapheresis and IVIg.
Reference: Kobashigawa J, Crespo-Leiro MG, Ensminger SM, et al. Report from a consensus conference on antibody-mediated rejection in heart transplantation. J Heart Lung Transplant. 2011; 30(3):252-269.

❖ IVIg has been used alone or in conjunction with appropriate anti-infective therapy to prevent or modify acute bacterial or viral infections (e.g., cytomegalovirus infections) in patients with iatrogenically induced or disease-associated immunosuppression such as patients undergoing major surgery (e.g., cardiac transplants) or patients with hematologic malignancies, extensive burns, or collagen-vascular diseases (AHFS 2014).[m]

❖ Jordan et al. (2011), in a review, addressed clinical applications of Ig in solid organ transplantation and suggested that IVIg has a much broader ability to regulate cellular immunity and is a modifier of complement activation and injury.[8]

- Published clinical data addresses the use of IVIg in desensitization and treatment of antibody-mediated rejection (AMR) and are supportive for use in kidney transplant recipients, however no clinical trials using IVIg in sensitized individuals have been performed.
- The available data regarding the use of IVIg for desensitization and treatment of AMR in cardiac and lung allograft recipients is not conclusive.
- The authors noted out that desensitization (immunomodulation) pre- and post-solid organ transplantation requires a coordinated approach so that AMR and infectious complications are minimized.
- There are currently no FDA approved drugs/protocols for desensitization.
  Reference: Jordan SC, Toyoda M, Kahwaji J, Vo AA. Clinical aspects of intravenous immunoglobulin use in solid organ transplant recipients. Am J Transplant. 2011; 11(2):196-202

DESENSITIZATION THERAPY

Prior to and Immediately after Solid Organ Transplantation

❖ **Kidney**

IVIg has been used in highly sensitized patients to reduce allosensitization, ischemiareperfusion injuries, and acute rejections episodes in renal allograft recipients.[1-5] IVIG has been used alone or after plasmapheresis. In one Phase III double-blind trial in patients with end stage renal disease (ESRD), IVIg was better than placebo in reducing anti-HLA antibody levels and improving transplantation rates in highly sensitized patients.[2]

Reference:

1. *Marfo K, Lu A, Ling M, Akalin E. Desensitization protocols and their outcome. Clin J Am Soc Nephrol. 2011;6:922-936.*
2. *Jordan SC, Tyan D, Stablein D, et al. Evaluation of intravenous immunoglobulin as an agent to lower allosensitization and improve transplantation in highly sensitized adult patients with end-stage renal disease: report of the NIH IG02 trial. J Am Soc Nephrol. 2004;15:3256-3262.*
3. *Jordan SC, Vo AA, Peng A, et al. Intravenous gammaglobulin (IVIG): a novel approach to improve transplant rates and outcomes in highly HLA-sensitized patients. Am J Transplant. 2006;6:459-466.*
4. *Shehata N, Palda VA, Meyer RM, et al. The use of immunoglobulin therapy for patients undergoing solid organ transplantation: an evidence-based practice guideline. Transfus Med. 2010;24(1 Suppl 1):S7-S27.*
5. *Jordan SC, Toyoda M, and Kahwaji J. Clinical aspects of intravenous immunoglobulin use in solid organ transplant recipients. Am J Transplant. 2011;11:196-202.*

❖ **Heart**

IVIG has been used as a desensitization agent in patients undergoing cardiac transplantation.[1-2] However, randomized trials are not available and many of the studies have not defined response. The studies have not shown that IVIG alone reduced antibody and results concerning survival after transplant are conflicting.

Reference:

1. *Shehata N, Palda VA, Meyer RM, et al. The use of immunoglobulin therapy for patients undergoing solid organ transplantation: an evidence-based practice guideline. Transfus Med. 2010;24(1 Suppl 1):S7-S27.*
2. *Jordan SC, Toyoda M, and Kahwaji J. Clinical aspects of intravenous immunoglobulin use in solid organ transplant recipients. Am J Transplant. 2011;11:196-202.*

❖ **Lung or Liver**

The role of IVIG or any other desensitization therapy in patients prior to *lung* transplantation who are sensitized to HLA is not known.[1] There is insufficient evidence to recommend for or against use of IVIG in these patients for desensitization or for treatment of rejection.[1-2] Regarding *liver* transplantation, antibody mediated rejection after transplantation is rare and patients are not routinely evaluated for HLA antibody formation.[1]

According to guidelines from the Canadian Blood Services and the National Advisory Committee on Blood and Blood Products of Canada[1] there is insufficient evidence to make a recommendation for or against routine use of IVIG in preparation for liver transplantation or for treatment of rejection/ABO-incompatible liver transplantation. Use of IVIG in combination with other therapies in patient undergoing lung or liver transplantation requires further study.

Reference:

1. *Shehata N, Palda VA, Meyer RM, et al. The use of immunoglobulin therapy for patients undergoing solid organ transplantation: an evidence-based practice guideline. Transfus Med. 2010;24(1 Suppl 1):S7-S27.*
2. *Jordan SC, Toyoda M, and Kahwaji J. Clinical aspects of intravenous immunoglobulin use in solid organ transplant recipients. Am J Transplant. 2011;11:196-202.*

❖ **Small Intestine**

Limited published information is available in sensitized recipients of small intestine transplants.[1-2] In a pilot study, highly sensitized patients (n = 6) with intestinal failure (short gut syndrome) who were awaiting isolated small bowel transplant received IVIG and immunosuppressive therapy pre-transplant.[1] Four of the six patients had reduction in high panel peak reactive antibody (PRA) and received intestinal transplantation. Patients continued on IVIG post-transplant at Days 1, 7 and 21. The waiting time for transplant and mortality was similar to non-sensitized patients. IVIG is also used post-transplant to treat acute antibody-mediated rejection and steroid-resistant acute cellular rejection.[1] These patients are hospitalized.

Reference:

1. *Gondolesi G, Blondeau B, Maurette R, et al. Pretransplant immunomodulation of highly sensitized small bowel transplant candidates with intravenous immune globulin. Transplantation. 2006;81:1743-1746.*
2. *Hawksworth JS, Rosen-Bronson S, Island E, et al. Successful isolated intestinal transplantation in sensitized recipients with the use of virtual crossmatching. Am J Transplant. 2012;12 Suppl 4:s33-s42.*

OTHER BACTERIAL OR VIRAL INFECTIONS

IVIg has been used alone or in conjunction with appropriate anti-infective therapy to prevent or modify acute bacterial or viral infections (e.g., cytomegalovirus infections) in patients with iatrogenically induced or disease-associated immunosuppression such as patients undergoing major surgery (e.g., cardiac transplants) or patients with hematologic malignancies, extensive burns, or collagen-vascular diseases (AHFS 2015).[m]

Cytomegalovirus (CMV) Infections, Prophylaxis or Treatment in Solid Organ Transplantation:

- Antiviral therapy is currently used.[1,2]
- Antiviral agents (ganciclovir, Valcyte™ [valganciclovir]) and Cytogam are effective in preventing and treating CMV in solid organ transplant recipients.

Reference:

1. *Preiksaitis JK, Brennan DC, Fishman J, et al. Canadian Society of Transplantation consensus workshop on cytomegalovirus management in solid organ transplantation final report. Am J Transplant. 2005;5:218-227.*
2. *Pereyra F, Rubin RH. Prevention and treatment of cytomegalovirus infection in solid organ transplant recipients. Curr Opin Infect Dis. 2004;17:357-361.*

Points for consideration:

- The drug of choice for prevention of CMV disease in solid-organ transplant patients is now valganciclovir.[9] Other than CMV retinitis, however, ganciclovir remains the mainstay of treatment, at least initially. The other options listed below are either second-line (foscarnet, cidofovir, or maribavir) or are used off-label (leflunomide).

  There is no consensus at this time as to whether prophylaxis versus preemptive therapy is the better approach for prevention of CMV infection in solid-organ transplant recipients. Recent data favors prophylactic therapy with either ganciclovir or valganciclovir in high risk liver transplant recipients.[10] Data also favor the use of valganciclovir prophylaxis over preemptive therapy in CMV-positive renal allograft recipients.[11]

- Current guidelines do not recommend routine treatment of CMV disease with CMV-Ig; however state that either CMV-Ig or regular IVIg may be considered in pneumonitis.

- No well-designed randomized controlled clinical trials were available regarding the use of CMV-Ig in the treatment of CMV disease.

- Trials available are almost entirely for CMV pneumonia and are largely uncontrolled, retrospective, observational, case-series or surveys; limited recent evidence is available.

- No trials comparing efficacy of IVIg and CMV-Ig for treatment. There is no clear evidence that CMV-Ig provides advantage over IVIg for treatment of CMV disease, and IVIg has also shown in some trials to be effective for adjunctive treatment of CMV pneumonia.

COMBINATION THERAPY WITH RITUXIMAB

IVIg is one of the most common therapies used to decrease antibody-mediated immunity. IVIg causes B cell apoptosis, reduces B cell numbers, and down-regulates several B cell surface antigens. It also blocks binding of donor-reactive antibodies and may inhibit complement activation. It has a relatively low side effect profile. The combination of IVIg and rituximab has also been used in the setting of organ transplantation. Firstly, IVIg ± rituximab has been administered to highly human leucocyte antigen (HLA)-sensitized patients to reduce anti-HLA antibody levels, thereby allowing transplantation in these patients. Secondly, IVIg in combination with rituximab is effective in the treatment of antibody-mediated rejection following transplantation.

- Rituximab, an anti-CD20 monoclonal antibody that causes B cell depletion, has been proven effective in the treatment of presensitized renal transplant recipients in conjunction with IVIG [2,3] through an open-label, phase 1-2, single-center study. This phase I-II trial examined if a treatment protocol, consisting of intravenous immune globulin (IVIG) and rituximab, administered prior to kidney transplantation would improve transplantation rates by reducing anti-HLA antibody levels in highly sensitized individuals.[2] These findings suggest that the combination of intravenous immune globulin and rituximab may prove effective as a desensitization regimen for patients awaiting a transplant from either a living donor or a deceased donor. Larger and longer trials are needed to evaluate the clinical efficacy and safety of this approach.
    - Twenty individuals, who were highly sensitized, were treated with the combination regimen of IVIg + rituximab between 2005 and 2007. In this protocol, 2 g/kg IVIg was delivered on week 0, followed by 1 g rituximab on weeks 3 and 4 and a second dose of IVIg on week 5.
    - Vo and colleagues (2008) reported that following this desensitization therapy:
        - Panel reactive antibodies (PRA) levels were "***reduced significantly*** (from 77 ± 19% before first infusion to 44 ± 30% after the second infusion)."
        - Serum creatinine levels, as a marker of kidney function, were normal in most patients, except for one who lost the graft.
        - No infections or progressive multi-focal leucoencephalopathy were observed.
        - 16 of the 20 participants received successful transplantation (6 received a deceased donor kidney; 10 received a living donor kidney) and mean follow-up was 22.1 ± 6 months with recipient with allograft survivals of 100% and 94%, respectively.
        - The remaining 4 participants had PRA levels greater than 50% and were awaiting a deceased donor kidney transplant. One graft was lost due to severe rejection after a reduction of immunosuppressive therapy. Acute rejection occurred in 50% of the transplanted individuals. Acute antibody-mediated rejections (AMR) occurred in 31% of the episodes and 2 individuals had late (greater than 6 months) AMR episodes. Individuals with AMR were treated with methylprednisolone, rabbit antithymocyte globulin and rituximab.
        - Recipients of deceased donor kidneys had a mean waiting list time of 12 years (range, 5-27) prior to desensitization, but received transplants within 5 to 6 months after receiving combination treatment with IVIG and rituximab.

- In 2010, Vo and colleagues reported on 76 HLA-sensitized individuals who were treated with IVIG and rituximab prior to kidney transplantation during 2006 and 2009.[4] The study examined the efficacy of IVIG and rituximab on the reduction of anti-HLA antibodies that led to kidney transplantation with incurring the risk of AMR and immediate graft loss. All participants were deemed high immunologic risks with PRA 30% - 79% in 25% of individuals and 75% of the participants had PRA ≥ 80%. Thirty-one individuals received living donor (LD) and 45 individuals received deceased donor (DD) kidney transplants. Recipients of deceased donor kidneys had a mean waiting list time of 95 ± 46 months prior to desensitization, but received transplants within 4 months after receiving combination treatment with IVIG and rituximab. Acute rejection (AR) occurred in 37% of participants (8% cell mediated rejection [CMR] and 29% AMR). Nine individuals had graft losses, with AMR involved in 6 cases. Recipient and allograft survivals

were 95% and 84%, respectively. The authors concluded, *"IVIG and rituximab seems to offer significant benefits in reduction of anti-HLA antibodies, allowing improved rates of transplantation for highly sensitized patients, especially those awaiting DD, with acceptable antibody-mediated rejection and survival rates at 24 months"* (Vo, 2010). Additional analysis in a randomized trial was encouraged.

Reference:

1. *Astor TL, Weill D, et al. Pulmonary capillaritis in lung transplant recipients: treatment and effect on allograft function. J Heart Lung Transplant 2005;24:2091–2097.*
2. *Vo AA, Lukovsky M, Toyoda M, et al. Rituximab and intravenous immune globulin for desensitization during renal transplantation. N Engl J Med 2008;359:242–251.*
3. *Colvin RB, Smith RN. Antibody-mediated organ-allograft rejection. Nat Rev Immunol 2005;5:807–817.*
4. *Vo AA, Peng A, Toyoda M, et al. Use of intravenous immune globulin and rituximab for desensitization of highly HLA-sensitized patients awaiting kidney transplantation. Transplantation. 2010; 89(9):1095-1102.*

- Current guidelines (Costanzo et al, 2010) recommend the use of rituximab for antibody mediated rejection in heart transplant recipients, with steroids, plasmapheresis and/or IVIG, to reduce the risk of recurrent rejection.[E] Initial therapy of antibody-mediated rejection can include immunoadsorption and corticosteroid or plasmapheresis/low dose of IVIG and corticosteroid. The guidelines state that rituximab can be added to reduce the risk of recurrent rejection. Changes in therapy, which can be considered for maintenance immunosuppression in patients who experience antibody mediated rejection, can include switch to tacrolimus in patients receiving cyclosporine-based immunosuppression, increased doses of mycophenolate mofetil, and corticosteroids.

EVIDENCE-BASED PRACTICE GUIDELINES[A]

- In 2010, the National Advisory Committee on Blood and Blood Products and Canadian Blood Services issued a guideline on the use of IVIg for solid organ transplantation; a panel of experts reviewed findings from a systematic review of evidence. In their literature search, they identified 3 RCTs, all on **kidney transplant**, and numerous observational studies or case series on several types of organ transplantation. Notable recommendations of the panel are as follows:
  - When kidney transplantation involves use of a living donor, IVIg is recommended to decrease **donor-specific sensitization.**
  - There is insufficient evidence to recommend for, or against, the use of IVIg for **ABO-incompatible** kidney transplantation
  - To reduce the risk of **acute antibody-mediated rejection,** IVIg is recommended for kidney transplant patients who have donor-specific antibodies preoperatively. IVIg is not recommended for kidney transplant patients who do not have donor-specific antibodies
  - IVIg is recommended after **plasmapheresis** for patients who have received a living donor or deceased kidney donor transplant and who have acute antibody-mediated rejection.
  - Consider IVIg when patients have **corticosteroid-resistant rejection**, when other therapies are deemed unacceptable or ineffective.

- The following recommendations were issued regarding **non**-kidney solid organ transplantation:[A]
  - There is insufficient evidence to recommend for, or against, the use of IVIg for **desensitization** for patients undergoing heart, lung, or liver transplantation.
  - There is insufficient evidence to recommend for, or against, the routine use of IVIg for desensitization for patients undergoing heart transplantation to improve graft/overall survival or to treat rejection; however, other factors may influence decision-making.
  - There is insufficient evidence to make a recommendation for or against the routine use of IVIg for desensitization for patients undergoing lung transplantation or for the treatment of rejection; however, other factors may influence decision-making.
  - There is insufficient evidence to make a recommendation for or against the routine use of IVIg for patients undergoing liver transplantation, or for the treatment of rejection/ABO-incompatible liver transplantation.

The Committee further indicated:[A]

- There is limited methodologically rigorous evidence for the use of IVIg for solid organ transplantation.
- Future studies are needed to delineate the effect of IVIg on desensitization using standardized methods for desensitization; the effect of IVIg on acute rejection rates, graft survival, and overall survival; the use of the combined modality IVIg and PP compared either to PP or IVIg alone; and the optimum dosage of IVIg (Shehata, 2010).

Reference: Shehata N, Palda VA, Meyer RM, et al. The use of immunoglobulin therapy for patients undergoing solid organ transplantation: an evidence-based practice guideline. Transfus Med Rev. 2010; 24 Suppl 1:S7-S27.

❖ International Consensus Guidelines: Solid Organ Transplantation[B]

- FDA approved for prophylaxis of CMV disease but remains controversial
- No randomized studies indicating superiority of adding CMV IG to ganciclovir or valganciclovir versus appropriate antiviral therapy alone
- Level III recommendation (opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees)
- CMV IVIg Role in adults unclear; may be adjunctive for severe infection like pneumonitis
- Recommended in pediatrics for treatment of pneumonitis & enteritis and for hypogammaglobulinemia; "on a selective basis" for other clinical entities

DEFINITIONS

N/A

APPENDIX

Appendix 1

There are several immune globulin products available. Each product varies with FDA-approved indications. SCIg products are currently only FDA approved for the treatment of primary immunodeficiency disease (PID) while other products are labeled for primary immunodeficiency diseases (PID), idiopathic thrombocytopenic purpura (ITP), B-cell chronic lymphocytic leukemia (CLL), chronic inflammatory demyelinating polyneuropathy (CIDP), Kawasaki disease and /or multifocal motor neuropath (MMN).

NOTE: The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.

Below is a table of products and their FDA approved indications.

Brand name	Route	PID	ITP	CLL	CIDP	KD	MMN
Bivigam	IV	X					
Carimune NF	IV	X	X				
Flebogamma DIF	IV	X					
Gammagard Liquid	IV/SC*	X					X
Gammagard S/D	IV	X	X	X		X	
Gammaked	IV/SC*	X	X		X		
Gammaplex	IV	X					
Gamunex-C	IV/SC*	X	X		X		
Hizentra	SQ	X					
HyQvia	SQ	X					
Octagam	IV	X					
Privigen	IV	X	X				

*Only PID is considered FDA approved for the subcutaneous route (SC), all conditions are FDA approved for the intravenous (IV) route. Applications of this product for conditions other than primary immunodeficiencies are considered off-label in the United States therefore will not be addressed in this policy.

Intravenous Immunoglobulin
Bivigam: 10% (1 g/10 mL) in 50 mL, 100 mL vials
Carimune NF powder for injection: 3 g, 6 g, 12 g bottles
Flebogamma: 5% (50 mg/mL) in 10 mL, 50 mL, 100 mL, 200 mL, 400 mL vials; 10% (5 g/50 mL) in 50 mL, 100 mL, 200 mL vials
Gammagard: 10% (1 g/10 mL) in 10 mL, 25 mL, 50 mL, 100 mL, 200 mL, 300 mL vials
Gammagard S/D powder for injection: 2.5 g, 5 g, 10 g bottles
Gammaked: 10% (1 g/10 mL) in 10 mL, 25 mL, 50 mL, 100 mL, 200 mL vials
Gammaplex: 5% (50 mg/mL) in 50 mL, 100 mL, 200 mL vials
Gamunex: 10% (1 g/10 mL) in 25 mL vials
Gamunex-C: 10% (1 g/10 mL) in 10 mL, 25 mL, 50 mL, 100 mL, 200 mL vials
Octagam: 5% (50 mg/mL) in 20 mL, 50 mL, 100 mL, 200 mL, 500 mL
Privigen: 10% (100 mg/mL) in 50 mL, 100 mL, 200 mL, 400 mL vials

Subcutaneous Immunoglobulin
Gammagard: 10% (1 g/10 mL) in 10 mL, 25 mL, 50 mL, 100 mL, 200 mL, 300 mL vials
Gammaked: 10% (1 g/10 mL) in 10 mL, 25 mL, 50 mL, 100 mL, 200 mL vials
Gamunex-C: 10% (1 g/10 mL) in 10 mL, 25 mL, 50 mL, 100 mL, 200 mL vials
Hizentra protein solution for subcutaneous injection: 20% (0.2 g/mL) in 5 mL, 10 mL, 20 mL vials

APPENDIX 2: Cytomegalovirus Intravenous Immune Globulin (CMV-IG; Cytogam®) n,q

FDA-Approved Indication:
Cytomegalovirus prophylaxis: For the prophylaxis of cytomegalovirus disease associated with transplantation of kidney, lung, liver, pancreas, and heart. In transplants of these organs other than kidney from CMV seropositive donors into seronegative recipients, prophylactic CMV-IGIV should be considered in combination with ganciclovir.

FDA-Approved Dosing and Administration

Time frame after transplant	Kidney transplant	Liver, lung, pancreas, heart
Within 72 hours of transplant	150 mg IG/kg	150 mg IG/kg
Weeks 2,4,6,8 post-transplant	100 mg IG/kg	150 mg IG/kg
Weeks 12 & 16 post-transplant	50 mg IG/kg	100 mg IG/kg

*Maximum recommended total dosage per infusion is 150 mg IG/kg; max rate: 60mg/kg/hr

CODING INFORMATION: THE CODES LISTED IN THIS POLICY ARE FOR REFERENCE PURPOSES ONLY. LISTING OF A SERVICE OR DEVICE CODE IN THIS POLICY DOES NOT IMPLY THAT THE SERVICE DESCRIBED BY THIS CODE IS A COVERED OR NON-COVERED. COVERAGE IS DETERMINED BY THE BENEFIT DOCUMENT. THIS LIST OF CODES MAY NOT BE ALL INCLUSIVE.

CPT	Description
90283	Immune globulin (IgIV), human, for intravenous use

HCPCS	Description
J1459	Injection, immune globulin (Privigen), intravenous, nonlyophilized (e.g., liquid), 500 mg
J1557	Injection, immune globulin, (Gammaplex), intravenous, nonlyophilized (e.g., liquid), 500 mg
J1561	Injection, immune globulin, (Gamunex/Gamunex-C/Gammaked), nonlyophilized (e.g., liquid), 500 mg
J1562	Injection, immune globulin (Vivaglobin), 100 mg
J1566	Injection, immune globulin, intravenous lyophilized (eg, powder), 500 mg
J1568	Injection, immune globulin, (Octagam), intravenous, nonlyophilized (e.g., liquid), 500 mg
J1569	Injection, immune globulin, (Gammagard liquid), intravenous, nonlyophilized, (e.g., liquid), 500 mg
J1572	Injection, immune globulin, (Flebogamma/Flebogamma Dif), intravenous, nonlyophilized (e.g., liquid), 500 mg

ICD-9	Description [For dates of service prior to 10/01/2015]
966.8	Complications of transplanted organ

ICD-10	Description [For dates of service on or after 10/01/2015]
T86.91	Unspecified transplanted organ and tissue rejection

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g. Gammaplex (immune globulin intravenous) [prescribing information]. Bio Products Laboratory: Elstree, Hertfordshire UK: September 2013.
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i. Octagam (immune globulin intravenous) [prescribing information]. Octapharma USA Inc: Centreville, VA; September 2013.
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AMR Peer Review Network

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