Commissioning Criteria Policy for the use of therapeutic immunoglobulin (Ig) England, 2021

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

Summary

The updated commissioning criteria for the use of therapeutic immunoglobulin (Ig) 2021 describes all conditions for which Ig is commissioned and provides the detail around the role, dose and place of Ig in the treatment pathway for individual indications alongside possible alternative treatment options for use of Ig in both adults and children. It has been built 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 expert working group following wide consultation with specialty experts, relevant scientific societies and the respective Clinical Reference Groups (CRGs) for haematology, immunology, neurology, infectious diseases, rheumatology and other specialities. The CRG will review the document as per NHS England and NHS Improvement policy review process or when there is a significant change in evidence. Recommendations on Ig dose and outcomes are based on a combination of available evidence and expert opinion. The colour coding scheme, which had been previously devised for demand management but was often utilised as a commissioning tool, has now been replaced by categorisation of Ig use; to routinely commissioned or not commissioned routinely (NRC) categories. This is now based on the strength of clinical evidence.

Commissioning criteria

These commissioning criteria are for all 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) and those grey indications (immune-mediated disorders with limited or little/no evidence) that have moved into routine commissioning.

This guideline supersedes previous clinical guidelines and NHS England and NHS Improvement guidance with the exception of those indications within the Department of Health and Social Care (DHSC) 2011 clinical guidelines for immunoglobulin use[1], which have not moved into routine commissioning.

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 should not proceed without prior panel approval; if this is not possible, for example in an urgent case, retrospective approval must be sought. For urgent approvals in hours – a process will need to be in place on the agreed pathway for approval. For those cases that require out of hours approval, panels will have local processes in place, to ensure robust governance for retrospective panel approval. Where local expertise is not available, panels will also be able to advise on dose optimisation and trials of treatment withdrawal.

All referrals should be carried out via the Medicine Database Solutions and Services (MDSAS) National Immunoglobulin Database e-referral platform. MDSAS data will be reviewed and findings reported to the Ig clinical expert working group and CRG with any recommendations on changes in policy will be updated in line with recommendations. MDSAS data will be analysed for ethnic groups to ensure any possible inequality in access is identified.

Indications or clinical scenarios not listed in “Commissioning Criteria Policy for the use of therapeutic immunoglobulin (Ig) England, 2021” are not routinely commissioned and will still require an Individual Funding Request (IFR) application subject to support by the Sub Regional Immunoglobulin Assessment Panels (SRIAPs), to be submitted to the national IFR Panel. If the IFR is approved, the diagnosis and locally agreed efficacy criteria are recorded on the immunoglobulin database.

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 dose-determining weight (DDW), derived from ideal body weight (IBW)[2,3] using the following formula (available at: https://ivig.transfusionontario.org/dose). In a small minority of patients where this approach may be sub-optimal, higher doses of Ig may be required.

Vial Dosing

Total treatment course should be calculated and then rounded down to the nearest dose which can be administered using whole vials. Note in an adult patient part vials should never be used. Where the dose is split over multiple days, daily dose may differ.

For example:

- Male patient; Height 170cm; Weight 84kg
- Diagnosed with Guillain-Barre syndrome and meets criteria for IVIg, plan to receive 2g/kg based on DDW to be given over 5 days as per guidelines.

IBW = 50 + (0.91 x [Height(cm) – 152.4]) = 50 + (0.91 x[170-152.4]) = 66kg.

DDW = IBW + (0.4 x [ABW(kg) – IBW (kg)]) = 66 + (0.4 x [84-66]) = 73.2kg
Total dose = 2 x 73.2kg = 146.4g rounded down to nearest 5g (vial size) vial = 145g. To be split over 5 days suggested dosing:

Day 1: 30g Day 2: 30g Day 3: 30g Day 4: 30g Day 5: 25g

Ig and the use of IBW for dosing in paediatric patients

In all paediatric patients Ig dosing should be based on IBW. Actual body weight (ABW) should not be used. In patients whose ABW is < IBW, IBW should still be used to ensure appropriate dosing and preventing underdosing.

The recommended methods suggested by the RCPCH and NPPG to calculate IBW, include the use of the table at the back of the BNFc[4]or methods suggested in the UKMI document[5]. In the future, the RCPCH and NPPG aim to work on a standardised approach in conjunction with the BNFc.

Where possible doses should be rounded down to the nearest vial size to prevent wastage.

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
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
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 In newly diagnosed patients with PID with no significant burden of infection, the decision to start Ig replacement should be based on a MDT discussion	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

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 • 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	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 consider	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 • Days in hospital • Database parameters will include entry of number of infections and days in hospital pre-treatment and 6 monthly thereafter. • Treatment courses of antibiotics	Yes

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
	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 • Use of Ig post-CAR-T therapy in B-cell acute lymphoblastic leukaemia (B-ALL) Because of the severity of B-cell aplasia and the longer time required for reconstitution, it is anticipated that virtually all patients (children and adults) with B-ALL will initially require Ig replacement following CAR-T cell therapy. As with the use of Ig post-CAR-T therapy in B-cell lymphoma, continued use of IVIg should be reviewed at regular intervals based on B-cell recovery, serum immunoglobulins and burden of infection • Use of Ig post-CAR-T cell therapy in B-cell lymphoma The need for immunoglobulin replacement in patients receiving CAR-T cell therapy for B-cell lymphoma is variable ranging between 31% to 64% in published studies[6] highlighting faster B-cell recovery in this group in contrast to patients with B-cell acute lymphoblastic leukaemia		temporary cessation of Ig in the summer			

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
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

* 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, “Don’t routinely give Ig replacement to adult HSCT recipients in the absence of recurrent infections regardless of the IgG level”[7].

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.

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
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 109 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	1.0 g/kg – 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
Alloimmune thrombocytopenia (foetal-maternal/neonatal) (FMAIT NAIT)	<u>Prevention or treatment of foetal thrombocytopenia or haemorrhage:</u> • 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).	No	Maternal: Immunoglobulin is the primary treatment and sometimes combined with steroids Neonatal: First line treatment is with HPA-1a/5b – negative platelets which covers 95% of HPA incompatibilities	Maternal: The dose of IVIG and the gestation at which to start treatment should be tailored according to the history of NAIT in earlier pregnancies. A patient with a low-risk obstetric history (where the previous infant had thrombocytopenia but no intracranial haemorrhage) should be commenced on 0.5g-1.0/kg/week from 20 weeks' gestation. In high-risk pregnancies, treatment should commence from as early as 12 weeks' gestation with a dose of 1g/kg/week (where the previous fetus or neonate had	• 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

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
	<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		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	intracranial haemorrhage after 28 weeks' gestation), or 2g/kg/week (where the previous fetus or neonate had intracranial haemorrhage before 28 weeks)[8-12] Neonatal: 1g/kg; a 2nd dose may be required if thrombocytopenia persists		
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
Coagulation factor inhibitors (alloantibodies and	<u>Acquired von Willebrand disease (VWD)</u> • Life- or limb-threatening haemorrhage,	Acquired VWD associated with IgM monoclonal gammopathy	Immunoglobulin is a therapeutic option in acquired VWD, particularly in cases	Either 0.4g/kg for five days or 1g/Kg for two days	• Rise of factor level • Resolution of bleeding	Yes** **If prior approval is

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
autoantibodies) – short term use:	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		associated with a IgG monoclonal gammopathy alongside other therapies – plasmapheresis, desmopressin, VWF-containing concentrates and recombinant Factor VII		• Number of bleeding episodes	not possible then treatment should proceed, and retrospective approval should be sought
Haemolytic disease of the newborn – short term use:	Adjunct to continuous multiple phototherapy in cases of Rhesus haemolytic disease, or ABO haemolytic disease: • Rising bilirubin despite intensive phototherapy (see NICE CG98[13]) • 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	No	Immunoglobulin is an adjunct to phototherapy Also see NICE CG98 guidance[13]	0.5g/kg over 4 hours	• Bilirubin level • Need for exchange transfusion • Long term morbidity	No
Haemophagocytic syndrome (Haemophagocytic lymphohistiocytosis or HLH) – short term use:	Diagnosis by a consultant haematologist or rheumatologist based on H-score* including: • pyrexia • organomegaly • multiple lineage cytopenias • triglycerides • fibrinogen • ferritin • serum aspartate aminotransferase • haemophagocytosis on bone marrow biopsy • long-term pharmacological immunosuppression * A score >169 is 93% sensitive and 86% specific for HLH)	No	Other therapies include IL-1 receptor inhibition (Anakinra) Please refer to NHS England policy[14]	2g/kg in two to five divided doses alongside corticosteroids (dexamethasone) as per HLH protocol. This may be repeated on relapse and for a 2nd relapse, where alternative therapies are not indicated or are contraindicated	• Improvement of cytopenias • Survival • Improvement of HLH markers – Ferritin/soluble CD25	Yes
Immune Thrombocytopenic	Immunoglobulin generally used in only 4 situations in ITP: 1) Life-threatening bleeding	No	Thrombopoietin mimetics may be useful substitutes in	Adults: 1g/kg as a single infusion.	• Increase in platelet count	No for acute ITP; the use of a 2nd dose

<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>Purpura (ITP) short term use:</td>
<td>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
4) Moderate severity bleeding in patient at higher risk of subsequent severe bleed. Patients with mucosal bleeding or bleeding from multiple sites or a previous history of severe bleeding are at higher risk of a subsequent severe bleed

Bleeding severity as defined by the “Updated international consensus report on the investigation and management of primary immune thrombocytopenia 2019”[15]

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>
<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</td>
<td></td>
<td>some patients (in situation 3) or as an adjunct in the other situations</td>
<td>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 platelet count is not achieved a 2nd dose (1g/kg) may be considered at day 5 to 7</td>
<td>• Resolution of bleeding
• Number of bleeding complications</td>
<td>should be discussed with the designated panel lead.

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

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
	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[16]. 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.					
Covid Vaccine-induced thrombosis and thrombocytopenia (VITT)	Confirmed/Probable diagnosis of VITT made by a haematologist conforming to up to date guidance from the Expert Haematology Panel - See British Society for Haematology website for details. Also see NICE NG200 guideline[17].	Isolated thrombocytopenia or thrombosis: • Reduced platelet count without thrombosis with D dimer at or near normal and normal fibrinogen. • Thrombosis with normal platelet count and D dimer	Treatment with intravenous immunoglobulin, irrespective of the degree of thrombocytopenia is urgent as this is the treatment most likely to influence the disease process. A repeat course of IVIg may be required depending on clinical course	1g/kg (divided over two days if required)	• Platelet count	No
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 <60g/L, with evidence of on-going intravascular haemolysis due to a delayed haemolytic transfusion/hyperhaemolysis). It is	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 • Maintenance of post-transfusion Hb at 1 – 3 weeks	No

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
associated hyperhaemolysis **Prevention of delayed haemolytic transfusion reaction**	recognised that some patients with an Hb > 60 g/l may require treatment. Patients who have had previous delayed haemolytic transfusion reactions/post-transfusion hyperhaemolysis or who have single or multiple allo-antibodies AND who may require a blood transfusion	Eculizumab is commissioned as a 2nd line treatment where 1st line treatment has failed; Rituximab is recommended as a 3rd line treatment[18].		1 – 2 g/kg over 2 to 5 days, given with IV methylprednisolone	• Avoidance of need for repeated transfusion	
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

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
Acute idiopathic/autoimmune dysautonomia/ganglionopathy	• Acute onset autonomic failure with presence of ganglionic (alpha3) acetylcholine receptor antibodies OR • Acute onset autonomic failure with clinical pattern consistent with above including pupillary involvement but without identifiable antibodies AND • Authorised by specialist autonomic unit	Non-immune causes of autonomic failure (for example primary autonomic failure (PAF) without pupillary involvement, MSA multisystem atrophy, diabetes mellitus	IVIG may be required to obtain rapid control, but may be substituted for by prednisolone, MMF, plasma exchange or other immunosuppressants which are preferable in the longer term	2g/kg over 5 days initially repeated at 6 weeks then titrated to optimal interval and minimum dose to achieve stability Annual reassessment with IVIG suspension as necessary	• Postural BP drop reduction with improved activities of daily living • Time to significant postural BP fall • Numbers of syncopal and pre-syncopal episodes • Oral dryness score • Diarrhoea and constipation frequency	Yes
Autoimmune encephalitides (AIE) (antibody associated)	• Non-infective encephalitis, with or without underlying teratoma or malignancy with known encephalitis associated antibody (e.g. LGI1, Caspr2, NMDAR, GAD, DPPX, AMPA, GABAb and others) AND • Functional disability caused by seizures, encephalopathy, stiffness, cognitive dysfunction or other relevant neurological sequelae	Infective encephalitis or other non-inflammatory cause of encephalopathy or seizures	Search for underlying malignancy and treat as appropriate Prednisolone/Methylprednisolone is first line, with or without Plasma Exchange (where this is available) Ongoing treatment with IVIG may be necessary where long-term oral immunosuppression, tumour removal and definitive strategies to reduce antibody levels (e.g. cyclophosphamide/rituximab) are ineffective or contra-indicated NB: Please note the Enceph-IG study is	2g/kg over 5 days initially repeated at 3 to 6 weeks. Repeat course 3 times if necessary. If repeated courses are required, consider institution of alternative longer-term strategy immediately	AIE outcomes for all types (except Ab titre in non-antibody associated) • Antibody titre (if relevant and measurable) • Modified Rankin Score • Seizure numbers • Improvement on one or more validated tests of memory or executive tasks • resolution of MR signal change (where present) • Resolution of hyponatraemia where present	Yes

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
			available[19]. Consider recruitment within the trial for suitable patients.			
Autoimmune encephalitides (no known antibody defined)	• Non-infective encephalitis, with or without underlying teratoma or malignancy without known encephalitis associated antibody AND • Functional disability caused by seizures, encephalopathy, stiffness, cognitive dysfunction or other relevant neurological sequelae AND • Evidence of inflammatory CNS disorder including active CSF, EEG defined seizures, MRI imaging changes consistent with AIE, known antibodies etc in the absence of infection	Infective encephalitis or other non-inflammatory cause of encephalopathy or seizures	Search for underlying malignancy and treat as appropriate. Prednisolone is first line, with or without Plasma Exchange (where this is available) Ongoing treatment with IVIG may be necessary where long-term oral immunosuppression, tumour removal and definitive strategies to reduce antibody levels (e.g. cyclophosphamide/ rituximab) are ineffective or contra-indicated NB: Please note the Enceph-IG study is available[19]. Consider recruitment within the trial for suitable patients.	2g/kg over 5 days initially repeated at 3 to 6 weeks. Repeat course 3 times if necessary If repeated courses are required, consider institution of alternative longer-term strategy immediately	AIE outcomes for all types • Modified Rankin Score • Seizure numbers • Improvement on one or more validated tests of memory or executive tasks • resolution of MR signal change (where present) • Resolution of hyponatraemia where present	Yes
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 Ig	Ig 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, Ig and plasma exchange are all available Ig 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	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[20]. 2g/kg initially followed by 1g/kg after 3 weeks and a further 1g/kg 3 weeks later[21].	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)	Short-term initiation treatment to assess Ig responsiveness – No Long-term treatment - Yes

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
			or plasma exchange are contra-indicated. Strong consideration should be given to the early use of steroids or plasma exchange in other circumstances	For maintenance dose optimisation see general note below	• Hand dynamometry • Inflammatory RODS score • 10-m walk (in seconds) • Up and go 10m walk (in seconds) • Berg Balance scale • Other validated disability score	
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	Patients with Miller-Fisher Syndrome do not usually require IVIg and unless associated with GBS overlap with weakness will recover normally PLEX is equally efficacious as IVIg in GBS and should be preferentially considered where it is clinically appropriate and easily accessible	2g/kg as soon as possible after the diagnosis is confirmed, given over 5 days. Administration over a shorter time frame not recommended because of fluid and protein overload and pro-coagulant effects. IVIG is unlikely to be effective if given more than 4 weeks after the onset of symptoms[22]. Second doses of IVIg are not effective in the treatment of GBS and may be associated with real potential harm[23].	None	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. Rituximab is recommended in IgM paraproteinaemic demyelinating peripheral	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[20]. 2g/kg initially followed by 1g/kg after 3 weeks and a further 1g/kg 3 weeks later[21].	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

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
			neuropathy in adults, in line with NHS England policy[24].	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	
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 Ig	Where progression is not rapid and in the absence of contra-indications, steroids should be considered first. In adult patients (and post-pubescent children through the NHS England and NHS Improvement Medicines for Children policy[25]) with refractory disease associated with myositis-specific antibodies, rituximab (or biosimilar) has been approved as a second line treatment by NHS England[26]. Abatacept is recommended in refractory idiopathic inflammatory myopathies (adults and children aged 2 and over), in line with NHS England policy as a third line treatment[27]. IVIg would be the fourth line treatment line. 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	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 determined on an individual basis	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 • CAT or DAS • FVC • CHAQ to include the childhood score PM: 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) • HAQ • FVC Efficacy outcomes should be recorded after the initiation course and regularly reassessed and recorded thereafter For Dermatomyositis (juvenile – JDM): • MMT-8	Yes

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
			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 attempted at least annually to establish on-going need for treatment		• CMAS score • CK for baseline and asses how a patient has improved after each infusion or at least after 3 infusions. • PGALs is used to assess how many inflamed or swollen joints a patient has.	
Opsoclonus-myoclonus syndrome - paediatric or adult non paraneoplastic	• Paediatric OMS diagnosed by a paediatric neurologist OR • OMS in an adult with no evidence of neoplasm, anti-neuronal antibodies, or focal structural or inflammatory alterative diagnosis	Structural disease. Multiple sclerosis or other inflammatory lesions associated with defined diagnoses where the primary treatment of that disease is not Ig	Corticosteroids should be tried first Consider other anti-inflammatory strategies including oral immunosuppressants, rituximab or cyclophosphamide as appropriate	2g/kg over 5 days initially repeated at 6 weeks then titrated to optimal interval and minimum dose to achieve stability	• OMS score	Yes
Paraneoplastic neurological syndromes (PNS) without evidence of autoantibodies	• Defined paraneoplastic syndrome (for example limbic encephalitis, sensory ganglionopathy, cerebellar degeneration etc) AND • Evidence of a PNS associated tumour (e.g. small cell lung, ovarian or testicular, breast, thymoma etc	See eligibility criteria	Treatment of primary tumour Consider steroids and plasma exchange	2g/kg over 5 days initially repeated at 6 weeks. If beneficial then titrated to optimal interval and minimum dose to achieve stability. Discontinue If not objectively effective after 2 doses.	• Modified Rankin Scale • 10m walk Any validated relevant disability measure appropriate to the condition	Yes

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 Ig	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[20]. 2g/kg initially followed by 1g/kg after 3 weeks and a further 1g/kg 3 weeks later[21] For maintenance dose optimisation see general note below If no significant measurable and functionally meaningful improved in abilities has been achieved after 3 doses IVIg should be stopped	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
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 prothrombotic risks of Ig	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	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	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

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
			centre with a specialist neuromuscular service, maintenance therapy may be considered A rituximab biosimilar agent is likely to be an equally effective alternative therapy and has been approved by NHS England[28] for this group of patients with resistant myasthenia	**Refer to dose optimisation section for maintenance**		
Neuromyotonia (Isaacs syndrome)	• Neuromyotonia from peripheral nerve hyperexcitablity associated with significant disability • AND • Supported by diagnostic electrophysiological changes with or without antibodies to the VGKCh complex (Caspr) and resistant to alternative agents	Non autoimmune myotonia syndromes	Anticonvulsants should be tried first from phenytoin, carbamazepine, sodium valproate and lamotrigine. Immunomodulation: Prednisolone +/- azathioprine or oral immunosuppressant Plasma exchange	2g/kg over 5 days initially repeated at 6 weeks then titrated to optimal interval and minimum dose to stability	• Timed up and go walk • Functional measure: e.g. Myotonia Behaviour Scale (MBS), Rivermead Mobility Index, or Brief Pain Inventory • Neurophysiological myotonia assessment	Yes
Non-MS CNS inflammatory disease covering the clinical phenotype of AQP4 ab disease, NMOSD, ADEM (with or without encephalopathy, including brainstem attacks), MOGAD, TM, ON **<u>Acute Disease: Short term use</u>**	• Acute disease attack* not responding to IVMP (5g-7g or equivalent in children) and PLEX. When PLEX is not available or delayed or contraindicated, IVIG can be used before PLEX	Mild relapses without: new neurological signs	Refractory to IV Methyl Prednisolone OR PLEX not available or contraindicated OR refractory to PLEX in cases of severe disability	2g/kg over 2-5 days	To be determined by disease features including 3 of: • Modified Rankin score • 10m walk • 9-hole peg test	No

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
	AND • Evidence of ongoing inflammation AND • Within 6 weeks unless evidence of active inflammation	OR reduced activities of daily living OR other inflammatory disease diagnoses (e.g. MS Sarcoid, Behcet's etc)	and ongoing inflammation (usually within 6 weeks)		• Validated neuropsychometric testing • Improvement of other relevant validated scale • Objective relevant imaging improvement If ON - clinical improvement of VA If TM - either 1. EDMUS OR 2. ASIA	
<u>Chronic relapse prevention:</u>						
MOGAD (Myelin Oligodendrocyte Glycoprotein Antibody Disease)	MOGAD - refractory to (relapse* breakthrough) at least two treatments; one must be prednisolone and an immunosuppressant (any of MMF/Rituximab/AZA/methotrexate) OR serious side effects with prednisolone (adequate dose and length of time)	Pseudorelapse OR MS (may have low positive MOGAbs)	Failed 2 first line therapies	1g/kg daily over 2 days then 1g/kg monthly for first year (titrate to 2g/kg if relapses occur despite on-going steroid and IVIg at 1g/kg) Annual reviews for dose optimisation	Suppression of further relapses* Treatment Failure – defined as objective evidence of true relapse* on treatment	Yes
AQP4 NMOSD	AQP4 NMOSD - Failed or intolerant to 3 or more 'usual treatments' resulting in relapse*, including at least prednisolone (unless severe prednisolone side effects from adequate dose and time) + immunosuppressant (aza/ritux/MMF/methotrexate /ciclosporin or tacrolimus /PLEX or new RCT treatment if available)	Pseudo relapse	As per selection criteria	1g/kg monthly for first year; if break through consider 2g/kg Review annually	Suppression of further relapses* Treatment Failure – defined as objective evidence of true relapse* on treatment	Yes
Ab negative phenotypes	Failed or intolerant to 3 or more 'usual treatments' resulting in relapse* including at least prednisolone (unless severe prednisolone side effects from adequate	Pseudo relapse OR Other inflammatory	As per selection criteria	1g/kg 2 then monthly for first year	Suppression of further relapses*	Yes

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
	dose and time) PLUS immunosuppressant (aza/ritux/MMF/methotrexate /ciclosporin or tacrolimus /PLEX or new RCT treatment if available)	disease diagnoses (e.g. MS Sarcoid, Behcets etc)		Review at one year try reducing interval /dose with alternative options	Failure – defined as objective evidence of true relapse* on treatment	

*Attack or Relapse is a new or extended neurological symptom with signs that reflects the anatomical location of the inflammatory lesion (note a minority of early MOGAD TM may be difficult to visualise) that is not a fluctuating residual symptom of an old lesion and that usually persists for at least one week. However, acute treatment should not be delayed. Contrast enhancement is present in the majority during the acute phase.

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 Ig	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, 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 Ig	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[20]. 2g/kg initially followed by 1g/kg after 3 weeks and a further 1g/kg 3 weeks later[21]. For maintenance dose optimisation see general note below. If no significant measurable and functionally meaningful	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

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
				improved in abilities had been achieved after 3 doses IVIG should be stopped		

For many disorders where rituximab is a potential longer-term alternative to IVIg, the speed of response should be considered in determining treatment choice. IVIg can provide more rapid but temporary control and is likely to be the preferred option in emergency situations where an immediate response is required, for example in dysphagia and/or difficulty in breathing in inflammatory myositis.

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[29].

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[20]. 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[30] 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[31].

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.

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.	Prior approval is via discussion with UKHSA health protection team* *Find your local protection team here: https://www.gov.uk/health-protection-team

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 (immune-suppressed individuals)	Immunosuppressed individuals (Group A and Group B based on level of immunosuppression[32]) 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	Prior approval is via discussion with UKHSA health protection team* *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. Advice is available at: https://www.gov.uk/government/publications/measles-post-exposure-prophylaxis	See eligibility criteria	For pregnant contacts, immunoglobulin is mainstay management for PEP For infants below 6 months immunoglobulin is mainstay treatment; For infants aged between 6-8 months, MMR vaccine can be offered if exposure occurred outside household setting AND ideally should be given within 72 hours	• For pregnant contacts, approximately 3000mg of human normal immunoglobulin (HNIG) • 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.	Prevention of measles	Prior approval is via discussion with UKHSA health protection team* *Find your local protection team here: https://www.gov.uk/health-protection-team

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	See eligibility criteria	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	Prior approval is via discussion with UKHSA health protection team* *Find your local protection team here: https://www.gov.uk/health-protection-team
Severe or recurrent Clostridium difficile infection (CDI) colitis - short term use	• Severe cases (WCC >15 and/or, acutely rising creatinine and/or signs/symptoms of colitis) not responding to routine 1st line vancomycin and metronidazole • If multiple recurrences, especially with evidence of malnutrition	See comments under position of Ig	For fulminant or recurrent CDI unresponsive to appropriate antibiotics (see under selection criteria) consider IV tigecycline or IVIg[33]. Faecal microbiota transplantation is approved by NICE for patients with recurrent CDI unresponsive to antibiotics and is likely to be an effective alternative[34].	0.4 g/kg, one dose, and consider repeating once	• Clearance of C. diff. • Duration of hospital in-patient stay	Yes
Staphylococcal (including PVL-associated sepsis) or streptococcal toxic shock syndrome (TSS) - short term use	• Diagnosis of streptococcal or staphylococcal TSS, preferably with isolation of organism, AND	See comments under position of Ig	IVIg is reserved for patients with life-threatening disease who fail to achieve rapid improvement with antibiotic therapy. However, for streptococcal TSS, it should be noted that	Total dose of 2g/kg, because of uncertainty regarding the timing and optimal dose of IVIg, it is recommended that patients are reviewed after an initial dose of	• Improvement of FBC, ALK, CPK,and acute phase markers • Reduction in hospital inpatient stay • Survival	No Ideally, prior approval is recommended but if this is

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
	• Failure to achieve rapid improvement with antibiotic therapy and other supportive measures, AND • Life-threatening		there has been significant controversy regarding the benefits of IVIg treatment prompting the Infectious Diseases Society of America (IDSA) not to recommend its use in patients with necrotising Group A streptococcal infections[35] Since then a systematic review and meta-analysis of IVIg in clindamycin-treated patients with streptococcal TSS suggests a reduction in mortality from 33.7% to 15.7%, though this finding may be confounded by differences in baseline characteristics between patients receiving IVIg and those who didn't[36] Based on the results of this meta-analysis, the use of IVIg as adjunctive therapy is supported by Stevens DL[37].	1g/kg. Should there be no evidence of improvement at 24 hours, a further 1g/kg may be considered.		not possible, treatment should proceed, and retrospective approval should be sought.
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")	See eligibility criteria	• 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 IU for individuals > 50kg See table below*	Resolution of tetanus infection	No
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[38].	See eligibility criteria	• 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 heavy contamination or following burns The dose is the same for adults and children	Prevention of tetanus infection	No

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
				Immunoglobulin: 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)		

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
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:	Mildly immunocompromised whose level of immunosuppression does not meet the criteria for	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	Prevention of chicken pox infection Prevention of severe chicken pox	Prior approval is via discussion with UKHSA health protection team*.

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
	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	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 administration of VZIG or IVIG		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 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*		*Find your local protection team here: https://www.gov.uk/health-protection-team
Viral pneumonitis post-transplantation: HSCT and solid organ	Definitive diagnosis of viral pneumonitis – Varicella Zoster Virus (VZV), Respiratory Syncytial Virus (RSV), Human Parainfluenza Virus (HPIV)	VZV - See comments under position of Ig RSV, HPIV – patients with mild disease confined to the upper respiratory tract	VZV - IVIg is reserved for patients with disseminated disease. For guidance on treatment of patients with significant exposure to chicken pox or herpes zoster please see use of Ig in specific infectious diseases. RSV, HPIV – patients with lower respiratory infections. In patients with RSV infection, Ig would be used as an adjunct to Ribavirin. For patients with RSV and HPIV upper respiratory infections post-HSCT, consider Ig in the presence of	1 – 2g/kg in divided doses	• Radiological improvement • Length of hospital stay • Survival	Yes. If prior approval is not possible then treatment should proceed, and retrospective approval should be sought.

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
			some or all of the following risk factors[39]: • Older age • GVHD • Lymphopenia : < 0.2 x 109/L • Neutropenia • Mismatched/unrelated donor • Immediate aftermath of HSCT (< 1 month)			

* 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

Use of immunoglobulin in "other" indications:

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
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	For those patients fulfilling eligibility criteria, there are no alternatives to IVIg	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 For further information please refer to the Clinical Commissioning Policy: Maternal intravenous immunoglobulin (IVIg) for the prevention of allo-immune fetal and neonatal haemochromatosis[40].
ANCA-associated systemic vasculitides (AAV)	• Patients with refractory/relapsing AAV in whom conventional immunosuppressive therapy is contra-indicated e.g. presence of severe infection or in pregnancy as bridging therapy • The role of IVIg in the treatment of ANCA negative small vessel vasculitis is unclear and each case will need to be assessed on individual grounds.	No specific exclusion criteria – see comments under selection criteria	IVIg is reserved as adjunctive or very rarely as sole therapy for the minority of patients in whom conventional immunosuppressive therapy is contra-indicated	Total dose of 2g/kg over 2 – 5 days every 4 weeks. The optimal duration of therapy is not known though most patients are likely to achieve remission after 3 months. IVIg should be discontinued after 3 months in the absence of clinical improvement.	• Improvement in Birmingham Vasculitis Score (BVAS)/PVAS to capture paediatric assessment tool • Fall in inflammatory markers • Improvement in organ function	Yes - Treatment cannot proceed without prior panel approval

Autoimmune uveitis - short term use	Severe aggressive sight-threatening disease unresponsive to conventional immunosuppressive treatment (topical and systemic steroids and oral or injectable immunosuppressants)	See comments under position of Ig	IVIg is reserved for exceptional cases where anti-TNF agents are contra-indicated or ineffective or associated with intolerable adverse effects and other corticosteroid and immunosuppressive agents are ineffective. Anti-TNF agents (Infliximab, Adalimumab) are regarded as the treatment of choice for the treatment of severe, refractory uveitis and are approved by NHS England[41])	1 - 1.5 g/kg/month – two to three infusions given 6 – 8 weeks apart to assess benefit	• Improvement or stabilisation in visual acuity • Imaging endpoints • Electrodiagnostic studies	Yes
Catastrophic antiphospolipid syndrome (CAPS)	Diagnosis of definite or probable CAPS: ▪ Thromboses in 3 or more organs developing in less than a week ▪ Histological evidence of microthrombosis in at least one organ ▪ Persistent anti-phospholipid antibody positivity (lupus anti-coagulant and or anti-cardiolipin/anti-B2GPI of IgG or IgM isotype	Chronic recurrent thrombosis due to other causes Thrombosis associated with stable anti-phospholipid syndrome in the context of other disorders	Steroids, anti-coagulants and plasma exchange (PLEX) represents optimal therapy IVIg is likely to be beneficial In selected cases associated with severe thrombocytopenia where PLEX is either unavailable or contra-indicated or in the event of deterioration following PLEX	2g/kg over 4-5 days	• Clinical improvement • Reduction in anti-phospholipid antibody levels	Yes - Treatment cannot proceed without prior panel approval
Immunobullous diseases - long term use	• Severely affected AND • conventional corticosteroid treatment with adjuvant immunosuppressive agents has failed or is inappropriate	See comments under position of Ig	IVIg is reserved as adjunctive therapy for patients with severe disease refractory to conventional immunosuppressive therapy. Rituximab is increasingly supplanting IVIg as the preferred treatment for resistant disease and is approved by NHS England[42] .In such patients it is listed as a 3rd line treatment	1 - 2 g/kg over 2–5 days. There may be a need for maintenance Ig in exceptional patients unresponsive or intolerant of Rituximab. In such cases every attempt should be made to define the minimal effective dose of Ig by undertaking periodic dose reduction and or lengthening the interval between treatment	• Reduction in recurrence of disease/relapse • Dose reduction/discontinuation of other immunosuppressive therapy • Improved quality of life • Resolution of blisters/healing affected skin • Resolution of pruritus	Yes

			alongside IVIg. However, Rituximab should be favoured over IVIg, given the stronger evidence base supporting its use			
Kawasaki disease – short term use **Paediatric inflammatory multisystem syndrome temporally associated to COVID-19 (PIMS-TS)**	Clinical diagnosis of Kawasaki disease by a paediatrician, paediatric infectious disease consultant or paediatric immunologist Clinical diagnosis of PIMS-TS by a paediatrician, paediatric consultant in infection or paediatric immunologist Clinical diagnosis of PIMS-TS in an adult (also known as MIS-A or AIMS-TS) by a consultant in infection or immunologist or appropriate specialist MDT" Because of the similarities between PIMS and Kawasaki disease, the use of IVIg is approved for any child fulfilling diagnostic criteria for PIMShttps://www.rcpch.ac.uk/	No	IVIg in combination with anti-inflammatory doses of Aspirin is the treatment of choice	2g/kg single dose, in conjunction with high-dose aspirin; a second dose may be given if no response, or if relapse within 48h	• Resolution of fever • Improvement in acute phase markers	No
Prevention of autoimmune congenital heart block (anti-Ro)	Prophylactic IVIg therapy has previously been given during pregnancy when: • There is a history of autoimmune congenital heart block in at least one previous pregnancy, AND	See comments under position of Ig	Hydroxychloroquine is regarded as the treatment of choice IVIg may be considered in exceptional cases refractory to hydroxychloroquine or if the patient is unable to tolerate hydroxychloroquine, but	Two infusions of 1g/kg/day, the first at 14 weeks and the second at 18 weeks of gestation	• Improvement in the degree of heart block at birth	Yes

	• Maternal anti-Ro and/or anti-La antibodies are present. However, more recent evidence has cast doubt on the beneficial effects of IVIg with hydroxychloroquine being regarded as first line therapy – see comments under position of Immunoglobulin		there is uncertainty regarding its efficacy. At a dose of 0.4 g/kg every 3 weeks administered from weeks 12 through to week 24 of gestation, IVIg was ineffective in preventing the development of CHB in neonates in two prospective open-label trials based on a case series a higher dose (1g/kg) alongside high dose oral prednisolone may possibly be effective.			
Transplantation (solid organ) – short term use	Antibody Incompatible Transplant (AIT): Patients in whom renal, heart, liver or lung transplant is prevented because of antibodies Antibody Mediated Rejection (AMR): Patients experiencing steroid resistant rejection or where other therapies are contraindicated after renal, heart, liver and/or lung transplant	See comments under position of Ig	While IVIg is included in many protocols, there is a paucity of high-quality evidence to support its use. A systematic review of AMR in kidney transplant recipients categorised the evidence supporting the use of IVIg as being 'very low'[43]. Where IVIg is used in combination with plasma exchange (PLEX), any beneficial effects of Ig are likely to be negated by subsequent PLEX. For this reason, the use of Ig immediately prior to PLEX is not supported. The addition of Rituximab to IVIg appears to be of benefit in lowering HLA antibody titres	AIT: Up to 2 g/kg to be repeated as per DSA; in renal desensitisation at 0.1 g/kg for 8–12 doses AMR: Treatment protocols vary in the UK ranging from low dose 100mg/kg after PLEX or high dose 2g/kg	AIT and AMR: Renal: • Type of renal transplant • HLA class DSA (where available) • Rejection episodes • Patient survival • Graft survival • Renal function = eGFR (MDRD) • Cardiothoracic: • DSA • Length of ITU and hospital stay Graft function (heart = rejection fraction; lung = spirometry; liver = liver function, clotting indices)	No

References

1. Department of Health and Social Care. *Clinical guidelines for immunoglobulin use (second edition update)*. Available from: https://www.gov.uk/government/publications/clinical-guidelines-for-immunoglobulin-use-second-edition-update
2. Chow S et al. Transfusion and apheresis science : official journal of the World Apheresis Association : official journal of the European Society for Haemapheresis 2012;46:349-52.
3. Grindeland JW et al. Ann Pharmacotherapy. 2020;54:205-212
4. MedicinesComplete. *BNF for Children*. Available from: https://about.medicinescomplete.com/publication/british-national-formulary-for-children/
5. Specialist Pharmacy Service. *UKMI NPPG - drug dosing in childhood obesity May 2021*. Available from: https://www.sps.nhs.uk/articles/how-should-medicines-be-dosed-in-children-who-are-obese/
6. Locke *et al.* Lancet Oncol 2020; 20:31-42, Wang *et al* NEJM 2020;382:1331-42, Schuster *et al* NEJM 2017;377:2545-54
7. Bhella et al. Biol Blood Marrow Transplant 2018;24:909-13
8. Pacheco et al. Fetal and neonatal alloimmune thrombocytopenia. Obst & Gyn 2011; 118: 1157-1163.
9. Peterson et al. Neonatal alloimmune thrombocytopenia: pathogenesis, diagnosis and management. Br J Haematol. 2013; 161: 3-14.
10. Regan et al. Prenatal Management of Pregnancies at Risk of Fetal Neonatal Alloimmune Thrombocytopenia (FNAIT). BJOG 2019; 126: 173-185.
11. Lieberman et al. Fetal and neonatal alloimmune thrombocytopenia: recommendations for evidence-based practice, an international approach. Br J Haematol. 2019; 185: 549-562.
12. Winkelhorst et al. Fetal and neonatal alloimmune thrombocytopenia: evidence based antenatal and postnatal management strategies. Exp Rev Hematol 2017; 10: 729-737.
13. National Institute for Health and Care Excellence. *Jaundice in newborn babies under 28 days Clinical guideline [CG98]*. Available from: https://www.nice.org.uk/guidance/cg98
14. National Health Service. *Clinical Commissioning Policy: Anakinra for Haemophagocytic Lymphohistiocytosis (HLH) for adults and children in all ages [210701P] (1924)*. Available from: https://www.england.nhs.uk/publication/anakinra-for-haemophagocytic-lymphohistiocytosis-for-adults-and-children-in-all-ages/
15. Provan et al. Blood Adv (2019) 3 (22): 3780–3817.
16. Provan et al. Blood 2010;115:168-186
17. National Institute for Health and Care Excellence. *COVID-19 rapid guideline: vaccine-induced immune thrombocytopenia and thrombosis (VITT). NICE guideline [NG200]*. Available from: https://www.nice.org.uk/guidance/ng200
18. National Health Service. *Clinical Commissioning Policy; Rituximab and eculizumab for the prevention and management of delayed haemolytic transfusion reactions and hyperhaemolysis in patients with haemoglobinopathies [URN 1821] [200602P]*.

Available from: https://www.england.nhs.uk/publication/rituximab-and-eculizumab-for-the-prevention-and-management-of-delayed-haemolytic-transfusion-reactions-and-hyperhaemolysis-in-patients-with-haemoglobinopathies/
19. University of Liverpool. *Enceph-IG Study - Institute of Infection, Veterinary and Ecological Sciences*. Available from: https://www.liverpool.ac.uk/infection-veterinary-and-ecological-sciences/research/groups/brain-infections-group/enceph-ig/
20. Lunn M et al. J Peripher Nerv Syst. 2016 Mar;21(1):33-7.
21. Hughes R et al. Expert Rev Neurother. 2009 Jun;9(6):789-95.
22. Hughes R et al. Cochrane Database Syst Rev. 2014 Sep 19;2014(9):CD002063
23. Lunn M et al. Lancet Neurol. 2021 Apr;20(4):249-251.
24. National Health Service. *Clinical Commissioning Policy: Rituximab for the treatment of IgM paraproteinaemic demyelinating peripheral neuropathy in adults*. Available from: NHS England » Policies: Routinely commissioned
25. National Health Service. *Commissioning Medicines for Children in Specialised Services*. Available from: https://www.england.nhs.uk/publication/commissioning-medicines-for-children-specialised-services/
26. National Health Service. *Clinical Commissioning Policy: Rituximab for the treatment of dermatomyositis and polymyositis (adults)*. Available from: https://www.england.nhs.uk/wp-content/uploads/2018/07/Rituximab-for-the-treatment-of-dermatomyositis-and-polymyositis-adults.pdf
27. National Health Service. Clinical Commissioning Policy: *Abatacept for refractory idiopathic inflammatory myopathies (adults and children aged 2 and over)*. Available from: NHS England » Policies: Routinely commissioned
28. National Health Service. *Clinical Commissioning Policy Statement: Rituximab bio-similar for the treatment of myasthenia gravis (adults)*. Available from: https://www.england.nhs.uk/wp-content/uploads/2021/04/Rituximab-biosimilar-for-the-treatment-of-myasthenia-gravis-adults-v2.pdf
29. Lucas M et al. J Clin Immunol. 2010 May;30 Suppl 1:S84-9.
30. Adrichem M et al. J Peripher Nerv Syst. 2016 Sep;21(3):121-7.
31. Foreman et al. Internal Med J 2017;47:112-115
32. Public Health England. *Guidelines on Post-Exposure Prophylaxis for measles*. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/814203/Guidance_for_measles_post-exposure_prophylaxsis.pdf
33. McDonald et al. Clinical Practice Guidelines for Clostridium difficile Infection in Adults and Children: 2017 Update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA) Clin Infect Dis 2018;66:e1-e48
34. National Institute for Health and Care Excellence. *Faecal microbiota transplant for recurrent Clostridium difficile infection. Interventional procedures guidance [IPG485]*. Available from: https://www.nice.org.uk/guidance/ipg485
35. Stevens DL et al. Practice guidelines for the diagnosis and management of skin and soft tissue infections. 2014 update by the IDSA. Clin Infect Dis 2014;59:e10-52

36. Parks T et al. Clin Infect Disease 2018;67:1434-6
37. UpToDate. *Invasive group A streptococcal infection and toxic shock syndrome: Treatment and prevention*. Available from: https://www.uptodate.com/contents/invasive-group-a-streptococcal-infection-and-toxic-shock-syndrome-treatment-and-prevention
38. Public Health England. *Tetanus: advice for health professionals*. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/820628/Tetanus_information_for_health_professionals_2019.pdf
39. Hirsch *et al*. Clin Infect Dis. 2013 Jan 15; 56(2): 258–266
40. National Health Service. *Clinical Commissioning Policy: Maternal intravenous immunoglobulin (IVIg) for the prevention of alloimmune fetal and neonatal haemochromatosis*. Available from: https://www.england.nhs.uk/wp-content/uploads/2019/12/1864_Maternal-intravenous-immunoglobulin-to-prevent-allo-immune-fetal-haemochromatosis.pdf?UNLID=743114393202131542541
41. National Health Service. *Clinical Commissioning Policy: Infliximab (Remicade) and Adalimumab (Humira) As Anti-TNF Treatment Options For Adult Patients with Severe Refractory Uveitis*. Available from: https://www.engage.england.nhs.uk/consultation/specialised-services-consultation/user_uploads/uveitis-adults-policy.pdf
42. National Health Service. *Clinical Commissioning Policy: Rituximab for Immunobullous Disease*. Available from: https://www.england.nhs.uk/wp-content/uploads/2021/06/cc-policy-rituximab-for-immonobullous-disease-ocular-v2.pdf
43. Roberts DM et al. The treatment of acute antibody-mediated rejection in kidney transplant recipients – a systematic review. Transplantation. 2012;94:775-783

Additional information

IFR form can be found at: https://www.england.nhs.uk/publication/specialised-services-individual-funding-requests/

More information on IFRs in general, including the application form, is available here: https://www.england.nhs.uk/commissioning/spec-services/key-docs/#ifr

Clinical Guidelines for Immunoglobulin Use (2nd edition update; July 2011): https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/216671/dh_131107.pdf

NHS England will monitor use of Ig in grey indications via the Ig database and provide SRIAPs and commissioners with data relating to use in grey indications.