CAREPATHrx™
Specialty Pharmacy & Infusion Solutions

GUIDELINES FOR OUTPATIENT INTRAVENOUS IMMUNE GLOBULIN (IVIG) THERAPY

Section: Nursing
Compliance: ACHC Infusion Pharmacy
ACHC Standards: N/A
URAC Standards: N/A
Policy ID: NUR241
Effective: 6/1/22
Reviewed:
Revised:
Approved by: Kathleen Patrick, President, 6/1/22

I. POLICY

Intravenous Immune Globulin (IVIG) is produced from pooled plasma containing polyclonal IgG from the serum of thousands of screened donors. The IgG molecule is the main component of IVIG. Numerous quality control procedures and manufacturing standards are in place to ensure highly purified and stable solutions, although slight differences exist among products. Multiple IVIG products are available, and choice of product depends on patient/disease factors and clinical judgment.

IVIG has been demonstrated to inactivate auto-reactive T-cells by competing for and interrupting their interaction with antigen presenting cells. The balance of cytokines also appears to be restored by IVIG, with studies showing that IVIG contains antibodies and antagonists to pro-inflammatory cytokines. In addition, IVIG is thought to interfere with and prevent the passage of auto-immune T-cells into the blood–nerve barrier. IVIG can affect innate immunity by interrupting the steps in the complement activation cascade and blocking Fc-receptor mediated activity, which results in down-regulation of macrophage activity.

In conclusion, IVIG has several immunosuppressive and anti-inflammatory properties that include modulation of immunoglobulin G (IgG) levels, lymphocyte and reticuloendothelial function, cytokine production, complement regulation, and clearance of pathogenic IgG. IVIG provides adequate concentrations of antibodies against a broad range of pathogens for patients with hypogammaglobinemia, antibody deficiency disorders, other immunodeficiency states, as well as certain infections.

The following outlines the procedures and protocols for coordination of servicing patients in need of outpatient IVIG home infusions.

II. PATIENT ACCEPTANCE CRITERIA

A. All candidates for home care service must be evaluated by the clinician(s) and deemed appropriate to receive home care based upon admission criteria.

B. The decision to administer a first dose in the home by a field nurse will be determined on a case-by-case basis and reviewed by nursing and pharmacy management. The following criteria will be evaluated:
    1. Prescriber preference

2. Allergy profile
3. Ability to secure contracted nursing for subsequent infusions
4. Other relevant social and/or medical history

C. Site specific treatment protocol for anaphylaxis will be instituted unless more comprehensive patient-specific orders are provided by physician. See policy NUR012 (Appendix A).

D. Physician's orders shall include
    1. Dose/Brand/Concentration
    2. Hourly rate of delivery (if one is not provided, may defer to package insert)
    3. Frequency of administration
    4. Standing orders for adverse reaction (epinephrine, diphenhydramine)

E. Additional clinical data needed for eligibility review may include but is not limited to:
    1. Documented low IgA or anti-IgA antibodies
    2. Loading dose regimen (if applicable)
    3. Indication for IVIG use
    4. Current and past medical history
    5. Patient and prescriber preference
    6. Baseline CBC/CMP results
    7. Prescriptions for IV/PO premedications are advised

F. Of clinical note, each intact IVIG product with a distinct lot/batch number as specified on the container, is comprised of a different donor plasma pool. Changes in clinical response/tolerance due to product variation cannot be ruled out

G. The decision to permit a patient or caregiver to administer IVIG without a nursepresent in the home will be made on an individual basis under the following circumstances:
    1. A second person must be present during administration
    2. The home must have an available telephone
    3. The caregiver will be taught emergency measures in the event of an allergic response

H. Contraindications
    1. All IVIG products are contraindicated in patients with a history of anaphylactic or severe systemic response to human immune globulin preparations, inactive ingredients, and those with selective IgA deficiency who have known antibody against IgA.

II. PHARMACOLOGY OVERVIEW

A. Indications
    1. Prevention of infections in immune-deficient patients
        a. Primary and secondary Immunodeficiency states (Chronic lymphocytic leukemia, multiple myeloma, hematopoietic stem cell transplantation)
        b. Infections and infection-related disorders (chronic parvovirus infection complicated by anemia, toxic shock syndrome, and measles post exposure prophylaxis if the patient is immunocompromised or nonimmune)
    2. Suppression of an inflammatory or autoimmune process
        a. Neuroimmunologic disorders (chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy, Guillain-Barré syndrome, myasthenia gravis)

b. Autoimmune/inflammatory conditions (immune thrombocytopenia, autoimmune hemolytic anemia, autoimmune neutropenia, acquired von Willebrand syndrome, Kawasaki disease)
c. Alloimmune processes (hemolytic disease of the fetus and newborn, post-transfusion purpura, antibody-mediated organ transplant rejection, hyperhemolytic crisis in individuals with sickle cell disease who have received transfusions)

B. Dosage
1. Prevention of infections in immune-deficient patients
a. 400 to 800 mg/kg every three to four weeks
b. Dosing is adjusted depending on the patient's progress and trough or steady-state IgG levels
2. Suppression of an inflammatory or autoimmune process
a. Usually requires higher doses
b. 1-2 grams/kg repeated as appropriate depending on disease state

C. Contraindications
1. Anaphylaxis or severe systemic reaction to human immunoglobulins or to any component of the product
2. Hereditary intolerance to fructose, including infants and neonates for whom sucrose or fructose tolerance has not been established
3. Hyperprolinemia (type I or II); Hizentra(R) and Privigen(R) contain the stabilizer L-proline
4. IgA deficiency with antibodies against IgA, and a history of hypersensitivity - IVIG products contain trace amounts of IgA
5. Severe thrombocytopenia or any coagulation disorder which would contraindicate IM injections

D. Warnings and Precautions
1. Pretreatment Testing
a. Bacterial infection screening
i. Rule out any infectious process
ii. TB test
b. Viral Infection Screening
i. Hepatitis B testing (CMV virus, EBV virus, etc. if immunosuppressed)
2. Infusion Reactions
a. Patients should be monitored for adverse events during and after the infusion
i. Stop administration with signs of infusion reaction (fever, chills, nausea, vomiting, and rarely shock)
ii. Risk may be increased with initial treatment, when switching brands of immune globulin, and with treatment interruptions of >8 weeks
b. Usually start 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
i. 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
3. Vaccines
a. Live vaccines
i. Passive transfer of antibodies may transiently impair the immune responses to live attenuated virus vaccines for up to a year or more
1) Inform the immunizing provider of recent IVIG therapy so

appropriate precautions can be taken

b. SARS-CoV-2 Infection and Inactivated Vaccines
    i. For patients with active infection of coronavirus or in the process of receiving a vaccine (initial and booster doses), please consult the current Center for Disease Control (CDC) guidelines
c. Inactivated vaccines
    i. IVIG should not interfere with the host's ability to respond, if that is intact
    ii. Patients receiving IVIG may receive inactivated vaccines to stimulate T cell immunity to the virus, which may help in recovery from viruses like influenza

E. Pharmacokinetics
1. Considerable intra- and interpopulation variability
2. Half-life ~ 30 days

F. Adverse Reactions
1. More common
    a. Headache
    b. Gastrointestinal disorders
    c. Fever
    d. Sore throat
    e. Rash
    f. Allergic reaction
    g. Increased cough
    h. Infusion site reactions
2. Anaphylaxis/hypersensitivity reactions
    a. Hypersensitivity and anaphylactic reactions can occur; patients with known antibodies to IgA are at greater risk; a severe fall in blood pressure may rarely occur with anaphylactic reaction
3. Hypertension
    a. Elevations of blood pressure (≥180 mmHg/120 mmHg) have been observed during and/or shortly following infusion, which resolved with either observation or changes in oral antihypertensive therapy
4. Thromboembolic events
    a. Thrombosis may occur with immune globulin products even in the absence of risk factors for thrombosis
    b. For patients at risk of thrombosis (advanced age, prolonged immobilization, hypercoagulable conditions, history of venous or arterial thrombosis, use of estrogens, indwelling central vascular catheters, hyperviscosity, and cardiovascular risk factors) administer at the minimum dose and infusion rate practicable
        i. Ensure adequate hydration before administration
5. Renal dysfunction and acute renal failure
    a. Acute renal dysfunction can rarely occur and has been associated with fatalities in predisposed patients
    b. For patients at risk of renal dysfunction or acute renal failure (elderly patients, patients with renal disease, diabetes mellitus, hypovolemia, volume depletion, sepsis, paraproteinemia, and nephrotoxic medications due to risk of renal dysfunction):
        i. Ensure adequate hydration prior to administration

ii. Minimize the dose, rate of infusion, and concentration of solution as much as possible
iii. Assess renal function prior to treatment and periodically thereafter
c. Discontinue if renal function deteriorates

6. Fluid overload
   a. High-dose regimens (1 g/kg for 1 to 2 days) are not recommended for individuals with fluid overload or where fluid volume may be of concern
7. Pulmonary edema - transfusion-related acute lung injury (TRALI)
   a. Non-cardiogenic pulmonary edema
   b. Characterized by severe respiratory distress, pulmonary edema, hypoxemia, and fever in the presence of normal left ventricular function
   c. Usually occurs within 1 to 6 hours after infusion
8. Aseptic meningitis
   a. May occur with high doses (≥1 g/kg) and/or rapid infusion
   b. Appears within several hours to 2 days following treatment and usually resolves within several days after product is discontinued
   c. Female patients or patients with a migraine history may be at higher risk for AMS
9. Hemolysis
   a. Acute or delayed
   b. Risk factors
      i. High doses (≥2 g/kg) given either as a single administration or divided over several days
      ii. Underlying associated inflammatory conditions, or underlying inflammatory states (elevated CRP or ESR)
      iii. Preexisting anemia and/or cardiovascular or pulmonary compromise

G. Drug/Lab Interactions
1. Live vaccines
   a. Interference with the immune response to the live vaccine when given concurrently with IVIG
   b. Withhold live virus vaccination for recommended number of months after IVIG administration according to formulation being used
2. 1,3-beta-D-glucan detection
   a. Immune globulin can lead to false positive readings in assays that depend on detection of beta-D-glucans for diagnosis of fungal infections and may persist for weeks following infusion of immune globulin
3. Coombs test - anti-human globulin
   a. After infusion of IVIG, the transitory rise of the various passively transferred antibodies in the patient's blood may yield false positive serological testing results (positive Coombs test), with the potential for misleading interpretation
4. Glucose measurement, blood
   a. IVIG may cause an interference in blood/plasma glucose measurement using the glucose dehydrogenase pyrroloquinoline quinone (GDH-PQQ) based test, producing falsely elevated blood glucose levels

III. ADMINISTRATIVE GUIDELINES

A. Administration

1. 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
2. Avoid vigorous mixing as excessive foaming could occur
3. Reconstituted lyophilized products should be inspected before administration to assure that the product has been completely dissolved and that the solution is uniform
4. 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

B. Dosing
    1. Weight based and dependent on indication
    2. Pretreatment
        a. Many patients receiving IVIG for immunoglobulin replacement therapy do not require premedication
            i. If premedication is needed, may use acetaminophen, a nonsteroidal anti-inflammatory drug (NSAID), steroids, and/or antihistamines 30 minutes prior to the infusion of IVIG
        b. An adverse reaction to IVIG requiring premedication, especially glucocorticoids, is an indication to switch to subcutaneous immune globulin (SCIG) or another IVIG product
    3. Pre-Hydration
        a. Patients receiving IVIG should be well hydrated prior to the infusion especially patients with risk factors for thrombosis and/or renal complications
        b. Hydration can be accomplished by ample oral fluid intake
        c. Intravenous fluids can be used for hydration - Normal saline 10 to 20 mL/kg is suggested for this purpose

C. Duration
    1. Duration of therapy should be dependent on patient response and adverse reaction
    2. No specific duration is noted in the package insert

D. Dose Adjustment
    1. High BMI
        a. Insufficient evidence to base recommendations for dosing
        b. A reasonable approach would be to start with a dose based on ideal body weight (IBW) or adjusted body weight and modify the dose accordingly
    2. Renal dosing adjustment
        a. Refer to package insert of IVIG product being used for specific recommendations
    3. Hepatic dosing adjustment
        a. Refer to package insert of IVIG product being used for specific recommendations

E. Patient Monitoring
    1. Obtain temperature, pulse, respirations, and blood pressure
        a. Prior to infusion initiation
        b. 15 minutes after infusion has started
        c. Every 30-60 minutes thereafter for the remainder of the infusion based on RN evaluation of the patient's response
        d. 15 minutes following end of infusion

IV. NURSING PROCEDURE

A. Supplies
1. Alcohol Swabs
2. Gloves
3. IVIG vials needed based on dose
4. Bag of sodium chloride 0.9% if needed for hydration
5. Dressing change kit
6. IV Pole
7. IV Start Kit
8. Peripheral IV catheter (ex. 22 Gauge x1" and 24 Gauge x ¾" for patients needing peripheral access)
9. Port access needle (ex. 22 Gauge x ¾ to 1" safe step for patients with a port)
10. Tape
11. Extension set 8" IV injection cap
12. Ambulatory pump
13. Batteries for ambulatory pump
14. Pump return box
15. IV administration set compatible with electronic pump (1.2- to 5-micron filter optional)
16. Sharps container

B. How Supplied, Storage and Handling, and IV Compatibility
1. Please refer to package insert of IVIG product being used for specific information

C. Procedures: Preparation of product, Infusion rates, post infusion monitoring time
1. Explain the reasoning for visit and use of IVIG.
2. Don gloves.
3. Establish venous access prior to preparation of drug.
4. Counsel patient on warnings, precautions, and potential side effects
5. Do not dilute IVIG further and give IVIG through a separate infusion line
    a. No other medications or fluids should be mixed with the IVIG preparation.
6. Before beginning the infusion, be sure solution is clear and at about room temperature
    a. All parenteral products must be inspected visually for particles and discoloration
7. Prepare Product and do not agitate the solution
    a. IV infusions should be given immediately after prepared/spiked
    b. Use within 1 hour of preparation per current USP Immediate-Use Guidelines
8. Begin infusion at prescribed rate
9. Obtain temperature, pulse, respirations, and blood pressure
    a. Prior to infusion initiation
    b. 15 minutes after infusion has started
    c. Every 30-60 minutes thereafter for the remainder of the infusion based on RN evaluation of the patient's response
    d. 15 minutes following end of infusion
    e. Caregiver may be taught vital sign monitoring
10. Adjust rate throughout infusion if necessary
    a. Mild adverse reaction
        i. Stop infusion until symptoms subside
        ii. Resume infusion at slower rate
    b. Moderate/Severe Reaction or Persistent Mild reaction
        i. Stop infusion
        ii. Administer emergency meds
        iii. Notify physician immediately and transfer patient to emergency room if

necessary
11. Discontinue infusion or heparinized line when complete
12. Document procedure and patient response

V. CLINICAL MONITORING

A. Pretreatment testing
    1. Evaluate hematologic parameters, renal function, metabolic status, glucose, and possible infections such as hepatitis (e.g., by testing hepatic transaminases)
    2. Repeat at six-month or yearly intervals

B. Positive Coombs test/ Hemolysis
    1. 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
    2. If a previously negative Coombs test becomes positive, one or more of the following may be done:
        a. Switch the patient to a different IVIG preparation in which isohemagglutinins have been reduced
        b. Delay or divide the remaining dose
        c. Evaluate and/or refer to hematology for evaluation of possible new development of autoimmune hemolytic anemia

C. Ig trough levels prior to next infusion
    1. Clinical experience suggests a target serum IgG trough level of at least 500 mg/dL

D. Renal function (prior to first infusion and periodically), urine output, volume status

E. CBC (prior to initiation and periodically)

F. Physicians follow up within 4 weeks of 1st dose

G. Assessment and documentation of any adverse reactions

H. Monthly weight assessment with dose adjustment if appropriate

REFERENCES:

Stangel M, Pul R. Basic principles of intravenous immunoglobulin (IVIg) treatment. J Neurol. 2006 Sep;253 Suppl 5:V18-24. doi: 10.1007/s00415-006-5003-1. Erratum in: J Neurol. 2008 Feb;255(2):308. PMID: 16998749.

Kaveri SV, Dietrich G, Hurez V, Kazatchkine MD. Intravenous immunoglobulins (IVIg) in the treatment of autoimmune diseases. Clin Exp Immunol. 1991 Nov;86(2):192-8. doi: 10.1111/j.1365-2249.1991.tb05794.x. Erratum in: Clin Exp Immunol 1992 May;88(2):373. PMID: 1934588; PMCID: PMC1554132.

Privigen [package insert]. Bern, Switzerland. CSL Behring LLC. 2017.

Gammagard [package insert]. Westlake Village, CA. Baxter Healthcare Corporation. 2012.

Hizentra [package insert]. Bern, Switzerland. CSL Behring LLC. 2021.

Ballow, M et al. Overview of Intravenous Immune Globulin Therapy. UpToDate. UpToDate; 2022. Accessed June 15, 2022.

Immune Globulin. Quick Answers. IBM Micromedex [database online]. Truven Health Analytics/IBM Watson Health; 2022. Accessed June 15, 2022. https://www.micromedexsolutions.com

APPENDIX A: ANAPHYLAXIS KIT INTRUCTIONS

Emergency Medication After Your Infusion

Please call your pharmacy if you have any questions or concerns. In the event of an emergency, always call 911.

Your nurse will tell you when you need to use Emergency Medications.
The epinephrine dose will be noted on the Anaphylaxis Protocol included with your kit.

Start with a clean work surface and clean hands.

Open the supply bag labeled Anaphylaxis Kit Contents.

You will need:

1. **Bag containing Pills** (2 Acetaminophen and 2 Diphenhydramine)
2. **Bag containing Alcohol Prep Pads**
3. **Bag labeled IM Epinephrine**

All other contents will not be needed.

Open the IM Epinephrine Bag

1. **Remove 1 of each item**
    a. 1 -syringe
    b. 1 – brown labeled filter needle (BD Filter Needle)- **for ampul use only**
    c. 1 – black labeled safety needle (Magellan Hypodermic Safety Needle 22G x 1”)
    d. 1 ampul of epinephrine

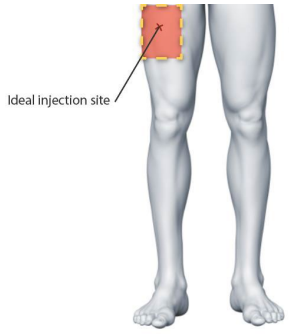
Prepare IM (intramuscular) injection of Epinephrine:

1. **Attach the brown filtered needle to syringe**

a. Be careful to not touch the tip of the syringe or the needle.

2. Using an **alcohol swab, wipe the neck of the epinephrine ampul.**
3. Holding the ampul upright, **swirl and flick the ampul until all fluid flows to the bottom chamber** (the top chamber should be empty).
4. Using a new alcohol wipe, grasp the neck of the ampul and with your other hand grasp the bottom chamber of the ampul. **Quickly snap the top of the ampul off, directing the snap way from you.**
5. **Place the tip of the brown filter needle inside the ampul**. Tilting the ampul, **withdraw dose of medication into the syringe** by gently pulling back on the plunger. Be careful to not pull the plunger out of the syringe.
6. Remove the needle from the ampul and h**old the syringe upright** with the needle pointing upward. **Gently tap the side of the syringe to bring any air to the top of the syringe.**
7. **Push the air out of the syringe by gently pushing on the plunger**.
8. Replace the cap on the brown filter needle. Discard remainder in ampul.
9. **Remove the brown filter needle and place the black safety needle onto the syringe.**

Give your IM Epinephrine injection



1. **Grasp your leg muscle at the outer mid-thigh** and **cleanse the area** with a new alcohol wipe.
2. **Push the needle into your leg muscle straight** in at a 90-degree angle.
3. **Inject the medication** by depressing the plunger in a slow and steady motion.
4. **Remove the needle** and wipe the site with the alcohol wipe.
5. May repeat dose every 5 minutes (**maximum 3 doses**) if ordered per protocol.

Take the pills by mouth.

a. 2 – Acetaminophen
b. 2 – Diphenhydramine

Place all trash in the bag the pills came in and take with you when you seek medical care. **Give the bag to the nurse or EMT**, so your doctor will know what medication you already took. They will properly dispose of the syringe and needles.
Call 911 or have someone drive you to the emergency department.