Updated Commissioning Criteria for the use of therapeutic immunoglobulin (Ig) in immunology, haematology, neurology and infectious diseases in England, November 2019

Prepared by NHS England Immunoglobulin Policy Working Group. Published by NHS England, in electronic format only

This updated commissioning criteria on the use of therapeutic immunoglobulin (Ig) in immunology, haematology, neurology and infectious diseases has been based on a previous review of the literature updated with a further evidence review, expert opinion and multi-organisational input. The criteria have been developed by the Ig policy working group following wide consultation with specialty experts, relevant scientific societies and the respective Clinical Reference Groups for haematology, immunology, neurology and infectious diseases. Recommendations on Ig dose and outcomes are based on a combination of available evidence and expert opinion. These criteria apply to the use of Ig in both adults and children.

As compared with the previous iteration of the Department of Health guidelines (2nd edition update; July 2011), it provides greater detail around the role, dose and place of Ig in the treatment pathway for individual indications alongside possible alternative treatment options. The colour coding scheme, which was previously devised for demand management but often utilised as a commissioning tool, has been replaced by categorisation of Ig use in to routinely commissioned or not commissioned categories based on the strength of evidence. Note: The Department of Health guidelines colour coding scheme will still apply if the demand management scheme is officially implemented in times of short supply.

This commissioning criteria has focused on those indications previously categorised as red (conditions for which Ig treatment is considered the highest priority because of a risk to life without treatment) and Blue (conditions for which there is a reasonable evidence base for the use of Ig but other treatment options are available). As a significant proportion of Ig use is in haematology, immunology and neurology, the first phase of the criteria review focused on those indications within these specialties. There have been a number of supply issues of pathogen specific immunoglobulin over the past year, so use of Ig in specific infectious diseases was also included in phase one of the overall Ig review.

A completed referral form is still required for use of Ig in all indications. If the “Prior panel approval required” column states “No” - treatment can proceed without panel approval but a completed application form should be submitted and retrospectively reviewed by the Panel. If the column states “Yes”, treatment cannot proceed without prior panel approval. Where local expertise is not available, panels will also be able to advise on dose optimisation and trials of treatment withdrawal.

The second phase of the update will review the use of Ig in those indications classified as red or blue under other within the current Clinical Guidelines for Immunoglobulin use. This will include:

- Autoimmune congenital heart block/paediatric myocarditis
- Autoimmune uveitis
- Kawasaki disease
- Necrotising (PVL associated) staphylococcal sepsis
- Severe or recurrent *Clostridium difficile* colitis
- Staphylococcal or streptococcal toxic shock syndrome
- Toxic epidermal necrolysis, including Steven Johnson Syndrome
- Transplantation (solid organ)

The third phase will be based on a detailed evidence review of the use of Ig in disorders previously categorised as grey indications (immune-mediated disorders with limited or little/no evidence), where the high quality evidence base was weak or absent, or the disease was rare. As with red and blue indications, only those grey indications which are supported by adequate evidence of Ig efficacy will be commissioned.

Whilst the 2nd and 3rd phases of the criteria review are underway NHS England will continue to commission Ig in other indications and in grey indications in line with the Current Clinical Guidelines for Immunoglobulin use (2nd edition update; July 2011).

In keeping with the advice included in previous iterations of these guidelines and to ensure cost-effective use and minimise dose-dependent adverse effects, Ig prescribing will be based on ideal body weight- adjusted dosing (Chow et al Transfusion and Apheresis Science 2012;46:349-52;Stump et al. Pharmacotherapy 2017; 37:1530-1536). In a small minority of patients where this approach may be sub-optimal, higher doses of Ig may be required.

Updates to V1.4 (November 2019)

Within this updated commissioning criteria, clarification on the need for prior panel approval has been provided. Updates also include guidance on “other” indications, correction to dosages in Infectious Diseases and hyperlink to local health protection teams for Hepatitis A referrals.

Version control

Version number	Summary of amends	Page	Date
1.4	Addition of Trough IgG to secondary antibody deficiency and specific antibody deficiency	3-4	October 2019
1.4	New guidance for Allo-immune neonatal haemochromatosis & Gestational allo-immune liver disease (GALD)	25	August 2019
1.4	Website link to local health protection teams for Hepatitis A referrals	18	August 2019
1.4	Updated dosage for HNIG in Measles in pregnant women and infants	19	August 2019
1.4	Recommended dosage of alternative immunoglobulin products for Tetanus prone injury (prophylaxis)	19-20	August 2019

Use of Immunoglobulin in Immunology:

Immunoglobulin is routinely commissioned in the following indications, under the circumstances described:

Indications	Selection criteria	Exclusion criteria:	Position of immunoglobulin, taking into account alternative therapies:	Recommended dose	Outcome measures to be recorded on the national database:	Prior panel approval required*
Primary immunodeficiencies associated with significant antibody defects (excluding specific antibody deficiency) – long term use	A specific PID diagnosis must be established by a clinical immunologist	No	Ig is the only definitive treatment for antibody deficiency	Initiate at 0.4–0.6 g/kg/month; dose requirements may increase and should be based on clinical outcome	Trough IgG Reduction in number of infections, treatment courses of antibiotics, days in hospital.	No
Thymoma with immunodeficiency – long term use	Profound B cell depletion and/or significant antibody deficiency	No	Ig is the only definitive treatment for antibody deficiency	Initiate at 0.4–0.6 g/kg/month; dose requirements may increase and should be based on clinical outcome	Trough IgG Reduction in number of infections, treatment courses of antibiotics, days in hospital.	No
HSCT in primary immunodeficiencies – long term use	PID patients undergoing HSCT	No	Ig is the only definitive treatment for antibody deficiency	Initiate at 0.4–0.6 g/kg/month; dosing requirements may increase and should be based on clinical outcome. Because of the possibility of B-cell reconstitution, evaluation of immune function (off Ig) is required at 2 years.	Trough IgG	No

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Indication	Eligibility criteria:	Exclusion criteria:	Position of immunoglobulin, taking into account alternative therapies:	Recommended dose:	Outcome measures to be recorded on the national database:	Prior panel approval required*
Specific antibody deficiency – long term use	• Diagnosis by a clinical immunologist • Severe, persistent, opportunistic or recurrent bacterial infections despite continuous oral antibiotic therapy for 6 months • Documented failure of serum antibody response to unconjugated pneumococcal or other polysaccharide vaccine challenge	No, but see comments in column of position of immunoglobulin	Many patients with specific antibody deficiency will achieve protection from bacterial infections with prolonged antibiotic prophylaxis. Ig is reserved for those patients in whom antibiotic prophylaxis proves to be ineffective.	Initiate trial at 0.4–0.6 g/kg/month for a period of 6 to 12 months; Long-term maintenance treatment should be based on clear evidence of benefit from this trial and require panel approval. Dose requirements may increase and should be based on clinical outcome.	Trough IgG Reduction in number of infections, treatment courses of antibiotics, days in hospital. Database parameters will include entry of number of infections and days in hospital pre-treatment and 6 monthly thereafter	Yes
Secondary antibody deficiency – long term use	• Underlying cause of hypogammaglobinaemia cannot be reversed or reversal is contraindicated; OR: • Hypogammaglobinaemia associated with drugs, therapeutic monoclonals targeted at B cells and plasma cells (rituximab and other anti-CD20,CD19 agents, daratumumab etc) post-HSCT*, NHL, CLL, MM or other relevant B-cell malignancy confirmed by haematologist; AND • Recurrent or severe bacterial infection despite continuous oral antibiotic therapy for 6 months • IgG <4 g/L (excluding paraprotein) • Documented failure of serum antibody response to unconjugated pneumococcal or other polysaccharide vaccine challenge	No, but see comments in column of position of immunoglobulin	Many patients with secondary antibody deficiency will achieve protection from bacterial infections with prolonged antibiotic prophylaxis. Ig is reserved for those patients in whom antibiotic prophylaxis proves to be ineffective. Since infection susceptibility in patients with haematological malignancies is frequently multifactorial, the reduction in overall burden of infections with long term Ig replacement may be variable. For this reason annual reviews of treatment are recommended. In patients with seasonal preponderance of infections, it may be appropriate to	• 0.4 – 0.6 g/kg/month modified to achieve an IgG trough level of at least the lower limit of the age-specific serum IgG reference range	Trough IgG Reduction in number of infections and days in hospital (Database parameters will include entry of number of infections and days in hospital pre-treatment and 6 monthly thereafter)	Yes

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	• It is recognised that vaccine challenge may be of limited value in patients with very low serum IgG (< 3g/L). In these circumstances vaccine challenge may be omitted if it is considered inappropriate clinically. • It is acknowledged that not all of the above criteria will need to be fulfilled for an individual patient. • In patients developing hypogammaglobinaemia associated with B-cell aplasia as a consequence of Chimeric Antigen Receptor – T cell therapy (CAR-T cells) targeted against B cell antigens, the prophylactic use of Ig in the absence of a burden of severe infections and vaccine challenge may be appropriate.		consider temporary cessation of Ig in the summer.			

*There is variable practice regarding Ig replacement in adult patients with hypogammaglobinaemia post-HSCT for haematological malignancy. The American Society for Blood and Marrow transplantation and the Canadian Blood and Marrow Transplant group have recently stated as follows:

- Don't routinely give Ig replacement to adult HSCT recipients in the absence of recurrent infections regardless of the IgG level (Bhella et al. Choosing Wisely BMT. Biol Blood Marrow Transplant 2018;24:909-13)

It is possible that patients with recurrent sino-pulmonary infections on a background of chronic pulmonary GVHD and hypogammaglobinaemia may benefit if they fulfil the criteria for secondary antibody deficiency.

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Use of Immunoglobulin in Haematology:

Immunoglobulin is routinely commissioned in the following indications, under the circumstances described:

Indication	Eligibility criteria:	Exclusion criteria:	Position of immunoglobulin, taking into account alternative therapies:	Recommended dose:	Outcome measures to be recorded on the national database:	Prior panel approval required*
Alloimmune thrombocytopenia (foetal-maternal/neonatal) (FMAIT NAIT):/	Prevention or treatment of foetal thrombocytopenia or haemorrhage: Clinical suspicion of FMAIT in the antenatal setting based on clinical and laboratory features: Unexplained previous foetal death, haemorrhage, hydrocephalus or thrombocytopenia or known affected sibling, AND the presence of maternal platelet-specific alloantibodies directed against current paternal antigens (most commonly HPA-1a or HPA-5b). <u>Prevention or treatment of neonatal thrombocytopenia or haemorrhage</u>: Clinical suspicion of NAIT in the neonatal setting based on clinical features suggestive of bleeding e.g. purpura and/or bruising and/or more serious bleeding and a low platelet count.	No	Immunoglobulin is the primary treatment and sometimes combined with steroids First line treatment is with HPA-1a/5b – negative platelets which covers 95% of HPA incompatibilities responsible for NAIT. Platelet transfusion is effective immediately. In contrast, immunoglobulin is a second line treatment and works in approximately 75% of cases. It has a delayed effect over 24 – 48 hours. Immunoglobulin may be of value if there is prolonged thrombocytopenia with the aim of minimising the need for platelet transfusions.	Maternal: 0.5 -1g/kg weekly throughout pregnancy. Dose and stage of gestation at which to start treatment to be tailored to individual risk profile primarily based on the history of NAIT in earlier pregnancies.Patients with a low-risk obstetric history should be commenced on 0.5.g/kg (Winkelhorst D et al. Fetal and neonatal alloimmune thrombocytopenia:evidence based antenatal and postnatal management strategies. Exp Rev Hematol 2017;10:729-737) Neonatal: 1g/kg; a 2nd dose may be required if thrombocytopenia persists	Successful outcome of pregnancy i.e. no severe haemorrhage such as intracranial haemorrhage Platelet count above $50x10^9$ /L at time of delivery Increment in neonatal platelet count	No – for NAIT Yes – for FMAIT

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<table>
<tr><th>Indication</th><th>Eligibility criteria:</th><th>Exclusion criteria:</th><th>Position of immunoglobulin, taking into account alternative therapies:</th><th>Recommended dose:</th><th>Outcome measures to be recorded on the national database:</th><th>Prior panel approval required*</th></tr>
<tr><td>Haemolytic disease of the newborn – short term use:</td><td>Adjunct to continuous multiple phototherapy in cases of Rhesus haemolytic disease, or ABO haemolytic disease:

• Rising bilirubin despite intensive phototherapy

• Prevention of foetal haemolytic disease in women with a previous history of this and confirmed red cell antibodies to current paternal or foetal antigens, to delay the need for intrauterine transfusions</td><td>No</td><td>Immunoglobulin is an adjunct to phototherapy</td><td>0.5g/kg over 4 hours</td><td>Bilirubin level

Need for exchange transfusion

Long term morbidity</td><td>No</td></tr>
<tr><td>Immune Thrombocytopenic Purpura (ITP) short term use:</td><td>Immunoglobulin generally used in only 3 situations in ITP:-
1) Life-threatening bleeding
2) Where an immediate increase in platelet count is required e.g. before emergency surgery or other procedure (see table for target platelet counts)
3) Where the patient is refractory to all other treatment to maintain the platelet count at a level to prevent haemorrhage. It may need to be given every 2-3 weeks during a period where other second line treatments are being tried.

Target platelet counts for surgery*
<table><tr><td>Procedure</td><td>Platelet count</td></tr><tr><td>Dentistry</td><td>>20</td></tr><tr><td>Simple dental extraction</td><td>>30</td></tr><tr><td>Complex dental extraction</td><td>>50</td></tr></table></td><td>No</td><td>Thrombopoietin mimetics may be useful substitutes in some patients</td><td><u>Adults</u>: 1g/kg as a single infusion.
A 2nd dose may be required after 24 – 48 hours, if severe or life-threatening bleeding:
e.g. Intracranial bleed or pulmonary haemorrhage
Otherwise, if a haemostatically adequate platelet count is not achieved a 2nd dose (1g/kg) may be considered at day 5 to 7

<u>Children</u>: 0.8 – 1g/kg as a single infusion.
A 2nd dose may be required after 24 – 48 hours, if severe or life-threatening bleeding, such as an intracranial bleed or pulmonary haemorrhage.
Otherwise, if a haemostatically adequate</td><td>Increase in platelet count

Resolution of bleeding

Number of bleeding complications</td><td>No for acute ITP; the use of a 2nd dose should be discussed with the designated panel lead.

Yes – for maintenance treatment</td></tr>
</table>

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	<table><tr><td>Regional dental block</td><td>>30</td></tr><tr><td>Minor surgery</td><td>>50</td></tr><tr><td>Major surgery</td><td>>80</td></tr><tr><td>Major neurosurgery</td><td>>100</td></tr></table> ITP in pregnancy: Maintenance treatment with Ig may be required antenatally to maintain platelets above $20x10^9$/l and/or to increase platelets to over 50 $x10^9$/l for delivery in women with symptomatic persistent or chronic ITP where other treatments have failed. *There is controversy regarding the target platelet count for epidural anaesthesia (Provan et al. Blood 2010;115:168-186). There are no data to support a minimum platelet count and each case must be carefully considered. In the absence of bruising, bleeding history, and anticoagulation and if the INR, APTT and fibrinogen levels are normal, a small consensus of obstetric anaesthetists agree no changes to normal practice are needed until the platelet count drops below 50.			platelet count is not achieved a 2nd dose (1g/kg) may be considered at day 5 to 7		
Acquired red cell aplasia associated with chronic parvovirus B19 infection– short term use	Parvovirus B19 infection: • Parvovirus B19 infection confirmed by PCR, AND • Evidence of high viral load, usually above 10^9 IU/ml In cases of foetal hydrops: • Likely to be associated with parvovirus B19	Infection other than parvovirus B19	Immunoglobulin is an adjunct to transfusion. Chronic parvovirus infection generally occurs on a background of immunosuppressive therapy, primary or HIV-related immunodeficiency and may resolve with a reduction in immunosuppression. Acute parvovirus infection associated with transient aplastic crisis requires urgent transfusion rather than Immunoglobulin.	1 – 1.2g/kg in divided doses. This may be repeated on relapse and for a 2nd relapse	Rise in haemoglobin Transfusion independence Reticulocyte count	Yes

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Indication	Eligibility criteria:	Exclusion criteria:	Position of immunoglobulin, taking into account alternative therapies:	Recommended dose:	Outcome measures to be recorded on the national database:	Prior panel approval required*
Autoimmune haemolytic anaemia (AHA, including Evans syndrome) – short term use	AHA, including Evans syndrome: • Symptomatic or severe anaemia, except in patients with co-morbidities), AND • Refractory to conventional treatment with corticosteroids, OR • Corticosteroids contra-indicated, OR • As a temporising measure prior to splenectomy AHA in pregnancy: • Pregnant women with warm AHA refractory to corticosteroids OR with evidence of fetal anaemia. • Neonates of mothers with AHA who have evidence of haemolysis and rising bilirubin despite intensive phototherapy	No	Immunoglobulin is reserved for patients unresponsive to steroids or where steroids are contra-indicated.	1-2g/kg in two to five divided doses. This may be repeated on relapse and for a 2nd relapse	Rise in haemoglobin Transfusion independence Reduction in haemolysis markers (bilirubin, lactate dehydrogenase)	No – for treatment of acute episodes Yes – for repeat courses
Post-transfusion hyperhaemolysis – short term use **Prevention of haemolysis in patients with a history of transfusion-**	Treatment of acute post-transfusion hyperhaemolysis: Symptomatic or severe anaemia (Hb <6g/dL, with evidence of on-going intravascular haemolysis due to a delayed haemolytic transfusion/hyperhaemolysis). It is recognised that some patients with an Hb > 6 g/dl may require treatment. Patients who have had previous delayed haemolytic transfusion reactions/post-transfusion hyperhaemolysis or who have	No	In combination with steroids, Immunoglobulin is used as first-line treatment.	2g/kg (usually over two days) given with IV methylprednisolone 1-2g/kg over two or five days given with steroids	Rise in haemoglobin Transfusion Independence Reduction in haemolysis markers (bilirubin, lactate dehydrogenase) No haemolysis	No

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associated hyperhaemolysis Prevention of delayed haemolytic transfusion reaction	single or multiple allo-antibodies AND who may require a blood transfusion			1 – 2 g/kg over 2 to 5 days, given with IV methylprednisolone	Maintenance of post-transfusion Hb at 1 – 3 weeks Avoidance of need for repeated transfusion	

Indication	**Eligibility criteria:**	**Exclusion criteria:**	**Position of immunoglobulin, taking into account alternative therapies:**	**Recommended dose:**	**Outcome measures to be recorded on the national database:**	**Prior panel approval required***
Coagulation factor inhibitors* (alloantibodies and autoantibodies) – short term use:	<u>Acquired von Willebrand disease (VWD)</u> • Life- or limb-threatening haemorrhage, AND • Failure to respond to other treatments, AND/OR • Prior to invasive procedure • Treatment directed by the haemophilia centre at which the patient is registered	Acquired VWD associated with IgM monoclonal gammopathy	Immunoglobulin is a therapeutic option in acquired VWD, particularly in cases associated with a IgG monoclonal gammopathy alongside other therapies – plasmapheresis, desmopressin, VWF-containing concentrates and recombinant Factor VII.	Either 0.4g/kg for five days or 1g/Kg for two days	Rise of factor level Resolution of bleeding Number of bleeding episodes	Yes
Haemophagocytic syndrome – short term use:	• Diagnosis by consultant haematologist based on bone marrow biopsy, AND OR • Pancytopenia, AND • Non-response to conventional treatment (e.g. corticosteroids, immunosuppressive agents, chemotherapy), OR • Conventional treatment is contra-indicated or inappropriate	No		2g/kg in two to five divided doses. This may be repeated on relapse and for a 2nd relapse	Improvement of cytopenias Survival Improvement of HLH markers – Ferritin/soluble CD25	Yes
Post-transfusion purpura – short term use:	• Sudden severe thrombocytopenia 5 to 10 days post-transfusion of blood products, AND • Active bleeding (typically occurs in Caucasian HPA-1a antigen negative females previously exposed to HPA-1a antigen in pregnancy or transfusion)	No	There are now very few cases in UK following the implementation of universal leucocyte-reduction of blood components in 1999.	1 - 2g/kg in divided doses over two to five days	Increase in platelet count Resolution of bleeding Number of bleeding complications	No

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Use of Immunoglobulin in Neurology:

Immunoglobulin is routinely commissioned in the following indications, under the circumstances described:

Indication	Eligibility criteria:	Exclusion criteria:	Position of immunoglobulin, taking into account alternative therapies:	Recommended dose:	Outcome measures to be recorded on the national database:	Prior panel approval required*
CIDP (including IgG or IgA associated paraprotein associated demyelinating neuropathy)	Probable or definite diagnosis of CIDP by a neurologist according to the EFNS/International Peripheral Nerve Society Guidelines; AND Significant functional impairment inhibiting normal daily activities. All patients should have an initial documented assessment after induction dosing and a further assessment after 2-3 doses to demonstrate meaningful functional improvement. Annual withdrawal/clinical reviews should be performed to document on-going need.	No specific exclusion criteria but see general comments regarding prothrombotic risks of IVIg	IVIg should not always be considered first line treatment for CIDP, although it may be where steroids are contra-indicated and plasma exchange is not available. Where steroids, IVIg and plasma exchange are all available IVIg would be considered preferable in patients with motor predominant CIDP, rapidly progressive disease where rapid response is required (particularly patients requiring admission to hospital) or where steroids or plasma exchange are contra-indicated. Strong consideration should be given to the early use of steroids or plasma exchange in other circumstances.	An initiation regimen of a maximum 4g/kg divided into at least two courses of 1-2g/kg each, and given over a 4 to 8 week period, with assessment at the end of the period. Regimens to establish response might include: 2g/kg given over 2 to 5 days and repeated after 6 weeks (Fig 1 Lunn et al J Peripheral Nerv Syst 2016;21:33-37) 2g/kg initially followed by 1g/kg after 3 weeks and a further 1g/kg 3 weeks later (Hughes et al Expert Rev Neurother 2009;9:789-95) For maintenance dose optimisation see general note below	Efficacy outcomes should be used to measure response after the chosen initial regimen and thereafter when assessing for dose optimisation Clinically meaningful improvement in any three of the following prespecified measures per patient: • MRC score (7 pairs of muscles in upper and lower limb scored 0–5, maximum 70) • INCAT sensory sum score • ONLS (Overall Neuropathy Limitation Score) • Hand dynamometry • Inflammatory RODS score • 10-m walk (in seconds) • Up and go 10m walk (in seconds) • Berg Balance scale • Other validated disability score	Short-term initiation treatment to assess Ig responsiveness – No Long-term treatment - Yes

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Indication	Eligibility criteria:	Exclusion criteria:	Position of immunoglobulin, taking into account alternative therapies:	Recommended dose:	Outcome measures to be recorded on the national database:	Prior panel approval required*
Guillain-Barre syndrome (GBS) (includes Bickerstaff's brain stem encephalitis and other GBS variants)	Diagnosis of GBS (or variant) in hospital, AND Significant disability (Hughes Grade 4); OR Disease progression towards intubation and ventilation OR mEGRIS score ≥ 3 OR Poor prognosis mEGOS ≥ 4	Patients with mild and/or non-progressive disease not requiring intubation. A second dose of IVIg is only indicated within 4 weeks and where there is a failure to increment IgG by ≥ 7g/l	Patients with Miller-Fisher Syndrome do not usually require IVIg and unless associated with GBS overlap with weakness will recover normally.	2g/kg given over 5 days (shorter time frame not recommended because of potential fluid overload and autonomic problems); Second dose may be considered at 14 days for non-responsive or late deteriorating patients if IgG not increased from baseline by ≥ 7g/l **NB: IVIg dosing beyond 4 weeks is unlikely to have clinical benefit**	Measure incremental increase in delta IgG at 2 – 7 days post-treatment. A further dose within 4 weeks of disease onset may be appropriate if delta IgG is <7g/l. If delta IgG ≥7g/l is attained no further dosing is necessary	No
IgM Paraprotein-associated demyelinating neuropathy	• Diagnosis by a neurologist, AND • Significant functional impairment inhibiting normal daily activities; AND • Other therapies have failed, are contra-indicated or undesirable	Mild disease with non progressive sensory loss and imbalance does not require treatment	IVIg is seldom significantly effective and response should be reviewed at least every 6 months if there is initial functional improvement. Alternative underlying haematological diagnoses should be considered which may direct treatment, or other therapies such as single agent rituximab (or biosimilars) should be considered.	An initiation regimen of a maximum 4g/kg divided into at least two courses of 1-2g/kg each, and given over a 4 to 8 week period, with assessment at the end of the period. Regimens to establish response might include: 2g/kg given over 2 to 5 days and repeated after 6 weeks (Fig 1 Lunn et al J Peripheral Nerv Syst 2016;21:33-37) 2g/kg initially followed by 1g/kg	Efficacy outcomes should be used to measure response after the chosen initial regimen and thereafter when assessing for dose optimisation Clinically meaningful improvement in any three of the following prespecified measures per patient: • MRC score (7 pairs of muscles in upper and lower limb scored 0–5, maximum 70) • INCAT sensory sum score • ONLS (Overall Neuropathy Limitation Score) • Hand dynamometry	Yes

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				after 3 weeks and a further 1g/kg 3 weeks later (Hughes et al Expert Rev Neurother 2009;9:789-95) For maintenance dose optimisation see general note below	• Inflammatory RODS score • 10-m walk (in seconds) • Up and go 10m walk (in seconds) • Berg Balance scale • Other validated disability score	

Indication	**Eligibility criteria:**	**Exclusion criteria:**	**Position of immunoglobulin, taking into account alternative therapies:**	**Recommended dose:**	**Outcome measures to be recorded on the national database:**	**Prior panel approval required***
Inflammatory Myopathies **Dermatomyositis (DM)** **Polymyositis (PM)**	• Diagnosis of myositis by a neurologist, rheumatologist, dermatologist or immunologist of DM or PM AND EITHER: • Patients with PM or DM who have significant muscle weakness; OR • Dysphagia and have not responded to corticosteroids and other immunosuppressive agents; OR • DM with refractory skin involvement.	No specific exclusion criteria but see general comments regarding prothrombotic risks of IVIg	Where progression is not rapid and in the absence of contra-indications, steroids should be considered first IVIg is seldom effective in isolation and is best used as an adjunct to immunosuppressive therapy. Maintenance treatment with IVIg for a prolonged period (usually less than 12 months) may be required in a small minority of patients with inflammatory myositis, as a third line treatment after consideration of rituximab (see comments under position of immunoglobulin). In these cases, every effort should be made to establish the minimum clinically effective dose by either reduction of dose or lengthening the intervals between infusions. Cessation trials should be	An initiation course of a maximum 4g/kg divided into at least two courses of 1-2 g/kg each, and given over a 4 to 8 week period, with assessment after dosing. Regimens to establish response might include: 2g/kg given over 2 to 5 days and repeated after 6 weeks For maintenance dose optimisation see general note below. The need for maintenance treatment in resistant juvenile dermatomyositis should be	Clinically meaningful improvement in three pre-defined measures from the list below: DM: functional/disability scores (ADLs): • semi-quantitative muscle scores (MRC sumscore) • other quantitative muscle strength (e.g. MMT8) • up and go 10-m walk (in secs) • CDASI • FVC • HAQ • PM: functional/disability scores (ADLs): • semi-quantitative muscle scores (MRC sumscore) • other quantitative muscle strength (e.g. MMT8)	Yes

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			attempted at least annually to establish on-going need for treatment In patients with refractory disease associated with myositis-specific antibodies, rituximab (or biosimilar) has been approved as a second line treatment by NHS England (policy reference 16036/P); with IVIg being considered as a third line treatment.	determined on an individual basis.	• up and go 10-m walk (in secs) • HAQ • FVC **Efficacy outcomes should be recorded after the initiation course and regularly reassessed and recorded thereafter**	

Indication	**Eligibility criteria:**	**Exclusion criteria:**	**Position of immunoglobulin, taking into account alternative therapies:**	**Recommended dose:**	**Outcome measures to be recorded on the national database:**	**Prior panel approval required***
Myasthenia Gravis (MG), includes Lambert-Eaton Myasthenic Syndrome (LEMs)	Diagnosis of MG or LEMS by a neurologist AND EITHER; Acute exacerbation (myasthenic crisis); OR Weakness requires hospital admission; OR Prior to surgery and/or thymectomy	No specific exclusion criteria but see general comments regarding prothromboti c risks of IVIg	All patients requiring urgent in patient treatment should receive plasma exchange first if available, including considering transfer to an appropriate neuroscience centre. IVIg could follow plasma exchange if required Where plasma exchange is not available, IVIg may be appropriate In rare circumstances where a patient has failed all standard treatments (including steroids and immunosuppression) and where authorised by a specialist in MG from a centre with a specialist neuromuscular service, maintenance therapy may be considered. A rituximab biosimilar agent is likely to be an equally effective alternative therapy	In acute exacerbation use plasma exchange first where available. Patients admitted to hospital should receive 1g/kg in the first instance, only receiving a further 1g/kg if there is further deterioration or no response. Patients with life threatening disease (ITU with respiratory and/ or bulbar failure) should receive 2g/kg. **Refer to dose optimisation section for maintenance**	Improvement in variation of myasthenic muscular strength and fatigue measures by the QMGS MG composite score. Additional efficacy may be monitored using: • Forward arm abduction time (up to 5 min) • Quantitative Myasthenia Gravis Score (Duke) • Respiratory function, e.g. forced vital capacity • Variation of another myasthenic muscular score • Dysphagia score • Dysarthria 1-50 counting • Diplopia or ptosis measurement	Myasthenic crisis – No Long-term treatment - Yes

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			and has been approved by NHS England here for this group of patients with resistant myasthenia.			

Indication	Eligibility criteria:	Exclusion criteria:	Position of immunoglobulin, taking into account alternative therapies:	Recommended dose:	Outcome measures to be recorded on the national database:	Prior panel approval required*
Multifocal Motor Neuropathy (MMN)	Diagnosis by a neurologist of multifocal motor neuropathy with or without persistent conduction block; AND Significant functional impairment inhibiting normal daily activities	No specific exclusion criteria but see general comments regarding prothrombotic risks of IVIg	No alternative treatments known	An initiation regimen of a maximum 4g/kg divided into at least two courses of 1-2g/kg each, and given over a 4 to 8 week period, with assessment at the end of the period. Regimens to establish response might include: 2g/kg given over 2 to 5 days and repeated after 6 weeks (Fig 1 Lunn et al J Peripheral Nerv Syst 2016;21:33-37) 2g/kg initially followed by 1g/kg after 3 weeks and a further 1g/kg 3 weeks later (Hughes et al Expert Rev Neurother 2009;9:789-95) For maintenance dose optimisation see general note below If no significant measurable and functionally meaningful	Improvement in 3 pre-specified measures from the below list: • MRC score • Power score from 7 pre-defined pairs of muscles including 4 most affected muscle groups neuro-physiologically • RODS for MMN • Hand dynamometry • ONLS • 10-m walk (in secs) • Any other validated MMN disability measure	Short-term treatment to assess Ig responsiveness – No Long-term treatment - Yes

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				improved in abilities has been achieved after 3 doses IVIg should be stopped		

Indication	Eligibility criteria:	Exclusion criteria:	Position of immunoglobulin, taking into account alternative therapies:	Recommended dose:	Outcome measures to be recorded on the national database:	Prior panel approval required*
Rasmussen's Encephalitis	When other therapies (such as steroids) have failed	No specific exclusion criteria but see general comments regarding pro-thrombotic risks of IVIg	Immunoglobulin is reserved for patients unresponsive to steroids and other therapies.	2g/kg given over 2-5 days and repeated monthly for three months for initial trial	Seizure frequency with expected reduction of 30% to continue therapy	Yes
Stiff person syndrome (SPS) or variant	Diagnosis of SPS or a variant (stiff limb, PERM, etc) by a consultant neurologist Supportive criteria: Demonstration of auto-antibodies to GAD, Glycine receptor, DPPX, amphyphysin, gephyrin or other stiff person associated antibodies AND/OR Continuous motor unit activity at rest on EMG testing in paraspinal or affected limb musculature	No specific exclusion criteria but see general comments regarding pro-thrombotic risks of IVIg	Consider plasma exchange as initial treatment. Rituximab is likely to be equally effective but is not commissioned for this indication.	An initiation regimen of a maximum 4g/kg divided into at least two courses of 1-2g/kg each, and given over a 4 to 8 week period, with assessment at the end of the period. Regimens to establish response might include: 2g/kg given over 2 to 5 days and repeated after 6 weeks (Fig 1 Lunn et al J Peripheral Nerv Syst 2016;21:33-37) 2g/kg initially followed by 1g/kg after 3 weeks and a further 1g/kg 3 weeks later (Hughes	Report on at least two of the measures below: • Reduction in stiffness • Up and go 10-m walk (in secs) • BRIT score • Number of spasms per day • Validated measure of functional abilities	Yes

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				et al Expert Rev Neurother 2009;9:789-95) For maintenance dose optimisation see general note below. If no significant measurable and functionally meaningful improved in abilities had been achieved after 3 doses IVIG should be stopped		

Dosing optimisation for maintenance – general notes:

An ongoing issue for diseases that require long-term immunoglobulin treatment is that once significant and functional responsiveness to intravenous immunoglobulin (IVIg) is demonstrated for a patient using standard immunomodulatory dosing, the 'maintenance' dosing required to maintain the therapeutic response is not well characterised. In this update, the dosing recommendations for some neurological indications include 'time to relapse' as the interval between doses. This approach is supported by recent evidence from The Oxford Programme for Immunomodulatory Immunoglobulin Therapy, which was set up to review multifocal motor neuropathy (MMN) and chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) treatment with immunoglobulin. In view of the uncertainty of both remission and disease progression in CIDP and MMN, The Oxford Programme reviewed the dose and infusion frequency of patients on a regular basis and showed that increasing the infusion interval proved successful in some patients and resulted in treatment discontinuation [Lucas et al J Clin Immunol 2010;Suppl 1:S84-9].

An alternative approach based on establishing the 'time to relapse' following the first or second dose followed by dose reduction has also been proposed and is equally feasible (see fig 1 Lunn et al J Peripheral Nerv Syst 2016;21:33-37). This ensures patients who need no more than 1 or 2 doses are not exposed to unnecessary doses and those with ongoing needs are optimised to a minimal dose.

Based on evidence from randomised trials, it is likely that up to 40% of patients with CIDP may be able to discontinue treatment (Adrichem et al J Peripheral Nerv Syst 2016) after 6-12 months, although a significant proportion may relapse and require retreatment. For this reason, periodic trials of cessation of treatment are recommended, especially in patients who appear to be stable even if optimally treated. The demonstration of continued IVIG requirement by forced suspension on more than 2 or 3 occasions over a 5-year period probably indicates ongoing long term dependence and further withdrawals are highly unlikely to be effective. Referral to a specialist neurology centre is recommended as early as possible.

In inflammatory myositis, maintenance treatment with IVIg for a prolonged period (usually less than 12 months) may be required in a small minority of patients. In these cases, every effort should be made to establish the minimum clinically effective dose by either reduction of dose or lengthening the intervals between infusions. Cessation trials should be attempted at least annually to establish on-going need for treatment. (Foreman et al Internal Med J 2017;47:112-115)

Specific exclusion criteria against the use of immunoglobulin have not been listed, but it is important to carry out benefit-risk analyses in certain patient groups: patients at high risk of thromboembolism (hypertension, diabetes, smoking, hypercoagulable states) should be counselled regarding the prothrombotic risks of immunoglobulin.

IgA deficiency is no longer considered a contra-indication to the use of immunoglobulin and should not be withheld because of theoretical concerns of adverse reactions. The role of anti-IgA antibodies in causing reactions is controversial and measurement of anti-IgA antibodies prior to undertaking treatment is not warranted.

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Use of Immunoglobulin in Infectious Diseases:

Immunoglobulin is routinely commissioned in the following indications, under the circumstances described:

Indication	Eligibility criteria:	Exclusion criteria	Position of immunoglobulin, taking into account alternative therapies:	Recommended dose:	Outcome measures to be recorded on the national database:	Prior panel approval required*
Hepatitis A	Immunoglobulin is recommended in addition to hepatitis A vaccine for contacts of hepatitis A who are less able to respond to vaccine • (those aged 60 or over, OR • those with immunosuppression and those with a CD4 count <200 cell per microlitre), OR • those at risk of severe complications (those with chronic liver disease including chronic hepatitis B or C infection)	See eligibility criteria	Hepatitis A vaccine is recommended in addition to immunoglobulin Vaccine should be administered within 2 weeks of exposure	Subgam: <10 years 500mg >10 years 1000mg To be given by intramuscular injection*. Given with vaccine in those at high risk, within 2 weeks of exposure (those over 60 years, immunosuppression, CD4 count <200 cell per microliter) and those at risk of severe complications. For those exposed between 2-4 weeks ago, immunoglobulin may also be offered to modify disease in those at risk of severe complications (i.e. chronic liver disease including chronic hepatitis B or C infection).	Outcome measures not routinely recorded on surveillance databases Immunoglobulin is issued nationally and locally, records are held of who immunoglobulin was issued for with respect to exposure to the hepatitis A virus.	Yes, in discussion with PHE* *Find your local protection team here: https://www.gov.uk/health-protection-team

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Indication	Eligibility criteria:	Exclusion criteria:	Position of immunoglobulin, taking into account alternative therapies:	Recommended dose:	Outcome measures to be recorded on the national database:	Prior panel approval required*
Measles (immunosuppressed individuals)	Immunosuppressed individuals (Group A and Group B based on level of immunosuppression - https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/637003/Guidance_for_measles_post-exposure_prophylaxsis.pdf) who have had a significant exposure to measles and are known to be susceptible (based on vaccine history and /or IgG testing).	See eligibility criteria	For immunosuppressed contacts IVIg is mainstay management	0.15g/kg of IVIg recommended ideally within 72 hours of exposure although can be given up to 6 days. Where exposure recognised late or found to be antibody negative between 6 and 18 days after exposure, IVIg may be considered following discussion with specialist clinician.	Prevention of measles	Yes, in discussion with PHE* *Find your local protection team here: https://www.gov.uk/health-protection-team
Measles (pregnant women and infants)	Pregnant women who have identified as susceptible based on vaccine history and /or antibody testing who have had a significant exposure to measles Infants under 9 months of age with a significant exposure to measles		For pregnant contacts, immunoglobulin is mainstay management for PEP. For infants below 6 months immunoglobulin is mainstay treatment; For infants aged	• For pregnant contacts, approximately 3000mg of human normal immunoglobulin (HNIG)	Prevention of measles	Yes, in discussion with PHE*

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	Advice is available at: https://www.gov.uk/government/publications/measles-post-exposure-prophylaxis		between 6-8 months, MMR vaccine can be offered if exposure occurred outside household setting AND ideally should be given within 72 hours	• Infants 0.6ml/kg up to a maximum of 1000mg of HNIG HNIG to be given within 6 days of exposure in pregnant women and infants.		*Find your local protection team here: https://www.gov.uk/health-protection-team

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Indication	Eligibility criteria:	Exclusion criteria:	Position of immunoglobulin, taking into account alternative therapies:	Recommended dose:	Outcome measures to be recorded on the national database:	Prior panel approval required*
Polio	To prevent or attenuate an attack: • An immunocompromised person inadvertently given live polio vaccine, OR • An immunocompromised person whose contacts are inadvertently given live polio vaccine		Immunoglobulin represents first –line treatment	<1 year: 250mg 1 – 2 years: 500mg >3 years: 750mg Stool samples from the immunosuppressed individual must be obtained one week apart. If poliovirus is grown from either sample, repeat immunoglobulin at 3 weeks. Continue weekly stool collection and administration of immunoglobulin three weekly until immunocompromised individual's stool is negative for poliovirus on two occasions.	Either: • Prevention of infection, or • Resolution of infection	Yes, in discussion with PHE* *Find your local protection team here: https://www.gov.uk/health-protection-team
Tetanus prone injury (prophylaxis) **(IM-TIg or SCIg)**	Tetanus specific immunoglobulin (TIG) has limited stock and is recommended for susceptible individuals sustaining high risk tetanus prone injuries as defined in guidance (**https://www.gov.uk/government/publications/tetanus-advice-for-health-professionals**)		• Thorough cleaning of wound essential • Immunoglobulin for Prophylaxis • Booster of tetanus-containing vaccine for long term protection	TIG: • 250 IU for most uses • 500 IU if more than 24 hours have elapsed or there is a risk of	Prevention of tetanus infection	No

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				heavy contamination or following burns The dose is the same for adults and children. <u>Immunoglobulin</u>: If TIG (for intramuscular use) cannot be sourced, immunoglobulin for subcutaneous or intra-muscular use may be given as an alternative. Based on testing for the presence of anti-tetanus antibodies of alternative immunoglobulin products, the volume required to achieved the recommended dose of 250IU are included. Although no time frame is specified in the guidance, im TIG /immunoglobulin following a tetanus prone wound is only likely to confer benefit when given within incubation period of tetanus (10-21 days).		

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Indication	Eligibility criteria:	Exclusion criteria:	Position of immunoglobulin, taking into account alternative therapies:	Recommended dose:	Outcome measures to be recorded on the national database:	Prior panel approval required*
Suspected tetanus case (IVIg)	Person with clinical symptoms suggestive of localised or generalised tetanus ("in the absence of a more likely diagnosis, an acute illness with muscle spasms or hypertonia AND diagnosis of tetanus by a health care provider")		• Wound debridement • Antimicrobials • IVIG based on weight • Supportive care • Vaccination with tetanus toxoid following recovery	Dosage based on equivalent dose of anti-tetanus antibodies of 5000 IU for individuals < 50kg and 10000 for individuals > 50kg See table below*	Resolution of tetanus infection	No
Varicella zoster	Individuals for whom intra-muscular injections are contra-indicated (e.g. those with bleeding disorders) and thus cannot receive prophylaxis with VZIG IVIg is indicated for these Individuals who fulfil all of the following three criteria: 1) Significant exposure to chickenpox (varicella) or shingles (zoster) during the infectious period 2) At increased risk of severe chickenpox i.e. immunosuppressed individuals, neonates and pregnant women 3) No antibodies to varicella-zoster virus (based on VZV antibody testing) Immunosuppressed individuals are assessed at time of exposure into Group A & Group B based on likely level of immunosuppression Restrictions on use of VZIG have been in place since August 2018. Updated guidance on post exposure prophylaxis have been published in June 2019. Advice is available at: https://www.gov.uk/government/publications/varicella-zoster-immunoglobulin	Mildly immunocompromised whose level of immunosuppression does not meet the criteria for either Group A or Group B do not require VZIG e.g. children on doses of prednisolone less than 2mg/kg/day, patients on doses of methotrexate 25mg/week or less A further dose of IVIg is not required if a new exposure occurs within 3 weeks of administratio	For those patients fulfilling eligibility criteria, there are no alternatives to IVIg.	0.2g IVIG per kg body weight (i.e. 4ml/kg for a 5% solution) Brands have not been specified as no formal testing of products has been undertaken. VZIG (or IVIg when VZIG contraindicated) should be administered ideally within 7 days of exposure in susceptible immunosuppressed individuals. Where the exposure has been identified beyond 7 days, VZIG can be offered up to 14 days after exposure. *Beyond this time for patients in both groups A and B, a discussion with the specialist caring*	Prevention of chicken pox infection Prevention of severe chicken pox	Yes, in discussion with PHE* *Find your local protection team here: https://www.gov.uk/health-protection-team

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		n of VZIG or IVIG		*for the individual should take place and IVIg (0.2g per kg body weight) may be considered in susceptible individuals for up to 21 days to attenuate infection*		

* Please note SPC currently indicates subcutaneous route of administration only (although previously indicate both s/c and im routes), PHE guidance recommends intramuscular administration for post exposure prophylaxis with Subgam.

*Dose of immunoglobulin in suspected tetanus cases:

IVIg Products tested for anti-tetanus antibodies	**Volume required (in ml)**	
	For individuals < 50kg	For individuals > 50kg
Gammaplex 5%, Intratect 5%, Flebogamma 5%, Vigam 5%, Octagam 5%	400ml	800ml
Privigen 10%, Octagam 10%, Intratect 10%, Flebogamma 10%, Panzyga 10%, Gammunex 10%	200ml	400ml

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Use of immunoglobulin in “other” indications:

Indications	Eligibility criteria:	Exclusion criteria:	Position of immunoglobulin, taking into account alternative therapies:	Recommended dose	Outcome measures to be recorded on the national database:	Prior panel approval required*
Allo-immune neonatal haemochromatosis or gestational allo-immune liver disease (GALD)	• Pregnant mothers with a previous adverse pregnancy outcome and clear post-mortem evidence of fetal haemochromatosis or, • women who have had an offspring with neonatal liver failure confirmed to be allo-immune neonatal haemochromatosis • Decision to treat with Ig made by a consultant obstetrician with input from a liver unit specialist	No		Immunoglobulin is administered by intravenous infusion at a dose of 1g/kg (dose capped at 60g per week) to at risk mothers at 14 weeks, 16 weeks and then weekly from 18 weeks gestation until delivery between 37 and 38 weeks. The weight used to calculate the dose will be the mother’s weight at booking.	• Fetal loss (including gestation) • Gestation at delivery • Neonatal outcomes	Yes

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