Blue Cross Blue Shield Blue Care Network of Michigan

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Effective Date: 04/11/2024

Immune Globulin Replacement Therapy Medication Use Guidelines

Brand	HCPCS
Alyglo™	J3590
Asceniv™	J1599, J1554
Bivigam®	J1556
Carimune® NF	J1566
Cutaquig®	J1599
Cuvitru™ (SC only)	J1555 J7799 (Medicare Use) J1599 (Commercial)
Flebogamma® DIF	J1572
GamaSTAN® S/D (IM)	J1460/J1560 CPT /90281
Gammagard® Liquid (IV & SC)	J1569
Gammagard® S/D	J1569
Gammaked™ (IV & SC)	J1561
Gammaplex®	J1557
Gamunex®-C (IV & SC)	J1561
Hizentra® (SC only)	J1559
HyQvia® (SC only)	J1575
Octagam®	J1568
Panzyga®	J1576
Privigen®	J1459
Xembify®	J1558

Policy:

Requests must be supported by submission of chart notes and patient specific documentation.

A. Coverage of the requested drug is provided when all the following are met:
   a. Coverage for Cutaquip, Cuvitru and HyQvia is provided when used for FDA-approved indications only
   b. Acquired hemophilia A (acquired factor VIII inhibitor)
      i. Confirmation of diagnosis with ALL of the following:
         1. Factor VIII activity level of greater than 50% of normal for the reference range of the laboratory

2. Anti-human factor VIII inhibitor level greater than 0.6 BU/mL

ii. Trial and failure of ONE of the following:
1. Corticosteroids
2. Corticosteroids + cyclophosphamide
3. Corticosteroids + rituximab or a rituximab biosimilar

c. Allogeneic bone marrow transplant (BMT) recipients or patients treated with an anti-CD19 directed chimeric antigen receptor T-cell therapy (CAR-T)
i. Patients with moderate hypogammaglobulinemia evidenced by IgG laboratory findings or an inability to produce an antibody response to protein or carbohydrate antigens, receiving adequate prophylactic antibiotic therapy, and are still have recurrent infections
OR
ii. Patients with severe hypogammaglobulinemia evidenced by IgG laboratory findings

d. Autoimmune encephalitis
i. Patient has completed ALL of the following testing:
1. Cerebral spinal fluid (CSF) antibody testing
2. Electroencephalography (EEG) testing to exclude nonconvulsive seizures. Autoimmune encephalitis findings include but are not limited to: focal or generalized slowing, epileptiform activity, or periodic lateralized epileptiform discharges (PLEDs)
3. Brain magnetic resonance imaging (MRI) to exclude a cerebrovascular event or metastatic disease. Autoimmune encephalitis findings include but are not limited to: signal hyperintensities on fluid-attenuated inversion recovery (FLAIR) or T2-weighted images in affected brain regoins

ii. Other conditions have been ruled out

e. Autoimmune hemolytic anemia (AIHA)
i. Diagnosis of warm-type AIHA confirmed with ALL of the following:
1. Hemoglobin < 10 g/dL
2. Documented evidence of hemolysis, such as, elevated lactate dehydrogenase levels, decreased haptoglobin level, or schistocytosis
3. A direct agglutination (Coombs) test positive for IgG autoantibodies

ii. Trial and failure of TWO of the following:
1. Corticosteroids
2. Rituximab or a rituximab biosimilar
3. Azathioprine
4. Cyclosporin
5. Danazol
6. Mycophenolate mofetil
7. Splenectomy

f. Dermatomyositis
i. Adults
1. Both muscle and cutaneous symptoms are present
a) Trial and failure, contraindication, or intolerance to corticosteroids used in combination with either methotrexate or azathioprine
2. Only cutaneous symptoms are present (examples include: Gottron's sign, Gottron's papules, heliotrope eruption)
a) Failure of a three-month trial of each of the following unless contraindicated or not tolerated:
1) Hydroxychloroquine
2) Methotrexate
3) Mycophenolate mofetil

ii. Pediatrics
1. Trial and failure, contraindication, or intolerance to corticosteroids used in combination with either methotrexate or cyclosporine

g. Fetal alloimmune thrombocytopenia
i. For patients with a previous infant with thrombocytopenia but no intracranial hemorrhage, therapy should be initiated at 20 weeks gestation
ii. For patients with a previous fetus or neonate with intracranial hemorrhage, therapy should be initiated at 12 weeks gestation

h. HIV infected children
i. Less than 13 years of age
ii. Hypogammaglobulinemia evidenced by laboratory findings of low serum IgG

i. Hypogammaglobulinemia associated with either chronic lymphocytic leukemia (CLL), multiple myeloma, or anti-CD-20 monoclonal antibody B-cell lymphoma
i. Patient is receiving adequate prophylactic antibiotic therapy supported by NCCN guidelines
ii. Patient has a history of recurrent or persistent severe bacterial infections despite adequate treatment
iii. Patients with severe hypogammaglobulinemia evidenced by IgG laboratory findings
OR
Patients with an inability to produce an antibody response to protein or carbohydrate antigens

j. Hypogammaglobulinemic neonates
i. Patients with low birth weight of less than 1500 g
ii. Patients less than 30 days of age

k. Inflammatory demyelinating polyneuropathy (acute)
i. Significant functional disability, including but not limited to:
1. Deteriorating pulmonary function tests
2. Rapid deterioration with symptoms for less than 2 weeks
3. Rapidly deteriorating ability to ambulate
4. Inability to walk independently for 10 meters
ii. Documentation of elevated spinal fluid protein on lumbar puncture
1. If lumbar puncture is non-confirmatory:
a) Documentation of slowing of nerve conduction velocity on EMG/NCS; or
b) An MRI showing enlarged or enhancing nerves confirming the diagnosis

l. Inflammatory demyelinating polyneuropathy (chronic, CIDP)
i. Significant functional disability
ii. Definitive diagnosis based on the electrodiagnostic criterion from the Joint Task Force of the European Federation of Neurological Societies (EFNS)/Peripheral Nerve Society (PNS)
iii. If probable CIDP based on the electrodiagnostic criteria from the Joint Task Force of the EFNS/PNS, then documentation of elevated spinal fluid protein on lumbar puncture or an MRI showing enlarged or enhancing nerves confirming the diagnosis

m. Idiopathic thrombocytopenia purpura (ITP, acute)
i. Current platelet count < 20,000/µL
OR
ii. Current platelet count < 30,000/µL and symptoms of active bleeding

n. Idiopathic thrombocytopenia purpura (ITP, chronic)
i. Thrombocytopenia with a platelet count < 100,000/µL for at least 12 months
AND
ii. The patient's platelet count is currently dangerously low defined as, platelet count < 30,000/µL in children or < 20,000/µL in adults, for patients concurrently receiving corticosteroids or other 2nd line chronic ITP therapies

o. Idiopathic thrombocytopenia purpura in pregnancy
i. Platelet count < 10,000/µL in the 3rd trimester

OR

ii. Platelet count < 30,000/µL and bleeding
OR

iii. After steroid failure and ONE of the following:
1. Platelet count < 10,000/µL in the 1st or 2nd trimester
2. Platelet count < 30,000/µL, asymptomatic
OR

iv. Platelet count < 50,000/µL and patient requires a higher platelet count for an invasive procedure; i.e. planned cesarean delivery

p. Kawasaki syndrome during the first 10 days of diagnosis

q. Lambert-Eaton myasthenic syndrome
i. Treatment with at least one oral immunosuppressant is ineffective or not tolerated. Examples of oral immunosuppressants include prednisone, azathioprine, mycophenolate mofetil, and cyclosporine

r. Multifocal motor neuropathy (MMN)
i. Patient has nerve conduction studies demonstrating focal demyelination and conduction block in the motor nerves and normal sensory nerves
ii. Documentation of slowly progressive, focal, asymmetric limb weakness; that is, motor involvement in the motor nerve distribution of at least two nerves for more than one month
iii. Patient does not have objective sensory abnormalities except for minor vibration sense abnormalities in the lower limbs

s. Myasthenia gravis (MG)
i. Patient is experiencing an acute decompensation presenting as dyspnea or dysphagia
OR

ii. Patient has refractory disease defined as
1. Must demonstrate profound muscle weakness throughout the body resulting in one or more of the following:
a) Slurred speech
b) Impaired swallowing and choking
c) Double vision
d) Upper and lower extremity weakness
e) Disabling fatigue
f) Shortness of breath due to respiratory muscle weakness
g) Episodes of respiratory failure
2. Failure of corticosteroids and at least 2 or more immunosuppressive agents (for example: azathioprine, cyclosporine, mycophenolate mofetil, methotrexate, and tacrolimus)
OR

iii. Using preoperatively as a bridge to thymectomy in patients with persistent respiratory impairment or dysphagia despite treatment with pyridostigmine or immunosuppression

iv. Must not be using with other biologic therapies for myasthenia gravis

t. Pediatric intractable epilepsy
i. Patient is NOT a candidate for surgical resection
OR

ii. Other interventions are ineffective or not tolerated, including but are not limited to, anticonvulsant medications, ketogenic diets, vagus nerve stimulation, and steroids

u. Polymyositis (PM)
i. Trial and failure, contraindication, or intolerance to corticosteroids used in combination with either methotrexate or azathioprine

v. Post-transfusion purpura
i. History of transfusion of platelet-containing blood products occurring within 14 days prior to symptom onset

ii. Severe thrombocytopenia defined as less than 10,000 platelets/μL
iii. Presence of mucocutaneous bleeding; common sites of bleeding include, but are not limited to, mucous membranes, the gastrointestinal tract, and the urinary tract
iv. Identification of platelet antibodies in the patient's serum against one of the following human platelet antigens (HPA): HPA-2a, HPA-2b, HPA-3a, HPA-3b, HPA-4a, HPA-5a, HPA-5b, HPA-15b, or CD36/GPIV

w. Primary humoral immunodeficiency diseases
i. Transient hypogammaglobulinemia of infancy
1. Patients is 24 months of age or under at the time of symptom onset
2. Patients with severe hypogammaglobulinemia evidenced by IgG laboratory
3. Patient has a history of recurrent or persistent severe bacterial infections despite adequate treatment
ii. X-linked agammaglobulinemia (congenital agammaglobulinemia)
1. Patients with severe hypogammaglobulinemia evidenced by IgG laboratory
2. Patient has less than 2% CD19+ B cells
3. Patient has a mutation in the BTX gene
OR
Patient has absent BTK mRNA on Northern blot analysis of neutrophils or monocytes
OR
Patient has absent BTK protein in monocytes or platelets
OR
Patient has maternal cousins, uncles, or nephews with less than 2% CD19+ B cells
iii. Common variable immunodeficiency (CVID)
1. Patients with severe hypogammaglobulinemia, evidenced by IgG laboratory findings
2. Patients with an inability to produce an antibody response to protein or carbohydrate antigens
iv. Immunoglobulin subclass deficiency (e.g., X-Linked immunodeficiency with hyper-IgM)
1. Patients with an inability to produce an antibody response to protein or carbohydrate antigens
2. Patient has a history of recurrent or persistent severe bacterial infections despite adequate treatment
3. Patient has a deficiency of one or more IgG subclasses, assessed on two occasions
4. Patient has normal total serum IgG levels
5. Patient has aggressive management of other conditions predisposing to recurrent sinopulmonary infections
v. Combined immunodeficiency syndromes
1. Patients with a combined immunodeficiency confirmed by molecular genetic testing
OR
2. Patients with absent or below normal levels of both B- and T-lymphocytes AND an inability to produce an antibody response to protein or carbohydrate antigens
vi. Idiopathic hypogammaglobulinemia
1. Patients without a diagnosed primary immunodeficiency
2. Patients with severe hypogammaglobulinemia evidenced by IgG laboratory findings
3. Patients with an inability to produce an antibody response to protein or carbohydrate antigens
4. Patient has a history of recurrent or persistent severe bacterial infections despite adequate treatment, including all of the following:
a) Aggressive management of other conditions predisposing to recurrent sinopulmonary infections
b) Prophylactic antibiotics

x. Prophylactic post exposure for hepatitis A, measles (rubeola), varicella, and rubella in early pregnancy (GammaSTAN only)
    i. Hepatitis A within two weeks following exposure
        1. Not to be administered if clinical manifestations of hepatitis A are present
    ii. Measles (rubeola) within less than 6 days of exposure
        1. Must be a susceptible person (one who has not been vaccinated and has not had measles previously) or a pregnant woman without evidence of immunity
        2. Measles vaccine may not be co-administered with GamaSTAN
    iii. Varicella in immunosuppressed patients when varicella zoster immune globulin (human) is unavailable
    iv. Rubella in exposed pregnant women who will not consider a therapeutic abortion
y. Pure red cell aplasia (PRCA)
    i. Diagnosis of pure red cell aplasia confirmed with ALL of the following:
        1. Normocytic, normochromatic red blood cells
        2. Absolute reticulocyte count < 10,000/µL (< 1% reticulocytes)
        3. Normal white blood cell and platelet counts in the absence of a concurrent disorder such as chronic lymphocytic leukemia (CLL)
        4. Less than 1% erythroblasts on bone marrow differential count
        5. No significant abnormalities in the myeloid, lymphocytic, or megakaryocyte lineages, unless the patient has a concurrent diagnosis of CLL or chronic myeloid leukemia (CML)
    ii. Postive test for parvovirus B19
z. Refractory pemphigus foliaceus
    i. Diagnosis of pemphigus foliaceus as supported by ALL the following:
        1. Cutaneous lesions, including superficial blisters and/or scaly, crusted erosions, in seborrheic skin areas (i.e. chest, scalp, face, interscapular region)
        2. Subcorneal or granular layer acantholysis found on biopsy
        3. Demonstration of intercellular deposition of immunoglobulin G (IgG) and/or C3 on direct immunofluorescence (DIF) OR demonstration of IgG antibodies to desmoglein 1 on enzyme-linked immunosorbent assay (ELISA)
    ii. Trial and failure of systemic corticosteroids and at least one of the following after 6 - 8 weeks of treatment unless contraindicated or not tolerated: azathioprine, mycophenolate mofetil, mycophenolate sodium, or rituximab/rituximab biosimilar
aa. Solid organ transplant
    i. For the prevention of antibody mediated rejection prior to solid organ transplant when patient is at high risk for antibody-mediated rejection OR
    ii. Following solid organ transplant for the treatment of antibody-mediated rejection
bb. Stiff-Person Syndrome
    i. Trial and failure, contraindication, or intolerance to maximally tolerated doses of oral diazepam or oral clonazepam
    ii. Trial and failure, contraindication, or intolerance to maximally tolerated doses of oral baclofen
cc. Systemic lupus erythematosus
    i. Diagnosis of lupus thrombocytopenia requiring acute treatment with platelets less than 30,000/mm^3
    ii. Trial and failure of, contraindication, or intolerance to high-dose glucocorticoids
dd. Trial and failure, contraindication, OR intolerance to the preferred drugs as listed in BCBSM/BCN's utilization management medical drug list and/or BCBSM/BCN's prior authorization and step therapy documents
ee. BCBSM/BCN does not consider intravenous immune globulins to be self-administered medications and they are covered under the medical benefit. Subcutaneously administered immune globulin may be considered under the pharmacy benefit
ff. Subcutaneous and intravenous immune globulin products are not to be used in combination

B. Quantity Limitations, Authorization Period and Renewal Criteria
    a. Quantity Limits: Please refer to table 1 for intravenous products. For subcutaneous products, quantity limits align with FDA recommended dosing
    b. Authorization Period: Please refer to table 2
    c. Renewal Criteria: Please refer to table 2

C. Investigational Uses Including But Not Limited to:
    a. Acute lymphocytic leukemia
    b. Acute renal failure
    c. Adrenoleukodystrophy
    d. Adult HIV infection
    e. Alzheimer's disease
    f. Aplastic anemia
    g. Asthma
    h. Atopic dermatitis
    i. Autism
    j. Behçet's syndrome (Behçet's disease)
    k. Cardiomyopathy, recent-onset dilated
    l. Chronic fatigue syndrome
    m. Clostridium difficile, recurrent
    n. Cystic fibrosis
    o. Diabetes
    p. Diamond-Blackfan anemia
    q. Endotoxemia
    r. Heart block, congenital
    s. Hemolytic anemia
    t. Hemolytic transfusion reaction
    u. Hemophagocytic syndrome
    v. Human T-lymphocyte virus-1 myelopathy
    w. Hyper IgE syndrome
    x. Immune mediated neutropenia
    y. Inclusion body myositis
    z. Infectious disease in high risk neonates and adults following surgery or trauma
    aa. Lumbosacral plexopathy
    bb. Miller-Fisher syndrome
    cc. Motor neuron syndromes
    dd. Multiple sclerosis
    ee. Narcolepsy/cataplexy
    ff. Neonatal hemochromatosis
    gg. Neonatal hemolytic disease
    hh. Nephropathy, membranous
    ii. Nephrotic syndrome
    jj. Neuromyelitis optica
    kk. Nonimmune thrombocytopenia
    ll. Ophthalmopathy, euthyroid
    mm. Opsoclonus myoclonus
    nn. Otitis media, recurrent
    oo. Paraproteinemic neuropathy
    pp. Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS)
    qq. Polyneuritis
    rr. Post-polio syndrome

ss. Recurrent spontaneous pregnancy loss/abortion
tt. Rheumatoid arthritis
uu. Sinusitis, chronic
vv. Stevens-Johnson Syndrome
ww. Still's Disease
xx. Surgery or trauma
yy. Thrombotic Thrombocytopenic Purpura/Hemolytic Uremic Syndrome (TTP/HUS)
zz. Thrombotic Thrombocytopenic Purpura, neonatal autoimmune – severe thrombocytopenia (TTP)
aaa. Thrombotic Thrombocytopenic Purpura, refractory to platelet transfusions. (TTP)
bbb. Tic disorder (DSM-IV)
ccc. Toxic epidermal necrolysis
ddd. Urticaria, delayed pressure
eee. Uveitis
fff. Vasculitic syndromes, systemic
ggg. Von Willebrand's syndrome
hhh. Wegener's granulomatosis

Note: Requests for use of IVIG in non-FDA approved indications must include documentation of a trial and failure of standard therapies for that diagnosis when applicable.

***Note: Coverage and approval duration may differ for Medicare Part B members based on any applicable criteria outlined in Local Coverage Determinations (LCD) or National Coverage Determinations (NCD) as determined by Center for Medicare and Medicaid Services (CMS). See the CMS website at http://www.cms.hhs.gov/. Determination of coverage of Part B drugs is based on medically accepted indications which have supported citations included or approved for inclusion determined by CMS approved compendia.

Table 1. Dosing per Indication*

Indication	Dose**
Acquired Factor VIII inhibitor	1000 mg/kg for 2 days OR 400 mg/kg for 5 days
Allogeneic bone marrow transplant	500 mg/kg on day 7 and day 2 prior to transplantation and then once weekly thereafter for 90 days after transplantation
Autoimmune encephalitis	400 mg/kg/day for 5 days
Autoimmune hemolytic anemia	400 mg/kg/day for 5 days
Dermatomyositis	2000 mg/kg every month
Fetal alloimmune thrombocytopenia	1000 mg/kg every week, 2 g/kg/week in refractory cases
HIV + children (< 13 years)	400 mg/kg every 4 weeks
Hypogammaglobulinemia associated with chronic lymphocytic leukemia or multiple myeloma	400 mg/kg IV every 4 weeks
Hypogammaglobulinemic neonates	400 – 600 mg/kg/month, administered as a single dose, or up to several months in duration
Inflammatory demyelinating polyneuropathy (acute), including Guillain-Barré syndrome	400 mg/kg/day for 5 days
Inflammatory demyelinating polyneuropathy (chronic; CIDP)	Loading dose: 2000 mg/kg, given in divided doses over 2 - 4 consecutive days Maintenance dose: 1000 mg/kg every 3 weeks OR 500 mg/kg/day, for 2 consecutive days every 3 weeks 400 mg/kg/5 days, repeated every 6 weeks
ITP (acute)	1000 mg/kg/day for 2 consecutive days OR 400 mg/kg once daily for 2 - 5 consecutive days
ITP (chronic)	1 – 2 g/kg as a single dose or divided into equal amounts and given over 2 - 5 days
ITP in pregnancy	400 mg/kg/day for 5 days
Kawasaki syndrome	2000 mg/kg as a single dose OR 400 mg/kg/day for 4 days
Lambert-Eaton myasthenic syndrome	2000 mg/kg administered over 2 - 5 days
Multifocal motor neuropathy	2000 mg/kg/month administered over 2 - 5 days
Myasthenia gravis	1 - 2 g/kg/month IV given over 2 - 5 days
Pediatric intractable epilepsy	2000 mg/kg over 4 days followed by 1000 mg/kg over 2 days every month for 6 months
Polymyositis	2000 mg/kg/month given over 2 - 5 days
Post-transfusion purpura	500 mg/kg/day for 2 consecutive days
Primary humoral immunodeficiency diseases	100 – 800 mg/kg/month
Pure red cell aplasia	400 mg/kg/day for 5 - 10 days OR 2000 mg/kg/day for 5 days
Refractory pemphigus foliaceus	1 - 2 g/kg over 3 days every 4 weeks
Solid organ transplant	2000 mg/kg/month for 4 months
Stiff-Person Syndrome	400 mg/kg/day for 3 - 5 days
Systemic lupus erythematosus	400 mg/kg/day for 5 days

* Dosing must be based on ideal body weight (IBW) unless the patient's BMI is ≥ 30 kg/m^2 or actual body weight is greater than ideal body weight (IBW) by 20% or more, then adjusted body weight (adjBW) must be used.

** Initial dosing will be approved at the lower end of the dose range. Increase in dose and dosing interval will be authorized based on indication and literature support of the dose/dosing interval

Table 2. Authorization Period and Renewal Criteria

Indications	Frequency	Authorization Duration				Reauthorization	
	IVIG may be given no more frequently than:	60 days	3 months	6 months	1 year	Yes/ No	Criteria
Acquired Factor VIII inhibitor	One treatment per month			X		Yes	Documented initial response to IVIG and presence of factor VIII inhibitor
Allogeneic bone marrow transplant	On days 7 and 2 prior to transplant, then once weekly for up to 90 days (total therapy duration of 97 days)			X		Yes	Reauthorization may be considered under hypogammaglobulinemia criteria
Autoimmune encephalitis	One treatment per month			X			Documentation of clinical improvement
Autoimmune hemolytic anemia	One treatment per month			X		Yes	Documented initial response to IVIG and recurrence of clinically significant, symptomatic anemia
Dermatomyositis	One treatment per month		X			Yes	Objective evidence of efficacy of initial three-month treatment, such as improvement in muscle strength or decreased CPK levels
Fetal alloimmune thrombocytopenia (FAIT)	One treatment per month			X		Yes	Documented previous history of FAIT. Treatment not to exceed the duration of pregnancy
HIV + children	One treatment per month				X	Yes	Documentation of clinical improvement
Hypogammaglobulinemia associated with chronic lymphocytic leukemia or multiple myeloma	One treatment per month				X	Yes	Documentation of clinical improvement and current IgG levels that are in the low to normal range.
Hypogammaglobulinemic neonates	One treatment per month			X		Yes	Documentation of clinical improvement and current IgG levels that are in the low to normal range
Inflammatory demyelinating polyneuropathy (acute)	One treatment per month		X			No	N/A
Inflammatory demyelinating polyneuropathy (chronic; CIDP)	One treatment per month			X		Yes	Documented initial response to IVIG and evidence of functional improvement
ITP (acute)	Up to 4 doses given every other day			X		No	N/A

Indication	Frequency	Authorization Duration				Reauthorization	
	IVIG may be given no more frequently than:	60 days	3 months	6 months	1 year	Yes/ No	Criteria
ITP (chronic)	One treatment per month			X		Yes	Platelet count equal to or greater than 30,000/ mm^3 but no more than 150,000/mm^3, OR less than 30,000/mm^3 but platelets have increased from base-line accompanied by resolution of previous bleeding. IVIG treatment only covered until conventional therapy takes effect
ITP in pregnancy	One treatment per month		X			Yes	Platelet count (see policy criteria). Treatment is not to exceed the duration of pregnancy
Kawasaki syndrome	One treatment given within 10 days of symptom onset	X				No	N/A
Lambert-Eaton myasthenic syndrome	One treatment per month			X		Yes	Documented initial response to IVIG and measurable improvement in muscle function/strength
Multifocal motor neuropathy	One treatment per month			X		Yes	Documented initial response to IVIG and measurable improvement in muscle function/strength
Myasthenia gravis (acute and chronic)	One treatment per month			X		Yes	Documented initial response to IVIG and measurable improvement in muscle function/strength.
Pediatric intractable epilepsy	One treatment per month			X		Yes	Documented initial response to IVIG and significantly reduced frequency and/or duration of seizures
Polymyositis	One treatment per month		X			Yes	Objective evidence of the efficacy of initial 3-month treatment, such as improvement in muscle strength and/or decreased CPK levels
Post-transfusion purpura	One or two treatments	X				No	N/A
Primary humoral immunodeficiency diseases	One treatment per month				X	Yes	Documented initial response to IVIG, current IgG levels that are in the low to normal range, and evidence of clinical improvement
Pure red cell aplasia	One treatment per month			X		Yes	Documentation of initial response to IVIG, parvovirus, and recurrence of significant anemia
Refractory pemphigus foliaceus	One treatment per month			X		No	N/A

Indication	Frequency	Authorization Duration				Reauthorization	
	IVIG may be given no more frequently than:	60 days	3 months	6 months	1 year	Yes/ No	Criteria
Solid organ transplant	Up to 4 doses pre-transplant, then 1 dose weekly for 4 weeks post-transplant		X			No	N/A
Stiff-Person Syndrome	One treatment per month		X			Yes	Objective evidence of the efficacy of initial 3-month treatment, such as improvement in mobility, ability to perform work-related or household tasks, and decreased fall frequency
Systemic lupus erythematosus	One treatment per month			X		Yes	Documentation of initial response to IVIG and evidence of clinical improvement
GamaSTAN Only-Prophylactic Post Exposure - Medicare Only							
Hepatitis A	Once for < 3 month stay in endemic region. Repeat every 4 to 6 months for > 3 month stay in endemic region				X	Yes	Recommended for persons who plan to travel in areas where hepatitis A is common
Measles (Rubeola)	Once post suspected exposure if fewer than 6 days previously				X	Yes	Prevention or to modify measles in a susceptible person exposed fewer than 6 days previously
Varicella	Once immediately post exposure				X	Yes	When VZIG is unavailable, given promptly post exposure
Rubella	Once				X	Yes	Exposed women who will not consider a therapeutic abortion

Background Information:

- Acquired hemophilia A (AHA)

  - Acquired hemophilia A is characterized by neutralizing autoantibodies against factor VIII (FVIII). It is a rare disorder typically affecting pregnant women and those over the age of 60 years. Approximately half of patients have concomitant disorders, most often other autoimmune disorders or malignancy. In approximately 1 − 5% of cases, diagnosis occurs during pregnancy or within 1 year following childbirth. The bleeding phenotype of acquired FVIII inhibitors is variable ranging from life-threatening bleeds to mild or no bleeding. Subcutaneous hematomas are characteristic of AHA and can be the first indication of the disease.

  - The 2020 International Recommendations on the Diagnosis and Treatment of Acquired Hemophilia A and the 2017 Updated Review of Evidence and Treatment Guidance state AHA should be considered in patients with recent onset of abnormal bleeding, an isolated prolongation in activated partial thromboplastin time (aPTT), and normal prothrombin time (PT). It should also be considered in nonbleeding patients not on anticoagulation, with an isolated prolonged aPTT, a mixing study consistent with an inhibitor, and a negative

lupus anticoagulant (LA). Diagnosis is confirmed when FVIII activity is less than 50% of normal for the laboratory reference range and the patient has an anti-human factor VIII inhibitor level greater than 0.6 BU/mL.

- Immunosuppression therapy should be started in all adult patients with the goal of therapy to reduce the risk of bleeding by shortening the time to remission. Both the 2017 and 2020 guidance for treatment of AHA recommend use of corticosteroids alone or in combination with either cyclophosphamide or rituximab as first-line therapy. The 2020 guidelines recommend use of steroids alone in patients with FVIII level greater than or equal to 1% and an anti-human factor VIII inhibitor level less than or equal to 20 BU/mL. For patients with a FVIII level less than 1% and an anti-human factor VIII inhibitor level greater than 20 BU/mL, combination therapy should be started immediately. Therapy should continue for at least 4 weeks as 60 – 80% of patients will see an improvement in FVIII activity levels within that timeframe.

- Use of immunoglobin therapy is not recommended by either the 2020 or the 2017 guidance. However, it has been shown to possible be efficacious when used as part of the modified Bonn-Malmo Protocol (MBMP). The protocol combines immunoadsorption for inhibitor elimination, factor VIII substitution, intravenous immunoglobulin, and immunosuppression. During this protocol, patients received 0.3 g/kg/day of IVIG on days 5 – 7 of each 7 day treatment cycle. Treatment cycles were repeated several times, depending on the clinical response and the coagulation factor activity. In addition, one prospective, multicenter study of high-dose IGIV in 19 patients with AHA has been conducted. Patients received induction therapy with IGIV at a dose of 1,000 mg/kg x 2 consecutive days or 400 mg/kg x 5 consecutive days followed by maintenance doses at intervals as clinically indicated. The study showed some patients may experience beneficial effects and a decrease in anti-human factor VIII inhibitor levels with the use of IVIG.

- Allogeneic bone marrow transplant (BMT) recipients or patients treated with an anti-CD19 directed chimeric antigen receptor T-cell therapy (CAR-T)

    - Allogenic bone marrow transplant patients receive stem cells from another individual, either a matched related or an unrelated donor. These patients require both long- and short-term infection prevention measures depending on their degree of immunosuppression. Infection is the primary cause of death in approximately 17% to 20% of allogenic BMT patients. Treatment plans for infection prevention include individualized antimicrobial therapy, along with IVIG in select patients.

    - International Guidelines for Preventing Infectious Complications among Hematopoietic Cell Transplantation Recipients (2009) recommend against the routine use of IVIG within the first 100 days after BMT, citing a meta-analysis of randomized controlled trials showing no improvement in survival, infection prevention, or other transplant complications. In BMT patients with severe hypogammaglobulinemia, evidenced serum IgG less than 400 mg/dL, IVIG is recommended for the prevention of bacterial infection. Guidelines recommend against its use beyond 100 days after BMT in patients without severe hypogammaglobulinemia.

    - Recommended dosing for adult or adolescent BMT patients with severe hypogammaglobulinemia is 500 mg/kg/week. Recommended dosing for pediatric BMT patients with severe hypogammaglobulinemia is 400 mg/kg/week. Guidelines suggest monitoring serum IgG levels every 2 weeks for patients receiving IVIG therapy.

- Autoimmune encephalitis

    - The autoimmune encephalitis syndromes have a wide clinical spectrum that ranges from typical limbic encephalitis to syndromes with complex neuropsychiatric symptoms such as deficits of memory, cognition, psychosis, seizures, abnormal movements, or coma. This group of disorders is associated with antibodies to neuronal cell surface/synaptic proteins. The target antigens usually play critical roles in synaptic transmission and plasticity. Clinical features include prodromal headache, fever, prominent psychiatric manifestations, insomnia, memory deficits, seizures, decreased level of consciousness, frequent dyskinesias, autonomic instability, and language dysfunction.

    - Autoimmune encephalopathy should be suspected in those with symptoms accompanied by cerebrospinal fluid (CSF) lymphocytic pleocytosis or oligoclonal bands; electroencephalography (EEG) with infrequent epileptic activity but frequent slow, disorganized activity that does not correlate with most abnormal movements; and brain magnetic resonance imaging (MRI) that is often normal or shows transient fluid-attenuated inversion recovery (FLAIR) or contrast-enhancing abnormalities in cortical (brain, cerebellum) or subcortical (hippocampus, basal ganglia, white matter) regions. CSF examination should be performed to evaluate for antibodies and should include cell count, protein, glucose, and viral cultures. Studies to exclude other pathogens should also be performed. EEG should be performed to exclude nonconvulsive seizures. In patients with paraneoplastic and autoimmune encephalitis, nonspecific EEG abnormalities are common and include focal or generalized slowing, epileptiform activity, and periodic lateralized epileptiform discharges (PLEDs). MRI is helpful in this clinical setting to exclude a cerebrovascular event or metastatic disease among others. Characteristic MRI findings in patients with paraneoplastic or autoimmune encephalitis include signal hyperintensities on fluid-attenuated inversion recovery (FLAIR) or T2-weighted images in affected brain regions (eg, medial temporal lobes and/or brainstem); subcortical regions and the cerebellum are sometimes affected as well.

    - The differential diagnosis of this clinical presentation includes primary psychiatric disorders, malignant catatonia, neuroleptic malignant syndrome, viral encephalitis, and encephalitis lethargica and should be ruled out before confirming a diagnosis of autoimmune encephalitis.

    - Based on observational studies and clinical experience, initial treatment with intravenous methylprednisolone and either 400 mg/kg IVIG per day for five days or plasma exchange in most patients. An alternative approach to stepwise escalation of immunotherapy is to use rituximab in combination with steroids and IVIG or plasma exchange as initial therapy. This approach is gaining favor in severely affected patients based on clinical experience and accumulating data supporting the effectiveness of rituximab in reducing relapses when used in the second-line setting.

- Autoimmune hemolytic anemia (AIHA)

    - AIHA is a decompensated acquired haemolysis caused by the host's immune system acting against its own red blood cell antigens. Warm AIHA is the most common type and is caused by antibodies that are active at body temperature. Patients may present with symptoms of anemia, hemolysis, pallor, splenomegaly, hepatosplenomegaly, or hemoglobinuria. Specific symptoms that occur may vary from one person to another and may depend upon the rate of onset, the rate of destruction of healthy red blood cells and the presence of an underlying disorder.

    - The 2017 British Diagnosis and Management of Primary Autoimmune Hemolytic Anemia guidelines state AIHA should be suspected based upon a thorough clinical evaluation, a detailed patient history, identification of characteristic symptoms, and a variety of tests. To confirm a diagnosis of warm AIHA, patients should have a hemoglobin less than 10 g/dL and also symptoms of hemolysis including increased

bilirubin, increased reticulocytes, decreased haptoglobin, normal or elevated lactate dehydrogenase, urinary hemosiderin, and/or blood in the urine. In addition, guidelines state patients should have a direct agglutination (Coombs) test performed and it should show they are positive for IgG autoantibodies.

- Immunosuppression therapy should be started in all patients with the goal of therapy to induce remission. The 2017 guidance for treatment of AIHA recommend use of corticosteroids alone as first-line treatment. If there is no response to steroids, rituximab should be started as second-line therapy. Third-line therapies include azathioprine, cyclosporin, danazol, mycophenolate mofetil, or splenectomy. The half-life of autoantibodies is approximately 2 – 3 weeks, so even if therapy halts production of autoantibodies, patients may still experience hemolysis for 2 – 3 weeks following therapy initiation. Therefore, patients should try each line of therapy for at least 21 days before failure is considered.

- Regular use of immunoglobin therapy is not recommended by the 2017 guidance. However, the guidelines do state IVIG may be useful in emergency situations. Evidence from case studies suggest 40% of patients respond to IVIG 0.4 – 0.5 g/kg/day for 5 days and most responders maintained their hemoglobin levels for greater than or equal to 3 weeks. Emergent treatment with IVIG is considered in the guidelines as short term treatment when patients have a pre-treatment hemoglobin level of less than 6 g/dL or as a temporizing measure prior to splenectomy.

- Dermatomyositis

  - Dermatomyositis (DM) is an idiopathic immune-mediated myopathy that can occur in children and adults. It commonly presents with progressive, symmetric, proximal muscle weakness and muscle inflammation that can affect a patient's ability to walk, run, and pick themselves up after a fall. Weakness typically begins with muscles closest to and within the trunk of the body, such as the neck, hip, back, and shoulder muscles. In addition to muscle symptomology, patients with DM typically present with a rash which is a key distinguishing feature of DM compared to polymyositis. Pathognomonic cutaneous features of DM are a heliotrope rash and Gottron's papules. Gottron's papules may resemble lesions of lupus erythematosus, lichen planus, or psoriasis; however, a heliotrope rash is rare in other disorders and therefore highly suggestive of dermatomyositis if present. Additional characteristic cutaneous features of DM include Gottron's sign, photodistributed erythema, nailfold changes, poikiloderma, psoriaform changes in the scalp, and calcinosis cutis. Systemic manifestations may also occur and include, but are not limited to, gastrointestinal ulcers, interstitial lung disease, dysphagia, and malignancy in adults. Most patients with DM exhibit both cutaneous disease and muscle weakness (classic DM), though the onset of cutaneous manifestations can precede myositis by several months in 30% of these patients or follow shortly after muscle involvement in about 10%. Cutaneous manifestations of DM may persist after successfully treating DM-associated myositis in patients with classic DM; these patients are termed as having post-myopathic DM. Additionally, a subset of patients may develop the characteristic cutaneous manifestations in the absence of muscle symptoms or related laboratory findings. These patients have a distinct form of DM referred to as clinically amyopathic DM and account for about 20% of patients with DM.

  - Diagnosis of DM is primarily clinical, generally depending on the presence of characteristic clinical and laboratory findings and may include laboratory tests, imaging studies, electromyography (EMG), and skin and/or muscle biopsy. Tests needed to aid in establishing a diagnosis vary between groups of patients depending on their presentation (i.e. highly characteristic clinical presentation, muscle weakness and nonspecific but typical findings, atypical findings, or cutaneous features without weakness). It is essential that DM be distinguished from other conditions that cause muscle weakness and/or a similar cutaneous presentation. Differential diagnoses may include but are not limited to drug-induced myopathy, myasthenia gravis, discoid lupus erythematosus, lichen planus, psoriasis, rosacea, sarcoidosis, discoid lupus erythematosus, graft versus host disease, subacute cutaneous lupus erythematosus, systemic lupus erythematosus, and tinea corporis.

- Classification criteria have been used historically for diagnostic purposes. These criteria have defined DM primarily for clinical and epidemiologic research and are useful for clinicians to identify key features of disease; however, there are limitations to the sensitivity and specificity of these criteria for diagnostic purposes. Additionally, there is a lack of consistency as several sets of classification criteria have been published throughout the literature.

    - The European League Against Rheumatism (EULAR) and the American College of Rheumatology (ACR) revised classification criteria for adults and juvenile idiopathic inflammatory myopathies in 2017, which classifies patients as having definite, probable, and possible disease based on a score and corresponding probability of disease with two different scoring systems depending on whether a muscle biopsy was performed. The criteria include four variables related to muscle weakness, three related to skin manifestations, and others related to lab findings and other clinical manifestations. If a patient meets classification criteria for IIM, a classification tree further subclassifies patients as having amyopathic DM, DM, or juvenile DM.

    - The Myositis Association lists comprehensive diagnostic criteria on their website both for classic DM, amyopathic DM, and juvenile DM that has been developed based on research data and expert clinical experience.

    - Different DM expert groups have proposed classification criteria for DM that solely presents with cutaneous manifestations. A group of dermatology experts suggest biopsy-confirmed hallmark cutaneous manifestations of classic DM occurring for six months or more, no clinical evidence of proximal muscle weakness and no serum muscle enzyme abnormalities for at least 6 months, absence of exclusion criteria (i.e. systemic immunosuppressive therapy, use of drugs that may produce DM-like skin changes), and normal results for more extensive muscle testing if pursued. An expert group of neurologists and rheumatologists proposed similar criteria but also included electrophysiologic studies in their classification criteria.

- The goals of treatment are to improve muscle strength, to avoid the development of extramuscular complications, and resolution of cutaneous disease manifestations. Cutaneous manifestations of DM frequently respond to agents used to treat the associated myositis; however, they can persist despite the myositis effectively being treated and may require additional treatment.

- Glucocorticoids are considered first-line therapy. They are typically initiated with prednisone at a dose of 1 mg/kg per day (maximum daily dose of 80 mg) in adults and 2 mg/kg per day (maximum daily dose of 80 mg) in pediatric patients. A steroid-sparing immunosuppressive agent is generally started along with glucocorticoid treatment so the patient can eventually begin to taper their steroids. Methotrexate or azathioprine are the recommended steroid-sparing immunosuppressive agents for adults, while methotrexate is preferred for pediatric patients with cyclosporine as an alternative. Tapering of glucocorticoids is based on a combination of the improvement in muscle enzymes and recovery of muscle strength. Ideally, normalization of enzymes and complete recovery of muscle strength should occur before glucocorticoids are tapered. The initial response to glucocorticoids in the patient with DM typically takes four to six weeks for normalization of creatine kinase (CK) levels or three to four months to regain muscle strength.

- Some patients either relapse after an initial response to therapy or fail to respond to glucocorticoids and immunosuppressant therapy. These patients are considered to have recurrent or resistant disease. IVIG is considered the next step when the patient experiences recurrent or resistant disease after glucocorticoids and immunosuppressant therapy, and its use for refractory DM in adults is supported by the 2012 American Academy of Neurology guidelines for IVIG in the treatment of neuromuscular disorders.

- The efficacy of IVIG in adults was demonstrated in a double-blind, placebo-controlled trial of 15 DM patients with resistant disease who continued prednisone and were randomly assigned to a monthly IVIG infusion (2 g/kg) or placebo for 3 months. Patients assigned to IVIG all had significant improvement in their muscle strength and neuromuscular symptom scores.

- The benefits of IVIG in pediatric patients has been reported in multiple observational studies of children with juvenile DM who previously failed glucocorticoid therapy and in the majority of cases immunosuppressants as well. Reported patients experienced improvement in skin disease and muscle strength; additionally, use of IVIG reduced the cumulative glucocorticoid dose for most patients. IVIG was commonly dosed at 2 g/kg (maximum dose 70 g) as a single dose every two weeks for three doses, then monthly according to the childhood arthritis and rheumatology research alliance (CARRA) consensus clinical treatment plans for juvenile DM.

- Other therapies that have been shown to have some effectiveness in adults with refractory DM either alone or in combination with other treatment modalities include cyclosporine, mycophenolate mofetil, chlorambucil, and cyclophosphamide. For pediatric patients, cyclosporine has also shown some effectiveness in refractory juvenile DM, while a number of other therapies are considered investigational and require further studies to determine their role in juvenile DM.

- Adult patients with amyopathic DM or post-myopathic DM with persistent cutaneous lesions require additional treatment. A multifaceted approach is generally necessary to achieve a response for cutaneous DM. This includes photoprotection, antipruritic agents, topical corticosteroids or topical calcineurin inhibitors, and systemic medications. Skin lesions of DM are often resistant to photoprotection and topical therapies alone, therefore necessitating initiation of systemic therapy. Glucocorticoids have limited evidence for efficacy for cutaneous DM and are not generally advised if they are no longer required for extracutaneous manifestations of DM. For mild cutaneous DM (< 10% BSA, minimal pruritis), hydroxychloroquine is suggested as initial systemic therapy. Response should be evident after 6 - 12 weeks of treatment with a 3 month trial appropriate to assess treatment efficacy. Methotrexate may be added for patients whose response to hydroxychloroquine is inadequate or used alone if hydroxychloroquine cannot be tolerated. For severe cutaneous DM (> 10% BSA involvement, intolerable pruritis, or otherwise disabling disease) methotrexate is recommended as initial systemic therapy with improvement expected within 8 - 12 weeks. Hydroxychloroquine may subsequently be added if there is an insufficient response to methotrexate or the two can be started simultaneously depending on the clinician's experience. Once a satisfactory response is achieved with hydroxychloroquine or methotrexate and is maintained for several months, slow tapering should be initiated to the lowest dose necessary to maintain the response.

- Patients with amyopathic DM or post-myopathic DM who fail to respond to methotrexate and/or hydroxychloroquine or who relapse after an initial response have refractory cutaneous disease and require more aggressive immunomodulatory and immunosuppressive agents. IVIG and mycophenolate mofetil are considered treatments of choice for cutaneous DM refractory to conventional therapies. Comparative studies have not been performed between these agents.

    - IVIG is administered monthly as a 2 g/kg infusion with clinical improvement expected within 2 - 3 cycles, but full benefit to be realized after about 6 months. The interval between treatments is typically lengthened in a progressive fashion once the patient is at a complete or near complete clinical response, however, relapse may occur upon treatment discontinuation. Improvement in cutaneous DM was reported in a randomized, placebo-controlled trial evaluating 2 g/kg IVIG monthly for DM-related myositis. Marked improvement in skin disease occurred in 8 of 12 patients treated with IVIG in either the initial or crossover phase of the trial with improvement evident 15

days after the first infusion and peaking between the second and third. Retrospective studies, case reports, and case series further support IVIG in refractory DM.

- Mycophenolate mofetil for cutaneous DM is supported by uncontrolled studies and a case series. These studies suggest higher doses may be required to effectively treat cutaneous manifestations of DM. Mycophenolate mofetil is started as 500 mg twice daily for two weeks then titrated, if tolerated, up to 1.5 g twice daily with improvement in skin disease expected within two to three months of treatment. Due to the slow onset of action, overlapping treatment (i.e. with methotrexate) may reduce the risk of disease flares during titration. If the response is poor after three months, transitioning to alternative treatment is recommended.

- Other therapies for refractory cutaneous DM may include azathioprine, cyclosporine, cyclophosphamide, chlorambucil, and dapsone. There is a lack of strong evidence supporting these therapies which, along with the serious adverse effect profile associated with many of these agents, suggests that they may best be suited for patients who have failed or cannot receive IVIG or mycophenolate mofetil.

- Fetal alloimmune thrombocytopenia

  - Fetal alloimmune thrombocytopenia is the most common type of severe thrombocytopenia in fetuses and neonates. It results from incompatibility between parents for platelet-specific antigens. These antigens are inherited in the fetus in an autosomal codominant fashion. Fetal-maternal passage of platelets leads to the development of specific antibodies to the exposed antigen in the pregnant patient.

  - The diagnosis is usually made after an affected pregnancy when either severe unexplained thrombocytopenia presents in a neonate or fetal or neonatal intracranial hemorrhage is diagnosed in the presence of thrombocytopenia. Confirmation of the diagnosis requires both demonstration of platelet-specific antigen incompatibility between the parents or between the mother and the neonate and the presence of maternal antibodies against the involved antigen. The most significant complication of fetal alloimmune thrombocytopenia is intracranial hemorrhage.

  - Because the majority of intracranial hemorrhages occur before the onset of labor, treatment must be initiated antenatally to prevent them. Treating the mother with IVIG is the mainstay of therapy for fetal alloimmune thrombocytopenia. Depening of the severity of disease in prior pregnancies, the 2011 Fetal and Neonatal Alloimmune Thrombocytopenia Management Algoirithm recommend initiation of therapy should begin at different gestational timeframes.

    - When the mother has had an infant with thrombocytopenia but no intracranial hemorrhage, IVIG should be started at 20 weeks gestation at a dose of 2 g/kg/week or 1 g/kg/week with 0.5 mg/kg/day of prednisolone. At 32 weeks gestation, the dose of IVIG is increased to 2 g/kg/week and should be given with 0.5 mg/kg/day of prednisolone.

    - When the mother has had a previous fetus or neonate with intracranial hemorrhage diagnosed at 28 or more weeks of gestation, IVIG should be initiated at a dose of 1 g/kg/week at 12 weeks gestation. At 20 weeks, the dose of IVIG can be increased to 2 g/kg/week or 0.5 mg/kg/day prednisolone can be added to the patient's drug regimen. At 28 weeks gestation, the patient should receive 2 g/kg/week IVIG with 0.5 mg/kg/day prednisolone.

    - When the mother has had a previous fetus with intracranial hemorrhage diagnosed at less than 28 weeks of gestation, IVIG should be initiated at a dose of 2 g/kg/week at 12 weeks gestation. At 20

weeks gestation, 1 mg/kg/day prednisolone should be added to the patient's drug regimen until delivery.

- HIV infected children
    - HIV infected children are at increased risk of infections and prevention of infections is a critical component of care.
    - Current guidelines, encompassing recommendations from CDC, the National Institutes of Health, the HIV Medicine Association of the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the American Academy of Pediatrics, strongly recommend IVIG use among HIV-infected children who have hypogammaglobulinemia to prevent serious bacterial infections (SBIs). The recommendation is based on evidence from trials where IVIG has been shown to decrease the frequency of bacterial infections, increase the time free from serious bacterial infections, and decrease the frequency of hospitalization in children with AIDS. The guidelines cite the supporting evidence is from studies that include children or children/adolescents, but not studies limited to post-pubertal adolescents.
    - The recommended dose is 400 mg/kg every 2-4 weeks to maintain the serum IgG level.
- Hypogammaglobulinemia associated with either chronic lymphocytic leukemia (CLL), multiple myeloma, or anti-CD20 monoclonal antibody treated B-cell lymphoma
    - Chronic lymphocytic leukemia
        - Chronic lymphocytic leukemia patients are at increased risk of infections and require management with infection prevention and antibiotic prophylaxis. Infections are the most common complication and cause of death in CLL patients. Patients with advanced disease and hypogammaglobulinemia are at in increased risk of serious infections.
        - National Comprehensive Cancer Network (NCCN) Chronic Lymphocytic Leukemia 2020 guidelines recommend IVIG in CLL patients with reduced serum IgG levels and recurrent infections requiring intravenous antibiotics or hospitalization. It is only recommended in patients with severe hypogammaglobulinemia, evidenced by serum IgG less than 400 - 500 mg/dL. Recommended dosing is 400 mg/kg every 4 weeks. Patients should receive concomitant prophylactic antibiotic therapy in accordance with the 2020 NCCN guidelines for Prevention and Treatment of Cancer-Related Infections.
        - In addition, American Academy of Allergy, Asthma, and Immunology 2016 guidelines recommend IVIG in patients with CLL with recurrent serious bacterial infections, along with reduced IgG, and subprotective antibody levels following diphtheria, tetanus, or pneumococcal immunizations. Monitoring of serum IgG levels during treatment is recommended to determine the need for continuation of therapy.
    - Multiple myeloma
        - Patients with multiple myeloma are at an increased risk of infections throughout the stages of the disease. Infections are a significant cause of morbidity and mortality in these patients, particularly those with advanced disease and hypogammaglobulinemia. Comprehensive treatment plans include infection prevention precautions, prophylactic antibiotics, and, in select patients, IVIG.

- The 2020 Multiple Myeloma NCCN treatment guidelines recommend considering IVIG for patients with reduced serum IgG levels and recurrent, life-threatening infections. It is only recommended in patients with severe hypogammaglobulinemia, evidenced by serum IgG less than 400 - 500 mg/dL. Recommended dosing is 400 mg/kg every 4 weeks. Patients should receive concomitant prophylactic antibiotic therapy in accordance with the 2020 NCCN guidelines for Prevention and Treatment of Cancer-Related Infections.

- American Academy of Allergy, Asthma, and Immunology 2016 guidelines recommend IVIG in patients with recurrent serious bacterial infections and sub protective antibody levels following diphtheria, tetanus, or pneumococcal immunizations. This recommendation is based off a meta-analysis and systematic review showing a reduction in serious infections and mortality in patients receiving IVIG.

- B-cell lymphoma

  - Patients with B-cell lymphoma who are being treated with an anti-CD20 monoclonal antibody or CAR-T therapy are at an increased risk of infections due to the cytotoxic nature of their treatment. Infections are a significant cause of morbidity and mortality in these patients, particularly those with advanced disease and hypogammaglobulinemia. Comprehensive treatment plans include infection prevention precautions, prophylactic antibiotics, and, in select patients, IVIG.

  - The 2020 B-cell lymphoma NCCN treatment guidelines state patients on these therapies may experience hypogammaglobulinemia and recommend IVIG for patients with reduced serum IgG levels and recurrent, life-threatening infections. Recommended dosing is 400 mg/kg every 4 weeks. Patients should receive concomitant prophylactic antibiotic therapy in accordance with the 2020 NCCN guidelines for Prevention and Treatment of Cancer-Related Infections.

- Hypogammaglobulinemic neonates

  - Preterm and low birth weight infants are deficient in IgG and often cared for in intensive care units, where they are at risk for sepsis. IVIG has been studied as an immune enhancing agent to reduce the risk of sepsis in these settings. In a study of patients with very low birth rate, defined as 700 grams to 1,300 grams, the prevalence of sepsis was reduced within the first 30 days of life. Typically, in clinical practive, physicians treat all patients with a birth weight of less than 1500 grams with IVIG. However, a more recent Cochrane review concluded that IVIG was not associated with a reduction in mortality, although it was associated with a 3% reduction in sepsis and 4% reduction in 1 or more episodes of a serious infection.

  - American Academy of Allergy, Asthma, and Immunology 2016 guidelines state that the use of prophylactic IVIG may provide benefit in preventing sepsis for preterm infants. While the routine use of IVIG in neonates for the prevention of infection is not recommended, high-risk patients in acute care settings may benefit from therapy. Published studies have shown IVIG dosing of 0.5 g/kg to 2 g/kg weekly for approximately 4 weeks to be safe and effective.

- Inflammatory demyelinating polyneuropathy (acute)

  - Historically, Guillain-Barré syndrome (GBS) was considered a single disorder. It now is recognized as a heterogeneous syndrome with several variant forms. Each form of GBS has distinguishing clinical, pathophysiologic, and pathologic features. Acute inflammatory demyelinating polyradiculoneuropathy (AIDP) is the most common form in the United States and Europe, representing approximately 85% - 90%

of cases. The typical clinical features are a progressive, fairly symmetric, muscle weakness accompanied by absent or depressed deep tendon reflexes. The weakness can vary from mild difficulty with walking to nearly complete paralysis of all extremity, facial, respiratory, and bulbar muscles. Severe respiratory muscle weakness necessitating ventilatory support develops in about 30% of patients and dysautonomia occurs in 70% of patients. GBS usually progresses over a period of about two weeks.

- The initial diagnosis of GBS is based upon clinical presentation. The certainty of the diagnosis is supported if cerebrospinal fluid (CSF) analysis and electrodiagnostic studies showing abnormalities typical of GBS. Therefore, these studies should be performed in all patients with suspected GBS. Lumbar puncture often reveals an elevated CSF protein with a normal CSF white blood cell count. This finding, known as albuminocytologic dissociation, is present in 50% - 66% of patients with GBS in the first week after the onset of symptoms and greater than or equal to 75% of patients in the third week. Nerve conduction studies (NCS) and needle electromyography (EMG) are valuable for confirming the diagnosis of GBS and for providing some information regarding prognosis. In addition, electrodiagnostic studies are useful in classifying the main variants of GBS as demyelinating (eg, acute inflammatory demyelinating polyneuropathy) or axonal (eg, acute motor axonal neuropathy). Demyelinating forms of GBS are supported by features of demyelination including decreased motor nerve conduction velocity, prolonged distal motor latency, increased F wave latency, conduction blocks, and temporal dispersion.

- The main modalities of therapy for Guillain-Barré syndrome (GBS) are plasma exchange and administration of IVIG. Patients recover sooner when treated early. IVIG is recommended in nonambulatory patients within 4 weeks of neuropathic symptom onset, and in ambulatory patients who are not yet recovering within 4 weeks of neuropathic symptom onset. The beneficial effects of plasma exchange and IVIG are believed to be equivalent while combining the two treatments is not beneficial. Intravenous immune globulin is given for five days at 0.4 g/kg per day.

- Inflammatory demyelinating polyneuropathy (chronic, CIDP)

  - CIDP, also known as chronic inflammatory demyelinating polyradiculoneuropathy, is an acquired, immune-mediated neuropathy affecting peripheral nerves and nerve roots. It is characterized by a relapsing-remitting or progressive course, glucocorticoid responsiveness, and electrodiagnostic or pathologic features of demyelination. In its classic form, CIDP manifests as a symmetric, motor-predominant neuropathy that results in both proximal and distal muscle weakness. Recognized variants include asymmetric and/or sensory-predominant forms. All share the common pathophysiology of inflammatory demyelination. Although relatively rare, CIDP is important to recognize among the varied causes of polyneuropathy as it is treatable with immunomodulatory therapies.

  - There is a temporal continuum between acute inflammatory demyelinating polyneuropathy (AIDP), which is the demyelinating form of Guillain-Barré syndrome (GBS), and CIDP. The time course of progression and the occurrence of relapses are used to distinguish between these entities. GBS commonly reaches its nadir within three to four weeks but does not progress beyond eight weeks. CIDP continues to progress or has relapses for greater than eight weeks. GBS is typically monophasic, but up to two relapses in the first eight weeks from onset can occur. Three or more relapses in the first eight weeks is highly suggestive of acute CIDP. Relapses closer to the eight week time period is more suggestive of CIDP.

  - The diagnosis of CIDP should be considered in patients presenting with a progressive or relapsing-remitting polyneuropathy involving both motor and sensory axons along with areflexia, particularly when weakness predominates and affects proximal and distal muscles simultaneously and symmetrically. While the initial suspicion for CIDP is clinical, the diagnosis is confirmed by evidence of peripheral nerve demyelination, which must be demonstrated by electrodiagnostic findings or rarely by nerve biopsy, and exclusion of other

disorders that may cause or mimic CIDP.

- Electromyography (EMG) should be performed in all patients with suspected CIDP and is a critical component of the evaluation. The characteristic electrophysiologic features of a definitive CIDP diagnosis per the EFNS/PNS guidelines are those of peripheral nerve demyelination which include at least one of the following:
    - Greater than or equal to 50% prolongation of motor distal latency above the upper limit of normal in two nerves
    - Greater than or equal to 30% reduction of motor conduction velocity below the lower limit of normal in two nerves
    - Greater than or equal to 20% prolongation of F-wave latency above the upper limit of normal in two nerves or greater than 50% if the amplitude of the distal negative peak compound motor action potention (CMAP) is less than 80% of the lower limit of normal
    - Absence of F waves in two nerves, if these nerves have amplitudes of distal negative peak CMAPs greater than or equal to 20% of the lower limit of normal, plus at least one other demyelinating parameter, meeting any of the definite criteria, in at least one other nerve
    - Partial motor conduction block, defined by a greater than 50% amplitude reduction of the proximal negative peak CMAP relative to distal, if distal negative peak CMAP is greater than or equal to 20% of the lower limit of normal, in two nerves, or in one nerve plus at least one other demyelinating parameter, meeting any of the definite criteria, in at least one other nerve
    - Abnormal temporal dispersion, defined by a greater than 30% duration increase between the proximal and distal negative peak CMAP in at least two nerves
    - Distal CMAP duration (interval between onset of the first negative peak and return to baseline of the last negative peak) increase in at least one nerve (median greater than or equal to 6.6 ms, ulnar greater than or equal to 6.7 ms, peroneal greater than or equal to 7.6 ms, tibial greater than or equal to 8.8 ms) plus at least one other demyelinating parameter, meeting any of the definite criteria, in at least one other nerve
- The EFNS/PNS guidelines state probable CIDP is considered when patients have greater than or equal to 30% amplitude reduction of the proximal negative peak CMAP relative to the distal, excluding the posterior tibial nerve, if the distal negative peak CMAP is greater than or equal to 20% of the lower limit of normal in two nerves or in one nerve plus at least one other demyelinating parameter meeting any of the definite criteria in at least one other nerve.
- Cerebrospinal fluid (CSF) analysis is recommended in patients with probable CIDP and particularly for patients in whom the clinical and electrophysiologic findings are inconclusive. Albuminocytologic dissociation is a hallmark of CIDP and represents supportive evidence in the EFNS/PNS diagnostic criteria for probable CIDP.
- Magnetic resonance imaging (MRI) with gadolinium of the spine (including spinal roots, cauda

equina), brachial plexus, lumbosacral plexus, and other nerve regions can be used to look for enlarged or enhancing nerves. MRI abnormalities are useful as supportive criteria for probable CIDP in the EFNS/PNS guideline.

- The initial dose of IVIG is 2 g/kg infused over two to five days (eg, 0.4 g/kg per day for five days). Many patients with CIDP require a treatment trial of repeat IVIG dosing every two to six weeks depending on clinical course.

- Idiopathic thrombocytopenia purpura (ITP, acute)

  - Immune thrombocytopenia (ITP), defined as a platelet count less than 100,000/µL, is an acquired form of thrombocytopenia that is primarily due to autoantibody-mediated destruction of platelets. The autoantibodies may also affect megakaryocytes and impair platelet production. ITP is a diagnosis of exclusion, characterized by isolated thrombocytopenia without a clinically apparent condition responsible for the low platelet count; there are no reliable laboratory tests to confirm the diagnosis.

  - The time elapsed since diagnosis determines whether ITP is referred to as newly diagnosed, persistent, or chronic. Patients are considered newly diagnosed up to three months since diagnosis. Patients have persistent disease if they are still experiencing low platelet counts in the 3 to 12 month timeframe from diagnosis. If symptoms persist more than 12 months from diagnosis, the disease is labeled as chronic.

  - The most commonly used agents for initial treatment of ITP for those who require it are glucocorticoids and IVIG. Intravenous anti-D immune globulin is a type of immune globulin that may be effective in patients who have an Rh+ blood type and have not had a splenectomy. IVIG raises the platelet count more rapidly than glucocorticoids and therefore, is often used for patients with active bleeding, patients who need an urgent invasive procedure, or patients who experience side effects with glucocorticoids. For all patients with severe bleeding and a platelet count less than 30,000/µL, immediate platelet transfusion along with ITP-specific therapy with IVIG and high-dose glucocorticoids are recommended. ITP-specific therapy should also be administered to patients with a new diagnosis of ITP and a platelet count less than 20,000/µL, even in the absence of bleeding symptoms, because the thrombocytopenia may be persistent and become more severe. Some patients with platelet counts greater than 30,000/µL may require treatment if they have an increased risk of bleeding (eg, peptic ulcer disease, high risk of falling), other hemostatic defects (eg, use of antiplatelet agents or anticoagulants), a history of bleeding at a higher platelet count, or a need for surgery/invasive procedures.

  - IVIG is administered at 1 g/kg daily for one or two days; 1 g/kg for one day is often sufficient. Alternative dosing can also be used, for example, 400 mg/kg daily for five days. The IVIG can be stopped when a response occurs even if the full course has not been completed.

- Idiopathic thrombocytopenia purpura (ITP, chronic)

  - Immune thrombocytopenia, defined as a platelet count less than 100,000/µL, is an acquired form of thrombocytopenia that is primarily due to autoantibody-mediated destruction of platelets. The autoantibodies may also affect megakaryocytes and impair platelet production. ITP is a diagnosis of exclusion, characterized by isolated thrombocytopenia without a clinically apparent condition responsible for the low platelet count; there are no reliable laboratory tests to confirm the diagnosis.

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persistent disease if they are still experiencing low platelet counts in the 3 to 12 month timeframe from diagnosis. If symptoms persist more than 12 months from diagnosis, the disease is labeled as chronic.

- The threshold for pharmacologic treatment depends on multiple factors including ongoing bleeding symptoms, risk factors for bleeding, such as, sports or an active lifestyle, concomitant medical conditions and medications, anxiety, fatigue, and access to medical care. Decisions should be individualized and made in collaboration with the patient and family. Children with chronic ITP should be managed by a pediatric hematologist whenever possible.

- IVIG is considered a rescue therapy for patients with chronic ITP rather than routine, ongoing therapy. It should only be used in patients meeting the requirements for acute treatment and who have had a platelet count less than 100,000/µL for more than 12 months. The most commonly used agents for treatment of acute drop in platelets in patients with chronic ITP are glucocorticoids and IVIG. Intravenous anti-D immune globulin is a type of immune globulin that may be effective in patients who have an Rh+ blood type and have not had a splenectomy. IVIG raises the platelet count more rapidly than glucocorticoids and therefore, is often used for patients with active bleeding, patients who need an urgent invasive procedure, or patients who experience side effects with glucocorticoids. For all patients with severe bleeding and a platelet count less than 30,000/µL, immediate platelet transfusion along with ITP-specific therapy with IVIG and high-dose glucocorticoids are recommended. ITP-specific therapy should also be administered to patients with a platelet count less than 20,000/µL, even in the absence of bleeding symptoms, because the thrombocytopenia may be persistent and become more severe. Some patients with platelet counts greater than 30,000/µL may require treatment if they have an increased risk of bleeding (eg, peptic ulcer disease, high risk of falling), other hemostatic defects (eg, use of antiplatelet agents or anticoagulants), a history of bleeding at a higher platelet count, or a need for surgery/invasive procedures.

- For patients with chronic ITP whose symptoms and risks are not adequately controlled using first-line therapies and for those who remain dependent on glucocorticoid therapy to control symptoms, second-line treatments include rituximab, eltrombopag, romiplostim, and splenectomy. Other agents that are sometimes used for patients who require chronic immunosuppression include azathioprine, 6-MP, or MMF. The choice among these options is complex and highly dependent on the values and preferences of the patient and family.

- Idiopathic thrombocytopenia purpura in pregnancy

  - ITP occurs in approximately 1 to 3 in 10,000 pregnancies with only a subset of patients having platelet counts less than 50,000/µL. This is approximately 10-fold greater than the incidence of ITP in the general population which is estimated to be 3 in 100,000 adults. As in non-pregnant individuals, the risk of bleeding is greater with platelet counts less than 20,000 to 30,000/µL, although there is no absolute platelet count threshold above which bleeding does not occur. Data indicates an increased risk of bleeding if platelet count is below 20,000 to 30,000/µL for a vaginal delivery or below 50,000/µL for a cesarean section.

  - The American Society of Hematology recommends medical management of ITP in pregnancy in the following scenarios: patients are in their 3rd trimester with platelets less than 10,000/µL; platelets are 10,000 to 30,000/µL with bleeding; platelets are less than 10,000 µL after steroid failure; platelets are 10,000 to 30,000/µL and the patient is experiencing bleeding after steroid failure; and the patient is in their 3rd trimester with platelets 10,000 to 30,000 µL and asymptomatic following steroid failure.

  - Due to their efficacy and low cost, many consider corticosteroids to be first line treatment for ITP in pregnancy. However, the many adverse effects of corticosteroids are amplified during pregnancy, and pregnancy-specific toxicities such as gestational diabetes, weight gain, acceleration of bone loss,

hypertension, and possibly placental abruption and premature labor must be recognized. Furthermore, some studies have associated the use of corticosteroids in the first trimester with congenital anomalies, such as orofacial clefts.

- Alternatively, others have suggested that IVIG should be the first line therapy for pregnancy-associated ITP, especially when a long duration of therapy may not be required. Compared to corticosteroids, IVIG is less likely to induce toxicities such as hypertension. ASH guidelines consider IVIG to be an appropriate first line agent for severe thrombocytopenia, or thrombocytopenic bleeding in the third trimester. However, responses to IVIG tend to be transient, and multiple courses of therapy may be required at significant cost and patient inconvenience. Treatment with 2 g/kg IVIG infused over two to five days is an effective means of raising the platelet count rapidly.

- Kawasaki syndrome

  - Kawasaki disease (KD) is one of the most common vasculitides of childhood. KD also occurs rarely in adults. It is typically a self-limited condition with fever and manifestations of acute inflammation lasting for an average of 12 days without therapy. However, complications such as coronary artery (CA) aneurysms, depressed myocardial contractility and heart failure, myocardial infarction, arrhythmias, and peripheral arterial occlusion may develop and lead to significant morbidity and mortality.

  - There is no single test to diagnose KD. Diagnosis requires the presence of fever lasting greater than or equal to 5 days combined with other physical findings, without an alternative explanation, that could include bilateral bulbar conjunctival injection, oral mucous membrane changes such as fissured lips or strawberry tongue, peripheral extremity changes such as erythema of palms or soles, edema of hands or feet, polymorphous rash, cervical lymphadenopathy.

  - Randomized, controlled studies and meta-analyses have confirmed that IVIG, in conjunction with aspirin, started within 10 days of fever onset reduces the risk of CA aneurysms from approximately 25% to less than 5%. IVIG has additional beneficial effects in KD, such as rapid resolution of the almost universal lymphocytic myocarditis seen in the disease. IVIG is not effective if more than ten days have elapsed from onset of symptoms. Expeditious diagnosis and timely treatment are critical to achieve the optimal clinical outcome. The usual dose of IVIG is 2 g/kg as a single dose, or 400 mg/kg daily for 5 days.

- Lambert-Eaton myasthenic syndrome (LEMS)

  - LEMS is a rare acquired autoimmune disorder characterized by proximal weakness of extremities, decreased reflexes, and dryness of mouth and eyes. Weakness normally spreads proximally (most common in the upper arms and legs) to distally (involving feet and hands) and from the posterior towards the head, finally reaching the oculobulbar region. This is in contrast to myasthenia gravis, in which weakness typically starts in the head and then descends. The characteristic weakness is thought to be caused by antibodies generated against the P/Q-type voltage-gated calcium channel (VGCC) present on presynaptic nerve terminals and by diminished release of ACh. More than one-half of LEMS cases are associated with small cell lung cancer which expresses functional VGCC.

  - The diagnosis of LEMS is confirmed by electrodiagnostic studies including repetitive nerve stimulation and anti-P/Q-type VGCC antibody testing. The electrodiagnostic evaluation of suspected LEMS typically involves the following elements: routine motor and sensory nerve conduction studies, high-frequency repetitive nerve stimulation and/or exercise testing, and electromyography (EMG). Antibodies against the P/Q-type VGCC) are present in approximately 85% to 95% of patients with LEMS.

- There are no clinical practice guidelines for LEMS. The most effective treatments increase the presynaptic release of acetylcholine and thereby reverse the underlying physiologic deficit present in LEMS. If adequate to induce stable functional muscle strength, no further treatment may be needed. Amifampridine is FDA approved to treat LEMS and used as a first line treatment option as it improves the release of acetylcholine. For patients who do not improve sufficiently second line treatment options include IVIG and oral immunosuppressants such as prednisone, azathioprine, mycophenolate mofetil, and cyclosporine. Some experts are reluctant to use oral immunosuppressive agents such as azathioprine in patients with cancer because of concerns that such treatment may exacerbate the malignancy.

- A number of small studies suggests benefit of IVIG in LEMS, with both clinical improvement such as improved muscle strength and a reduction in the voltage-gated calcium channel antibodies. The recommended dose of IVIG is 2 g/kg administered over 2 – 5 days every 4 - 12 weeks depending on duration of response.

- Multifocal motor neuropathy (MMN)

  - MMN is a rare disorder in which focal areas of multiple motor nerves are attacked by one's own immune system. Typically, MMN is slowly progressive resulting in asymmetrical weakness of a patient's limbs. Patients frequently develop weakness in their hand(s) causing them to drop objects or be unable to turn a key in a lock. The weakness associated with MMN can be recognized as fitting a specific nerve territory. There is essentially no objective sensory abnormalities, such as, numbness, tingling, or pain. Patients with MMN can have other symptoms, including twitching, or small random dimpling of the muscle under the skin which neurologists call fasciculations. MMN is associated with increased levels of specific antibodies to GM1, a ganglioside or sugar-containing lipid found in peripheral nerves. Elevated titers of anti-GM1 antibodies are present in 30% to 80% of patients. However, it is unclear whether anti-GM1 antibodies are involved in the pathogenesis of MMN.

  - The European Federation of Neurological Societies/Peripheral Nerve Society (EFNS/PNS) have specific requirments for the diagnosis of MMN to be made. Two core criteria must be present in a patient. The first is a slowly progressive, focal asymmetric limb weakness defined as motor involvement in the moror nerve distribution of at least two nerves for more than one month. If signs and symptoms are present only in the distribution of one nerve, only a possible diagnosis can be made. The second core criterion is a lack objective sensory abnormalities except for minor vibration sense abnormalities in the lower limbs. The diagnosis is supported by nerve conduction studies that demonstrate focal demyelination and condution block in motor nerves and normal sensory nerves. Additional supportive clinical criteria include predominant upper limb involvement, decreased or absent tendon reflexes in the affected limb, absence of cranial nerve involvement, cramps and fasciculations in the affected limb, and a response in terms of disability or muscle strength to immunomodulatory treatment. MMN can be ruled out if the patient has upper motor neuron signs, marked bulbar involvement, sensory impairment more marked than minor vibration loss in the lower lilmbs, or diffuse symmetric weakness during the initial weeks.

  - MMN is treatable with IVIG. However, unlike chronic inflammatory demyelinating polyneuropathy, MMN is generally unresponsive to glucocorticoids or plasma exchange, and these therapies have been associated with clinical worsening in some cases. The EFNS/PNS and the American Academy of Neurology treatment guidelines recommend IVIG 2 g/kg given over two to five days for initial treatment of patients with MMN who require treatment due to disease progression or disability has been shown to be effective.

- Myasthenia gravis (MG)

    - Myasthenia gravis is a rare autoimmune disease resulting from an immunologic attack of AChR, muscle-specific tyrosine kinase (MuSK), and/or other receptors found on the postsynaptic neuromuscular junction. It typically initially presents as asymmetric ptosis and diplopia and is known as ocular MG of the eyelids and extraocular muscles. As weakness extends beyond the ocular muscles, the disease progresses into generalized MG with patients experiencing widespread fatigue and muscle weakness most commonly in the head, neck, and extremities.

    - Approximately 10-15% of MG cases will become refractory resulting in profound debilitating muscle weakness and fatigue and difficulty breathing, swallowing, speaking, and walking. Refractory disease is defined by the 2016 international consensus guidance for management of myasthenia gravis as worsening or unchanged disease despite use of corticosteroids and at least two different immunosuppressive therapies used in adequate doses for an adequate duration with persistent symptoms and/or side-effects that limit function.

    - A proportion of patients with myasthenia gravis will experience myasthenic crisis. Impending myasthenic crisis is defined as rapid clinical worsening of myasthenia gravis that, in the opinion of the treating clinician, could lead to crisis within days to weeks. Myasthenic crisis is defined by increasing respiratory muscle and/or bulbar muscle weakness severe enough to necessitate intubation and/or mechanical ventilation. Patients experiencing symptoms of crisis should be admitted to the hospital and assessed for the need for ventilation. The 2016 international consensus guidance for management of myasthenia gravis state therapy with immunoglobulin or plasma exchange (PLEX), also known as rapid therapy, should initiated. These interventions provide a quick reversal of the exacerbation but benefits only last a few weeks. Therefore, immunosuppressive therapy should also be started to provide a longer benefit over the rapid therapies.

    - The thymus plays an important role in the pathogenesis of MG. Studies have shown that muscle-like myoid cells in the thymic medulla expressing AChR could be driving the antibody mediated response seen in MG. The 2016 international consensus guidance for management of myasthenia gravis state thymectomy can be considered for patients with generalized MG without thymoma based on Class II evidence from a meta-analysis. Thymectomy should only be performed once a patient's MG has stabilized. In patient with persistent mild residual respiratory impairment or dysphagia despite treatment with pyridostigmine and immunosuppression, a course of IVIG or PLEX can be given/done preoperatively. This practice is empiric, with a goal of reducing the risk of a postoperative flare evolving quickly into myasthenic crisis. Treatment should be timed to end the week prior to surgery so that the effects of the rapid therapy peak and persist through the perioperative period.

    - Standard therapies recommended by the 2016 international consensus guidance for management of myasthenia gravis include acetylcholinesterase inhibitors, corticosteroids, immunosuppressants, IVIG, and PLEX.

        - Acetylcholinesterase inhibitors are used for temporary symptomatic relief of MG symptoms. Their use is limited as an adjunct therapy to immunotherapy in those with residual or refractory MG or for treatment of ocular and mild generalized disease in those who cannot receive immunosuppressants.

        - Corticosteroids are effective in ocular MG and in patients with general MG with unsatisfactory responses to acetylcholinesterase inhibitors. They produce improvement in up 80% of MG patients often beginning within 2 weeks. However, they are associated with significant dose-dependent adverse events and are typically started with an immunosuppressant and then tapered slowly.

- Azathioprine and mycophenolate mofetil are standard immunosuppressant therapies and act as steroid-sparing agents. Other options include cyclosporin, methotrexate, and tacrolimus. Onset of action is slow and may take up to 9 to 12 months. Guidelines recommend dose adjustments no more frequently than every 3 to 6 months. Once the patient experiences treatment effect and doses should be maintained for six months to two years of therapy and then tapered to the lowest effect dose.

- Cyclophosphamide is typically used after failure of standard therapy in severe MG. It has several serious potential side effects. Since there are effective agents with less toxicity cyclophosphamide is usually reserved for patients refractory to the other immunosuppressive therapies.

- PLEX and IVIG provide short-term symptomatic relief during exacerbations for surgical preparation or in patients with septicemia through downregulating autoantibodies and/or inducing antiidiopathic antibodies. IVIG has been shown to be effective in reducing the time of mechanical ventilation in myasthenic crisis, in management of severe generalized MG, to stabilize MG before surgery, and prior to high-dose corticosteroid therapy to minimize or prevent steroid-induced exacerbations. IVIG may be a maintenance treatment option for patients intolerant to or not responding to an adequate course of non-steroid immunosuppressive therapy. In contrast, the clinical effects of PLEX last only a few weeks unless concomitant immunosuppressants are given. Studies indicate that there is no long-term immunosuppressive effect of PLEX.

- There is good rationale for the use of rituximab in MG as the disease is B-cell mediated and rituximab targets CD20 on the B-cell membrane. A number of case reports and case series support the efficacy of rituximab in patients with refractory MG. In a prospective study of 22 patients with refractory MG treated with rituximab, the mean time to relapse was 17 months. Among 14 patients taking prednisone, the mean daily dose decreased from 25 mg at baseline to 7 mg after treatment with a mean follow-up of 29 months. In an observational study of 72 patients with new-onset or refractory generalized MG, those treated with low-dose rituximab had shorter time to remission, lower use of adjunctive treatments, and fewer adverse events than patients treated with conventional immunosuppressive therapy.

- Pediatric acute-onset neuropsychiatric syndrome (PANS)/pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS)

  - PANDAS is a clinical diagnosis in children who have an acute manifestation of varied neuropsychiatric symptoms following a streptococcal (strep) infection. A child may be diagnosed with PANDAS when obsessive compulsive disorder (OCD), a tic disorder, or both suddenly appear or become worse after an illness caused by streptococci, such as strep throat or scarlet fever. The symptoms are usually dramatic, happening "overnight and out of the blue." In addition to OCD and tics, children may become moody or irritable, experience anxiety attacks, show concerns about separating from parents or loved ones, or have issues with attention and concentration. PANS has similar features to PANDAS including OCD, eating restrictions, anxiety, attention deficit disorder, and academic decline and develops following a viral or bacterial infection. Although PANS/PANDAS are emerging autoimmune encephalopathic diseases, these two conditions are unique from autoimmune encephalitis (AE) which presents with seizures or new focal CNS findings, MRI abnormalities, and/or elevated white blood cell count in the cerebral spinal fluid. AE patients also have cognitive dysfunction whereas cognitive function remains intact with PANS/PANDAS. In addition, PANS/PANDAS patients often experience a relapsing/remitting course with rapid progression to maximum symptoms and rapid return to previous function.

  - While the etiology of PANDAS is still unclear, studies suggest that the condition is brought on by a cross-reaction between antibodies to Streptococcus pyogenes and structures on neuronal cells in the brain.

GABHS bacteria use molecular mimicry to appear nearly identical to molecules found in normal human tissues, thereby allowing the bacteria to evade detection for long periods of time. Once the GABHS bacteria is recognized as foreign to the body, the immune system reacts not only to the strep infection but also to the human host molecules that were mimicked. The result is an abrupt onset of PANDAS symptoms.

- PANDAS/PANS is a diagnosis of exclusion. Differentiating PANDAS from phenotypically similar conditions, such as OCD, tic disorders, and autism spectrum disorder (ASD), remains challenging and controversial due to both heterogeneous presentations and the likelihood that at least some instances of these other disorders share overlapping pathophysiology. Currently, PANDAS is characterized by five working diagnostic criteria including: OCD and/or tic disorder; pediatric onset between the age of 3 and the start of puberty; an abrupt onset and episodic course of symptoms; a temporal relationship between GABHS infection and onset and/or exacerbation; and neurologic abnormalities, such as motoric hyperactivity, choreiform movements, or tics during exacerbations. Children who present with abrupt onset of OCD and/or tic disorder, separation anxiety, or urinary frequency should be evaluated for PANDAS by testing for GABHS infection. The diagnosis is considered probable when patients present with an abrupt onset of neuropsychiatric symptoms, have evidence of recent GABHS infection, and remission of neuropsychiatric symptoms with antibiotic therapy. Because clinical diagnostic classification is challenging, more research is clearly needed to identify reliable diagnostic biomarkers of active disease including autoantibodies, inflammatory cells, metabolic profiles, and/or neuroimaging signatures. The quality of the evidence for the use of IVIG in ASD is still below what is commonly accepted for a routinely used treatment with the bulk of the studies being uncontrolled. Many studies demonstrated bias, including selection bias (lack of randomization), performance bias (lack of blinding), detection bias (lack of standardized outcomes), attrition bias (retrospective studies are prone to losing patients to follow-up), and reporting bias (case studies tend to report positive rather than negative outcomes). Thus, the current set of studies presented should be used to design and implement well-controlled, blinded randomized clinical trials in the future. Additionally, the populations used in these studies are very heterogeneous with many different immune system abnormalities, making it hard to determine if there is a particular subset of children with ASD in which the treatment may be most effective. Consensus guidelines are silent on the use of IVIG to treat symptoms related to autism.

- If PANDAS is an autoimmune disorder, and this remains controversial, then immunomodulatory treatments might be beneficial, but as of yet are unproven. Most of the medical treatment approaches targeting immune modulation are supported by weak or conflicting evidence. A recent comprehensive review by Sigra et al identified 12 treatment studies with published outcomes data. Eleven of the 12 studies were judged to have a moderate or high risk of bias, including selection bias, performance bias, detection bias, attrition, reporting bias, other bias, or a combination of these issues. The one exception was a randomized, controlled clinical trial conducted by Williams et al comparing IVIG with placebo for treatment of PANDAS OCD in 35 children which showed no difference between the IVIG and placebo groups in OCD severity scores or proportion of responders. In contrast, follow-up open-label treatment trials in these patients reported improvement in all participants regardless of their initial treatment group assignment. The follow-up data suggests patients and care givers are experiencing a placebo effect and not true treatment related resolution of symptoms.

- In addition to the Sigra et al review, Hayes completed an additional evidence-based review of the use of IVIG in PANDAS. Of the 92 records reviewed, 3 studies reported met inclusion requirements which consisted of enrollment of at least 10 patients, reporting of aggregate data for the patient population, published in 2001 or later, and assessment of patient-oriented efficacy and/or safety outcomes. The first included study by Perlmutter et al was a randomized-controlled trial of 30 pediatric patients with severe, infection-triggered exacerbations of OCD or tic disorders comparing treatment with IVIG, plasma exchange, or placebo. While results suggest that IVIG was both effective in reducing neuropsychiatric symptoms severity when compared w/ placebo, the study also had a significant number of limitations. First, there was

a small sample size with no power analysis and no intent to treat analysis. Eighteen percent (3 of 17) of patients underwent additional treatment with IVIG, PE, or other additional treatments from 1 month to 1 year. Also the authors note results may not be generalizable due to strict inclusion criteria. Hayes also included the Williams et al along with the Lyon et al study. The analysis resulting in the same conclusions citing study limitations, smaller than expected effect size due to greater placebo effect and lower treatment benefit of IVIG which led to the study being underpowered. In addition, select outcome measures relied on parent report with the potential for recall bias, and the long-term outcomes may reflect benefit from the additional treatment in the follow-up months. The final study included in the Hayes report was completed by Melamed et al. It was a prospective, open-label, single-arm pretest/posttest study evaluating the use of IVIG in 21 patients with PANS. Results suggest that patients with moderate-to-severe PANS treated with IVIG experienced improvement in neuropsychological symptoms. In a subset of patients with long-term follow-up, up to 46 weeks post-treatment, symptom relief was sustained. There were significant limitations to this study as well, including no control or comparator group; a small sample size with no power analysis; an open-label trial; no intent to treat analysis; and only a subset of patients had long-term data available. Evaluating the strength of evidence in both the Sigra and Hayes reviews, there is currently insufficient data to clearly support the use of any immune modulating treatment, including IVIG, for PANDAS due to significant flaws in clinical trial design and multiple sources of bias.

- Pediatric intractable epilepsy

    - Patients with epilepsy whose seizures do not successfully respond to antiseizure drug therapy are considered to have drug-resistant epilepsy (DRE). This condition is also referred to as intractable, medically refractory, or pharmacoresistant epilepsy. As many as 20% to 40% of patients with epilepsy are likely to have refractory epilepsy.

    - Epilepsy surgery should be considered in appropriate patients with DRE when seizures are sufficiently frequent or severe as to significantly increase the mortality risk or disrupt the patient's quality of life. Surgery is a reasonable option for people with refractory epilepsy if seizures start in one area of the brain and that area can be removed safely. Vagus nerve stimulation (VNS) therapy is a way of controlling seizures in people who do not respond to medications and may not respond to surgery. The vagus nerve sends information from your neck down to the chest and stomach and then back up again. The vagus nerve then sends information up to the brain. Stimulation of the vagus nerve can change the likelihood of the brain to have seizures. The "classic" ketogenic diet is a special high-fat, low-carbohydrate diet that helps to control seizures in some people with epilepsy. It is prescribed by a physician and carefully monitored by a dietitian. It is usually used in children with seizures that do not respond to medications.

    - The efficacy of IVIG treatment for severe childhood epilepsy was evaluated in a retrospective, multicenter study comprising 64 consecutive patients treated with IVIG for either epileptic encephalopathy or refractory epilepsy. Nine patients (14%) demonstrated complete resolution and 10 (15.6%) exhibited partial improvement. Of these 19 responders (29.7%), eight relapsed. Although IVIG is not suitable for all cases of epilepsy, it may prove efficacious for specific epileptic syndromes, mainly idiopathic West syndrome and electrical status epilepticus during sleep.

- Polymyositis (PM)

    - Polymyositis is a type of inflammatory myopathy characterized by proximal skeletal muscle weakness and muscle inflammation. Muscle weakness usually happens over days, weeks, or months. It can affect a patient’s ability to walk, run, and pick themselves up after a fall. The weakness typically begins with muscles closest to and within the trunk of the body, such as the muscles of the neck, hips, back, and shoulders. The exact cause of the disease is unknown but it shares many characteristics with autoimmune

disorders. In some cases, the disease may be associated with viral infections, connective tissue disorders, or an increased risk for malignancies.

- Diagnosis is based on a clinical examination that may include laboratory tests, imaging studies, electromyography (EMG), and a muscle biopsy. There is no agreed upon criteria for diagnosis with multiple methods published throughout the literature. The 2005 International Consensus Guidelines for Trials of Therapies in the Idiopathic Inflammatory Myopathies guidelines suggest diagnosis can be made with an abnormal biopsy consistent with PM and no pathognemic rash suggestive of dermatomyositis. In contrast, the Myositis Association lists comprehensive diagnostic criteria on their website stating patients should present without skin symptoms and four of the following: symmetrical muscle weakness in the shoulders/upper arms or hips/upper legs and trunk; elevated skeletal muscle-associated enzymes; muscle pain on grasping or spontaneous pain; a triad of muscle-related changes on EMG including short, small, low-amplitude polyphasic motor unit potentials, fibrillation potentials, and bizarre high-frequency repetitive discharges; positive for any of the myositis-specific autoantibodies; nondestructive arthritis or arthralgias; signs of systemic inflammation; or muscle biopsy findings compatible with inflammatory myositis. In addition, Dalakas MC & Hohlfeld developed their own diagnostic requirements. Due to the lack of consistent diagnostic criteria, PM is generally considered a disease of exclusion and is typically diagnosed when all other disorders are ruled out.

- The goals of treatment are to improve muscle strength and to avoid the development of extramuscular complications. Glucocorticoids are considered first-line therapy for PM. They are typically initiated with prednisone at a dose of 1 mg/kg per day, to a maximum daily dose of 80 mg. A steroid-sparing immunosuppressive agent, either methotrexate or azathioprine, is generally started along with glucocorticoid treatment so the patient can eventually begin to taper their steroids. Tapering of glucocorticoids is based on a combination of the improvement in muscle enzymes and recovery of muscle strength. Ideally, normalization of enzymes and complete recovery of muscle strength should occur before glucocorticoids are tapered. The initial response to glucocorticoids in the patient with PM typically takes four to six weeks for normalization of creatine kinase (CK) levels or three to four months to regain muscle strength.

- Some patients either relapse after an initial response or fail to respond to glucocorticoids and immunosuppressant therapy. These patients are considered to have recurrent or resistant disease. Multiple options exist as second-line therapy for those who do not respond adequately to glucocorticoids plus azathioprine or methotrexate. IVIG is considered the next step when the patient experiences recurrent or resistant disease. In PM, no controlled studies have been conducted, but IVIG has seems to be effective in approximately 70% of patients. Other therapies that have been shown to have some effectiveness either alone or in combination with other therapies include cyclosporin, mycophenolate mofetil, chlorambucil, and cyclophosphamide.

- Post-transfusion purpura

  - Post-transfusion purpura (PTP) is a rare but serious transfusion-associated complication characterized by thrombocytopenia developing within 2 weeks of transfusion accompanied by bleeding of variable severity that can be life-threatening. The prevalence of PTP is unknown and difficult to establish as the disease is difficult to differentiate from other thrombocytopenic conditions. According to case reports and series, previously pregnant women are the most commonly affected group with likelihood of developing PTP increasing with prior exposure to a specific human platelet antigen (HPA) absent on the patient's platelets. Subsequent transfusions re-expose recipients to the antigen triggering an immune response that induces platelet destruction. The most commonly implicated antibody is anti-HPA-1a made by patients with an HPA-1b/1b genotype.

  - PTP presents as severe thrombocytopenia with less than 10,000 platelets/μL sometimes accompanied by

life-threatening bleeding with symptoms occurring 5 - 10 days after transfusion of blood products containing platelets (including whole blood, packed RBCs, platelets, and plasma). Bleeding is typically mucocutaneous (e.g. petechiae, epistaxis, gingival bleeding) with the most common sites of bleeding being the mucous membranes, the gastrointestinal tract, and the urinary tract. PTP is considered a self-limited disease with recovery of platelet counts seen in approximately 20 days.

- Diagnosis of PTP can be challenging due to the wide array of thrombocytopenic syndromes with symptomatic overlap. Differential diagnosis includes immune thrombocytopenic purpura (ITP), drug-induced thrombocytopenia (DITP), thrombotic thrombocytopenic purpura (TTP), heparin-induced thrombocytopenia (HIT), disseminated intravascular coagulation (DIC), sepsis, and pseudo thrombocytopenia.

- Patients with acute, severe thrombocytopenia that develops approximately 5-10 days following a blood transfusion, together with primarily mucocutaneous bleeding and the presence of potent HPA-specific platelet antibodies, is diagnostic of PTP. Platelet antibody testing is required to confirm diagnosis. HPA genotyping may also be of additional benefit.

- Antibodies against HPA-1, HPA-2, HPA-3, HPA-4, HPA-5, and HPA-15 have been detected in the sera of patients with PTP. Direct and indirect antibody testing can be used to detect these platelet-specific antibodies; indirect methods test for antibodies in the patients plasma or serum while direct methods detect antibodies attached the patient's platelets. Direct testing can be limited in the presence of severe thrombocytopenia.

- Enzyme-linked immunosorbent assays (ELISA) are the most widely available technique for platelet antibody testing and can be used for both direct and indirect testing. Examples of platelet antibody assays that are widely used include the antigen capture ELISA (ACE), the modified antigen capture ELISA (MACE), the monoclonal antibody immobilization of platelet antigens (MAIPA) assay, and the platelet antibody bead array (PABA). Highly sensitive and specific antigen capture tests like the PABA or MAIPA assays should be performed since a strong HPA antibody is the hallmark of PTP. It is common for sera to contain platelet antibodies targeting multiple HPA even though HPA-1a antibodies are the most frequently detected in the serum of suspected PTP patients.

- HPA typing confirms HPA antibody specificity and guides clinical care for future transfusions. Two commonly used techniques include polymerase chain reaction using sequence-specific primers (PCR-SSP) and 5'exonuclease strategies. The typical result in PTP cases is the presence of HPA-1a antibodies in the patient's serum and an HPA-1b/1b (HPA-1a negative) genotype.

- The treatment of choice for PTP is intravenous immunoglobulin (IVIG) with recommended doses of 400 - 500 mg/kg/day for 1 - 10 days or 1 - 2 g/kg/day for 2 - 5 days. A favorable response to treatment is noted within as little as 2 days, with response rates of up to 90% having been reported. Corticosteroids may be given in addition to IVIG; however, the effectiveness of corticosteroids has not been proven. Platelet transfusions are generally ineffective at increasing platelet counts; however, they should be administered to patients with life-threatening bleeding. For cases refractory to IVIG or for more complex cases, whole blood or plasma exchange may be considered to quickly reduce the levels of autoantibodies.

- Recurrence of PTP following subsequent transfusion is not common; however, previously affected patients who require transfusion should receive HPA-compatible blood products.

- Primary humoral immunodeficiency diseases

  - Transient hypogammaglobulinemia of infancy (THI)

- Transient hypogammaglobulinemia of infancy is a type of primary immunodeficiency characterized by reduced IgG levels beginning at 5 to 24 months of age. Diagnosis of other common variable immunodeficiencies are not excludable until after this transient period. THI typically resolves at age 2 to 6 years old in the absence of diagnosis of another immunodeficiency disorder. While many patients remain asymptomatic, some experience recurrent infections such as upper and lower respiratory infections. Severe infections, including urinary tract infections, gastroenteritis, and invasive infections, may occur in severe cases. IVIG is recommended in THI patients with severe, life-threatening infections, or recurrent infections despite antibiotic therapy. Dosing of 400 mg/kg every 3 weeks has been effective in published studies

- X-linked agammaglobulinemia (congenital agammaglobulinemia)

  - X-linked agammaglobulinemia (congenital agammaglobulinemia) occurs in male infants, usually presenting in the first 3 years of life. Patients have either agammaglobulinemia or hypogammaglobulinemia, along with very low or absent CD19+ cells. Diagnosis is confirmed by molecular genetic testing for the BTK gene or protein expression. Lack of protein expression is considered when the patient has absent BTK mRNA on Northern blot analysis of neutrophils or monocytes or has absent BTK protein in monocytes or platelets. Probable diagnosis can also be made based off a family history of documented agammaglobulinemia or hypogammaglobulinemia. Diagnosis can also be confirmed when a patient has maternal cousins, uncles, or nephews with less than 2% CD19+ B-cells.

  - The most common clinical manifestations of this condition are bacterial infections, which can lead to sepsis, osteomyelitis, septic arthritis, and central nervous system infections. Patients are also susceptible to viral, fungal, and parasitic infections. Some patients may be diagnosed more proactively if there is a document history of the disease in the family. Median age of onset is 2.6 years in patients with a family history and 5.4 years in patients without a family history of the disease.

  - Immunoglobulin replacement therapy is the cornerstone of therapy in X-linked agammaglobulinemia. Observational studies show that it lowers morbidity and mortality in these patients. American Academy of Allergy, Asthma, and Immunology 2016 guidelines recommend lifelong immunoglobulin replacement therapy as both necessary and lifesaving. It must be used in combination with infection avoidance measures, vaccinations, and aggressive antibiotic therapy for infections. Recommended dosing for IVIG is 400 - 600 mg/kg every 3 - 4 weeks. Recommended dosing for subcutaneous IVIG is 100 - 200 mg/kg per week.

- Common variable immunodeficiency (CVID)

  - Common variable immunodeficiency is a heterogeneous primary immunodeficiency disorder affecting both children and adults. CVID comprises a group of hypogammaglobulinemia syndromes, stemming from multiple genetic defects, where patients have impaired B-cell differentiation and immunoglobulin production. Diagnosis is contingent on significantly reduced serum IgG levels, low levels of IgA and/or IgM, reduced response to immunizations, and exclusion of other immunodeficiency disorders.

  - Most patients experience chronic lung disease, autoimmune disorders, gastrointestinal disease, an increased susceptibility to lymphoma, and recurrent infections. Approximately 25% of patients

have symptom onset during childhood or adolescence. Children, in particular, present with recurrent ear infections and concomitant autoimmune cytopenias and allergic disease. In severe cases, children present with failure to thrive.

- IVIG has proven to reduce recurrent infections and complications in these patients. It is recommended for patients with significant impairments in immune globulin production, evidenced by approximately two standard deviations below the normal range for IgG and lack for response to protein and polysaccharide vaccines. IVIG with close monitoring may be considered in patients with less severe impairments in immune globulin production and minor responses to some vaccines. While the recommended maintenance dose is 400 mg/kg every 4 weeks, higher doses may be used in patients with recurrent major infections, chronic lung disease, enteropathy, and in pregnancy.

- Immunoglobulin subclass deficiency (e.g., X-Linked immunodeficiency with hyper-IgM)

  - Immunoglobulin subclass deficiency is a rare primary immunodeficiency diagnosed in adults and children with recurrent infections. Patients with immunoglobulin subclass deficiency have reduced serum concentrations of one or more subclasses of IgG, but normal total concentrations of IgG. Patients with laboratory findings of reduced subclasses of IgG, recurrent infections, and inadequate response to a vaccine challenge are considered to have clinically significant immunoglobulin subclass deficiency. Levels of IgG subclasses, including IgG1, IgG2, IgG3, or IgG4, should be confirmed on two occasions at least 2 - 4 weeks apart. Approximately 15% of patients also have an IgA deficiency. Many patients have concomitant asthma, chronic obstructive pulmonary disease (COPD), vasculitis, and cytopenias.

  - Like patients with other primary immunodeficiencies, these patients most often present with recurrent sinopulmonary infections. They require comprehensive treatment plans, including infection prevention precautions, along with management of COPD, asthma, and other conditions that would predispose them to infections. Aggressive antibiotic therapy and prophylaxis are recommended for patients with recurrent infections. Immunoglobulin replacement therapy is recommended in patients with recurrent infections not resolved with prophylactic antibiotics. Evidence from retrospective studies have shown that IVIG treatment demonstrated reduced infections, decreases antibiotic use, and improved quality of life. American Academy of Allergy, Asthma, and Immunology 2016 guidelines state that IVIG may provide benefit in patients with isolated IgG subclass deficiency and recurrent infections. Recommended dosing is 400 - 600 mg/kg every 4 weeks.

- Combined immunodeficiency syndromes

  - Combined immunodeficiency syndromes include Wiskott-Aldrich syndrome, Severe Combined Immune Deficiency (SCID), DiGeorge Syndrome, and Ataxia Telangiectasia and are rare, inherited syndromes. These patients are prone to many opportunistic infections, and susceptibility often increases with age. Disease severity and degree of immunodeficiency is often dependent on the genetic defect. Patients with mild defects may not present with symptoms until early adulthood. SCID is often differentiated from other combined immunodeficiencies as a more severe condition with significant mortality as an infant due to infection.

  - American Academy of Allergy, Asthma, and Immunology 2016 guidelines recommend immunoglobulin replacement therapy in patients with primary immune defects with absent B-cells,

hypogammaglobulinemia, and impaired specific antibody production. Immunoglobulin replacement therapy is also FDA approved for the treatment of combined immunodeficiency syndromes, including Wiskott-Aldrich syndrome and SCID. There are many combined immunodeficiencies, each with different molecular genetic defects. Please refer to clinical guidelines and literature to determine disease-specific diagnostic criteria and information about specific molecular genetic defects. Recommended dosing is usually 400 - 600 mg/kg every 4 weeks.

- Idiopathic hypogammaglobulinemia

    - Hypogammaglobulinemia is a general term describing serum levels of IgG which are below the lower limits of normal. Diagnosis of a primary immunodeficiency is often retrospective and of exclusion. Patients with hypogammaglobulinemia should receive a comprehensive treatment plan, including infection prevention precautions, antibiotic prophylaxis, and adequate management of disease states that would predispose them to infections, including asthma and COPD. In patients with recurrent infections despite these measures, immunoglobulin replacement therapy is appropriate. American Academy of Allergy, Asthma, and Immunology 2016 guidelines recommend immunoglobulin replacement therapy in patients with hypogammaglobulinemia and impaired specific antibody production. Recommended dosing is usually 400 - 600 mg/kg every 4 weeks in these patients.

- Prophylactic post exposure for hepatitis A, measles (rubeola), varicella, and rubella in early pregnancy (GammaSTAN only)

    - Human immune globulin (IG) is a blood product used to provide antibodies for short-term prevention of infectious diseases. GamaSTAN is the only intravenous immunoglobulin product approved for the use of post-exposure prophylaxis for Hepatitis A, measles, varicella, and rubella in early pregnancy. Its labeled indications are as follows:

        - Prophylaxis following exposure to hepatitis A. It is not indicated in persons with clinical manifestations of hepatitis A or in those exposed more than 2 weeks previously.

        - To prevent or modify measles in a susceptible person, one who has not been vaccinated and has not had measles previously, exposed fewer than 6 days previously. GamaSTAN is also indicated for pregnant women without evidence of immunity and may be especially indicated for susceptible household contacts of measles patients, particularly contacts under 1 year of age, for whom the risk of complications is highest.

        - To modify varicella. Passive immunization against varicella in immunosuppressed patients is best accomplished by use of varicella zoster immune globulin (human). If unavailable, GamaSTAN, promptly given, may also modify varicella.

        - To modify rubella in exposed women who will not consider a therapeutic abortion.

    - Hepatitis A

        - IG provides protection against hepatitis A through passive transfer of antibody and has been shown to be 80 - 90% effective at preventing hepatitis A when administered within 2 weeks of exposure. Efficacy is greatest for post-exposure prophylaxis when IG is administered early in the incubation period. When administered later in the incubation period, IG might only attenuate the clinical expression of HAV infection.

- According to the Advisory Committee on Immunization Practices (ACIP) recommendations for prevention of hepatitis A through active or passive immunization, people who have recently been exposed to Hepatitis A and have not been previously vaccinated should receive a single dose of IG as soon as possible within two weeks of exposure as efficacy when administered after 2 weeks has not been established.

- If the hepatitis A vaccine is recommended for the person receiving IG, it may be administered simultaneously at a separate injection site.

- Measles (Rubeola)

  - IG has historically been the blood product of choice for short-term measles prophylaxis and has been used as prophylaxis to prevent or attenuate measles disease since the 1940s, when it was demonstrated that IG can reduce the risk for measles or modify disease if administered within 6 days of exposure with a dose response effect.

  - The ACIP recommends IG to prevent or modify measles in persons who are nonimmune within 6 days of exposure. It is not indicated for people who have received at least 1 dose of measles-containing vaccine at an age of greater than or equal to 12 months unless they are severely immunocompromised. Susceptible patient groups at risk for severe disease and complications from measles who should receive IG according to the ACIP recommendations include infants less than 12 months of age, pregnant women without evidence of measles immunity, and severely immunocompromised persons regardless of immunologic or vaccination status.

  - Nonimmune patients 12 months of age or older who were exposed to measles and received GamaSTAN should also receive a measles vaccine, however, measles vaccine must be administered separately at least 5 months after GamaSTAN at which point the measles antibody titer will have disappeared.

  - IG is not recommended to control measles outbreaks, but rather to reduce the risk for infection and complications in the person receiving it. IG has not been shown to prevent rubella or mumps infection after exposure and is not recommended for that purpose.

- Varicella

  - VariZIG®, a varicella zoster immune globulin preparation, is approved by the FDA and recommended by the ACIP for use as post-exposure prophylaxis of varicella in patients at high risk for severe disease who lack evidence of varicella immunity and for whom the vaccine is contraindicated. VariZIG is approved to be administered as soon as possible following varicella exposure, ideally within 96 hours for greatest effectiveness and after no more than 10 days. VariZIG is intended to reduce the severity of varicella. There is no convincing evidence that it will reduce the incidence of infection after exposure or modify established varicella infections. High risk groups for whom VariZIG is indicated include: immunocompromised children and adults, newborns of mothers with varicella shortly before or after delivery, premature infants, neonates and infants less than 1 year of age, adults without evidence of immunity, and pregnant women.

  - If VariZIG is unavailable, GamaSTAN may be given promptly to modify varicella post-exposure in immunosuppressed patients.

- Rubella

- Rubella infection in pregnant women, especially during the first trimester, can result in miscarriages, stillbirths, and congenital rubella syndrome (CRS; an array of birth defects that often includes cataracts, hearing loss, mental retardation, and congenital heart defects). In addition, infants with CRS frequently exhibit both intrauterine and postnatal growth retardation. The risk for congenital infection and defects is highest during the first 12 weeks of gestation, and the risk for any defect decreases after the 12th week of gestation.

- MMR vaccines should not be administered to women known to be pregnant or attempting to become pregnant. Additionally, post exposure MMR vaccination has not been shown to prevent or alter the clinical severity of rubella or mumps and is therefore not recommended for this purpose.

- Some studies have suggested that the use of GamaSTAN in susceptible women post-rubella exposure can lessen the likelihood of infection and fetal damage. As such, GamaSTAN may be beneficial to modify rubella in pregnant women who will not consider a therapeutic abortion. GamaSTAN is not, however, recommended or approved for routine prophylaxis in early pregnancy in unexposed women.

- Pure red cell aplasia (PRCA)

  - Pure red cell aplasia is a syndrome defined by a normocytic normochromic anemia with severe reticulocytopenia and marked reduction or absence of erythroid precursors from the bone marrow. Acquired PRCA may be either a primary disorder or secondary to some other disorder or agent. Primary acquired PRCA is an autoimmune disorder that is frequently antibody-mediated. Myelodysplastic syndromes may also present with the morphologic appearance of PRCA. Secondary acquired PRCA may be associated with collagen vascular or autoimmune disorders such as systemic lupus erythematosus; lymphoproliferative disorders such as chronic lymphocytic leukemia or large granular lymphocyte leukemia; infections, particularly parvovirus B19; thymoma and other solid tumors; or a variety of other disorders, drugs, or toxic agents.

  - Diagnosis of PRCA is established when the patient meets all of the following: normocytic, normochromatic red blood cells; an absolute reticulocyte count less than 10,000/µL (less than 1% reticulocytes); normal white blood cell and platelet counts in the absence of a concurrent disorder such as CLL; less than 1% erythroblasts on bone marrow differential count; and no significant abnormalities in the myeloid, lymphocytic, or megakaryocyte lineages, unless the patient has a concurrent diagnosis of CLL or CML.

  - Once a diagnosis is confirmed, the next step is to determine the cause which dictates the patient's treatment course. Testing should be done to distinguish between idiopathic, myelodysplastic, or secondary PRCA. All individuals who do not have CLL, CML, or myelodysplastic syndrome should have nucleic acid testing of peripheral blood for parvovirus B19 and treatment should not begin until those results are back. If the patient is taking a drug known to cause PRCA, the drug should be discontinued immediately. All other possible secondary causes should be investigated as appropriate as well.

  - For most causes of PRCA, immunosuppression is considered first-line therapy. However, if the patient is found to have PRCA due to parvovirus B19, IVIG is considered first-line therapy. IVIG contains antibodies against parvovirus and can reverse PRCA. Responses have been reported with doses as low as 400 mg/kg, although some have used the 2 g/kg dose divided over two to five days. While good response with IVIG is seen in patients with parvovirus B19, IVIG has not shown good efficacy in PRCA due to other causes.

- Refractory Pemphigus Foliaceous

- Pemphigus is a group of potentially life-threatening blistering disorders characterized by intraepithelial blisters in mucous membranes and skin that form due to a loss of keratinocyte adhesion. There are four major types: pemphigus vulgaris, pemphigus foliaceus, immunoglobulin A (IgA) pemphigus, and paraneoplastic pemphigus. Each form is distinguished by their own clinical features, autoantigens, and laboratory findings. Pemphigus vulgaris and pemphigus foliaceus are the two most common forms of pemphigus.

- Pemphigus foliaceus is an autoimmune skin disorder characterized by the loss of intercellular adhesion of keratinocytes in the upper parts of the epidermis that results in the formation of superficial blisters. The most common sites of involvement include the scalp, face, and trunk. Skin lesions are typically small, scattered, superficial blisters that rapidly evolve into scaly and crusted erosions that can remain localized or converge to cover large areas of the skin. The Nikolsy sign, induction of skin blistering with manual pressure, is often present. Variants of pemphigus foliaceus include endemic pemphigus foliaceus, which presents similarly to the idiopathic form but is related to an environmental trigger, and pemphigus erythematosus, which describes pemphigus foliaceus localized to the malar region of the face. Pemphigus foliaceus may also be drug-induced with manifestations similar to idiopathic disease.

- Assessing clinical, histologic, immunopathologic, and serologic findings is essential to proper diagnosis. Diagnosis requires clinical presentation and histopathology consistent with pemphigus foliaceus with either a positive DIF microscopy or serologic detection of autoantibodies against epithelial cell surface antigens. The following tests can confirm diagnosis of disease: lesional skin or mucosal biopsy for routine hematoxylin and eosin (H&E) staining; perilesional skin or mucosal biopsy for direct immunofluorescence (DIF); serum collection for enzyme-linked immunosorbent assay (ELISA) and indirect immunofluorescence (IIF). All patients with pemphigus foliaceus have positive DIF results demonstrating intercellular deposition of IgG, though negative DIF studies may occur in patients with drug-induced pemphigus. IIF demonstrates intercellular deposits of IGG. Greater than 80% of patients with pemphigus foliaceus have circulating antibodies detectable by IIF. IIF cannot distinguish between pemphigus foliaceus and vulgaris. ELISA for IgG antibodies to desmoglein 1 and desmoglein 3 is more sensitive and specific than IIF for diagnosing pemphigus vulgaris and pemphigus foliaceus, with a sensitivity greater than 90%. Desmoglein 1 autoantibodies are found on ELISA for pemphigus foliaceus.

- Differential diagnosis includes seborrheic dermatitis, impetigo, subacute cutaneous lupus erythematosus, IgA pemphigus, and the non-IgA pemphigus form of subcorneal pustular dermatosis.

- Pemphigus foliaceus is associated with the potential for severe morbidity and mortality therefore, treatment is indicated at the time of disease onset regardless of presenting disease severity. The goal of treatment is to induce complete remission while minimizing treatment-related adverse effects.

- An international consensus of experts supports the use of systemic glucocorticoids as first-line therapy for pemphigus foliaceus. Systemic glucocorticoids are typically given to attain rapid disease control with clinically significant improvement seen within 2 - 3 weeks. Their use is supported by randomized trials and studies documenting improvement in pemphigus with glucocorticoid monotherapy as well as extensive clinical experience. Oral therapy with prednisone, methylprednisolone, or prednisolone is the most common mode of administration at 0.5 to 1.5 mg/kg/day of prednisone or prednisolone, though higher doses can also be used. Full disease control requires 6 - 8 weeks. Tapering should begin once disease activity is under control with a goal of reaching the lowest dose needed to keep the disease controlled.

- Immunomodulators are used adjunctively to minimize glucocorticoid consumption and reduce the risk of adverse effects of long-term and high-dose glucocorticoid therapy. They can be used at the onset of therapy particularly in cases of increased risk with corticosteroid therapy, complications due to prolonged use, or dose dependency above 10 mg/day of prednisone. First-line corticosteroid-sparing

immunomodulator agents according to an international consensus of experts include azathioprine and mycophenolate mofetil. Adjuvant therapy is maintained until oral glucocorticoids have been completely discontinued and dose reduction begins 8 weeks after discontinuation of glucocorticoids. There is limited evidence that adding adjuvants is superior to corticosteroid monotherapy. Evidence has shown that the primary benefit of adjuvant therapy is in its glucocorticoid-sparing effect rather than a disease-modifying effect.

- Rituximab may also be used as a first-line treatment in new-onset moderate-to-severe pemphigus along with prednisone to allow for reduced prednisone doses, lower rates of corticosteroid-induced side effects, and more rapid corticosteroid tapering. A limiting factor to this regimen for initial treatment, however, is the high cost of rituximab.

- Disease activity is considered under control after a period of weeks during which no new lesions form, the Nikolsy sign is no longer present, and the majority of lesions have healed. Therapy at this point should be slowly reduced to the lowest dose required to prevent new lesions from appearing. Glucocorticoids are tapered first followed by a gradual reduction of non-steroidal adjuvant.

- Patients with refractory pemphigus foliaceus unresponsive to traditional first-line treatment may benefit from rituximab, IVIG, immunoadsorption, plasmapheresis, or cyclophosphamide. There is a lack of robust, high-quality literature on the treatment of refractory pemphigus in addition to a lack of definitive guidelines on how to best approach refractory treatment. Choice of treatment is influenced by patient tolerability, treatment availability, and treatment-specific contraindications.

- IVIG in refractory pemphigus foliaceus is typically combined with systemic corticosteroids initially and immunomodulator adjuvants. The recommended dose of IVIG for refractory pemphigus foliaceus is 2 g/kg over 2 to 5 days per month.

- Solid organ transplant

  - Patients at high risk for antibody mediated rejection (AMR) includes but is not limited to highly sensitized patients based on panel reactive antibody evaluation, those receiving an ABO incompatible organ, specific characteristics of donor-specific antibodies such as type and strength. AMR can occur after transplant, most commonly within 6 months.

  - Pre-treatment with IVIG (desensitization) has been shown to reduce the risk of AMR in highly sensitized solid organ transplant patients. The goal of therapy is early antibody elimination with IVIG, pheresis, or a combination of modalities. A variety of protocols have been developed for the use of IVIG in treating AMR after solid organ transplant. The usual dose of IVIG is 2 g/kg every 4 weeks.

- Stiff Person Syndrome

  - Stiff-person syndrome (SPS, also referred to as stiff-man syndrome) is a rare disorder involving progressive muscle stiffness, rigidity, and spasm involving the axial muscles that results in severely impaired ambulation. Women are affected two to three times more often than men with the average age of presentation between 20 and 50 years. SPS is often associated with type 1 diabetes mellitus and other autoimmune disorders.

  - The three major types of SPS include Classic SPS, partial SPS, and paraneoplastic SPS. Classic SPS accounts for 70 - 80% of SPS patients; characteristics of classic SPS include truncal stiffness, generalized rigidity, and frequent muscle spasms, all of which result in a wide-based, awkward gait. The

clinical hallmark of SPS is an extreme degree of muscle stiffness and rigidity. Partial SPS accounts for 10 - 15% of SPS patients, the most common form being stiff-limb syndrome where patients present with difficulty ambulating due to stiffness and lack of mobility affecting one limb (typically the leg) while sparing the trunk. Paraneoplastic SPS is extremely rare and seen in less than 2% of SPS patients. Clinically, paraneoplastic SPS is indistinguishable from classic SPS; however, paraneoplastic SPS patients are usually glutamic acid decarboxylase (GAD) antibody-negative and often have concurrent features of an underlying neoplasm. Malignancies associated with SPS include breast cancer, lung cancer, and Hodgkin lymphoma. Remission of neurologic symptoms has been noted after excision of the tumor and subsequent glucocorticoid treatment.

- There are no formally accepted criteria for diagnosing SPS. Muscle hardening to a board-like sensation is probably the most specific clinical observation establishing diagnosis. The presence of the following is generally considered necessary for diagnosis: stiffness in axial and limb muscles resulting in impaired ambulation; presence of superimposed episodic spasms precipitated by sudden movement, noise, or emotional upset; a positive therapeutic response to oral diazepam or findings of continuous motor-unit activity on electromyography (EMG) are abolished by IV diazepam; and absence of other neurologic disorders that could explain the clinical features.

- Diagnostic evaluation may include:

    - Anti-glutamic acid decarboxylase (GAD) antibody testing, which is positive in approximately 2/3 of patients. If present, anti-GAD antibodies support diagnosis; however, they may be absent.

    - A therapeutic trial of diazepam starting at 5 mg orally four times daily and slowly titrating up to the max dose required for symptom control without excessive sedation.

    - EMG testing including to evaluate response to oral diazepam

- In patients with characteristic clinical findings, anti-GAD antibodies, and a positive response to diazepam, diagnosis can be made without an EMG. The pain and stiffness characteristic of SPS, however, may mimic other conditions including ankylosing spondylitis, Parkinson disease, tetanus, axial dystonia, and focal limb or joint disorders. Alternative diagnoses must be ruled out.

- Treatment of SPS is directed at controlling symptoms to improve mobility and function. Benzodiazepines are considered the ideal initial symptomatic treatment for SPS with either diazepam 20 - 80 mg/day in three to four divided doses or clonazepam 10 - 30 mg orally two to four times daily. Diazepam daily doses to control disease may be as high as 100 – 200 mg/day while clonazepam can reach a maximum of 24 – 32 mg/day.

- In patients intolerant to high doses of benzodiazepines or with an unsatisfactory response, clinical experience supports the use of baclofen beginning at 10 mg 2 - 3 times daily with a gradual upward titration to a maximum of 80 mg daily in divided doses. Baclofen can be used as monotherapy or in conjunction to benzodiazepine therapy depending on the extent of benefit achieved from the maximally tolerated benzodiazepine. The use of baclofen is supported by clinical experience thought it has not been tested in randomized trials.

- For patients with continued inadequate symptomatic relief and in patients with severe disease where

symptoms continue to significantly interfere with activities of daily living, the use of immune modulating therapy is recommended. IVIG is generally initiated in patients lacking symptomatic relief after the use of benzodiazepines and/or baclofen, corresponding to the European Federation of Neurological Societies (EFNS) 2008 guidelines for the use of IVIG in the treatment of neurological diseases. IVIG is administered initially at 2 g/kg given in a treatment course over 2 - 3 infusions, each usually separated by 3 - 5 days. If the first round of IVIG does not produce a significant change in function, a second round can be tried with dosing of 2 g/kg per infusion given every 2 weeks for up to 4 doses.

- Additional therapies that may be beneficial for SPS based on findings from case reports and small uncontrolled series include corticosteroids, azathioprine, levetiracetam, valproic acid, gabapentin, plasma exchange, and rituximab/rituximab biosimilars.

- Systemic Lupus Erythematous (SLE)

  - Systemic lupus erythematosus (SLE) is a chronic autoimmune disease that can affect virtually any organ in the body. SLE is a clinically heterogenous disease with patients presenting with variable clinical manifestations that range from mild joint and skin involvement to life-threatening renal, hematologic, or central nervous system involvement. The diagnosis is generally based on clinical grounds in the presence of characteristic serological or laboratory abnormalities after having excluded alternative diagnoses. A prominent feature of disease is the production of antinuclear antibodies (ANA). Constitutional symptoms, such as, fatigue, fever, and weight loss, are typically present in most SLE patients at some point during the disease course with fatigue being the most common complaint. Arthritis and arthralgias occur in over 90% of SLE patients and often present as one of the earliest manifestations of disease. Mucocutaneous, cardiac, renal, gastrointestinal, pulmonary, neuropsychiatric, hematologic, and ophthalmologic involvement may also occur.

  - The goals of SLE therapy are to ensure long-term survival, have the lowest possible disease activity, prevent organ damage, minimize drug-related toxicities, and improve quality of life. Treatment is individualized based on the clinical manifestations, disease activity and severity, and patient comorbidities.

  - Treatment in SLE should aim at remission or low disease activity and prevention of flares in all organs while maintained on the lowest possible dose of steroids. SLE flares can be treated according to the severity of organ involvement via adjusting current ongoing therapies to higher doses, switching medications, or adding new therapies. Treatment of organ or life-threatening SLE includes an initial treatment with high-intensity immunosuppressive therapy to control disease activity followed by less intensive long-term therapy to consolidate the response and prevent relapse.

  - According to the 2019 update of the EULAR recommendations for the management of SLE, hydroxychloroquine is recommended for all patients with SLE unless contraindicated. Glucocorticoids can provide rapid symptom relief and may be used with hydroxychloroquine. The dose and route of administration of glucocorticoids are dependent on the type and severity of organ involvement. Immunosuppressive therapies such as methotrexate, azathioprine, and mycophenolate should be considered if a patient is not responding to hydroxychloroquine with or without glucocorticoids or is unable to reduce glucocorticoid doses to under 7.5 mg/day for chronic use. They can also be included as initial therapy for organ-threatening disease. Cyclophosphamide is another immunosuppressant option, however, it's recommended only to be used for severe organ threatening or life-threatening SLE or as rescue therapy for patients unresponsive to other immunosuppressants.

  - Hematologic manifestations of SLE frequently requiring treatment include thrombocytopenia and autoimmune hemolytic anemia (AIHA). The 2019 EULAR recommendations suggest first-line treatment of

significant lupus thrombocytopenia, platelets less than 30,000/mm^3, with high dose glucocorticoids in combination with an immunosuppressant, such as, azathioprine, mycophenolate mofetil, or cyclosporine. The role of the immunosuppressant is primarily for maintenance of response after acute treatment and as a glucocorticoid-sparing agent. IVIG may be considered in the acute phase after an inadequate response to high-dose glucocorticoids or to avoid glucocorticoid-related complications. The recommended dose of IVIG per the guidelines is 1 g/kg/day for 1 - 2 days. Refractory cases may be treated with rituximab/rituximab biosimilar or cyclophosphamide.

- The use of IVIG in SLE outside of significant lupus thrombocytopenia is not recommended by or addressed in the 2019 EULAR guidelines. Some small case reports and series have shown some benefit of IVIG in cutaneous lupus erythematosus, central nervous system lupus, and lupus myocarditis, however, there is a paucity of robust data or literature definitively supporting the clinical efficacy and use of IVIG for these and other manifestations of SLE.

- There are multiple IVIG treatment options. There an no clinical trials comparing the efficacy of one therapy to another. Choice of therapy should be based on patient characteristics, side effect profiles, cost, and availability.

- Immune globulin replacement therapy is indicated for many labeled and off-label indications and is traditionally dosed using a patient's actual body weight. IVIG and SCIG products have insignificant distribution into fat tissue and are only present in the intravascular space and extracellular fluids. Clinical literature supports alternative dosing strategies that provide comparable drug exposure without altering the clinical outcomes of treatment. Therefore, pateints should be dosed using adjusted body weight in situations where the pateint's dody mass index is 30 kg/m^2 or greater or their actual body weight is 20% to 30% higher than their ideal body weight.

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Policy History		
#	Date	Change Description
3.7	Effective Date: 04/11/2024	Annual review of criteria was performed, no changes were made
3.6	Effective Date: 04/01/2024	UM medical management system update for MAPPO and BCNA for Alyglo
3.5	Effective Date: 02/08/2024	Updated to add Flebogamma DIF and Alyglo
3.4	Effective Date: 01/18/2024	UM medical management system update for BCBS and BCN for Alyglo
3.3	Effective Date: 06/08/2023	Updated Inflammatory demyelinating polyneuropathy (acute) criteria due to Medical director's feedback to require lumbar puncture and if non-confirmotory, then require EMG/NCS or an MRI
3.2	Effective Date: 04/06/2023	Updated to allow approval for no less than 60 days for any indication
3.1	Effective Date: 10/06/2022	Updated to not allow use of IVIG with any other biologic therapy for myasthenia gravis
2.9	Effective Date: 02/10/2022	Annual review of criteria was performed, no changes were made
2.8	Effective Date: 02/04/2021	Updated all criteria to reflect current recommendations for diagnosis and treatment
2.7	Effective Date: 09/28/2020	UM medical management system update for BCNA and MAPPO for Cutaquig and Xembify
2.6	Effective Date: 04/16/2020	Updated weight based dosing changes and cost table
2.5	Effective Date: 02/03/2020	UM medical management system update for BCNA and MAPPO for Cuvitru and Panzyga
2.4	Effective Date: 11/07/2019	Removed Flebogamma DIF and updated weight based dosing requirements
2.3	Effective Date: 10/01/2019	UM medical management system update for BCNA and MAPPO for Asceniv
2.2	Effective Date: 08/15/2019	UM medical management system update for BCBSM and BCN for Xembify Added Xembify and Gammaked

2.1	Effective Date: 06/01/2019	UM medical management system update for BCBSM and BCN for Asceniv
2.0	Effective Date: 02/14/2019	Added Cutaquig
1.9	Effective Date: 12/06/2018	Added Panzyga
1.8	Effective Date: 11/01/2018	Reviewed policy for new Hizentra indication but no changes required. Updated criteria for hypogammaglobulinemia – added IgG levels, removed necessity for immunization after no response to vaccines.
1.7	Effective Date: 05/03/2018	Added criteria for autoimmune encephalitis and PANDAS was placed under investigational use
1.6	Effective Date: 08/10/2017	Updated CIDP criteria.
1.5	Effective Date: 02/09/2017	Added Cuvitru (new product) and GamaSTAN. Updated criteria for MMN.
1.4	Effective Date: 11/10/2016	Annual Review of Policies
1.3	Effective Date: 02/12/2015	Updated criteria – Require 2 vs. 1 preferred IG products; Added HyQvia (new product)
1.2	Effective Date: 05/08/2014	Updated criteria - include preferred product
1.1	Effective Date: 05/02/2013	Added Bivigam (new product)
1.0	Effective Date: 11/2012	Initial Dose changed to Usual Doses Investigational indications updated: Add: • Atopic dermatitis • Autism • Hemolytic anemia • Hyper IgE syndrome • Miller-Fisher syndrome • Neuromyelitis optica • Steven's Johnson syndrome • Wegener's granulomatosis

Line of Business	PA Required in Medical Management System (Yes/No)
BCBS	Yes
BCN	Yes
MAPPO	Yes
BCNA	Yes

** The prescribing information for a drug is subject to change. To ensure you are reading the most current information it is advised that you reference the most updated prescribing information by visiting the drug or manufacturer website or http://dailymed.nlm.nih.gov/dailymed/index.cfm.*