Intravenous Immune Globulin –
Adult/Pediatric – Inpatient/Ambulatory
Clinical Practice Guideline

Note: Active Table of Contents – Click to follow link
Committee Approvals/Dates:
Pharmacy & Therapeutics Committee (Last Periodic Review: 12/2016)
  • Interim revisions: None

Release Date: December 2016 | Next Review Date: December 2018
Executive Summary
Guideline Summary
The guideline provides evidence-based recommendations for managing disorders treated with intravenous immune globulin and for safely infusing it. Individual clinician experience may suggest stronger recommendations for some indications; however the evidence-based conclusions are based on the currently available evidence.

Key Revisions (2016 Periodic Review)
1. Comparison table of formulary immune globulins added
2. Timing of live vaccine administration in relation to IVIG administration is added
3. Recommendations and supporting evidence are designated according to Grading of Recommendations Assessment, Development, and Evaluation (GRADE), the UW Health standard
4. Recommendations for management of the following disorders were added
   4.1 Autoimmune encephalitis
   4.2 Persisting hypogammaglobulinemia secondary to rituximab therapy
   4.3 BK virus associated nephropathy
   4.4 Cytomegalovirus (CMV) associated nephropathy
   4.5 Pemphigus vulgaris when IVIG is used concurrently with rituximab
   4.6 Steven Johnson Syndrome/Toxic Epidermal Necrolysis (SJS/TENS)
   4.7 Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)
   4.8 Lupus erythematosus: cutaneous/systematic
5. Recommendations for management of the following disorders were removed:
   5.1 Use of cytomegalovirus immune globulin to manage CMV disease in solid organ transplant patients
6. Fluid management strategies are specified
7. Need for infusion filter by product has been added
8. Frequencies of adverse events have been added
9. Initial infusion rates for adults are modified to be weight-based instead of fixed volume per time. An infusion rate calculator, similar to that available for pediatric rates, is available for adults.
10. Pediatric infusion rate for Kawasaki’s Disease has been added
11. A prolonged infusion rate for inpatients is suggested, as long as a dedicated line is available and discharge is not unnecessarily delayed.
12. Information about subcutaneous administration for appropriate patients is provided.

List any MAJOR revisions which were made between full periodic reviews or during last review.
1. None
Key Practice Recommendations

1. All patients must have a current documented weight and height prior to writing orders for IVIG. Adult doses should be based on ideal body weight (IBW) unless dosing to a specific and measurable IgG level.\(^1,2\) (UW Health GRADE Low quality evidence; strong recommendation)

2. If actual weight is less than IBW, dose according to actual weight. (UW Health GRADE Very low quality evidence; strong recommendation)

3. Actual body weight should be used to calculate the dose for pediatric patients.\(^3,4\) (UW Health GRADE High quality evidence; strong recommendation)

4. Maximum administration rate is based on patient specific tolerability.\(^3,4\) (UW Health GRADE High quality evidence; strong recommendation)

5. Rationale and evidence for initial and continued use should be provided. (UW Health GRADE Very low quality evidence; strong recommendation)

6. Patient tolerability is always the first consideration for determining the infusion rate. Monitoring for adverse effects is recommended.\(^3,4\) (UW Health GRADE High quality evidence; strong recommendation)

Companion Documents

1. Intravenous Administration of Formulary Medications – Adult – Inpatient/ Ambulatory Clinical Practice Guideline: https://uconnect.wisc.edu/clinical/cckm-tools/content/?path=/content/cpg/medications/name-97579-en.cckm

2. Intravenous Administration of Formulary Medications – Pediatric/ Neonatal–Inpatient/ Ambulatory Clinical Practice Guideline: https://uconnect.wisc.edu/clinical/cckm-tools/content/?path=/content/cpg/medications/name-97571-en.cckm

3. Inpatient Immune Globulin Infusion Adult Supplement Order Set #1317

4. Inpatient Immune Globulin Infusion Pediatric Supplemental Order Set #4161

5. UWRX Infusion Center Order Set #930
**Scope**
This guideline is intended to help direct the use of intravenous immune globulin (IVIG) in UW Health inpatient and ambulatory populations, both adult and pediatric.

**Disease/Condition(s):** Intravenous immune globulin (IVIG) is used to treat disorders related to immunodeficiency, autoimmunity, inflammation, infection, and alloimmunity.

**Clinical Specialty:** Clinical specialties that will use the guideline include Allergy/Immunology, Dermatology, Infectious Disease, Hematology, Neurology, and Transplant.

**Intended Users:** Physicians, advanced practice providers, nurses, pharmacists, technical support, and the medication prior authorization team will utilize the guideline.

**Objective(s):** The objective of the guideline is to use a costly resource in an evidence based and safe manner.

**Target Population:** The target populations are adult and pediatric (including neonate) patients in the ambulatory and inpatient settings.

**Major Outcomes Considered:** Patient outcomes are considered by measuring patient function and lab based monitoring of immune globulin repletion and efficacy.
**Methodology**

**Methods Used to Collect/Select the Evidence:**
Electronic database searches (e.g., PUBMED) were conducted by the guideline author(s) and workgroup members to collect evidence for review. Expert opinion and clinical experience were also considered during discussions of the evidence.

**Methods Used to Formulate the Recommendations:**
The workgroup members agreed to adopt recommendations developed by external organizations and/or arrived at a consensus through discussion of the literature and expert experience. All recommendations endorsed or developed by the guideline workgroup were reviewed and approved by other stakeholders or committees (as appropriate).

**Methods Used to Assess the Quality of the Evidence/Strength of the Recommendations:**
Internally developed recommendations, or those adopted from external sources without an assigned evidence grade, were evaluated by the guideline workgroup using an algorithm adapted from the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology (see Figure 1 in Appendix A).

**Rating Scheme for the Strength of the Evidence/Recommendations:**
See Appendix A for the rating scheme(s) used within this document.

**Cost Analysis:**
Cost analyses were not performed to prepare this guideline.

**Recognition of Potential Health Care Disparities:**
Insurance coverage may differ depending on source. Therefore there may be barriers to consistent access depending on insurance coverage or financial circumstances.
Definitions
1. GVHD: Graft Versus Host Disease
2. Acute Idiopathic Thrombocytopenic Purpura: Acute bleeding with platelet count < 20,000/mm³

Table I. UW Health Formulary Intravenous Immune Globulin Products**

<table>
<thead>
<tr>
<th>Immune Globulin Product</th>
<th>Targeted Population</th>
<th>Commercial preparation</th>
<th>Health Link Medication Record Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gammagard Liquid®A</td>
<td>General immune globulin replacement</td>
<td>10% liquid</td>
<td>Immune globulin 10% (Gammagard Liquid®)</td>
</tr>
<tr>
<td>Gammagard S/D®B less IgA</td>
<td>IgA deficient pts. with antibodies to IgA Gammagard® liquid®</td>
<td>Freezedried powder</td>
<td>Immune globulin 10% (Gammagard S/D® Low IgA)</td>
</tr>
</tbody>
</table>

** Alternative nonformulary immune globulin products are available for patients that experience hypersensitivity to Gammagard® products. However, nonformulary products must be special ordered.
A. Gammagard Liquid® may be diluted to a 5% concentration with dextrose 5%.
B. Gammagard S/D® less IgA may be prepared in a 5% or 10% concentration (product specific diluent).

Introduction
Intravenous Immunoglobulin (IVIG) is isolated from pooled human plasma and was originally developed as prophylaxis against infections for individuals with primary immunodeficiency disorders.5,6 Currently IVIG is used to prevent and treat a growing number of indications. The expanded use of IVIG is supported by varying quality of evidence. Numerous published guidelines highlight the uses associated with this agent. UW Health monitors the use of IVIG because of its association with both adverse events and high cost. Practice guidelines tailored to UW Health have been available to optimize use of this resource. The current effort is a regularly scheduled review of available evidence to keep the practice guidelines timely.
Recommendations

1. All patients must have a current documented weight and height prior to writing orders for IVIG.  (UW Health GRADE Very low quality evidence; strong recommendation)

2. Adult doses should be based on ideal body weight (IBW) unless dosing to a specific and measurable IgG level$^{1,2}$ (UW Health GRADE Low quality evidence; strong recommendation)
   2.1. If the actual weight is less than IBW, dose according to actual weight.

3. Actual body weight should be used to calculate the dose for pediatric patients.$^{3,4}$ (UW Health GRADE High quality evidence; strong recommendation)

4. Doses should be titrated to patient’s response. Aim for the minimum dose required to maintain optimal clinical response defined by the disease specific monitoring parameters presented in the tables below.$^{3,4}$ (UW Health GRADE High quality evidence; strong recommendation)

5. Doses are not to exceed a maximum of 2 g/kg or 140 grams per day. (UW Health GRADE Very low quality evidence; strong recommendation)

6. IVIG must be used according to the specified criteria listed for each indication listed in the table below. (UW Health GRADE: quality of evidence varies; strength of recommendation varies)

7. Documentation must clearly state the medical necessity for initiation and continued use of IVIG.  (UW Health GRADE Very low quality evidence; strong recommendation) Documentation should include:
   7.1. History and physical
   7.2. Test results, including written interpretation
   7.3. Prior treatment therapies
   7.4. When used for an appropriate indication, there should be evidence of a significant deficiency in IgG blood levels prior to initiation of treatment and impaired ability to make specific antibodies
   7.5. History of severe and recurrent infections when appropriate
   7.6. Treatment goals/expected response from IVIG initiation and subsequent treatment. For immune deficiency disorders, the prescriber should provide an IgG target goal when writing the order.
   7.7. Evidence that IVIG therapy is effective when writing orders for continued therapy.

8. IVIG may limit the effectiveness of live attenuated virus vaccines, including the measles, mumps, rubella (MMR) and varicella vaccines. These vaccines should be administered 2 weeks prior to IVIG administration or delayed until 8 months after replacement of IVIG or 11 months following Kawasaki Disease treatment. The following live vaccines are not affected by IVIG administration: influenza, oral typhoid, zoster, yellow fever, and rotavirus vaccines.  (UW Health GRADE Moderate quality evidence; strong recommendation)

9. Disease specific recommendations are presented in the tables below.  (UW Health GRADE quality of evidence and strength of recommendation varies based on disorder.)
## Immunology

<table>
<thead>
<tr>
<th>Indication</th>
<th>Criteria for Use</th>
<th>Dose and Duration</th>
<th>Monitoring Parameters</th>
<th>Evidence Ranking</th>
<th>UW Health Recommendation Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Immunodeficiency</td>
<td>IgG value 2 standard deviations below normal for age or normogammaglobulinemia with impaired specific antibody production along with clinical correlate for humoral deficiency.</td>
<td>400-600 mg/kg every 4 weeks</td>
<td>Goal of therapy is to prevent infections (i.e. bronchiectasis). Ideal trough IgG values: within age and gender appropriate normal range.</td>
<td>Low</td>
<td>Strong</td>
</tr>
<tr>
<td>Kawasaki syndrome</td>
<td>Progressive form of the disease, ongoing inflammation, and/or elevated acute inflammatory markers and fever</td>
<td>2 g/kg once, beginning within 7 days of onset of fever</td>
<td>Inflammatory markers. • Defervescence • CRP • ESR</td>
<td>High</td>
<td>Strong</td>
</tr>
<tr>
<td>Idiopathic Thrombocytopenic Purpura (ITP)</td>
<td>Management of acute bleeding due to severe thrombocytopenia and/or platelet count less than 20,000/mm³ in adults, or less than 30,000/mm³ in children.</td>
<td>Acute: 1 g/kg daily for 1-2 days Chronic: 1 g/kg intermittently as to maintain platelet count Documented bleeding episodes</td>
<td>Maintain platelet count ≥ 20,000/mm³ in adults, or ≥ greater than 30,000/mm³ in children: • Acute: Monitor platelet count daily • Chronic: Monitor platelet count every 4 weeks</td>
<td>Moderate</td>
<td>Strong</td>
</tr>
<tr>
<td>Secondary Immunodeficiency due to CLL</td>
<td>IgG of less than 400 mg/dL</td>
<td>400 mg/kg every 4 weeks</td>
<td>Maintain a serum trough level IgG values ≥400 mg/dL</td>
<td>Moderate</td>
<td>Strong</td>
</tr>
<tr>
<td>Systemic Juvenile Rheumatoid Arthritis (JRA)</td>
<td>Resistant to other forms of therapy</td>
<td>1 to 2 g bimonthly for the first 2 months, then monthly for up to 6 months.</td>
<td>Efficacy appears to be short lived, Substantial clinical improvement must be shown and documented after 4-6 courses</td>
<td>Moderate</td>
<td>Weak/Conditional</td>
</tr>
<tr>
<td>Normogammaglobulinemia with impaired specific antibody production (Qualitative antibody deficiency)</td>
<td>Recurrent infections requiring antibiotic treatment and well-documented severe polysaccharide non-responsiveness</td>
<td>400 mg/kg every 4 weeks; Consider discontinuation or drug holiday (5 months) preferably in temperate climate) to assess efficacy</td>
<td>Decrease number of infections</td>
<td>Very Low</td>
<td>Weak/Conditional</td>
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<tr>
<td>Indication</td>
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<td>Evidence Ranking</td>
<td>UW Health Recommendation Rating</td>
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<tr>
<td>Autoimmune Encephalopathy</td>
<td>Used in combination with corticosteroids or plasmapheresis.</td>
<td>400 mg/kg for 5 days</td>
<td>Improvement in functional status (neurologic, psychiatric)</td>
<td>Very low</td>
<td>Weak/Conditional</td>
</tr>
<tr>
<td>Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)</td>
<td>Used as monotherapy</td>
<td>Induction: 400 mg/kg for 5 days or 1g/kg for 2 days</td>
<td>IVIG should be used for 3–6 months (3–6 courses) before determining whether the patient has responded.</td>
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<td></td>
<td>Can be used in combination with corticosteroids or immunosuppressants or as an alternative to plasmapheresis</td>
<td>Maintenance: 400 mg/kg to 1 g/kg every 2-6 weeks</td>
<td>If there is no benefit after 3–6 courses, IVIG therapy should be discontinued.</td>
<td>High</td>
<td>Strong</td>
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<td></td>
<td></td>
<td></td>
<td>Aim for minimum dose to maintain optimal functional status. (i.e. physical function; mobility/ambulation, fatigue)</td>
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<tr>
<td>Guillain-Barre Syndrome (GBS)</td>
<td>Used as first line agent for rapidly progressive form of disease.</td>
<td>400 mg/kg daily for 5 days or 1g/kg for 2 days</td>
<td>Improvement in functional status (i.e. physical function, mobility, respiratory status)</td>
<td>High</td>
<td>Strong</td>
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<td></td>
<td>May be used as an alternative to plasmapheresis</td>
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<tr>
<td>Moderate-Severe Myasthenia Gravis (MG)</td>
<td>Used when other treatments have been ineffective.</td>
<td>Induction: 400 mg/kg daily for 5 days or 1g/kg for 2 days</td>
<td>Measurable response must be documented within 6 months. (i.e. physical function; mobility/ambulation, fatigue)</td>
<td>High</td>
<td>Strong</td>
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<tr>
<td></td>
<td>Unresponsive/Intolerant to steroids</td>
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<td></td>
<td>Myasthenic Crisis: First line therapy</td>
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<td></td>
<td>As an alternative treatment to plasma exchange or thymectomy</td>
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<tr>
<td></td>
<td>Maintenance: 400mg/kg every 4 weeks</td>
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<tr>
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<tr>
<td>Multifocal Motor Neuropathy (MMN)⁴³</td>
<td>Multifocal motor neuropathy with persistent conduction block as diagnosed by a neurologist</td>
<td>Induction: 2 g/kg in 2 to 5 divided doses. Maintenance: 400 mg/kg to 1 g/kg every 2-6 weeks after induction dosing regimen The amount per dose should be titrated to the individual’s response. Aim for minimum dose to maintain optimal functional status.</td>
<td>Improvement in functional status</td>
<td>Moderate</td>
<td>Weak/ Conditional</td>
</tr>
<tr>
<td>Relapsing-Remitting Multiple Sclerosis (RRMS)⁴⁴-⁴⁷</td>
<td>After failure or intolerance to corticosteroids or in patients receiving plasmapheresis to maintain Ig levels</td>
<td>Induction: 400 mg/kg daily for 5 days or 1 g/kg for 2 days Maintenance: 400 mg/kg every 4 weeks</td>
<td>Measurable response must be documented within 6 months, (i.e. physical function; mobility/ambulation, fatigue) If there is no benefit after 6 courses, IVIG therapy should be discontinued.</td>
<td>High</td>
<td>Strong</td>
</tr>
<tr>
<td>Refractory Polymyositis⁴⁸,⁴⁹</td>
<td>Second line therapy for patients not responding to immunosuppressive treatment</td>
<td>1 g/kg x 2 consecutive days monthly for 3 to 6 months</td>
<td>Improved clinical status (increase muscle strength, decrease rash and CK level); able to taper steroids</td>
<td>Low</td>
<td>Weak/Conditional</td>
</tr>
<tr>
<td>Refractory Dermatomyositis⁴⁹-⁵¹</td>
<td>Unresponsive/intolerant to steroids and immunosuppressants; Significant skin vasculitis</td>
<td>1 g/kg x 2 consecutive days monthly for 3 to 6 months</td>
<td>Improved clinical status (increase muscle strength, decrease rash and CK level); able to taper steroids</td>
<td>Moderate</td>
<td>Weak/Conditional</td>
</tr>
<tr>
<td>Stiff Person Syndrome (SPS)⁵²,⁵³</td>
<td>Significant functional impairment in patients who have a verified diagnosis of stiff person syndrome made by a neurologist Used when standard treatment with diazepam is no longer effective</td>
<td>Induction: 2 g/kg in 2 to 5 divided doses Maintenance: 1 g/kg x 2 days monthly x 3 months</td>
<td>Improvement in functional status Duration of benefit ranges from 6 weeks to one year.</td>
<td>Moderate</td>
<td>Strong</td>
</tr>
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<tr>
<td>Bone Marrow Transplantation (prevention of Graft Versus Host Disease (GVHD) and infection) Adult and Pediatric</td>
<td>Low Ig levels pre-transplant defined as IgG of less than 400 mg/dL.</td>
<td>Pre-transplant: 250 mg/kg to a maximum of 20 grams on days -7 and -2 before transplant.</td>
<td>IgG values &gt;400 mg/dL. IgG levels be monitored every 2 weeks in patients receiving IVIG due to the shorter half-life</td>
<td>Moderate</td>
<td>Strong</td>
</tr>
<tr>
<td>Autoimmune Hemolytic Anemia</td>
<td>Following failure of immunosuppression with corticosteroids and cytotoxic agents prior to consideration for splenectomy</td>
<td>0.5 grams/kg/day for 5 days</td>
<td>Hemoglobin level ; Clinical status</td>
<td>Low</td>
<td>Weak/Conditional</td>
</tr>
<tr>
<td>Persisting hypogammaglobulinemia secondary to rituximab therapy</td>
<td>Documentation of recurrent and/or severe infections, significant hypogammaglobulinemia, and impaired specific antibody production</td>
<td>200 – 400 mg/kg monthly until IVIG level exceed 550 mg/dL; then as needed to maintain IVIG nadir between 550-600 mg/dL</td>
<td>Resolution of severe infection and IVIG level</td>
<td>Very Low</td>
<td>Weak/Conditional</td>
</tr>
</tbody>
</table>
## Transplantation

<table>
<thead>
<tr>
<th>Indication</th>
<th>Criteria for Use</th>
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</tr>
</thead>
</table>
| Antibody Mediated Rejection<sup>60-73</sup>     | Evidence of acute or chronic active rejection; presence of rejection established by biopsy and laboratory test to assess the presence and strength of antibodies to donor. | See Solid Organ Transplant Departmental Protocol for definitions of rejection type by Banff criteria and timing. Also see concurrent therapy.  
  - Early rejection: 100 mg/kg for 4-6 doses after plasma exchange  
  - Late rejection: 200 mg/kg every 2 weeks for 3 doses  
  - Persistent rejection: 500 mg/kg/week for 4 doses | Reduction in donor-specific antibodies and graft function by biopsy             | Moderate               | Weak/Conditional               |
| BK virus (polyoma) associated nephropathy<sup>71</sup> | Failure of decreased immunosuppression in combination with leflunomide to clear viremia | 500 mg / kg (maximum of 70 grams) every week for four doses;  
  Viral clearance and graft function | Very Low                       | Weak/Conditional               |
| Cytomegalovirus associated disease<sup>76-77</sup> | Failure of decreased immunosuppression in combination with anti-viral therapy to clear viremia | 500 mg/kg once; may repeat weekly for three doses with severe disease; total dose should not exceed 2 g/kg  
  Viral clearance and graft function | Low                           | Weak/Conditional               |
| Transplant Desensitization<sup>78-84</sup>      | Dependent on type of transplant (living or deceased) and amount of preformed antibodies detected in solid antigen bead testing done prior to transplant | See Solid Organ Transplant Departmental Protocol for live (D2) and deceased (D5c) donors  
  - 100 mg/kg after each plasma exchange  
    - D2- X2-3 doses before and after transplant  
    - D5c- one dose before transplant and X2-3 doses after transplant  
  Post reperfusion biopsy | Low                           | Weak/Conditional               |
| Waitlist Desensitization<sup>85-87</sup>        | Candidates on the kidney transplant waitlist approved for waitlist desensitization by the desensitization committee. | Solid Organ Transplant Departmental Protocol should be followed and referred to as a resource OR 2 g/kg administered monthly for 6 months with monitoring of donor specific antibodies  
  After 6 months, the clinical response is assessed by the desensitization committee to determine whether the patient should receive second cycle of 6 monthly doses of IVIG. | Low                           | Weak/conditional             |
<table>
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<tr>
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</thead>
<tbody>
<tr>
<td>Pemphigus Vulgaris/Pemphigus Foliaceus with IVIG as monotherapy⁸⁸-⁹²</td>
<td>Treatment refractory patients failure of systemic corticosteroids and immunosuppressants</td>
<td>1-2 g/kg; total dose divided equally and given daily for 3-5 days every 4 weeks; decrease frequency after disease controlled (every 6, 8, 10, 12, 14, 16 weeks) When given 16 weeks × 2 consider discontinuation for disease remission</td>
<td>Reduction or discontinuation of steroid; disease remission</td>
<td>Moderate</td>
<td>Weak/Conditional</td>
</tr>
<tr>
<td>Pemphigus Vulgaris Rituximab + IVIG⁹³-⁹⁴</td>
<td>Treatment refractory (inadequate response to conventional immune suppressive therapy + IVIG) patients when given in combination with rituximab</td>
<td>2 g/kg every 3 weeks for 2 doses starting in week 3 of rituximab therapy; then once monthly for 4 doses</td>
<td>Discontinuation of steroid; disease remission</td>
<td>Low</td>
<td>Weak/conditional</td>
</tr>
<tr>
<td>Bullous pemphigoid and Mucous-membrane (cicatricial) pemphigoid⁸⁸,9⁰-⁹²</td>
<td>Treatment refractory patients; failure of systemic corticosteroids and immunosuppressants</td>
<td>1-2 g/kg; total dose divided equally and given daily for 3-5 days every 4 weeks; decrease frequency after disease controlled (every 6, 8, 10, 12, 14, 16 weeks) When given 16 weeks × 2 consider discontinuation for disease remission</td>
<td>Reduction or discontinuation of steroid; disease remission</td>
<td>Low</td>
<td>Weak/Conditional</td>
</tr>
<tr>
<td>Stevens-Johnson Syndrome; toxic epidermal necrolysis⁹⁵-⁹⁹ (not Mycoplasma associated)</td>
<td>First line for treatment of severe disease in conjunction with withdrawal of offending medication and supportive care</td>
<td>1-2 g/kg daily for up to 3 consecutive days or until symptoms resolve; pt should be evaluated daily before each dose</td>
<td>Symptom resolution</td>
<td>Low</td>
<td>Weak/ Conditional</td>
</tr>
<tr>
<td>Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)¹⁰⁰, ¹⁰¹,¹⁰²</td>
<td>Life-threatening reaction refractory to corticosteroids</td>
<td>1 g/kg daily for up to 3 consecutive days or until symptoms resolve; pt should be evaluated daily before each dose</td>
<td>Symptom resolution</td>
<td>Low</td>
<td>Weak/ Conditional</td>
</tr>
</tbody>
</table>
## Infectious Disease

<table>
<thead>
<tr>
<th>Indication</th>
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<th>Evidence Ranking</th>
<th>UW Health Recommendation Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Refractory Clostridium Difficile Infection</td>
<td>Treatment refractory C. diff after failure of oral therapies (ex. metronidazole, vancomycin, fidaxomicin): see UW C. diff guidelines at <a href="https://uconnect.wisc.edu/clinical/cckm-tools/content/?path=/content/cpg/infection-and-isolation/name-97536-en.cckm">https://uconnect.wisc.edu/clinical/cckm-tools/content/?path=/content/cpg/infection-and-isolation/name-97536-en.cckm</a></td>
<td>No standard dose; suggested 150 – 500 mg/kg over 1 to 6 doses</td>
<td>Resolution of C. diff infection</td>
<td>Low</td>
<td>Weak/Conditional</td>
</tr>
<tr>
<td>HIV-associated thrombocytopenia</td>
<td>When platelets are less than 50,000</td>
<td>1.0 gram/kg/day for two consecutive days per week for 4 weeks</td>
<td>Platelet count; Signs and symptoms of IVIG adverse effects</td>
<td>Moderate</td>
<td>Weak/Conditional</td>
</tr>
<tr>
<td>Necrotizing Fasciitis</td>
<td>Critically ill patients with staph or strep necrotizing soft tissue infection</td>
<td>0.2-2g/kg day for 1 to 5 days</td>
<td>Improvement of soft tissue infection</td>
<td>High</td>
<td>Weak/Conditional</td>
</tr>
</tbody>
</table>

## Connective Tissue Disease

<table>
<thead>
<tr>
<th>Indication</th>
<th>Criteria for Use</th>
<th>Dose and Duration</th>
<th>Monitoring</th>
<th>Evidence Ranking</th>
<th>UW Health Recommendation Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lupus erythematosus (cutaneous or systemic)</td>
<td>Severe, refractory disease</td>
<td>1 g/kg on 2 consecutive days then Systemic: 1 g/kg once monthly until symptoms resolve Cutaneous: 400 mg/k once monthly until symptoms resolved</td>
<td>Erythrocyte sedimentation rate, C-reactive protein, urine protein, serum creatinine, anti-double stranded RNA, and complement (C3 &amp; C4)</td>
<td>Low</td>
<td>Weak/Conditional</td>
</tr>
</tbody>
</table>

## Inappropriate Uses

1. Alzheimer’s disease (UW Health GRADE Moderate quality evidence; strong recommendation)
2. Wegener’s granulomatosis (UW Health GRADE Moderate quality evidence; strong recommendation)
Administration Instructions for all patients

1. The fluid status of the patient should be evaluated prior to administration. Overdose may lead to fluid overload and hyperviscosity. Patients at risk of complications of fluid overload and hyperviscosity include elderly patients and those with cardiac or renal impairment.\textsuperscript{120} (UW Health GRADE Moderate quality evidence; strong recommendation)

1.1. Strategies to lower risk of hyperviscosity:
   1.1.1. Do not exceed the recommended dose
   1.1.2. Large doses may need to be infused over several days
   1.1.3. Ensure adequate hydration
   1.1.4. Infuse at the slowest practical rate
   1.1.5. Use a low osmolar product
   1.1.6. Encourage the patient to limit immobility in the days immediately following the infusion.

1.2 Strategies to lower risk of fluid overload are to use a low sodium product. The IVIG products available on the UW Health formulary are low sodium products; Gammagard Liquid\textsuperscript{®} (undetectable sodium) and Gammagard S/D\textsuperscript{®} low IgA (0.85% sodium).

2. Not all patients require premedication for successful administration, and it may be reasonable to consider foregoing it. However, premedication increases the tolerability of IVIG for many patients.\textsuperscript{121} Effective options are presented in the table below. They should be administered 30 minutes prior to the initiation the IVIG infusion. (UW Health GRADE Moderate quality evidence; strong recommendation)

**Table 2. Frequently used premedications**

<table>
<thead>
<tr>
<th>Therapeutic Class</th>
<th>Adults</th>
<th>Pediatrics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Analgesic</strong></td>
<td>Acetaminophen 650 mg orally once</td>
<td>Acetaminophen 10 – 15 mg/kg orally once; maximum = 650 mg</td>
</tr>
<tr>
<td><strong>Antihistamine</strong></td>
<td>• Diphenhydramine 25 – 50 mg orally or intravenous once&lt;br&gt;• Loratadine 10 mg orally once&lt;br&gt;• Cetirizine 10 mg oral once&lt;br&gt;• Fexofenadine 180 mg oral once</td>
<td>• Diphenhydramine 0.5 – 1 mg/kg oral or IV once; maximum = 50 mg&lt;br&gt;• Loratadine oral once&lt;br&gt;  o 2-5 yrs: 5 mg&lt;br&gt;  o ≥ 6 yrs: 5 – 10 mg&lt;br&gt;• Cetirizine oral once&lt;br&gt;  o 6 month – 2 yrs: 2.5 mg&lt;br&gt;  o 2 – 5 yrs: 2.5 – 5 mg&lt;br&gt;  o ≥ 6 yrs: 5 – 10 mg&lt;br&gt;• Fexofenadine oral once&lt;br&gt;  o 2 – 11 yrs.: 60 mg&lt;br&gt;  o ≥ 12 yrs: 180 mg</td>
</tr>
<tr>
<td><strong>Corticosteroid</strong></td>
<td>Dexamethasone 4 mg oral or IV once</td>
<td>Dexamethasone 0.5 mg/kg oral or IV once; maximum 4 mg</td>
</tr>
</tbody>
</table>
Methylprednisolone 20 – 60 mg IV once

Methylprednisolone 0.5 – 1 mg/kg IV once (max 40 mg)

3. Filters: Gammagard Liquid® product requires no filtration. Gammagard S/D® low IgA requires filtration with a 15 micron filter. (UW Health GRADE Moderate quality evidence; strong recommendation)

4. Infusion rates: Infusion rates are determined by patient tolerability. Generally infusion rates should be slower for the first infusions or when IVIG products are changed. The infusion rate for the first two administrations is presented for adults and pediatric patients below. If patients tolerate the initial infusions, a incrementally faster rate can be used for subsequent infusions. For all infusions, a gradual titration approach to the maximal infusion rate is recommended. (UW Health GRADE High quality evidence; strong recommendation)

5. Infusion related reactions that occur with IVIG are typically due to an infusion rate that is too fast for patient tolerability. If there is an infusion reaction stop or slow the rate of infusion and treat as presented in Table 3 below. (UW Health GRADE Moderate quality evidence; strong recommendation)

<table>
<thead>
<tr>
<th>Table 3. Treatment of Adverse Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Therapeutic Class</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Antihistamine</td>
</tr>
<tr>
<td>Corticosteroid</td>
</tr>
</tbody>
</table>

6. Restart the infusion at a slower rate once the reaction subsides. Decrease the infusion rate by one half the rate at which the reaction occurred. (UW Health GRADE High quality evidence; strong recommendation)

7. The rate can be titrated to a faster rate again as the patient tolerates. (UW Health GRADE High quality evidence; strong recommendation)

8. If the patient has a history of infusion reactions, the prescriber should indicate in the order the maximum infusion rate desired (gram/hr). (UW Health GRADE Very low quality evidence; strong recommendation)

9. Consider checking for anti-IgA antibodies in patients with infusion reactions and consider product change to low IgA product (Gammagard S/D). (UW Health GRADE Low quality evidence; weak/conditional recommendation)
Monitoring and cautions\textsuperscript{3,4}

1. All patients should be continually monitored for adverse effects related to the administration of IVIG and the infusion rate. \textit{(UW Health GRADE High quality evidence; strong recommendation)}

2. The following vital signs can be monitored to assess the safety of the infusion: blood pressure, heart rate, respiratory rate, oxygen saturation, and temperature. They can be measured before, during, and/or after the infusion OR if the patient experiences new or worsening symptoms of an infusion reaction. \textit{(UW Health GRADE High quality evidence; strong recommendation)}

3. Minor or mild reactions (with frequency) include:
   3.1. Headache 30.6%
   3.2. Nausea and/or vomiting 22%
   3.3. Chills 19.4%
   3.4. Hypotension 14%
   3.5. Lightheadedness ≤ 13%
   3.6. Fever 11.1%
   3.7. Fatigue 11.1%
   3.8. Backache 8.3%
   3.9. Urticaria 8%
   3.10. Leg cramps 6%
   3.11. Flushing 5.6%

4. Rare (<1%), but serious, side effects include: hemolysis transfusion-related acute lung injury, arterial thrombosis, deep vein thrombosis, pulmonary embolism, myocardial infarction, thromboembolism, aseptic meningitis syndrome, and acute renal failure.

5. Monitor for signs and symptoms of thrombosis, blood hyperviscosity, hemolysis, hemolytic anemia, and acute lung injury. \textit{(UW Health GRADE High quality evidence; strong recommendation)}

6. Certain patient populations may be predisposed to renal dysfunction when receiving IVIG products that contain sucrose. No UW Health formulary IVIG products contain sucrose.
   6.1. Patients over 65 yrs. old
   6.2. Patients with diabetes mellitus
   6.3. Patients with renal impairment prior to treatment with IVIG.

7. Periodic monitoring of renal function is recommended in patients that are judged to be at risk of acute renal failure. \textit{(UW Health GRADE High quality evidence; strong recommendation)}

8. IVIG should not be infused rapidly in patients with underlying renal disease or who are at risk for developing thrombotic events. To decrease these risks, the patient should be optimally hydrated. A product with a lower osmolality should be considered.\textsuperscript{3,4} \textit{(UW Health GRADE High quality evidence; strong recommendation)}
Administration Instructions for Adults
1. Patient tolerability is always the first consideration for infusion rate. (UW Health GRADE High quality evidence; strong recommendation)
   1.1. See the adult infusion calculator for 10% immune globulin product: URL = https://uconnect.wisc.edu/clinical/cckm-tools/content/cpg/medications/related/name-119307-en.cckm

2. The following is the recommended initial titration (first two doses) for immune globulin 10% (1 mL=100 mg)
   2.1. 0.5 mL/kg/hr. x 15 minutes
   2.2. 1 mL/kg/hr. x 15 minutes
   2.3. 1.5 mL/kg/hr x 15 minutes
   2.4. Infuse remaining volume at 2 mL/kg/hr

3. Subsequent infusions:
   3.1. If patient tolerates the initial infusions, the dose can be infused at a faster rate, however a gradual titration to the maximal rate is recommended for all doses. The maximum infusion rate is 5 mL/kg/hr.3,4 (UW Health GRADE High quality evidence; strong recommendation)

Administration Instructions for Pediatrics
1. Infusion rates: Infusion rates are determined by patient tolerability. The first two infusions should be infused at the rates summarized below, if the patient tolerates the initial infusion, a faster rate can be used for subsequent infusions.3,4 (UW Health GRADE High quality evidence; strong recommendation)
   1.1. See the pediatric infusion calculator for 10% immune globulin product: URL = https://uconnect.wisc.edu/clinical/cckm-tools/content/cpg/medications/related/name-114172-en.cckm

2. The following is the recommended initial titration (first dose) for 10% product for all indications except Kawasaki Disease (1mL=100 mg):
   2.1. 0.5 mL/kg/hr. x 30 min
   2.2. 1 mL/kg/hr. x 30 min
   2.3. 2 mL/kg/hr. x 30 min
   2.4. 3 mL/kg/hr. x 30 min
   2.5. Infuse remaining volume at 4 mL/kg/hr or max of 110 mL/hr (whichever is reached first)

3. Subsequent infusions:
   3.1. If the patient tolerates initial infusion, subsequent doses can be infused at a faster rate. However a gradual titration to the maximum rate is recommended for all doses. The maximum infusion rate is 5 mL/kg/hr.3,4 (UW Health GRADE High quality evidence; strong recommendation).
Administration Instructions for Kawasaki Disease

1. The following is the recommended titration rate for 10% product for Kawasaki Disease. Note that patients treated for Kawasaki Disease receive a high dose of IVIG at a slower rate due to the high oncotic volume load. The minimum infusion rate should not be less than 12 hours.\textsuperscript{125} (UW Health GRADE Moderate quality evidence; strong recommendation) See the pediatric Kawasaki infusion calculator for 10% immune globulin: URL = https://uconnect.wisc.edu/clinical/cckm-tools/content/cpg/medications/related/name-111816-en.cckm

2. The following is the recommended infusion rate for 10% product for Kawasaki Disease (1 mL = 100 mg):
  2.1. 0.5 mL/kg/hr x 30 min
  2.2. 0.8 mL/kg/hr x 30 min
  2.3. 1 mL/kg/hr x 30 min
  2.4. 1.5 mL/kg/hr x 30 min
  2.5. Infuse remaining volume at 1.8 mL/kg/hr
  2.6. Total infusion time should not be less than 12 hours

Administration Instructions for Inpatients

1. An infusion time longer than the maximum calculated infusion duration (8-12 hours) may be considered for inpatients in order to decrease the risk of adverse reactions. A prolonged infusion time in excess of the maximum calculated infusion duration may be considered when:
   1.1. A dedicated line will be available for the full duration of the infusion and the administration of other medications will not be delayed
   1.2. The patient’s discharge time is not anticipated within 24 hours and will not be postponed in order to complete infusion. (UW Health GRADE Very low quality evidence; weak/conditional recommendation)

Immune globulin administered by the subcutaneous route

1. Administration by the subcutaneous route may be considered in patients who are treated for immunodeficiencies and are receiving doses of reasonably low volume. Subcutaneous administration is less likely to result in adverse effects. Traditional immune globulin products labeled for subcutaneous administration and available on the UW Health formulary include Gammagard Liquid\textsuperscript{\textregistered}. HyQvia\textsuperscript{\textregistered}, indicated for hyaluronidase facilitated subcutaneous administration, is also available on the UW Health formulary on a restricted basis. The goal is to ultimately transition patients to self-administration in the home. However HyQvia\textsuperscript{\textregistered} is approved for outpatient administration during the initial dose ramp-up in patients naïve to immune globulin or those transitioning from intravenous administration. (UW Health GRADE High quality evidence; strong recommendation)
2. Independent insurance screening is necessary for subcutaneous immune globulin products and administration. Previous insurance coverage of intravenous administration may not extend to subcutaneous administration, even when using the same product.
UW Health Implementation

Potential Benefits:
The predominant benefit of implementation of this guideline is that IVIG will be used in a consistent, cost-effective manner throughout UW Health

Potential Harms:
- Patients may experience an adverse reaction, including serious events. These events may be related to an infusion rate that is too fast for patient tolerability.

Pertinent UW Health Policies & Procedures
1. UW Health Policy #: Policy 15.2 Medication Use in Outpatient Care Areas (Pharmacy)
2. UWHC Policy #: Policy 1.24 Alaris System (Nursing Patient Care)
3. UW Health Policy: Policy 4.1 Medication Delivery via Tube System

Patient Resources
1. Health Facts For You #6868- Intravenous Immune Globulin (IVIG)
2. Lexicomp- Immune Globulin IV

Guideline Metrics
1. Adverse event reporting
Implementation Plan/Clinical Tools

1. The restriction of IVIG use to appropriate, evidence-based indications will be operationalized by linking the guideline to the electronic prescription in health link and by pharmacist review for appropriate indication.

2. The use of IVIG for appropriate indications will continue to be audited through an electronic prescription record-based question regarding indication for utilization which will be updated to reflect the indications in the current clinical practice guideline and a follow-up medication use evaluation (MUE).

3. Applicable medication records and orders sets will be revised to reflect current recommendations in the guideline.

4. Decentralized clinical pharmacists and infusion center pharmacists will be educated about this guideline through pharmacy team meetings.

5. Pharmacists will review the indication, dose, pertinent monitoring parameters to evaluate appropriate use. Recommendations for changes in dosing, frequency, etc., will be communicated to the prescribing physician for possible interventions.

Disclaimer
This Clinical Practice Guideline provides an evidence-based approach for the use of IVIG. It is understood that occasionally patients will not match the conditions considered in the guideline.
Appendix A. Evidence Grading Scheme(s)

Figure 1. GRADE Methodology adapted by UW Health

Figure 1. GRADE Algorithm and Grading Scheme

Table 1. GRADE Ranking of Evidence

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>We are confident that the effect in the study reflects the actual effect.</td>
</tr>
<tr>
<td>Moderate</td>
<td>We are quite confident that the effect in the study is close to the true effect, but it is also possible it is substantially different.</td>
</tr>
<tr>
<td>Low</td>
<td>The true effect may differ significantly from the estimate.</td>
</tr>
<tr>
<td>Very Low</td>
<td>The true effect is likely to be substantially different from the estimated effect.</td>
</tr>
</tbody>
</table>

Table 2. GRADE Ratings for Recommendations For or Against Practice

<table>
<thead>
<tr>
<th>Rating</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong</td>
<td>The net benefit of the treatment is clear, patient values and circumstances are unlikely to affect the decision.</td>
</tr>
<tr>
<td>Weak/conditional</td>
<td>Recommendation may be conditional upon patient values and preferences, the resources available, or the setting in which the intervention will be implemented.</td>
</tr>
</tbody>
</table>

Methods for evidence grading are described in detail by Guyatt et al.¹²⁶
References


4. Immune globulin infusion (human) IgA less than 1 microgram per mL in a 5% solution (Gammagard S/D®)[prescribing information]. Baxter Healthcare Corporation; Westlake Village, CA. 2014.


