BlueCross BlueShield of Alabama

Immune Globulins
Prior Authorization Criteria
Program Summary

This prior authorization applies to Commercial and Health Insurance Marketplace formularies only.

OBJECTIVE
The intent of the prior authorization criteria for the immune globulins is to direct use to Food and Drug Administration approved label indications as well as indications supported by clinical guidelines. Currently available immune globulin preparations are produced from pooled human plasma involving a number of processes and there is limited supply of product. Use of immune globulins should be carefully considered. The prior authorization criteria for the immune globulins will consider use of these agents for unlabeled indications if there is evidence available or submitted by the prescriber supporting its intended use.

TARGET DRUGS
Cuvitru™ SCIG
Gammagard® Liquid IVIG
Gammaked™ Liquid IVIG
Gamunex®-C SCIG/IVIG
Hizentra™ SCIG
Hyqvia SCIG

PRIOR AUTHORIZATION CRITERIA FOR APPROVAL
Initial Evaluation
Immune Globulins will be approved when ALL of the following are met:
Choose ONE of the following:

1. The patient has been diagnosed with:
    a. ONE of the following Primary immunodeficiencies:
        i. Selective IgG subclass deficiency AND ALL of the following:
            1. Deficiency of 1 or more IgG subclasses (e.g. IgG1, IgG2, IgG3, or IgG4) < 2 standard deviations (SD) below age-specific mean, assessed on 2 separate occasions during infection free period
            AND
            2. Poor antibody response to vaccines (and/or absent isohaemagglutinins); i.e. absence of protective levels despite vaccination)
            AND
            3. Evidence of recurrent, persistent, severe, difficult-to-treat infections (e.g. recurring otitis media, bronchiectasis, recurrent infections requiring IV antibiotics, etc.) despite aggressive management and treatment with antibiotics

        OR

        ii. Specific antibody deficiency (SAD) AND normal levels of immunoglobulin and normal levels of IgG subclasses with BOTH of the following:
            1. Poor antibody response to vaccines (and/or absent isohaemagglutinins); i.e. absence of protective levels despite vaccination)

AND

2. Evidence of recurrent, persistent, severe, difficult-to-treat infections (e.g. recurring otitis media, bronchiectasis, recurrent infections requiring IV antibiotics, etc.) despite aggressive management and treatment with antibiotics

OR

iii. All other Primary immunodeficiencies [including, but not limited to, Common variable immunodeficiency (CVID), X-linked agammaglobulinemia (XLA)/congenital agammaglobulinemia/Bruton's agammaglobulinemia, Autosomal Recessive Agammaglobulinemia (ARA), primary hypogammaglobulinemia, X-linked immunodeficiency, severe combined immunodeficiency (SCID), combined immunodeficiency syndromes (e.g. Ataxia Telangiectasia, DiGeorge syndrome, Wiskott-Aldrich Syndrome, zeta chain-associated protein 70, Hyper-IgM syndrome), any other humoral immunodeficiency] and ONE of the following:

1. Agammaglobulinemia and ONE of the following:
    a. Total IgG < 200 mg/dL (at baseline prior to immune globulin therapy) **OR**
    b. Patients with an abnormal Bruton tyrosine kinase (BTK) gene/absence of BTK protein **OR**
    c. Absence of B lymphocytes

OR

2. Hypogammaglobulinemia and ALL of:
    a. Total IgG < 700 mg/dL (at baseline prior to immune globulin therapy)
    AND
    b. Poor antibody response to vaccines (and/or absent isohaemagglutinins); i.e. absence of protective levels despite vaccination
    AND
    c. Evidence of recurrent, persistent, severe, difficult-to-treat infections (e.g. recurring otitis media, bronchiectasis, recurrent infections requiring IV antibiotics, etc.) despite aggressive management and treatment with antibiotics

OR

b. Chronic lymphocytic leukemia with reduced IgG and **BOTH** of the following:
    i. The patient has hypogammaglobulinemia (total IgG < 700 mg/dL at baseline prior to immune globulin therapy)
    AND
    ii. ONE of the following:
        1. One severe bacterial infection within the last year **OR**
        2. Evidence of specific antibody deficiency

OR

c. Prevention of bacterial infections in HIV-treated patients **AND** the patient is currently on antiretroviral therapy

OR

d. Idiopathic thrombocytopenia purpura and **ONE** of the following:
    i. The patient has failed conventional therapy (e.g. corticosteroids) **OR**
    ii. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to all conventional therapy agents (e.g. corticosteroids)

OR

e. Dermatomyositis and **ONE** of the following:
    i. The patient has failed conventional therapy (e.g. immunosuppressants, corticosteroids) **OR**
    ii. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to all conventional therapy agents **OR**
    iii. The patient has been diagnosed with juvenile dermatomyositis

OR

f. Polymyositis and **ONE** of the following:
    i. The patient has failed conventional therapy (e.g. immunosuppressants, corticosteroids) **OR**
    ii. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to all conventional therapy agents

OR

g. Severe rheumatoid arthritis and **ONE** of the following:
    i. The patient has failed conventional therapy (e.g. tumor necrosis factor antagonists, DMARDS, Remicade, Xeljanz, Xeljanz XR) **OR**
    ii. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to all conventional therapy agents

OR

h. Myasthenia Gravis (MG) and **ONE** of the following:
    i. The patient is in acute myasthenic crisis with decompensation (e.g. acute episode of respiratory muscle weakness/respiratory failure/dysphagia/aspiration/major functional disability responsible for the discontinuation of physical activity) OR has severe refractory MG (e.g. major functional disability/weakness) **OR**
    ii. Immuneglobulin will be used prior to surgery (i.e. thymectomy) in a patient with MG crisis **OR**
    iii. The patient failed/has not been controlled with maximally tolerated immunomodulator therapy (e.g. corticosteroids, mycophenolate, cyclosporine, and/or azathioprine) **OR**
    iv. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to all immunomodulator therapy agents **OR**
    v. The patient has received plasma exchange within the last 30 days

OR

i. Multiple sclerosis and BOTH of the following:
    i. The patient has a diagnosis of relapsing remitting multiple sclerosis (RRMS) **AND**
    ii. The patient has had an insufficient response, documented failure, or FDA labeled contraindication to TWO Disease Modifying Agents FDA indicated for RRMS (e.g. Avonex, Aubagio, Betaseron, Copaxone (Glatopa), Extavia, Gilenya, Lemtrada, Plegridy, Rebif, Tecfidera, Tysabri or Zinbryta)

OR

j. Multiple myeloma **AND** the following:
    i. The patient has stable disease (i.e. not progressive) **AND** has recurrent infections despite antibiotic prophylaxis **AND** is currently (within past 30 days) on chemotherapy

OR

k. Acquired von Willebrand hemophilia and **ONE** of the following:
    i. The patient has failed conventional therapy (e.g. DDAVP, corticosteroids, cyclophosphamide, von Willebrand factor replacement therapy, FEIBA (factor eight inhibitor bypassing activity), rituximab, or recombinant factor VIIa) **OR**
    ii. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to all conventional agents

OR

l. Hemolytic disease of the newborn and **BOTH** of the following:
    i. The patient is using concurrent phototherapy **AND**
    ii. The patient has either Rhesus or ABO hemolytic disease

OR

m. Provision of passive immunity in **ONE** of the following susceptible individuals:
    i. Hepatitis A: The patient requires pre-exposure prophylaxis within 14 days **OR** the patient requires post exposure prophylaxis within 14 days **AND** falls under 1 of the following populations:
        1. Patients who cannot be vaccinated due to age (<12 months) **OR**
        2. Has a vaccination allergy or refusal of vaccination **OR**
        3. Infants born to mothers with acute hepatitis A prevention

    OR

    ii. Measles: For patients that have been exposed to measles within 6 days and are unvaccinated, and who have not previously had measles **OR**
    iii. Rubella: The patient is a pregnant woman, who will not consider therapeutic abortion, and requires post exposure prophylaxis within 72 hours of exposure to reduce the risk of infection and fetal damage **OR**
    iv. Varicella: For immunosuppressant patients that require post exposure prophylaxis because varicella zoster immune globulin is not available (cannot obtain vaccine within 96 hours of exposure)

OR

n. Prevention of bacterial infection in HIV-infected children and **ALL** of the following:
    i. Patient is <13 years old **AND**
    ii. CD4 count is >200 µL **AND**
    iii. Patient's IgG is <400 mg/dL (at baseline prior to immune globulin therapy)

OR

o. Refractory pemphigus vulgaris and **ALL** of the following:
    i. The patient has progressive, severe/extensive and/or debilitating disease

    AND

    ii. ONE of the following:
        1. The patient has failed conventional immunosuppressive therapy (e.g. azathioprine, cyclophosphamide, mycophenolate, corticosteroids)

        OR

        2. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to all conventional immunosuppressive therapy agents

OR

p. Primary immune defects with absent B cells

OR

q. Prior to solid organ transplant, treatment for patients at high risk of antibody-mediated rejection (AMR) including highly sensitized patients and those receiving ABO incompatible organ

OR

r. Post solid organ transplant, treatment of AMR

OR

s. Adult HIV associated thrombocytopenia

OR

t. Prevention and treatment of neonatal sepsis

OR

u. Graves Ophthalmopathy

OR

v. Fetomaternal alloimmune thrombocytopenia

OR

w. Post transfusion purpura

OR

x. Guillain-Barre syndrome

OR

y. Chronic inflammatory demyelinating polyneuropathy (CIDP)

OR

z. Multifocal motor neuropathy

OR

aa. Paraprotein associated demyelinating neuropathy – (IgM, IgA, or IgG)

OR

bb. Lambert-Eaton myasthenia syndrome (LEMS)

OR

cc. Intractable childhood epilepsy **OR**

dd. Rasmussen syndrome **OR**

ee. Kawasaki disease **OR**

ff. CMV-induced pneumonitis in solid organ transplant **OR**

gg. Rotaviral enterocolitis **OR**

hh. Bacterial infections in lymphoproliferative disease **OR**

ii. Prevention in acute graft vs. host disease (GVHD) after bone marrow transplant (BMT) **OR**

jj. Delayed pressure urticaria **OR**

kk. Prevention of acute humoral rejection in renal transplant **OR**

ll. Pediatric autoimmune psychiatric disorders associated with streptococcal infections **OR**

mm. Severe invasive group A streptococcal disease **OR**

nn. Severe, persistent, high-dose asthma **OR**

oo. Toxic epidermal necrolysis and Stevens-Johnson syndrome **OR**

pp. Low serum IgG levels induced by chemotherapy or following hematopoietic stem cell transplant (HSCT) for malignancy

OR

qq. Stiff-man syndrome (Moersch-Woltmann)

OR

rr. Monoclonal gammopathy

OR

ss. The use of the immune globulin product is supported by clinical evidence or the prescriber has submitted documentation in support of therapy with immune globulin for the intended diagnosis which has been reviewed and approved by the Clinical Review pharmacist

AND

2. ONE of the following:
    a. The dose is supported by FDA labeling, compendia, or clinical evidence
    OR
    b. The prescriber submitted clinical evidence supporting the requested dose for the intended use

Length of approval: 12 months unless otherwise indicated below (refer to Table 1)

Renewal Evaluation
Immune Globulins will be renewed when ALL of the following are met:
1. The patient has been previously approved for the requested agent through the Medical Drug Review Process
   AND
2. ONE of the following:
    a. The patient was previously approved for immune globulin (IG) therapy for short term use (i.e. ≤ 3 months) (refer to Table 1) **AND** the following:
        i. The prescriber has provided clinical documentation supporting continued use of the requested agent
    OR
    b. The patient was previously approved for chronic immune globulin (IG) therapy (e.g. for a diagnosis not noted in Table 1) **AND** one of the following:
        i. The patient has had clinical improvement OR disease stabilization (e.g. IgG level has improved from pre-treatment levels with the requested agent, reduction in the number and/or severity of difficult to treat infections, reduction in seizure frequency)
        OR
        ii. The prescriber has provided clinical documentation supporting continued use of the requested agent
   AND
3. ONE of the following:
    a. The dose is supported by FDA labeling, compendia, or clinical evidence
    OR
    b. The prescriber submitted clinical evidence supporting the requested dose for the intended use

Length of Approval: 12 months unless otherwise indicated below (refer to Table 1)

Table 1

Indication	Length of Approval
Measles, Rubella, Varicella	Once
Adult HIV associated thrombocytopenia	1 month
Rotaviral enterocolitis	1 month
Delayed pressure urticaria	1 month
Prevention of acute humoral rejection in renal transplant	1 month
CMV induced pneumonitis in solid organ transplant	3 months
Guillain-Barre Syndrome	3 months
Hepatitis A	3 months
Idiopathic thrombocytopenia purpura	3 months

Acquired von Willebrand hemophilia	3 months
Hemolytic disease of the newborn	3 months
Lambert-Eaton myasthenia syndrome	3 months
Myasthenia gravis crisis	3 months
Kawasaki disease	3 months
Prior to solid organ transplant, treatment for patients at high risk of antibody-mediated rejection (AMR) including highly sensitized patients and those receiving ABO incompatible organ	3 months
Post solid organ transplant, treatment of AMR	3 months
Prevention and treatment of neonatal sepsis	3 months
Severe invasive group A streptococcal disease	3 months
Toxic epidermal necrolysis and Steven Johnsons syndrome	3 months
Graves Ophthalmopathy	3 months
Post transfusion purpura	3 months
Prevention in acute graft vs. host disease (GVHD) after bone marrow transplant (BMT)	3 months
Pediatric autoimmune psychiatric disorders associated with streptococcal infections	3 months

FDA APPROVED INDICATIONS AND DOSAGE[1-10, 18-20,23,26,27,29,30,33]

	PID	CLL	ITP	KAWASAKI SYNDROME	OTHER	ROUTE	DOSE FORM
Bivigam™	✓					IV	10% solution
Carimune® NF	✓		✓			IV	Lyophilized powder
Cuvitru™ 20%	✓					SC	**20% solution**
Flebogamma®	✓					IV	5% solution
Flebogamma® 5% DIF	✓						10% Solution
Flebogamma® 10% DIF	✓		✓[d]				
GamaSTAN™ S/D					✓[a]	IM	16.5% solution
Gammagard® S/D, 5%, 10%	✓	✓	✓	✓		IV	Lyophilized powder
Gammagard® S/D, 5% IgA < 1 mcg/mL	✓	✓	✓	✓		IV	5% solution
Gammagard Liquid®	✓				✓[c]	SC, IV	10% solution
Gammaked	✓		✓		✓[b]	SC (PID only), IV	10% solution
Gammaplex Liquid®	✓		✓			IV	5% solution
Gamunex®-C	✓		✓		✓[b]	SC (PID only), IV	10% solution
Hizentra™	✓					**SC**	**20% solution**
Hyqvia	✓					**SC**	**10% solution**
Octagam®	✓					IV	**5% solution 10% solution**
Privigen™	✓		✓			IV	**10% solution**

PID=primary immunodeficiencies, CLL=chronic lymphocytic leukemia, HIV=human immunodeficiency virus, ITP=idiopathic thrombocytopenic purpura

[a] Prophylactic therapy for Hepatitis A, measles, Varicella, and Rubella

[b] Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)

[c] Multifocal Motor Neuropathy (MMN)

[d] Treatment of ITP in patients 2 years of age or older

CLINICAL RATIONALE

Immune globulin is a pooled blood product prepared from the serum of between 1000 and 15,000 donors.[11,12] Immune globulin is the treatment of choice for patients with antibody deficiencies and is often dosed 200-400 mg/kg every three weeks.[11,12] High dose (2

g/kg/month) regimens have been used in a variety of autoimmune and inflammatory disorders.[11,12] Clinical specialties that use immune globulin include: neurology, hematology, immunology, nephrology, rheumatology, and dermatology.[11] Immune globulin is FDA approved for six different indications.[12] Licensed indications account for less than 50% of the worldwide usage. The use of IVIG for additional conditions has more than doubled in the last decade.[23] There are numerous additional indications for immune globulin therapy as supported by clinical guidelines.[13, 20]

Adverse events of immune globulin therapy can be difficult to classify due to the diversity of components in the formulation.[13] Mild adverse events are common and may include low grade fever, headache, nausea, malaise, and myalgia. Infusion related reactions such as urticaria and fever can be prevented by premedicating patients with diphenhydramine and acetaminophen.[12,14] Tension headache is the most common adverse event associated with immune globulin use and ranges in frequency from 26%-61%.[13] Migraine headaches also occur and are more common in patients with a history of migraines.[14]

Serious adverse reactions with immune globulin therapy are rare. Acute renal failure was reported in 114 patients in the first 17 years of use, of which 17 patients died.[14] Acute renal failure has been associated with high dose immune globulin (2g/kg) and with use of sucrose containing products.[13,14] The FDA now recommends a maximum infusion rate of 3 mg sucrose/kg/min for sucrose containing preparations of immune globulin.[13,14] Aseptic meningitis has been reported in patients receiving high dose immune globulin, with the majority of patients recovering within five days of symptom onset. Immune globulin preparations may increase blood viscosity, which has been identified as a possible cause of stroke, MI, and thrombosis in patients receiving immune globulin.[13,14] Anaphylaxis has rarely occurred with immune globulin.[13,14] Because immune globulin products are derived from donor plasma, the transmission of infectious particles is possible.

DISEASE STATES OF FDA APPROVED INDICATIONS

Primary immunodeficiency

Immune globulin is the current mainstay of therapy for patients with primary immunodeficiencies. Immune globulin protects against infection by providing protective antibodies and humoral immunity. A study in 31 children with X-linked agammaglobulinemia showed that immune globulin reduced the incidence of infection from 0.4 per patient year to 0.06 per patient year ($p<0.001$).[15] In a study of adults with common variable immunodeficiency, immune globulin reduced the incidence of bacterial pneumonia from 84% before treatment to 11% after treatment with immune globulin.[15]

Idiopathic thrombocytopenic purpura (ITP)

Patients are often asymptomatic but may exhibit signs of bleeding including bruising, purpura, and mild mucosal hemorrhage. Use in ITP is often reserved for patients with overt bleeding[32] or need an immediate increase in platelet count or in patients who have failed corticosteroids.[15]

Kawasaki disease

The disease is characterized by a remittent fever, erythematous rash (often on the trunk), and red swollen lips and tongue.[17] Cardiac complications including coronary artery aneurysm, myocardial infarction, CHF, and arrhythmias are the most common cause of death in patients with Kawasaki disease.[16] A meta-analysis of randomized control trials (RCTs) found a significant decrease in new coronary artery aneurysms with the use of immune globulin.[15]

Chronic lymphocytic leukemia (CLL), bone marrow transplant, pediatric HIV
CLL, bone marrow transplant (BMT), and HIV are all associated with immunosuppression and an increased risk of infection. Immune globulin can provide additional protection against infection by supplementing humoral immunity. Trials comparing immune globulin to placebo in these disease states has shown decreased bacterial infections but not a decrease in mortality.[15] The advent of antimicrobial prophylaxis and Highly Active Anti-Retroviral Therapy (HAART) (in the case of HIV) has decreased the need for immune globulin.

Hepatitis A (HAV) [27,28]
The disease is usually transmitted via the fecal-oral route either by person-to-person contact or ingestion of contaminated food or water. Transmission is facilitated by poor personal hygiene, poor sanitation, and intimate contact (e.g., intrahousehold or sexual exposure). Illicit drug users are the most common source of HAV. The incubation period for HAV infection following exposure to the virus ranges from 15-50 days (average of 28 days). Use in HAV patients is to provide passive immunity for pre-exposure or post-exposure prophylaxis in susceptible individuals who are at risk of or have been exposed to the virus. Immune globulin (GamaSTAN S/D) is used for short-term protection against HAV in unvaccinated patients.

Measles[27,28,29]
Measles is a highly contagious respiratory disease caused by the measles virus. Measles spread through the air by breathing. Symptoms of measles include fever, runny nose, cough and rash all over the body. Immune globulin (GamaSTAN S/D) is used to prevent or modify symptoms of measles in susceptible persons (unvaccinated and has not had measles) exposed to the disease within 6 days previously.

Rubella[27,28]
Rubella, also known as German Measles, or three-day measles is a contagious viral infection caused by the rubella virus. The virus is spread through the air or close contact. Immune globulin (GamaSTAN S/D) is recommended as post exposure prophylaxis in susceptible pregnant women who are exposed to a confirmed case of rubella early in pregnancy, and who do not consider terminating the pregnancy under any circumstances. These women should receive immune globulin within 72 hours of rubella exposure.

Varicella[27,28]
Varicella, commonly called the chickenpox, is a common childhood disease. It is caused by the varicella-zoster virus (VZV). The virus is spread through airborne particles, droplets in exhaled air, and fluid from the blisters or sores. Symptoms include fever, weakness, and rash and usually appear 14-16 days. Immune globulin (GamaSTAN S/D) is recommended for post exposure prophylaxis when Varicella-Zoster Immune Globulin is unavailable (e.g., cannot be obtained within 96 hours of exposure).

ADDITIONAL INDICATIONS SUPPORTED BY EVIDENCE[13, 21, 22, 24, 25, 31]

IVIG EVIDENCE BASED INDICATIONS		
Indication	**Guideline**	**Recommendation / Evidence Level**
Primary immune defects with absent B cells	AAAAI	B, 2b
Impaired specific antibody production (normogammaglobulinemia, agammaglobulinemia, hypogammaglobulinemia	AAAAI / NHS	B, 2b / C, 3
Prior to solid organ transplant, treatment of patients at high risk of antibody-mediated rejection, including highly sensitized patients, and those receiving ABO incompatible organ	NHS	Grey Indication / 1b
Following solid organ transplant, treatment of antibody-mediated rejection	NHS	Grey Indication / 1b
Chronic lymphocytic leukemia with reduced IgG and history of infections	AAAAI / NHS	A, 1b / A, 1b
Adult HIV associated thrombocytopenia	NHS	A, 1b
Prevention in neonatal sepsis	AAAAI	A, 1a
Graves Ophthalmopathy	AAAAI	A, 1b
Dermatomyositis	AAAAI / NHS	B, 2a / B, 2a
Polymyositis	AAAAI	B, 2a
Severe rheumatoid arthritis	AAAAI	B, 2b
*Fetomaternal alloimmune thrombocytopenia	AAAAI / NHS	C, 3
*Post transfusion purpura	AAAAI / NHS	C, 3
Guillain-Barre syndrome	AAAAI / NHS	A, 1a / A, 1a
Chronic demyelinating polyneuropathy	AAAAI / NHS	A, 1a / A, 1a
Multifocal motor neuropathy	AAAAI / NHS	A, 1a / A, 1a
Paraprotein associated demyelinating neuropathy - (IgM)	AAAAI / NHS	A, 1b / A, 1b
Paraprotein associated demyelinating neuropathy - (IgG or IgA)	NHS	A, 1b
Lambert-Eaton myasthenia syndrome (LEMS)	AAAAI / NHS	A, 1b / A, 1b

IVIG EVIDENCE BASED INDICATIONS		
Indication	**Guideline**	**Recommendation / Evidence Level**
Myasthenia Gravis - myasthenia crisis	AAAAI / NHS	B, 1b-2a / B, 1a
Stiff-man syndrome	AAAAI / NHS	A, 1b / A, 1b
Monoclonal gammopathy - multiple sclerosis	AAAAI	A, 1a
Intractable childhood epilepsy	AAAAI	A, 1a
Rasmussen syndrome	AAAAI / NHS	B, 2b
CMV-induced pneumonitis in solid organ transplant	AAAAI / NHS	A, 1b / A, 1b
Treatment of neonatal sepsis	AAAAI	A, 1a
Rotaviral enterocolitis	AAAAI	A, 1b
Bacterial infections in lymphoproliferative disease	AAAAI	B, 1b
Delayed pressure urticaria	AAAAI	B, 2b
Prevention of acute humoral rejection in renal transplant	AAAAI	A, 1b
Pediatric autoimmune psychiatric disorders associated with streptococcal infections	AAAAI	B, 2b
Severe invasive group A streptococcal disease	NHS	B, 1b
Severe, persistent, high-dose asthma	AAAAI	A, 1b
Toxic epidermal necrolysis and Stevens-Johnson syndrome	AAAAI / NHS	B, 2a / B, 2a
Low serum IgG levels following HSCT for malignancy	NHS	B, 2b
Multiple myeloma	NHS	A, 1b
Acquired von Willebrand hemophilia	NHS	B, 2a
Hemolytic disease of the newborn	NHS	B, 3

*Adding with limited evidence due to life threatening nature

Recommendation

Requires at least 1 randomized controlled trial as part of a body of literature of overall good quality and consistency addressing specific recommendation. (Evidence levels 1a, 1b).	A
Requires the availability of well conducted clinical studies but no randomized clinical trials on the topic of recommendation. (Evidence levels 2a, 2b)	B
Requires evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities. Indicates an absence of directly applicable clinical studies of good quality. (Evidence levels 3, 4)	C

Evidence Grade

From meta-analysis of randomized controlled studies	1a
From at least 1 randomized controlled study	1b
From at least 1 controlled trial without randomization	2a
From at least one other type of quasi-experimental study	2b
From non-experimental descriptive studies, such as comparative, correlation, or case-control studied	3
From expert committee reports or opinions or clinical experience of respected authorities or both	4

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