Medical Policy:

IVIG – IMMUNE GLOBULINS (immunoglobulin) Intravenous

POLICY NUMBER	LAST REVIEW	ORIGIN DATE
MG.MM.PH.86	February 16, 2024	

The treating physician or primary care provider must submit to EmblemHealth, or ConnectiCare, as applicable (hereinafter jointly referred to as "EmblemHealth"), the clinical evidence that the member meets the criteria for the treatment or surgical procedure. Without this documentation and information, EmblemHealth will not be able to properly review the request preauthorization or post-payment review. The clinical review criteria expressed below reflects how EmblemHealth determines whether certain services or supplies are medically necessary. This clinical policy is not intended to pre-empt the judgment of the reviewing medical director or dictate to health care providers how to practice medicine. Health care providers are expected to exercise their medical judgment in rendering appropriate care. Health care providers are expected to exercise their medical judgment in rendering appropriate care.

EmblemHealth established the clinical review criteria based upon a review of currently available clinical information (including clinical outcome studies in the peer reviewed published medical literature, regulatory status of the technology, evidence-based guidelines of public health and health research agencies, evidence-based guidelines and positions of leading national health professional organizations, views of physicians practicing in relevant clinical areas, and other relevant factors). EmblemHealth expressly reserves the right to revise these conclusions as clinical information changes and welcomes further relevant information. Each benefit program defines which services are covered. 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 and/or paid for by EmblemHealth, as some programs exclude coverage for services or supplies that EmblemHealth considers medically necessary.

If there is a discrepancy between this guideline and a member's benefits program, the benefits program will govern. Identification of selected brand names of devices, tests and procedures in a medical coverage policy is for reference only and is not an endorsement of any one device, test or procedure over another. In addition, coverage may be mandated by applicable legal requirements of a state, the Federal Government or the Centers for Medicare & Medicaid Services (CMS) for Medicare and Medicaid members. All coding and web site links are accurate at time of publication.

EmblemHealth may also use tools developed by third parties, such as the MCG™ Care Guidelines, to assist us in administering health benefits. The MCG™ Care Guidelines are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice. EmblemHealth Services Company, LLC, has adopted this policy in providing management, administrative and other services to EmblemHealth Plan, Inc., EmblemHealth Insurance Company, EmblemHealth Services Company, LLC, and Health Insurance Plan of Greater New York (HIP) related to health benefit plans offered by these entities. ConnectiCare, an EmblemHealth company, has also adopted this policy. All of the aforementioned entities are affiliated companies under common control of EmblemHealth Inc.

Length of Authorization

1. Initial and renewal authorization periods vary by specific covered indication.
2. The initial authorization will be provided up to 6 months unless otherwise specified and may be renewed.

Dosing Limits [Medical Benefit]

A. Max Units (per dose and over time):

Indication	Billable Units	Max Units Per # days (unless otherwise specified)
PID	184	21
CIDP	Load: 460	4
	Maintenance: 230	21
Immune thrombocytopenia/ITP	460	28

FAIT	200	7
Kawasaki's Disease (*Pediatric Patients only*)	232	1 dose only
Multifocal Motor Neuropathy	460	28
CLL/MM	92	21
ALL	92	21
HIV (Pediatric Patients only)	47	28
Guillain-Barre	460	5 (*for one cycle only)*
Myasthenia Gravis	460	28
Auto-immune blistering diseases	460	28
Bone Marrow or Stem Cell Transplant	115	7
Dermatomyositis/Polymyositis	460	28
Complications of transplanted solid organ *(kidney, liver, lung, heart and pancreas transplants)*	460	28
Stiff Person	460	28
Toxic shock syndrome	460	5 *(for one cycle only)*
NAIT	16	2 doses only
Management of Immune Checkpoint Inhibitor Related Toxicity	460	5 *(for one cycle only)*
Management of CAR T-Cell-Related Toxicity	115	28

Guideline

I. Initial Approval Criteria

Intravenous Immune Globulins may be considered medically necessary if one of the below conditions are met **AND** use is consistent with the medical necessity criteria that follows:

The following indications require IVIG to be requested by one of the following specialists:

1. **Primary immunodeficiency (PID) and Chronic lymphocytic leukemia**
   - Allergist/Immunologist, Hematologist/Oncologist, or Infectious Disease Specialist
2. **Idiopathic thrombocytopenia purpura (ITP)**
   - Hematologist/Oncologist
3. **Chronic Inflammatory Demyelinating Polyneuropathy (CIDP), Guillain-Barre Syndrome (Acute inflammatory polyneuropathy), Multifocal Motor Neuropathy, Myasthenia Gravis, and Relapsing-Remitting Multiple Sclerosis**
   - Neurologist
4. **Dermatomyositis/Polymyositis**
   - Dermatologist or Rheumatologist

Coverage is provided in the following conditions:

Primary immunodeficiency (PID)/Wiskott - Aldrich syndrome †

Such as: x-linked agammaglobulinemia, common variable immunodeficiency, transient hypogammaglobulinemia of infancy, IgG subclass deficiency with or without IgA deficiency, antibody deficiency with near normal immunoglobulin levels) and combined deficiencies (severe combined immunodeficiencies, ataxia-telangiectasia, x-linked lymphoproliferative syndrome) [***list not all inclusive***]

1. Patient's IgG level is < 200 mg/dL **OR** both of the following
   a. Patient has a history of multiple hard to treat infections as indicated by at least **one** of the following:
      i. Four or more ear infections within 1 year
      ii. Two or more serious sinus infections within 1 year
      iii. Two or more months of antibiotics with little effect
      iv. Two or more pneumonias within 1 year
      v. Recurrent or deep skin abscesses
      vi. Need for intravenous antibiotics to clear infections
      vii. Two or more deep-seated infections including septicemia; **AND**
   b. The patient has a deficiency in producing antibodies in response to vaccination; **AND**
      i. Titers were drawn before challenging with vaccination; **AND**
      ii. Titers were drawn between 4 and 8 weeks of vaccination

Immune thrombocytopenia/Idiopathic thrombocytopenia purpura (ITP) †

For acute disease state:

1. To manage acute bleeding due to severe thrombocytopenia (platelet counts less than 30 X 10^9/L); **OR**
2. To increase platelet counts prior to invasive surgical procedures such as splenectomy. (Platelets less than 100 X 10^9/L); **OR**
3. Patient has severe thrombocytopenia (platelet counts less than 20 X 10^9/L) and is considered to be at risk for intracerebral hemorrhage

Note: Authorization is valid for 1 month only and cannot be renewed

Chronic Immune Thrombocytopenia (CIT):

1. The patient is at increased risk for bleeding as indicated by a platelet count less than 30 X 10^9/L; **AND**
2. History of failure, contraindication, or intolerance to corticosteroids; **AND**
3. Duration of illness > 6 months; **AND**
4. Member age ≥ 2 years

Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) †

1. Patient's disease course is progressive or relapsing and remitting for 2 months or longer; **AND**
2. Patient has abnormal or absent deep tendon reflexes in upper or lower limbs; **AND**
3. Electrodiagnostic testing indicating demyelination; **AND**
   a. Partial motor conduction block in at least two motor nerves or in 1 nerve plus one other demyelination criterion listed here in at least 1 other nerve; **OR**

b. Distal CMAP duration increase in at least 1 nerve plus one other demyelination criterion listed here in at least 1 other nerve; **OR**
c. Abnormal temporal dispersion conduction must be present in at least 2 motor nerves; **OR**
d. Reduced conduction velocity in at least 2 motor nerves; **OR**
e. Prolonged distal motor latency in at least 2 motor nerves; **OR**
f. Absent F wave in at least two motor nerves plus one other demyelination criterion listed here in at least 1 other nerve; **OR**
g. Prolonged F wave latency in at least 2 motor nerves; **AND**

4. Refractory or intolerant to corticosteroids (e.g., prednisolone, prednisone, etc.) given in therapeutic doses over at least three months; **AND**
5. Baseline in strength/weakness has been documented using an objective clinical measuring tool (e.g., INCAT, Medical Research Council (MRC) muscle strength, 6-MWT, Rankin, Modified Rankin, etc.)

Note: Initial authorization is valid for 3 months

Guillain-Barre Syndrome (Acute inflammatory polyneuropathy) ‡

1. Disease is severe (i.e., patient requires assistance to ambulate); **AND**
2. Onset of symptoms are recent (i.e., less than 1 month); **AND**
3. Patient has abnormal or absent deep tendon reflexes in upper or lower limbs; **AND**
4. Patient diagnosis is confirmed using a cerebrospinal fluid analysis; **AND**
5. Approval will be granted for a maximum of 2 rounds of therapy within 6 weeks of onset

Note: Authorization is valid for 2 months only and cannot be renewed

Multifocal Motor Neuropathy †

1. Patient has progressive, focal, asymmetric weakness (without sensory symptoms) for > 1 month; **AND**
2. Complete or partial conduction block or abnormal temporal dispersion conduction must be present in at least 2 motor nerves **AND**
3. Patient has normal sensory nerve conduction on all nerves tested; **AND**
4. Baseline in strength/weakness has been documented using an objective clinical measuring tool (e.g., INCAT, Medical Research Council (MRC) muscle strength, 6-MWT, Rankin, Modified Rankin, etc.)

Note: Initial authorization is valid for 3 months

HIV infected children: Bacterial control or prevention †‡

1. Patient age does not exceed 13 years of age; **AND**
2. Patient's IgG level is less than 400 mg/dL

Myasthenia Gravis ‡

1. Patient has a positive serologic test for anti-acetylcholine receptor (AchR) antibodies; **AND**
2. Patient has an acute exacerbation resulting in impending myasthenic crisis (i.e., respiratory compromise, acute respiratory failure, and/or bulbar compromise); **AND**

3. Patient is failing on conventional immunosuppressant therapy alone (e.g., corticosteroids, azathioprine, cyclosporine, mycophenolate, methotrexate, tacrolimus, cyclophosphamide, etc.); **AND**
4. Patient will be on combination therapy with corticosteroids or other immunosuppressant (e.g., azathioprine, mycophenolate, cyclosporine, methotrexate, tacrolimus, cyclophosphamide, etc.)

Note: Authorization is valid for 1 course per month and it can be renewed on a case by case basis.

Dermatomyositis †/Polymyositis ‡

1. Patient has severe active disease; **AND**
2. Patient has proximal weakness in all upper and/or lower limbs; **AND**
3. Diagnosis has been confirmed by muscle biopsy; **AND**
4. Patient has failed a trial of corticosteroids (i.e., prednisone); **AND**
5. Patient has failed a trial of an immunosuppressant (e.g., methotrexate, azathioprine, etc.); **AND**
6. Must be used as part of combination therapy with other agents; **AND**
7. Patient has a documented baseline physical exam and muscular strength/function

Note: Initial authorization is valid for 3 months

Complications of transplanted solid organ (kidney, liver, lung, heart, pancreas) and bone marrow transplant ‡

Coverage is provided for one or more of the following (list not all-inclusive):

1. Suppression of panel reactive anti-human leukocyte antigen (HLA) antibodies prior to transplantation
2. Treatment of antibody-mediated rejection of solid organ transplantation
3. Prevention or treatment of viral infections (e.g., cytomegalovirus, Parvo B-19 virus, and Polyoma BK virus)

Stiff-Person Syndrome ‡

1. Patient has anti-glutamic acid decarboxylase (GAD) antibodies; **AND**
2. Patient has failed at least 2 of the following treatments: benzodiazepines, baclofen, gabapentin, valproate, tiagabine, or levetiracetam; **AND**
3. Patient has a documented baseline on physical exam

Allogeneic Bone Marrow or Stem Cell Transplant † ‡

1. Used for prevention of acute Graft-Versus-Host-Disease (aGVHD) or infection; **AND**
2. Patient's BMT or hematopoietic stem cell (HSCT) transplant was allogeneic; **AND**
3. Patient's IgG level is less than 400 mg/dL

Note: Initial authorization is valid for 3 months

Kawasaki's disease (Pediatric) †

Note: Authorization is valid for 1 course (1 month) only and cannot be renewed

Fetal alloimmune thrombocytopenia (FAIT) ‡

1. Patient has a history of one or more of the following:
    a. Previous FAIT pregnancy
    b. Family history of the disease
    c. Screening reveals platelet alloantibodies

Note: Authorization is valid through the delivery date only and cannot be renewed

Neonatal Alloimmune Thrombocytopenia ‡

Note: Authorization is valid for 1 course (1 month) only and cannot be renewed

Auto-immune Mucocutaneous Blistering Diseases ‡

1. Patient has been diagnosed with one of the following:
    a. Pemphigus vulgaris
    b. Pemphigus foliaceus
    c. Bullous Pemphigoid
    d. Mucous Membrane Pemphigoid (a.k.a. Cicatricial Pemphigoid)
    e. Epidermolysis bullosa acquisita
    f. Pemphigus gestationis (Herpes gestationis)
    g. Linear IgA dermatosis; **AND**
2. Patient has severe disease that is extensive and debilitating; **AND**
3. Diagnosis has been confirmed by biopsy; **AND**
4. Patient's disease is progressive; **AND**
5. Disease is refractory to a trial of conventional therapy with corticosteroids and concurrent immunosuppressive treatment (e.g., azathioprine, cyclophosphamide, mycophenolate mofetil, etc.); **AND**
6. Patient has a documented baseline on physical exam

Acquired Immune Deficiency secondary to Acute Lymphoblastic Leukemia (ALL) ‡

1. Used for prevention of infection; **AND**
2. Patient's IgG level is less than 400 mg/dL

Acquired Immune Deficiency secondary to Chronic lymphocytic leukemia † or Multiple Myeloma † ‡

1. Patient's IgG level is <200 mg/dL **OR** both of the following
2. Patient has a history of multiple hard to treat infections as indicated by at least **one** of the following:
    a. Four or more ear infections within 1 year
    b. Two or more serious sinus infections within 1 year
    c. Two or more months of antibiotics with little effect
    d. Two or more pneumonias within 1 year
    e. Recurrent or deep skin abscesses
    f. Need for intravenous antibiotics to clear infections
    g. Two or more deep-seated infections including septicemia; **AND**
3. The patient has a deficiency in producing antibodies in response to vaccination; **AND**
    a. Titers were drawn before challenging with vaccination; **AND**

b. Titers were drawn between 4 and 8 weeks of vaccination

Note: other secondary immunodeficiencies resulting in hypogammaglobulinemia and/or B-cell aplasia will be evaluated on a case-by-case basis

Toxic Shock Syndrome ‡

Note: Authorization is valid for 1 course (1 month) only and cannot be renewed

Management of Immune-Checkpoint-Inhibitor Related Toxicity ‡

1. Patient has been receiving therapy with an immune checkpoint inhibitor (e.g. nivolumab, pembrolizumab, atezolizumab, avelumab, durvalumab, etc.); **AND**
2. Patient has one of the following toxicities related to their immunotherapy:
   a. Severe (G3) or life-threatening (G4) bullous dermatitis as an adjunct to rituximab
   b. Stevens-Johnson syndrome (SJS)
   c. Toxic epidermal necrolysis (TEN)
   d. Severe (G3-4) myasthenia gravis
   e. Transverse myelitis
   f. Myocarditis as further intervention if no improvement within 24-48 hours of starting pulse-dose methylprednisolone
   g. Moderate (G2) or severe (G3-4) Guillain-Barre Syndrome or severe (G3-4) peripheral neuropathy used in combination with pulse-dose methylprednisolone
   h. Moderate (G2) pneumonitis if no improvement after 48-72 hours of corticosteroids
   i. Severe (G3-4) pneumonitis if no improvement after 48 hours of methylprednisolone
   j. Encephalitis used in combination with pulse-dose methylprednisolone for severe or progressing symptoms or if oligoclonal bands are present
   k. Moderate, severe, or life-threatening steroid-refractory myalgias or myositis

Management of CAR T-Cell-Related Toxicity ‡

1. Patient has been receiving treatment with anti-CD19 chimeric antigen receptor (CAR) T-cell therapy (e.g., axicabtagene ciloleucel, brexucabtagene autoleucel, idecabtagene vicleucel, lisocabtagene maraleucel, tisagenlecleucel, etc.); **AND**

   a. Used for the management of G4 cytokine release syndrome that is refractory to high-dose corticosteroids and anti-IL-6 therapy (e.g., tocilizumab); **OR**

   b. Patient has hypogammaglobulinemia as confirmed by serum IgG levels <600 mg/dL **AND** serious or recurrent infections; **OR**

2. Used as prophylactic therapy prior to receiving treatment with anti-CD19 chimeric antigen receptor (CAR) T-cell therapy (e.g., axicabtagene ciloleucel, brexucabtagene autoleucel, idecabtagene vicleucel, lisocabtagene maraleucel, tisagenlecleucel, etc.); **AND**

a. Patient has hypogammaglobulinemia as confirmed by serum IgG levels ≤400 mg/dL **AND** serious, persistent, or recurrent bacterial infections

PANDAS/PANS

As per Massachusetts DOI Bulletin 2021-06, coverage for the following indication will be covered for Massachusetts residents under the Commercial line of business, starting 1/1/2022:

1. Treatment of pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS) and pediatric acute-onset neuropsychiatric syndrome (PANS).

*For Reference Use Only

Brand Name/ Formulation	FDA Indication	Contraindications	Product Specs	Comments
Asceniv (liquid)	PID ((≥12 yo)	History of anaphylaxis to IgG IgA-deficient with IgA antibodies	**IgA:** ≤200 mcg/Ml **Osmolality**: N/A **Stabilizer**: glycine	Other stabilizer used is Polysorbate 80
Bivigam (liquid)	PID (peds ≥6)	History of anaphylaxis to IgG IgA-deficient with IgA antibodies	**IgA**: ≤200 mcg/mL **Osmolality**: 510 mOsm/kg **Stabilizer**: glycine	
Flebogamma 5% (liquid)	PID (peds ≥2)	History of anaphylaxis to IgG IgA-deficient with IgA antibodies	**IgA**: <50 mcg/mL **Osmolarity**: 240 to 370 mOsm/kg **Stabilizer**: sorbitol	
Flebogamma 10% (liquid)	PID (peds ≥2) ITP (peds ≥2)	History of anaphylaxis to IgG IgA-deficient with IgA antibodies	**IgA**: <32 mcg/mL **Osmolarity**: 240 to 370 mOsm/L **Stabilizer**: sorbitol	
Gammagard (liquid)	PID (peds ≥2) MMN (adults)	History of anaphylaxis to IgG IgA-deficient with IgA antibodies	**IgA**: 37 mcg/mL **Osmolality**: 240 to 300 mOsm/kg **Stabilizer**: glycine	May be used SC (see policy for criteria
Gammagard S/D (lyophilized)	PID ITP CLL Kawasaki *(adults/peds for all indx)*	History of anaphylaxis to IgG IgA-deficient with IgA antibodies	**IgA**: <1 mcg/mL (5% solution) **Osmolality**: 636 mOsm/L (5% soln) **Stabilizer**: glycine	Contains some sugar (20mg/mL when prepared)
Gammaked (liquid)	PID (peds ≥2) ITP (peds/adults) CIDP (adults)	History of anaphylaxis to IgG IgA-deficient with IgA antibodies	**IgA**: 46 mcg/mL **Osmolality**: 258 mOsm/kg **Stabilizer**: glycine	May be used SC (see policy for criteria
Gammaplex 5% (liquid)	PID (peds ≥2) cITP (adults)	History of anaphylaxis to IgG IgA-deficient with IgA antibodies Fructose intolerance	**IgA**: <10 mcg/mL **Osmolality**: 420 to 500 mOsm/kg **Stabilizer**: glycine	Other stabilizer used is Polysorbate 80
Gammaplex 10% (liquid)	PID (adults) cITP (adults)	History of anaphylaxis to IgG IgA-deficient with IgA antibodies	**IgA**: <20 mcg/mL **Osmolality**: 280 mOsm/kg **Stabilizer**: glycine	Other stabilizer used is Polysorbate 80

Gamunex-C (liquid)	PID (peds ≥2) ITP (peds/adults) CIDP (adults)	History of anaphylaxis to IgG IgA-deficient with IgA antibodies	**IgA**: 46 mcg/mL **Osmolality**: 258 mOsm/kg **Stabilizer**: glycine	May be used SC (see policy for criteria
Octagam 5% (liquid)	PID (peds≥6)	History of anaphylaxis to IgG IgA-deficient with IgA antibodies Corn allergy	**IgA**: ≤200 mcg/mL **Osmolality**: 310 to 380 mOsm/kg **Stabilizer**: maltose	
Octagam 10% (liquid)	ITP (adults)	History of anaphylaxis to IgG IgA-deficient with IgA antibodies	**IgA**: 106 mcg/mL **Osmolality**: 310 to 390 mOsm/kg **Stabilizer**: maltose	
Privigen (liquid)	PID cITP (ped ≥15) CIDP (adults)	History of anaphylaxis to IgG IgA-deficient with IgA antibodies Hyperprolinemia	**IgA**: ≤25 mcg/mL **Osmolality**: 320 mOsm/kg **Stabilizer**: L-proline	
Panzyga	PID (peds ≥2) cITP (adults)	History of anaphylaxis to IgG IgA-deficient with IgA antibodies	**IgA**: ≤100 mcg/mL **Osmolality**: 240-310 mOsm/kg **Stabilizer**: Glycine	
– All intravenous immunoglobulins are derived from human plasma. – Products with higher IgA content pose a greater risk for anaphylactic reactions, especially in patients with IgA deficiencies. – All products may predispose patients to nephrotoxicity especially those with sugar-based or proline-based stabilizers. To lower risks, lower concentration products and infusions rates should be used as well as using products with osmolality/osmolarity that is near physiologic range (around 300 mOsm/kg or mOsm/L). – Premedications (e.g., acetaminophen, antihistamine, etc.) are recommended to reduce the risk of infusion related reactions.				
– *Adapted from: Professional Resource, Comparison of IVIG Products. Pharmacist's Letter/Prescriber's Letter. December 2016.*				

II. RENEWAL CRITERIA

Note: unless otherwise specified, renewal authorizations are provided for 1 year

Coverage can be renewed based upon the following criteria:

1. Absence of unacceptable toxicity from the drug. Examples of unacceptable toxicity include the following: acute kidney injury, thrombosis, hemolysis, hypersensitivity, pulmonary adverse reactions, volume overload, etc.; **AND**

2. Patient meets the disease-specific criteria identified below:

Primary Immunodeficiency (PID)

1. Disease response as evidenced by one or more of the following:
   a. Decrease in the frequency of infection
   b. Decrease in the severity of infection

Chronic Immune Thrombocytopenia/ITP

1. Disease response as indicated by the achievement and maintenance of a platelet count of at least 30×10^9/L and at least doubling the baseline platelet count

Chronic Inflammatory Demyelinating Polyneuropathy

1. Renewals will be authorized for patients that have demonstrated a clinical response to therapy based on an objective clinical measuring tool (e.g., INCAT, Medical Research Council (MRC) muscle strength, 6-MWT, Rankin, Modified Rankin, etc.)

Multifocal Motor Neuropathy

1. Renewals will be authorized for patients that have demonstrated a clinical response to therapy based on an objective clinical measuring tool (e.g., INCAT, Medical Research Council (MRC) muscle strength, 6-MWT, Rankin, Modified Rankin, etc.)

HIV infected children: Bacterial control or prevention

1. Disease response as evidenced by one or more of the following:
    a. Decrease in the frequency of infection
    b. Decrease in the severity of infection; **AND**
2. Patient continues to be at an increased risk of infection necessitating continued therapy necessitating continued therapy as evidenced by an IgG level < 400 mg/dL

Dermatomyositis/Polymyositis

1. Patient had an improvement from baseline on physical exam and/or muscular strength and function

Note: Renewal authorizations are provided for 6 months

Complications of transplanted solid organ (kidney, liver, lung, heart, pancreas) and bone marrow transplant

1. Disease response as evidenced by one or more of the following:
    a. Decrease in the frequency of infection
    b. Decrease in the severity of infection; **AND**
2. Patient continues to be at an increased risk of infection necessitating continued therapy

Stiff Person Syndrome

1. Documented improvement from baseline on physical exam

Allogeneic Bone Marrow or Stem Cell Transplant

1. Patient's IgG trough is less than 400 mg/dL

Note: Renewal authorizations are provided for 3 months

Auto-Immune Mucocutaneous Blistering Diseases

1. Documented improvement from baseline on physical exam

Note: Renewal authorizations are provided for 6 months

Acquired Immune Deficiency secondary to Chronic Lymphocytic Leukemia or Multiple Myeloma

1. Disease response as evidenced by one or more of the following:
    a. Decrease in the frequency of infection
    b. Decrease in the severity of infection; **AND**
2. Patient continues to be at an increased risk of infection necessitating continued therapy

Acquired Immune Deficiency secondary to Acute Lymphoblastic Leukemia (ALL)

1. Disease response as evidenced by one or more of the following:
    a. Decrease in the frequency of infection
    b. Decrease in the severity of infection; **AND**
2. Patient continues to be at an increased risk of infection necessitating continued therapy

Management of Immune Checkpoint Inhibitor related Toxicity ‡

1. May not be renewed.

Note: Renewal authorizations are provided for 6 months where applicable

Management of CAR T-Cell-Related Toxicity

1. Patient is still receiving treatment with anti-CD19 CAR T-cell therapy (e.g., axicabtagene ciloleucel, brexucabtagene autoleucel, lisocabtagene maraleucel, tisagenlecleucel, etc.); AND
2. Patient has serum IgG levels <600 mg/dl

Dosing Recommendations:

1. Patient's dose should be reduced to the lowest necessary to maintain benefit for their condition. Patients who are stable, or who have reached the maximum therapeutic response, should have a trial of dose reduction (e.g., 25-50% reduction in dose every 3 months).
2. Patients who have tolerated dose reduction and continue to show sustained improvement (i.e. remission) should have a trial of treatment discontinuation; with the following exceptions:
    a. PID would be excluded from a trial of discontinuation
    b. HIV-infected children should show satisfactory control of the underlying disease [e.g., undetectable viral load, CD4 counts elevated above 200 or >15% (ages 9 months – 5 years) on antiretroviral therapy, etc.]
    c. Solid organ transplant, CLL, and MM patients should not be at an increased risk of infection

III. DOSAGE/ADMINISTRATION

Dosing should be calculated using adjusted body weight if one or more of the following criteria are met:

1. Patient's body mass index (BMI) is 30 kg/m^2 or more; **OR**
2. Patient's actual body weight is 20% higher than his or her ideal body weight (IBW)

Use the following dosing formulas to calculate the adjusted body weight (round dose to nearest 5-gram increment in adult patients):

Dosing formulas
BMI = 703 x (weight in pounds/height in inches^2)
IBW (kg) for males = 50 + [2.3 (height in inches – 60)]
IBW (kg) for females = 45.5 + [2.3 x (height in inches – 60)]
Adjusted body weight = IBW + 0.5 (actual body weight – IBW)

This information is not meant to replace clinical decision making when initiating or modifying medication therapy and should only be used as a guide. Patient-specific variables should be taken into account.

Indication	Dose
PID	200 to 800 mg/kg every 21 to 28 days
CIDP	2 g/kg divided over 2-5 days initially, then 1 g/kg administered in 1-2 infusions every 21 days
ITP	2 g/kg divided over 5 days or 1 g/kg once daily for 2 consecutive days in a 28-day cycle
FAIT	1 g/kg/week until delivery
Kawasaki's Disease (Pediatric Patients)	1 g/kg to 2 g/kg x 1 course
Multifocal Motor Neuropathy	Up to 2 g/kg divided over 5 days in a 28-day cycle
Acquired immune deficiency: CLL, MM and ALL	400 mg/kg every 3 to 4 weeks
Pediatric HIV	400 mg/kg every 2 to 4 weeks
Guillain-Barre	2 g/kg divided over 5 days x 1 course
Myasthenia Gravis	1-2 g/kg divided as either 0.5 g/kg daily x 2 days or 0.4 g/kg daily x 5 days x 1 course
Auto-immune blistering diseases	Up to 2 g/kg divided over 5 days in a 28-day cycle
Dermatomyositis/Polymyositis	2 g/kg divided over 2 to 5 days in a 28-day cycle
Bone Marrow or Stem Cell Transplant	500 mg/kg once weekly x 90 days, then 500 mg/kg every 3 to 4 weeks
Complications of transplanted solid organ: (kidney, liver, lung, heart, pancreas) transplant	2 g/kg divided over 5 days in a 28-day cycle
Stiff Person	2 g/kg divided over 5 days in a 28-day cycle

Indication	Dose
Toxic shock syndrome	2 g/kg divided over 5 days x 1 course
Neonatal Alloimmune Thrombocytopenia	1 g/kg x 1 dose, may be repeated once if needed
Management of Immune Checkpoint Inhibitor Related Toxicity	2 g/kg divided over 5 days x 1 course
PANDAS/PANS	2 g/kg (maximum dose up to 120 g) OR as supported by literature
Management of CAR T-Cell Related Toxicity	400-500 mg/kg every 28 days
**Dosing for IVIG is highly variable depending on numerous patient specific factors, indication(s), and the specific product selected. For specific dosing regimens refer to current prescribing literature.*	

IV. Limitations/Exclusions

Immune Globulins (immunoglobulin) is not considered medically necessary for indications other than those listed above due to insufficient evidence of therapeutic value.

Applicable Procedure Codes and Applicable NDCs:

Drug	Manufacturer	J-Code C-Code	1 Billable Unit Equivalent	IgG (grams) per SDV	NDC
Asceniv	ADMA Biologics	J1554	500 mg	5	69800-0250-XX
		C9072	500 mg		
Bivigam	Biotest Pharmaceuticals	J1556	500 mg	5	59730-6502-XX
				10	59730-6503-XX
Flebogamma 10% DIF	Instituto Grifols, S.A.	J1572	500 mg	5, 10, 20	61953-0005-XX
Flebogamma 5% DIF				2.5, 5, 10, 20	61953-0004-XX
Gamunex-C	Grifols Therapeutics	J1561	500 mg	1, 2.5, 5, 10, 20, 40	13533-0800-XX
Gammagard Liquid	Baxalta	J1569	500 mg	1, 2.5, 5, 10, 20, 30	00944-2700-XX
				5	00944-2656-XX

Gammagard S/D Less IGA	Baxalta	J1566	500 mg	10	00944-2658-XX
Gammaked	Grifols Therapeutics	J1561	500 mg	1, 2.5, 5, 10, 20	76125-0900-XX
Gammaplex 5%	Bio Products Laboratory	J1557	500 mg	5, 10, 20	64208-8234-XX
Gammaplex 10%				5, 10, 20	64208-8235-XX
Octagam 10%	Octapharma USA Inc	J1568	500 mg	2, 5, 10, 20	68982-0850-XX
Octagam 5%				1, 2.5, 5, 10, 25	68982-0840-XX
Privigen	CSL Behring LLC	J1459	500 mg	5	44206-0436-XX
				10	44206-0437-XX
				20	44206-0438-XX
				40	44206-0439-XX
Panzyga	Octapharma USA Inc	J1599	500mg	1, 2.5, 5, 10, 20, 30	68982-0820-XX
Injection, immune globulin, intravenous, non-lyophilized (e.g., liquid), not otherwise specified	N/A	J1599	500 mg	N/A	N/A

ICD-10 Diagnoses

Code	Description
A48.3	Toxic shock syndrome
B20	Human immunodeficiency virus (HIV) disease
B25.0	Cytomegaloviral pneumonitis
B25.1	Cytomegaloviral hepatitis
B25.2	Cytomegaloviral pancreatitis
B25.8	Other cytomegaloviral diseases
B25.9	Cytomegaloviral disease, unspecified
C91.10	Chronic lymphocytic leukemia of B-cell type not having achieved remission

C91.11	Chronic lymphocytic leukemia of B-cell type in remission
C91.12	Chronic lymphocytic leukemia of B-cell type in relapse
C90.00	Multiple Myeloma not having achieved remission
C90.01	Multiple Myeloma in remission
C90.02	Multiple Myeloma in relapse
C90.10	Plasma cell leukemia not having achieved remission
C90.11	Plasma cell leukemia in remission
C90.12	Plasma cell leukemia in relapse
C90.00	Acute lymphoblastic leukemia not having achieved remission
C90.01	Acute lymphoblastic leukemia, in remission
C90.02	Acute lymphoblastic leukemia, in relapse
D69.3	Immune thrombocytopenic purpura
D69.41	Evans syndrome
D69.42	Congenital and hereditary thrombocytopenic purpura
D69.49	Other primary thrombocytopenia
D69.59	Other secondary thrombocytopenia
D80.0	Hereditary hypogammaglobulinemia
D80.1	Nonfamilial hypogammaglobulinemia
D80.3	Selective deficiency of immunoglobulin G [IgG] subclasses
D80.5	Immunodeficiency with increased immunoglobulin M [IgM]
D80.7	Transient hypogammaglobulinemia of infancy
D81.0	Severe combined immunodeficiency [SCID] with reticular dysgenesis
D81.1	Severe combined immunodeficiency [SCID] with low T- and B-cell numbers
D81.2	Severe combined immunodeficiency [SCID] with low or normal B-cell numbers
D81.6	Major histocompatibility complex class I deficiency
D81.7	Major histocompatibility complex class II deficiency
D81.89	Other combined immunodeficiencies
D81.9	Combined immunodeficiency, unspecified
D82.0	Wiskott-Aldrich syndrome
D82.1	DiGeorge's syndrome
D83.0	Common variable immunodeficiency with predominant abnormalities of B-cell numbers and function
D83.2	Common variable immunodeficiency with autoantibodies to B- or T-cells
D83.8	Other common variable immunodeficiencies
D83.9	Common variable immunodeficiency, unspecified
D89.81	Acute graft-versus-host disease
D89.81	Acute on chronic graft-versus-host disease
D89.89	Other specified disorders involving the immune mechanism, not elsewhere classified
G03.8	Meningitis due to other specified causes
G03.9	Meningitis, unspecified
G04.81	Other encephalitis and encephalomyelitis
G04.89	Other myelitis
G04.90	Encephalitis and encephalomyelitis, unspecified
G04.91	Myelitis, unspecified
G25.82	Stiff-man syndrome
G35	Multiple Sclerosis
G56.80	Other specified mononeuropathies of unspecified upper limb

G56.81	Other specified mononeuropathies of right upper limb
G56.82	Other specified mononeuropathies of left upper limb
G56.83	Other specified mononeuropathies of bilateral upper limbs
G56.90	Unspecified mononeuropathy of unspecified upper limb
G56.91	Unspecified mononeuropathy of right upper limb
G56.92	Unspecified mononeuropathy of left upper limb
G56.93	Unspecified mononeuropathy of bilateral upper limbs
G57.80	Other specified mononeuropathies of unspecified lower limb
G57.81	Other specified mononeuropathies of right lower limb
G57.82	Other specified mononeuropathies of left lower limb
G57.83	Other specified mononeuropathies of bilateral lower limbs
G57.90	Unspecified mononeuropathy of unspecified lower limb
G57.91	Unspecified mononeuropathy of right lower limb
G57.92	Unspecified mononeuropathy of left lower limb
G57.93	Unspecified mononeuropathy of bilateral lower limbs
G61.0	Guillain-Barre syndrome
G61.1	Serum neuropathy
G61.81	Chronic inflammatory demyelinating polyneuritis
G61.82	Multifocal motor neuropathy
G61.89	Other inflammatory polyneuropathies
G61.9	Inflammatory polyneuropathy, unspecified
G62.89	Other specified polyneuropathies
G70.00	Myasthenia gravis without (acute) exacerbation
G70.01	Myasthenia gravis with (acute) exacerbation
G90.09	Other idiopathic peripheral autonomic neuropathy
J70.2	Acute drug-induced interstitial lung disorders
J70.4	Drug-induced interstitial lung disorders, unspecified
L10.0	Pemphigus vulgaris
L10.2	Pemphigus foliaceous
L12.0	Bullous pemphigoid
L12.1	Cicatricial pemphigoid
L12.30	Acquired epidermolysis bullosa, unspecified
L12.31	Epidermolysis bullosa due to drug
L12.35	Other acquired epidermolysis bullosa
L12.5	Other acquired epidermolysis bullosa
L13.8	Other specified bullous disorders
M30.3	Mucocutaneous lymph node syndrome [Kawasaki]
M33.00	Juvenile dermatomyositis, organ involvement unspecified
M33.01	Juvenile dermatomyositis with respiratory involvement
M33.02	Juvenile dermatomyositis with myopathy
M33.03	Juvenile dermatomyositis without myopathy
M33.09	Juvenile dermatomyositis with other organ involvement
M33.10	Other dermatomyositis, organ involvement unspecified
M33.11	Other dermatomyositis with respiratory involvement
M33.12	Other dermatomyositis with myopathy
M33.13	Other dermatomyositis without myopathy

M33.19	Other dermatomyositis with other organ involvement
M33.20	Polymyositis, organ involvement unspecified
M33.21	Polymyositis with respiratory involvement
M33.22	Polymyositis with myopathy
M33.29	Polymyositis with other organ involvement
M33.90	Dermatopolymyositis, unspecified, organ involvement unspecified
M33.91	Dermatopolymyositis, unspecified with respiratory involvement
M33.92	Dermatopolymyositis, unspecified with myopathy
M33.93	Dermatopolymyositis, unspecified without myopathy
M33.99	Dermatopolymyositis, unspecified with other organ involvement
M36.0	Dermato(poly)myositis in neoplastic disease
O26.40	Herpes gestationis, unspecified trimester
O26.41	Herpes gestationis, first trimester
O26.42	Herpes gestationis, second trimester
O26.43	Herpes gestationis, third trimester
P61.0	Transient neonatal thrombocytopenia
T86.00	Unspecified complication of bone marrow transplant
T86.01	Bone marrow transplant rejection
T86.02	Bone marrow transplant failure
T86.03	Bone marrow transplant infection
T86.09	Other complications of bone marrow transplant
T86.10	Unspecified complication of kidney transplant
T86.11	Kidney transplant rejection
T86.12	Kidney transplant failure
T86.13	Kidney transplant infection
T86.19	Other complication of kidney transplant
T86.20	Unspecified complication of heart transplant
T86.21	Heart transplant rejection
T86.22	Heart transplant failure
T86.23	Heart transplant infection
T86.290	Cardiac allograft vasculopathy
T86.298	Other complications of heart transplant
T86.30	Unspecified complication of heart-lung transplant
T86.31	Heart-lung transplant rejection
T86.32	Heart-lung transplant failure
T86.33	Heart-lung transplant infection
T86.39	Other complications of heart-lung transplant
T86.40	Unspecified complication of liver transplant
T86.41	Liver transplant rejection
T86.42	Liver transplant failure
T86.43	Liver transplant infection
T86.49	Other complications of liver transplant
T86.810	Lung transplant rejection
T86.811	Lung transplant failure
T86.812	Lung transplant infection
T86.818	Other complications of lung transplant

T86.819	Unspecified complication of lung transplant
T86.890	Other transplanted tissue rejection
T86.891	Other transplanted tissue failure
T86.892	Other transplanted tissue infection
T86.898	Other complications of other transplanted tissue
T86.899	Unspecified complication of other transplanted tissue
Z48.21	Encounter for aftercare following heart transplant
Z48.22	Encounter for aftercare following kidney transplant
Z48.23	Encounter for aftercare following liver transplant
Z48.24	Encounter for aftercare following lung transplant
Z48.280	Encounter for aftercare following heart-lung transplant
Z48.290	Encounter for aftercare following bone marrow transplant
Z94.0	Kidney transplant status
Z94.1	Heart transplant status
Z94.2	Lung transplant status
Z94.3	Heart and lungs transplant status
Z94.4	Liver transplant status
Z94.81	Bone marrow transplant status
Z94.83	Pancreas transplant status
Z94.84	Stem cells transplant status

Revision History

Company(ies)	DATE	REVISION
EmblemHealth & ConnectiCare	2/16/2024	Annual Review: no criteria changes
EmblemHealth & ConnectiCare	6/23/2023	Annual Review: Dosage Limits chart: added “Management of CAR T-Cell-Related Toxicity” Chronic Inflammatory Demyelinating Polyneuropathy (CIDP): Initial Criteria: Removed “4. Cerebrospinal fluid analysis indicates the following: a. CSF white cell count of <10 cells/mm3; AND b. CSF protein is elevated; AND” Multifocal Motor Neuropathy: Initial Criteria: Removed ” Patient has progressive, multi-focal, weakness (without sensory symptoms); AND” replaced with “Patient has progressive, focal, asymmetric weakness (without sensory symptoms) for > 1 month; AND” Removed “Complete or partial conduction block or abnormal temporal dispersion conduction must be present in at least 2 nerves with accompanying normal sensory nerve conduction study across the same nerve that demonstrated the conduction block; AND” Replaced with “Complete or partial conduction block or abnormal temporal dispersion conduction must be present in at least 2 motor nerves AND” Added “Patient has normal sensory nerve conduction on all nerves tested; AND” Allogeneic Bone Marrow or Stem Cell Transplant: Initial Criteria: Removed “Patient’s BMT was allogeneic; AND” and replaced with

		"Patient's BMT or hematopoietic stem cell (HSCT) transplant was allogeneic; AND" Acquired Immune Deficiency secondary to Acute Lymphoblastic Leukemia (ALL): Initial Criteria: Removed "Patient age is less than 18 years old; AND"Management of Immune-Checkpoint-Inhibitor Related Toxicity: Initial Criteria: Removed a. "Myasthenia gravis refractory to high-dose corticosteroids b. Severe transverse myelitis c. Moderate or severe Guillain-Barre Syndrome or peripheral neuropathy toxicity used in combination with pulse-dose methylprednisolone d. Severe pneumonitis refractory to methylprednisolone after 48 hours of therapy e. Encephalitis used in combination with pulse-dose methylprednisolone" Replaced with "a. Severe (G3) or life-threatening (G4) bullous dermatitis as an adjunct to rituximab b.Stevens-Johnson syndrome (SJS) c. Toxic epidermal necrolysis (TEN) d. Severe (G3-4) myasthenia gravis e. Transverse myelitis f. Myocarditis as further intervention if no improvement within 24-48 hours of starting pulse-dose methylprednisolone g. Moderate (G2) or severe (G3-4) Guillain-Barre Syndrome or severe (G3-4) peripheral neuropathy used in combination with pulse-dose methylprednisolone h. Moderate (G2) pneumonitis if no improvement after 48-72 hours of corticosteroids i. Severe (G3-4) pneumonitis if no improvement after 48 hours of methylprednisolone j. Encephalitis used in combination with pulse-dose methylprednisolone for severe or progressing symptoms or if oligoclonal bands are present k. Moderate, severe, or life-threatening steroid-refractory myalgias or myositis" Removed Relapsing-Remitting Multiple Sclerosis Initial Criteria Added: Management of CAR T-Cell-Related Toxicity Initial Criteria and renewal criteria Removed Carimune from Reference chart Chronic Immune Thrombocytopenia/ITP Renewal Criteria Removed: "Disease response as indicated by the achievement and maintenance of a platelet count of at least 50 X 10^9/L as necessary to reduce the risk for bleeding" Replaced with "Disease response as indicated by the achievement and maintenance of a platelet count of at least 30 X 10^9/L and at least doubling the baseline platelet count"

		HIV Infected Children Renewal Criteria: Added "necessitating continued therapy as evidenced by an IgG level < 400 mg/dL"
EmblemHealth & ConnectiCare	7/22/2022	Transferred policy to new template
EmblemHealth & ConnectiCare	4/7/2022	Removed Site of Service language. Refer to Site of Service policy effective 7/1/2022
EmblemHealth & ConnectiCare	7/22/2021	Added PANDAS/PANS coverage as per Massachusetts DOI Bulletin 2021-06 for Massachusetts residents under the Commercial line of business, starting 1/1/2022
EmblemHealth & ConnectiCare	7/2/2021	Updated Asceniv code to J1554
EmblemHealth & ConnectiCare	4/6/2021	Removed BUN/SCr requirement from criteria
EmblemHealth & ConnectiCare	1/1/2021	Added C-Code: C9072 Injection, immune globulin (Asceniv), 500 mg
EmblemHealth & ConnectiCare	9/11/2020	Removed the following statement from Renewal criteria: Patient continues to meet criteria identified in section I above;
EmblemHealth & ConnectiCare	02/06/2020	For myasthenia gravis indication, we changed the approval from 1 course per 28 days and cannot be renewed. To 1 course per 28 days and it can be renewed on a case-by-case basis (approved in Medical Policy Subcommittee on 02/06/2020).
EmblemHealth & ConnectiCare	01/26/2020	Added Asceniv J-code J1599 and applicable NDC
EmblemHealth & ConnectiCare	09/11/2019	Added Mandatory Site of Service, effective 04/01/2020 (Effected lines of business: Commercial and Healthcare Exchange). Other lines of business pending further review.

References

1. Asceniv® [package insert]. Boca Raton, FL: ADMA Biologics; April 2019. Accessed January 2020.
2. Bivigam™ [package insert]. Boca Raton, FL; Biotest Pharmaceuticals; April 2019.
3. Carimune®NF [package insert]. Berne, Switzerland; CSL Behring AG; November 2016. Accessed August 2018.
4. Flebogamma® 10% DIF [package insert]. Barcelona, Spain; Instituto Grifols, S.A.; March 2019
5. Flebogamma® 5% DIF [package insert]. Barcelona, Spain; Instituto Grifols, S.A.; March 2019
6. Gammagard Liquid [package insert]. Westlake Village, CA; Baxalta US Inc.; June 2016.
7. Gammagard S/D Less IgA [package insert]. Westlake Village, CA; Baxalta US Inc.; September 2016.
8. Gamunex®-C [package insert]. Research Triangle, NC; Grifols Therapeutics, Inc.; June 2018.
9. Gammaked™ [package insert]. Research Triangle, NC; Grifols Therapeutics, Inc; June 2018
10. Gammaplex® 5% [package insert]. Durham, NC; Bio Products Laboratory Ltd.; December 2018. Gammaplex® 10% [package insert]. Durham, NC; Bio Products Laboratory Ltd.; December 2018.
11. Octagam® 5% [package insert]. Hoboken, NJ; Octapharma USA Inc; November 2018.
12. Octagam® 10% [package insert]. Hoboken, NJ; Octapharma USA Inc; November 2018.

13. Privigen® [package insert]. Berne, Switzerland; CSL Behring LLC; March 2019.
14. Panzyga® [package insert]. Hoboken, NJ; Octapharma USA Inc; January 2019.
15. Skeie GO, Apostolski S, Evoli A, et al. Guidelines for the treatment of autoimmune neuromuscular transmission disorders. Eur J Neurol. 2010;17(7):893-902.
16. Van den Bergh PY, Hadden RD, Bouche P, et al. European Federation of Neurological Societies/Peripheral Nerve Society guideline on management of chronic inflammatory demyelinating polyradiculoneuropathy: report of a joint task force of the European Federation of Neurological Societies [trunc]. Eur J Neurol 2010 Mar;17(3):356-63
17. Patwa HS, Chaudhry V, Katzberg H, et al. Evidence-based guideline: intravenous immunoglobulin in the treatment of neuromuscular disorders: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology. 2012 Mar 27;78(13):1009-15.
18. French CIDP Study Group. Recommendations on diagnostic strategies for chronic inflammatory demyelinating polyradiculoneuropathy. J Neurol Neurosurg Psychiatry 2008; 79: 115–118.
19. Donofrio PD, Berger A, Brannagan TH, et al. Consensus statement: The use of intravenous immunoglobulin in the treatment of neuromuscular conditions report of the AANEM ad hoc committee. Muscle Nerve. 2009; 40:890-900.
20. Feasby T, Banwell B, Benstead T, et al. Guidelines on the use of intravenous immune globulin for neurologic conditions. Transfus Med Rev. 2007;21(2 suppl 1): S57-107.
21. Gajdos P, Tranchant C, Clair B, et al; Myasthenia Gravis Clinical Study Group. Treatment of myasthenia gravis exacerbation with intravenous immunoglobulin: a randomized double-blind clinical trial. Arch Neurol. 2005;62(11):1689-1693.
22. Elovaara I, et al. EFNS guidelines for the use of intravenous immunoglobulin in treatment of neurological diseases: EFNS task force on the use of intravenous immunoglobulin in treatment of neurological diseases. European Journal of Neurology 2008;15(9):893-908.
23. Joint Task Force of the EFNS and the PNS. European Federation of Neurological Societies/Peripheral Nerve Society guideline on management of multifocal motor neuropathy. Report of a joint task force of the European Federation of Neurological Societies and the Peripheral Nerve Society--first revision. J Peripher Nerv Syst. 2010 Dec;15(4):295-301. doi: 10.1111/j.1529-8027.2010.00290. x.
24. Hahn AF, Bolton CF, Pillay N, et al. Plasma exchange therapy in chronic inflammatory demyelinating polyneuropathy. A double-blind, sham controlled, cross-over study. Brain 1996; 119:1055–66.
25. The National Institute of Child Health and Human Developments Intravenous Immunoglobulin Study Group. Intravenous immune globulin for the prevention of bacterial infections in children with symptomatic human immunodeficiency virus infection. N Engl J Med. 1991 Jul 11;325(2):73-80.
26. Silberry GK, Abzug MJ, Nachman, S, et al. Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Exposed and HIV-Infected Children: Recommendations from the National Institutes of Health, Centers for Disease Control and Prevention, the HIV Medicine Association of the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the American Academy of Pediatrics. J Pediatric Infect Dis Soc. 2013 Nov; 32 Suppl 2: i-KK4.
27. Wolfe GI, Barohn RJ, Foster BM, et al; Myasthenia Gravis-IVIG Study Group. Randomized, controlled trial of intravenous immunoglobulin in myasthenia gravis. Muscle Nerve. 2002;26(4):549-552.
28. Hughes RA, Wijdicks EF, Barohn R, et al; Quality Standards Subcommittee of the American Academy of Neurology. Practice parameter: immunotherapy for Guillain-Barré syndrome: report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology. 2003;61(6):736-740.
29. Hughes RA, Swan AV, Raphael JC, Annane D, van Koningsveld R, van Doorn PA. Immunotherapy for Guillain-Barré syndrome: a systematic review. Brain. 2007;130(pt 9):2245-2257.
30. Bussel, JB et al. Antenatal management of alloimmune thrombocytopenia with Intravenous Immunoglobulin: A randomized trial of low dose steroid to intravenous immunoglobulin. Am J Obstet Gynecol 1996; 174 1414-23.

31. Ratko TA, Burnett DA, The Univ Hospital Consortium Expert Panel for the Off-label Use of Polyvalent Intravenously Administered Immunoglobulin Preparations, et al. Recommendations for the off-label use of intravenously administered immunoglobulin preparations. JAMA 1995; 273:1865-70.
32. Ahmed AR, Spigelman Z, Cavacine LA et al. Treatment of pemphigus vulgaris with rituximab and intravenous immune globulin. N Eng J Med 2006; 1772-9
33. American Academy of Pediatrics Subcommittee on Hyperbilirubinemia. Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. Pediatrics 2004; 114:297-316
34. Gottstein R, Cooke R. Systematic Review of intravenous immunoglobulin in haemolytic disease of the newborn. Arch Dis Child Fetal Neonatal Ed 2003; 88: F6-10
35. Anderson D, Ali K, Blanchette V, et al. Guidelines on the use of intravenous immune globulin for hematologic conditions. Transfus Med Rev. 2007;21(2 Suppl 1): S9-56.
36. Orange J, Hossny E, Weiler C, et al. Use of intravenous immunoglobulin in human disease: A review of evidence by members of the Primary Immunodeficiency Committee of the American Academy of Allergy, Asthma and Immunology. J Allergy Clin Immunol 2006;117(4 Suppl): S525-53.
37. Stasi R, Evangelista ML, Stipa E, et al. Idiopathic thrombocytopenic purpura: current concepts in pathophysiology and management. Thrombosis and Hemostasis 2008;99(1):4-13.
38. Amagai M, Ikeda S, Shimizu H, et al. A randomized, double-blind trial of intravenous immunoglobulin for pemphigus. J Am Acad Dermatol 2009; 60:595-602
39. Ahmed AR. Intravenous immunoglobulin therapy in the treatment of patients with pemphigus vulgaris unresponsive to conventional immunosuppressive treatment. J Am Acad Dermatol 2001; 45:679-90.
40. Hughes R, Bensa S, Willison H, Van den Bergh P, Comi G, Illa I, Nobile-Orazio E, van Doorn P, Dalakas M, Bojar M, Swan A; Inflammatory Neuropathy Cause and Treatment (INCAT) Group. Randomized controlled trial of intravenous immunoglobulin versus oral prednisolone in chronic inflammatory demyelinating polyradiculoneuropathy. Ann Neurol. 2001 Aug;50(2):195-201.
41. Zinman L, Ng E, Bril V. IV immunoglobulin in patients with myasthenia gravis: a randomized controlled trial. Neurology. 2007 Mar 13;68(11):837-41.
42. Koski CL, Baumgarten M, Magder LS, et al. Derivation and validation of diagnostic criteria for chronic inflammatory demyelinating polyneuropathy. Journal of the Neurological Sciences 2009; 277:1-8.
43. Sullivan KM, Storek J, Kopecky KJ, et al. A controlled trial of long-term administration of intravenous immunoglobulin to prevent late infection and chronic graft-vs.-host disease after marrow transplantation: clinical outcome and effect on subsequent immune recovery. Biol Blood Marrow Transplant 1996;2:44-53.
44. Alejandria MM, Lansang MA, Dans LF, Mantaring JB. Intravenous immunoglobulin for treating sepsis and septic shock. Cochrane Database Syst Rev 2002;CD001090.
45. American College of Obstetricians and Gynecologists (ACOG), Committee on Practice Bulletins -- Obstetrics. Thrombocytopenia in pregnancy. ACOG Practice Pattern No. 6. Washington, DC: ACOG; September 1999.
46. Centers for Disease Control and Prevention. Guidelines for preventing opportunistic infections among hematopoietic stem cell transplant recipients: recommendations of CDC, the Infectious Disease Society of America, and the American Society of Blood and Marrow Transplantation. MMWR 2000;49(No. RR-10):1-128.
47. Emerson GG, Herndon CN, Sreih AG. Thrombotic complications after intravenous immunoglobulin therapy in two patients. Pharmacotherapy. 2002; 22:1638-1641.
48. Department of Health (London). Clinical Guidelines for Immunoglobulin Use: Update to Second Edition. August, 2011.
49. Provan, Drew, et al. "Clinical guidelines for immunoglobulin use." Department of Health Publication, London (2008).
50. Sussman J, Farrugia ME, Maddison P, et al. Myasthenia gravis: Association of British Neurologists' management guidelines. Pract Neurol 2015; 15: 199-206.
51. Sanders DB, Wolfe GI, Benatar M, et al. International consensus guidance for management of myasthenia gravis-Executive Summary. Neurology. 2016 Jul 26; 87(4): 419-25.

52. Orange JS, Ballow M, Stiehm, et al. Use and interpretation of diagnostic vaccination in primary immunodeficiency: A working group report of the Basic and Clinical Immunology Interest Section of the American Academy of Allergy, Asthma & Immunology. J Allergy Clin Immunol Vol 130 (3).
53. Neunert C, Lim W, Crowther M, et al. The American Society of Hematology 2011 Evidence-based practice guidelines for immune thrombocytopenia. Blood April 2011; Vol 117 (16).
54. Jeffrey Modell Foundation Medical Advisory Board, 2013. 10 Warning Signs of Primary Immunodeficiency. Jeffrey Modell Foundation, New York, NY.
55. Bonilla FA, Khan DA, Ballas ZK, et al. Practice Parameter for the diagnosis and management of primary immunodeficiency. J Allergy Clin Immunol 2015 Nov;136(5):1186-205.e1-78.
56. Kuitwaard K, de Gelder J, Tio-Gillen AP, et al. Pharmacokinetics of intravenous immunoglobulin and outcome in Guillain-Barré syndrome. Ann Neurol. 2009;66(5):597.
57. 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.
58. 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.
59. Yuan XP, Wang CX, Gao W, et al: Kidney transplant in highly sensitized patients after desensitization with plasmapheresis and low-dose intravenous immunoglobulin. Exp Clin Transplant 2010; 8(2):130-135.
60. Jordan SC, Quartel AW, Czer LSC, et al: Posttransplant therapy using high-dose human immunoglobulin (intravenous gamma globulin) to control acute humoral rejection in renal and cardiac allograft recipients and potential mechanism of action. Transplantation 1998; 66(6):800-805.
61. Sullivan KM, Kopecky KJ, Jocom J, et al: Immunomodulatory and antimicrobial efficacy of intravenous immunoglobulin in bone marrow transplantation. N Engl J Med 1990; 323:705-712.
62. Bhatti AB, Gazali ZA. Recent Advances and Review on Treatment of Stiff Person Syndrome in Adults and Pediatric Patients. Cureus. 2015 Dec 22;7(12):e427
63. Tanimoto K, Nakano K, Kano S, et al. Classification criteria for polymyositis and dermatomyositis. J Rheumatol. 1995 Apr;22(4):668-74.
64. Kyriakides T, Angelini C, Schaefer J, et al. EFNS guidelines on the diagnostic approach to pauci- or asymptomatic hyperCKemia. Eur J Neurol. 2010 Jun 1;17(6):767-73.
65. Feliciani C, Joly P, Jonkman MF, et al. Management of bullous pemphigoid: the European Dermatology Forum consensus in collaboration with the European Academy of Dermatology and Venereology. Br J Dermatol. 2015 Apr;172(4):867-77.
66. Hertl M, Jedlickova H, Karpati S, et al. Pemphigus. S2 Guideline for diagnosis and treatment--guided by the European Dermatology Forum (EDF) in cooperation with the European Academy of Dermatology and Venereology (EADV). J Eur Acad Dermatol Venereol. 2015 Mar;29(3):405-14.
67. Harman KE, Albert S, Black MM; British Association of Dermatologists. Guidelines for the management of pemphigus vulgaris. Br J Dermatol. 2003 Nov;149(5):926-37.
68. Perez EE, Orange JS, Bonilla F, et al. Update on the use of immunoglobulin in human disease: A review of evidence. J Allergy Clin Immunol. 2017 Mar;139(3S):S1-S46.
69. Dantal J. Intravenous Immunoglobulins: In-Depth Review of Excipients and Acute Kidney Injury Risk. Am J Nephrol 2013;38:275-284.
70. Rajabally YA et al. Validity of diagnostic criteria for chronic inflammatory demyelinating polyneuropathy: A multicentre European study. J Neurol Neurosurg Psychiatry 2009 Dec; 80:1364.
71. Referenced with permission from the NCCN Drugs & Biologics Compendium (NCCN Compendium®) Management of Immunotherapy-Related Toxicities, Version 1.2018. National Comprehensive Cancer Network, 2018. The NCCN Compendium® is a derivative work of the NCCN Guidelines®. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc." To view the most recent and complete version of the Compendium, go online to NCCN.org. Accessed August 2018.

72. Postow, MA. Managing Immune Checkpoint-Blocking Antibody Side Effects. American Society of Clinical Oncology Education Book. 2015; 76-83.
73. Williams TJ, Benavides DR, Patrice KA. Association of Autoimmune Encephalitis with combined immune checkpoint inhibitor treatment for metastatic cancer. *JAMA Neurol* .928-933:(8)73;2016 doi:10.1001/jamaneurol.2016.1399
74. Tomblyn M, Chiller T, Einsele H, et al. Guidelines for preventing infectious complications among hematopoietic cell transplantation recipients: a global perspective. Biol Blood Marrow Transplant. 2009;15(10):1143-1238. doi: 10.1016/j.bbmt.2009.06.019. [PubMed 19747629]
75. Willison HJ, Jacobs BS, van Doom PA. Guillain-Barré Syndrome. Lancet. 2016 Aug;388(10045):717-27. Epub 2016 Mar 2
76. Sanders DB, Wolfe GI, Benetar M, et al. International consensus guidance for management of myasthenia gravis. Neurology 2016;87:1–7
77. Van Winkle P, Burchette R, Kim R, et al. Prevalence and Safety of Intravenous Immunoglobulin Administration During Maintenance Chemotherapy in Children with Acute Lymphoblastic Leukemia in First Complete Remission: A Health Maintenance Organization Perspective. Perm J. 2018; 22: 17-141.
78. First Coast Service Options, Inc. Local Coverage Determination (LCD): Intravenous Immune Globulin (L34007). Centers for Medicare & Medicaid Services, Inc. Updated on 4/13/2018 with effective date 4/12/2018. Accessed August 2018.
79. Noridian Administrative Services, LLC. Local Coverage Determination (LCD): Immune Globulin Intravenous (IVIg) (L34074; L34314). Centers for Medicare & Medicaid Services, Inc. Updated on 5/25/2018 with effective date 07/1/2018. Accessed August 2018.
80. Novitas Solutions, Inc. Local Coverage Determination (LCD): Intravenous Immune Globulin (IVIG) (L35093). Centers for Medicare & Medicaid Services, Inc. Updated on 7/20/2018 with effective date 4/13/2018. Accessed August 2018.
81. Wisconsin Physicians Service Insurance Corporation. Local Coverage Determination (LCD): Immune Globulins (L34771). Centers for Medicare & Medicaid Services, Inc. Updated on 12/19/2017 with effective date 1/1/2018. Accessed August 2018.
82. CGS, Administrators, LLC. Local Coverage Determination (LCD): Intravenous Immune Globulin (L35891). Centers for Medicare & Medicaid Services, Inc. Updated on 3/28/2018 with effective date 3/1/2018. Accessed August 2018.
83. Palmetto GBA. Local Coverage Determination (LCD): Intravenous Immunoglobulin (IVIG) (L34580). Centers for Medicare & Medicaid Services, Inc. Updated on 7/20/2018 with effective date 7/26/2018. Accessed August 2018.
84. National Coverage Determination (NCD) for Intravenous Immune Globulin for the Treatment of Autoimmune Mucocutaneous Blistering Diseases (250.3). Centers for Medicare and Medicaid Services, Inc. Updated on 12/01/2015 with effective date 10/1/2015. Accessed August 2018.
85. National Government Services, Inc. Local Coverage Article for Intravenous Immune Globulin (IVIG) - Related to LCD L33394 (A52446). Centers for Medicare & Medicaid Services, Inc. Updated on 9/22/2017 with effective date 10/7/2017. Accessed August 2018.
86. Noridian Healthcare Solutions, LLC. Local Coverage Article for Intravenous Immune Globulin (IVIG)-NCD 250.3 – Related to LCD L34314, L34074 (A54641, A54643). Centers for Medicare & Medicaid Services, Inc. Updated on 1/18/2017 with effective date 11/7/2015. Accessed August 2018.
87. Noridian Healthcare Solutions, LLC. Local Coverage Article: Coverage of Intravenous Immune Globulin for Treatment of Primary Immune Deficiency Diseases in the Home – Medicare Benefit Policy Manual, Chapter 15, (A54660, A54662). Centers for Medicare & Medicaid Services, Inc. Updated 4/2/2018 with effective date 4/12/2018. Accessed August 2018.
88. MA Senate Bill 2984 (Chapter 26 of the Acts of 2020) – An Act promoting a resilient health care system that puts patients first (the Act); passed by the Legislature on 12/23/2020; signed by Governor Baker on 1/1/202.
89. Jennifer Frankovich, Susan Swedo, Tanya Murphy, Russell C. Dale, Dritan Agalliu, Kyle Williams, Michael

Daines, Mady Hornig, Harry Chugani, Terence Sanger, Eyal Muscal, Mark Pasternack, Michael Cooperstock, Hayley Gans, Yujuan Zhang, Madeleine Cunningham, Gail Bernstein, Reuven Bromberg, Theresa Willett, Kayla Brown, Bahare Farhadian, Kiki Chang, Daniel Geller, Joseph Hernandez, Janell Sherr, Richard Shaw, Elizabeth Latimer, James Leckman, Margo Thienemann, and PANS/PANDAS Consortium.Journal of Child and Adolescent Psychopharmacology.Sep 2017.574-593.http://doi.org/10.1089/cap.2016.0148