Guideline

Clinical guideline for immunoglobulin treatment: East of England Immunoglobulin Assessment Panel

1 Scope

This clinical guideline outlines the following standards by indication:

- Patient selection criteria
- Exclusion criteria (when not to treat)
- Place of immunoglobulin treatment vs. alternative therapies
- Dosing recommendations
- Clinical and laboratory outcomes to be assessed for efficacy
- Actions required for clinical approval by panel

Trust-wide in all named Trusts affiliated in with the East of England Immunoglobulin Assessment Panel:

- Bedfordshire Hospitals NHS Foundation Trust
    - Excluding Luton and Dunstable University Hospital
- Cambridge University Hospitals NHS Foundation Trust
- East & North Hertfordshire NHS Trust
- East Suffolk and North East Essex NHS Foundation Trust
- James Paget University Hospitals NHS Foundation Trust
- Mid and South Essex NHS Foundation Trust
- Norfolk & Norwich University Hospitals NHS Foundation Trust
- North West Anglia NHS Foundation Trust
- Princess Alexandra Hospital NHS Trust
- Queen Elizabeth Hospital Kings Lynn NHS Trust
- Royal Papworth Hospital NHS Foundation Trust
- West Suffolk Hospital NHS Foundation Trust

2 Purpose

This guideline outlines the standards for best clinical practice with immunoglobulins. This includes ensuring standardised:

- Selection criteria for treatment per indication
- Exclusion criteria for treatment per indication
- Doses align with national commissioning and clinical advice
- Understanding for prescribers for expected monitoring outcomes per indication

This guideline reflects and adds to the latest commissioning guidelines from NHS England and the Department of Health. As such all NHS prescribing of immunoglobulins within the jurisdiction of the East of England Immunoglobulin Assessment Panel should follow the advice in this guideline or by agreement with the East of England Immunoglobulin Assessment Panel. Prescribing of immunoglobulins is restricted to approved indications where clinical teams consent to record listed baseline and outcomes data for approved measures. This data facilitates the evaluation of the efficacy of immunoglobulin treatment for short-term indications and the continuing need for therapy at annual reviews, including the review of dosing regimens.

3 Definitions

ABW	actual body weight
ALK	alkaline phosphatase
CLL	chronic lymphocytic leukaemia
DDW	dose determining weight
ENRAD	Eastern Network of Rare Autoimmune Diseases
EOEIAP	East of England Immunoglobulin Assessment Panel
FBC	full blood count
fSCIG	facilitated subcutaneous immunoglobulin (with hyaluronidase)
g/Kg	grams per kilogram of body weight
Hb	haemoglobin
HSCT	haematopoietic stem cell transplant
IBW	ideal body weight
IEI	inborn errors of immunity
IgA	immunoglobulin type A
IgG	immunoglobulin type G
IgM	immunoglobulin type M
IM	intramuscular
IVIG	intravenous immunoglobulin
LFT	liver function test
MDT	multi-disciplinary team
MM	multiple myeloma
NHL	non-Hodgkin's lymphoma
NHSE	NHS England
NICE	National Institute for Health and Care Excellence
PCR	polymerase chain reaction
PID	primary immunodeficiencies
SCIG	subcutaneous immunoglobulin
TSS	toxic shock syndrome
WCC	white cell count

4 Undertaken by (staff groups)

All staff involved in any of the following aspects of immunoglobulin management:

- prescribing
- monitoring of clinical outcome(s) of therapy
- clinically checking and/or dispensing against prescriptions
- adjudication of clinical requests to the EOEIAP

To be used in conjunction with the Immunoglobulin policy and procedure.

5 Inclusion

This guideline covers neonatal, paediatric and adult treatment with immunoglobulins. While most of the indications are expected to be treated with IVIg, some may be treated with SCIg or fSCIG where appropriate training and homecare infrastructure are established. Immunodeficiency (all types), long-term neurology indications and certain infectious disease indications are most suitable for treatment with SCIg.

Appropriate pre-medication (an antihistamine, paracetamol +/- corticosteroid) is expected to be given before commencing immunoglobulin therapy to correct immunodeficiency. Pre-treatment assessment for immunomodulation involves ensuring euvolaemia and assessing VTE risks. Infusion reactions are uncommon in immunocompetent individuals.

Patients with capacity should be provided the regional Patient Information Leaflet which explains immunoglobulin therapy, the role of the EOE panel and the use of patient data. This should be used to inform the patient consent process before treating.

6 Exclusion

Patients at high risk of thromboembolism (hypertension, diabetes, smoking, hypercoagulable states) should be counselled regarding the prothrombotic risks of immunoglobulin.

Test doses of SCIg are not routinely recommended. These are only indicated in isolated immunodeficiency cases and should be agreed with a consultant immunologist before prescribing.

IgA deficiency is no longer considered a contraindication to the use of immunoglobulin therapy. Measurement of anti-IgA antibodies is not warranted.

Plasmapheresis / plasma exchange, where this is part of the clinical treatment deemed necessary for the condition, should be commenced before immunoglobulin therapy, unless there is a specific agreement in place with the EOE panel. In clinical emergencies where plasmapheresis is indicated but not immediately available, IVIG may be commenced provided:

- only the minimum number of infusions are given prior to plasmapheresis
- IVIG therapy is halted on the day plasmapheresis is due to commence

It is recognised that in some cases, subsequent to plasmapheresis, further IVIG may remain a treatment option. The exposure to IVIG prior to plasmapheresis is not usually factored into post-exchange dosing regimens for IVIG.

This guideline does not provide guidance for any immunoglobulin products other than 'normal' polyvalent immunoglobulin which is predominantly IgG in content.

Specifically it does not provide guidance for:

- IgM-enriched immunoglobulin (e.g. Pentaglobin)
- Hyperimmune immunoglobulins such as:
    - Rabies IgG
    - Tetanus IgG
    - CMV IgG
    - Hepatitis B IgG (Hepatect)
    - Anti-thymocyte immunoglobulin (equine or lapine)
    - Any other specific infection (viral or bacterial) targeted immunoglobulin

7 National guidelines

In 2024, NHS England published comprehensive Commissioning Guidelines including and updating 2021 guideline and the 2019 Commissioning Guidance for haematology, neurology and infectious disease indications which came before.

These documents in turn supersede the 2nd edition updated clinical guidelines for immunoglobulins published by the Department of Health (2011) and the 2019 NHS England Commissioning Guidance.

The East of England Immunoglobulin Assessment Panel seeks to provide comprehensive clinical guidelines which reflect best practice. At times this may be following changes to the national commissioning structure, but also before the national guidelines are updated (such as historically with Covid vaccine-induced thrombosis with thrombocytopenia or maternal treatment of alloimmune thrombocytopenia) or advice may reflect augmented good practice advice which supplements the information in the national clinical and commissioning guidance.

The information in this document aims to combine and reflect the latest commissioning and practice advice from each authority.

8 Applications to the East of England Immunoglobulin Assessment Panel (EOEIAP)

Electronic applications can be submitted to:

- add-tr.iap-eastofengland@nhs.net

Forms for application to panel are found on the EOEIAP webpage:

- https://www.cuh.nhs.uk/health-care-professionals/east-england-immunoglobulin-assessment-panel-eoe-iap/

Application forms can also be accessed via direct URL links:

- Immunoglobulin Clinical Application Request
- Immunodeficiency Clinical Application Form

For CUH applications:

- Where single panel member approval is required (Class II only), the name of the approving consultant / panel member should be documented on the Immunoglobulin Treatment Request Form and also in Epic.
- Where a panel consensus decision is required (Class III & IV), the approval email should be printed and attached to the accompanying Immunoglobulin Treatment Request Form.

See the Policy and Procedure for Immunoglobulins for further details and responsibilities.

- Cambridge University Hospitals Immunoglobulins Policy and Procedure
- CUH Immunoglobulins Policy and Procedure (external website)
- Other affiliated Trusts, refer to internal intranet for local policy and procedure

9 Dosing based on weight

All immunoglobulin doses are based on weight for initial dosing.

- **Immunoreplacement therapy (immunodeficiency)**
  - Use Actual Body Weight (ABW) then adjust in line with response
- **Immunomodulation (autoimmune disease)**
  - In adults (for the majority of cases)
    - Use Dose Determining Weight (DDW)
      - Use ABW if <154cm, if <60kg OR if IBW > ABW
      - In pregnancy, use the Booking Weight
  - In paediatrics, use the Ideal Body Weight, unless either height >154cm or weight >60kg. Where either threshold for height and weight are reached, use DDW.

DDW = IBW + 0.4(ABW-IBW)

IBW = {males} [(height(cm) – 154) x 0.9] + 50
= {females} [(height(cm) – 154) x 0.9] + 45.5

Total doses per treatment must use whole vials. Round calculated doses down to the nearest whole vial. For IVIg, this will mean rounding down to the nearest 5g.

Worked example for ♂ 84kg 170cm with GBS (2g/kg over 5 days)

IBW(kg) = (170 – 154) * 0.9 + 50 = 64.4

DDW = 64.4 + 0.4(84 – 64.4) = 72.24

@2g/kg = 144.48… round down to nearest 5g = 140g
Days 1-3: 30g, Days 4-5: 25g

10 Classification of indications

Historical classifications of indications into RED, BLUE, GREY and BLACK no longer exist. Treatment nationally is now either ‘commissioned’ or ‘not commissioned’, however the approval process for all indications except those which both 1) threaten life or limb and 2) demonstrate clear efficacy of IVIg over other treatment (i.e. Class I indications) require approval from the EOE Panel **prior** to treatment.

Indications in neither ‘commissioned’ nor ‘not commissioned’ categories are classified as **‘not routinely commissioned’** and require 1) **clinical approval** from the EOE Panel and 2) **funding approval** from NHS England via the IFR application process **prior** to treatment.

Classifications are divided into Class I to V in order help the panel and clinicians to prioritise treatment and IVIg stocks to those who are most likely to benefit from treatment, as detailed in Indication Classification.

11 Emergency treatment of conditions with high risk of mortality or morbidity; Class I

Treatment with IVIG may proceed without prior approval from the EOE Panel in the following conditions, where the stated inclusion criteria are met and;

- Alternative treatment is known to be clinically inferior, is contra-indicated or is not available.
- Failure to administer IVIG in a timely manner would risk life or limb
- The need for treatment is established by a consultant with specialist knowledge of the condition to be treated

Note: All Class I treatment must be notified retrospectively to the EOE panel. Pharmacists must ensure consultant approval and appropriate Class I indication prior to supply.

Class I indications

- Acute ITP with significant bleeding or the urgent need for emergency surgery
  - First dose only
- Autoimmune haemolytic anaemia (AHA) including Evans syndrome
- Coagulation factor inhibitors (allo- and autoantibodies)
  - Treatment may commence pending panel decision
- Haemolytic disease of the newborn
- Neonatal alloimmune thrombocytopenia (NAIT)
- Post-transfusion hyperhaemolysis
  - Treatment or prevention
- Post-transfusion purpura
- VITT (post Covid-vaccine)
  - First dose only
- Guillain-Barré syndrome
  - Respiratory and/or bulbar failure and PLEX not available
- Myasthenia Gravis
  - Myasthenic crisis (respiratory and/or bulbar failure)
- Hepatitis A
- Measles (if immunosuppressed or pregnant)
- Polio
- Staphylcoccal or streptococcal toxic shock syndrome
- Tetanus prone injury or suspected Tetanus
  - See also place of tetanus Ig in therapy
- Kawasaki disease

All other indications require individual approval by the EOE panel **prior** to treatment. Failure to obtain the appropriate approval risks the ability to continue treatment and notification to NHS England who may withhold the reimbursement of costs.

12 Indication classification

Class I indications	• **Short-term indications only – typically a single course with further treatment subject to panel approval (class II)**
	• **Immunoglobulin is the accepted first-line treatment (either alone or in combination with other treatments).**
	• **No alternative treatment is possible or available**
	• **Life/limb threatening or patient may incur harm if treatment is delayed.**
	• Patients must be assessed by the treating consultant as meeting set clinical eligibility criteria
	  ○ See indication specific treatment guidelines below
	• EOEIAP approval is not required for initial treatment providing an appropriate medical consultant specialist in the field of medicine for the indication has confirmed the minimum eligibility criteria are met.
	  ○ EOEIAP requires notification of treatment for all indications including retrospectively for Class I
	  ○ EOEIAP approval is required for re-treatment.
	• Out of hours treatment permitted for specified life/limb threatening indications
	• During shortages – to be available at all times because of risk to life or high likelihood of harm.
	• Response to treatment must be assessed against criteria, documented and made available to EOEIAP as required.

Class II indications	• **Acute or chronic treatment as per indication where alternative treatment may be possible, but evidence supports efficacy of immunoglobulins**
	• **Risk of harm from a short delay of access to treatment is low, or following initiation of class I treatment where further treatment is deemed necessary**
	• Proposal to treat must originate from the treating consultant/ consultant specialist in the field of medicine for the indication.
	• Patients must be assessed as meeting set treatment criteria.
	  ○ See selection criteria for indication
	• Clinical approval from EOEIAP is required before treatment may commence.
	  ○ Do not consent patients for treatment with immunoglobulins until clinical approval is granted.
	  ○ Triage to the appropriate EOEIAP SubPanel is the favoured mechanism for approval (immunology IAP, neurology IAP, ENRAD MDT or full panel submission).
	  ○ In the absence of a SubPanel, or where there is a risk of deterioration, an individual panel member may approve treatment (± panel pharmacist verification) providing there has been appropriate dialogue – written or verbal – between the requesting consultant and panel expert to assure the panel of the validity of the treatment request and need to use immunoglobulin over alternative treatments. However treatment decisions for Class II indications should involve at least 2 panel members where possible.
	• Treatment to be assessed against alternative treatment modalities and for long-term treatment plan.
	• Out of hours treatment is not permitted.
	• During shortages – use should be reviewed / modified in times of national shortage (eg dose reductions, alternative treatment).
	• Short-term/ long-term response to treatment must be assessed against criteria, documented and made available to EOEIAP as required.

Class III Indications	**Class III indications are commissioned and funded by NHS England providing there is clear and documented approval by the EoEIAP and where alternative therapy is not feasible or appropriate.** **Class III indications have LIMITED evidence for efficacy and access to treatment may be restricted during supply shortages.** • Proposal to treat must originate from the treating consultant / consultant specialist in the field of medicine for the indication. • Out of hours treatment is not permitted. • IFR submission is not required if the EOEIAP have granted clinical approval for treatment. • During shortages – use should be reviewed/ modified in times of national shortage (eg dose reductions, alternative treatment). • Response to treatment (short- and long-term) must be assessed and reported to East of England IAP meetings. Failure to submit details for panel review may result in clinical approval being revoked. • Clinical criteria to monitor treatment efficacy are required (as agreed by EOEIAP).

Class IV indications	• **Indications that are not included in any version of national clinical guidelines (DH) or national commissioning guidelines (NHSE); i.e. 'unlisted' indications or indications formerly listed, but removed from the current NHS England commissioning guideline.** • These indications are '**not routinely commissioned**' • Proposal to treat must originate from the treating consultant/ consultant specialist in the field of medicine for the indication. A **second opinion** from a consultant within the same specialism is preferred where available. • These indications do not have specified eligibility criteria, dosing strategies or outcome criteria. These should be suggested by the treating clinician at the point of request for review by EOEIAP, subject to modification as necessary. Clinical approval from the EOEIAP is restricted to dosing and monitoring specified at the time of approval. Any treatments approved by the EOEIAP must have patient specific parameters agreed. This detail must be included in the subsequent IFR application. • Uncommissioned indications require both EOEIAP clinical approval and NHS England funding approval or internal funding arrangement prior to treatment* • It is the responsibility of the treating team to submit an IFR for uncommissioned indications. • Out of hours treatment is not permitted. • During shortages – use should be reviewed/ modified in times of national shortage (e.g. dose reductions, alternative treatment). • Response to treatment (short- and long-term) must be assessed and reported to East of England IAP meetings. Failure to submit details for panel review may result in clinical approval being revoked.
Class V indications	• These indications have good quality primary medical literature which confirm immunoglobulin therapy is not effective. • Applications automatically rejected • Not recommended for use

13 Indication specific guidelines

Immunology indications

For all immunodeficiency treatment (all indications for immunoreplacement therapy):

- **Use ABW to guide initial dosing**
- **If using IVIG, premedication must be given before the first infusion**
  - **Antihistamine**
  - **Paracetamol**
  - **Plus, an 'as required' order for a corticosteroid**
- **If there is evidence of an infusion reaction during the first or subsequent doses, further premedication should be considered and the patient should be assessed by clinical immunology**

Indication	Selection criteria	Exclusion criteria	Position of immunoglobulin, taking into account alternative therapies	Recommended dose	Clinical outcomes	Prior panel approval required
Primary immunodeficiencies associated with significant antibody defects (excluding specific antibody deficiency) **LONG TERM**	A specific PID (IEI) diagnosis must be established by a **clinical immunologist**. In newly diagnosed patients with PID (IEI) and no significant burden of infection, the decision to commence Ig replacement should be recommended by immunology sub-panel / MDT.	No	Ig is the only definitive treatment for antibody deficiency	Initially: • 0.4-0.6 g/kg/month; Dose requirements may increase or decrease within the range 0.2-0.8g/kg/month and should be based on clinical outcomes. EOEIAP: Refer to dosing and patient management advice at the beginning of this section.	Raised: • Trough IgG level compared to baseline. Reduction in: • Number of infections • Days in hospital • Treatment courses with antibiotics	A single dose may be given at the discretion of the **consultant immunologist** prior to panel review. All patients must be discussed at the next available Immunology

						MDT (panel subgroup) to optimise patient treatment and for periodic review thereafter. **Class II indication (non-emergency)**
Haematopoeitic stem cell transplant (HSCT) in primary immunodeficiencies (PID) / inborn errors of immunity (IEI) **LONG TERM**	PID patients undergoing HSCT	No	Ig is the only definitive treatment for antibody deficiency	Initially: • 0.4-0.6 g/kg/month; Dose 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. EOEIAP: Refer to dosing and patient management advice at the beginning of this section.	• Raised trough IgG level compared to baseline.	All patients must be discussed at EOE Immunology MDT at the start of treatment and for periodic review thereafter. **Class II indication (non-emergency)**

Specific antibody deficiency **LONG TERM**	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	None, but see comments in column of position of immuno-globulin	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.	Initially: • 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 requires EOEIAP approval. Dose requirements may increase and should be based on clinical outcome. EOEIAP: Refer to dosing and patient management advice at the beginning of this section.	**6 monthly reviews (compared to baseline)** Raised: • Trough IgG level compared to baseline. Reduction in: • number of infections • days in hospital • treatment courses with antibiotics Database parameters will include entry of number of infections and days in hospital pre-treatment and 6 monthly thereafter.	All patients must be discussed at EOE Immunology MDT at the start of treatment and for periodic review **Class II indication (non-emergency)**
Secondary antibody deficiency **LONG TERM**	• Underlying cause of hypogammaglobinaemia cannot be reversed or reversal is contra-indicated; OR: • Hypogammaglobinaemia associated with drugs, therapeutic monoclonals targeted at B cells and plasma cells (rituximab and other	None, but see comments in column of position of immuno-globulin	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.	Initially: • 0.4-0.6 g/kg/month; Dose should be modified to achieve an IgG trough level of at least the lower limit of the age-specific serum IgG reference range. EOEIAP: Refer to dosing and patient management	**6 monthly reviews (compared to baseline)** Raised: • Trough IgG level compared to baseline. Reduction in: • number of infections • days in hospital • treatment with	All patients must be discussed at EOE Immunology MDT at the start of treatment and for periodic review **Class II**

	anti-CD20, CD19 agents, daratumumab etc.) post-HSCT, NHL, CLL, MM or other relevant B-cell malignancy confirmed by a haematologist; AND: **a)** Recurrent or severe bacterial infection despite continuous oral antibiotic therapy for 6 months **b)** IgG <4g/L (excluding paraprotein) **c)** Documented failure of serum antibody response to unconjugated pneumococcal or other polysaccharide vaccine challenge **NOTE:** 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 (a-c) will need to be fulfilled for an individual patient.		Since infection susceptibility in patients with haematological malignancies is frequently multifactorial, the reduction in overall burden of infections with long term Ig replacement therapy may be variable. For this reason biannual reviews of treatment are recommended. In patients with seasonal preponderance of infections, it may be appropriate to consider temporary cessation of Ig in the summer.	advice at the beginning of this section.	antibiotic courses Database parameters will include entry of number of infections and days in hospital pre-treatment and 6 monthly thereafter.	**indication (non-emergency)**

	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. 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 Transplantation group have jointly stated: "Do not routinely give Ig replacement to adult HSCT patients in the absence of infection regardless of the Ig level".					

	It is possible that patients with recurrent sino-pulmonary infections on a background of chronic pulmonary GVHD and hypogammaglobinaemia may benefit from Ig replacement therapy if they fulfil the criteria for secondary antibody deficiency.					
Thymoma with immunodeficiency **LONG TERM**	• Profound B cell depletion **AND / OR** • Significant antibody deficiency	None	Ig is the only definitive treatment for antibody deficiency	Initially: • 0.4-0.6 g/kg/month; Dose requirements may increase and should be based on clinical outcome EOEIAP: Refer to dosing and patient management advice at the beginning of this section.	Raised: • Trough IgG level compared to baseline. Reduction in: • Number of infections, • Treatment courses of antibiotics, • Days in hospital	All patients must be discussed at EOE Immunology MDT at the start of treatment and for periodic review **Class II indication (non-emergency)**

*There is controversy 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 states 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: 909-913.

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.

Indication	Selection criteria	Exclusion criteria	Position of immunoglobulin, taking into account alternative therapies	Recommended dose	Clinical outcomes	Prior panel approval required
Haematological indications						
Acquired red cell aplasia associated with chronic parvovirus B19 infection **SHORT TERM**	**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.	1g/kg to 1.2g/kg in divided doses. This may be repeated on relapse and for a 2nd relapse. EOEIAP: Use DDW for dosing.	• Rise in haemoglobin • Rise in reticulocyte count • Transfusion independence	Apply to EOEIAP **Out of hours** No. **Class II indication**
Alloimmune thrombocytopenia **- Foetal-maternal (FMAIT)**	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,	None	**FMAIT** Immunoglobulin is the primary treatment and sometimes combined with steroids.	**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	Successful outcome of pregnancy – i.e. no severe haemorrhage such as intracranial haemorrhage Platelet count above $50x10^9$/L at time of delivery.	FMAIT – apply to EOEIAP **Class II indication** **Out of hours** No

	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).			previous infant had thrombocytopenia but no intracranial haemorrhage) should be commenced on 0.5g-1.0g/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 foetus or neonate had intracranial haemorrhage after 28 weeks gestation), or 2g/kg/week (where the previous foetus or neonate had intracranial haemorrhage before 28 weeks).[8-12] EOEIAP: Use 'booking weight' for dose calculations in the treatment of pregnant patients. Monitor for IVIG-associated haemolysis in all patients but especially those with the blood groups: A, AB or B	Increment in neonatal platelet count.	

Alloimmune thrombocytopenia **- Neonatal (NAIT)**	<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.		**NAIT** 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 and 24-48 hours. Immunoglobulin may be of value if there is a prolonged thrombocytopenia with the aim of minimising the need for platelet transfusions.	**Neonatal:** Use IBW dosing in line with specialist paediatric advice. 1g/kg; a 2nd dose may be required if thrombocytopenia persists.		Consultant may approve – for NAIT **Class I indication** **Out of hours** Neonatal treatment only
Autoimmune haemolytic anaemia (AHA) including Evans syndrome **SHORT TERM**	**AHA – including Evans syndrome** • Symptomatic or severe anaemia, except in patients with co-morbidities, **AND** • Refractory to conventional treatment with corticosteroids	None	Immunoglobulin is reserved for patients unresponsive to steroids or where steroids are contraindicated.	1-2g/kg divided over two to five days. This may be repeated on relapse and for a 2nd relapse. **EOEIAP**: Use DDW for dosing in adults, IBW in infants or booking weight in	Rise in haemoglobin Transfusion independence Reduction in haemolysis markers (bilirubin, lactate dehydrogenase)	Consultant may approve – for treatment of acute episodes Apply to EOEIAP for

	OR • Corticosteroids contraindicated, **OR** • As a temporising measure prior to splenectomy **AHA in pregnancy:** • Pregnancy women with warm AHA refractory to corticosteroid OR with evidence of foetal anaemia • Neonates of mothers with AHA who have evidence of haemolysis and rising bilirubin despite intensive phototherapy			pregnancy.		repeat courses **Out of hours** No – unless emergency **First dose Class I indication** **Subsequent doses – Class II indication**
Coagulation factor inhibitors* (alloantibodies and autoantibodies) Including Acquired von Willebrand disease (vWD) **SHORT TERM**	• Life- or limb-threatening haemorrhage, **AND** • Failure to responds to other treatments, **AND/OR** • Prior invasive procedure Treatment is directed by the haemophilia centre at which the patients is registered	Acquired VWD associated with IgM monoclonal gammopathy	Immunoglobulin is a therapeutic option in acquired VWD, particularly in cases associated with an IgG monoclonal gammopathy alongside other therapies – plasmapheresis, desmopressin, VWF containing concentrates and recombinant Factor VII.	Either: **0.4g/kg/day for 5 days** OR **1g/kg/day for 2 days** EOEIAP: Use DDW for dosing.	Rise in factor level Resolution of bleeding Reduction in number of bleeding episodes	Apply to EOEIAP. If life-threatening, can commence treatment while panel decision pending. **Out of hours** No **Class II**

						indication
Haemolytic disease of the newborn **SHORT TERM**	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.	None	Immunoglobulin is an adjunct to phototherapy Also see NICE CG98 guidance[13]	0.5g/kg over 4 hours EOEIAP: Use **IBW** for dosing paediatrics, in line with specialist paediatric advice.	Reduction in bilirubin level Reduced need for exchange transfusion Long-term morbidity	Consultant may approve **Out of hours** Permitted **Class I indication**
Haemophagocytic syndrome **(Haemophagocytic lymphohistiocytosis or HLH)** **SHORT TERM**	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	Corticosteroid treatment may be contra-indicated e.g. in lymphoma	Other therapies include IL-1 inhibition (anakinra) on specialist advice only. Please refer to NHS England policy[14]. Depending on the underlying cause (e.g. EBV reactivation or HIV) alternative management following initial treatment with IVIG and corticosteroid may be appropriate. Primary HLH may have	Initially 2g/kg in divided doses over two to five days with corticosteroid (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. EOEIAP: Use DDW for dosing.	Improvement of cytopenias Survival Improvement of HLH markers – Ferritin / soluble CD25.	Apply to EOEIAP **Out of hours** No **Class II indication**

	(*H-score >169 is 93% sensitive and 86% specific for HLH)		additional management strategy to prepare for bone marrow transplant.	CUH operates an HLH panel. Referrals to the EOE panel for HLH may be triaged for specialist input and management.		
Immune Thrombocytopenic Purpura (ITP) **SHORT TERM**	Immunoglobulin generally used in only FOUR 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. 4) Moderate severity bleeding in patient with higher risk of subsequent severe bleed. Patients with mucosal bleeding or bleeding from multiple	None	Thrombopoietin mimetics may be useful substitutes in some patients (e.g. in situation #3) or as an adjunct in other situations. Relevant NICE CG/TA: Eltrombopag TA293 Romiplostim TA221 Other therapy listed by NICE for later treatments for ITP management include: • Rituximab (not licensed) • Splenectomy • Azathioprine, mycophenolate, ciclosporin, dapsone, danazol. Refer to specialist regional ITP services for specific guidance regarding chronic management.	**Acute ITP:** 0.8g/kg as a single infusion; not exceeding 1g/kg. EOEIAP: Use DDW for dosing. A 2nd infusion 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 second dose may be considered at day 5-7 **Persistent ITP:** While establishing a second line treatment, 0.8g/kg as a single infusion every 2-3 weeks (depending on response)	Increase in platelet count Resolution of bleeding Reduction in number of bleeding complications	Consultant haematologist may approve 1st dose for acute ITP; the use of a 2nd dose should be discussed with the EOEIAP Apply to EOEIAP – for maintenance treatment **Out of hours** Permitted for first acute treatment Repeat courses require EOEIAP application **First dose Class I indication**

	sites or a previous history of severe bleeding are at higher risk of a subsequent severe bleed. These eligibility criteria are also applicable when considering the short-term use of Ig in patients with **Chronic ITP** experiencing acute bleeding or requiring invasive procedures. Bleeding severity is defined by the "Updated international consensus report on the investigation and management of primary immune thrombocytopenia 2019"[15] Target platelet counts for surgery* Procedure / Platelet count Dentistry >20 Simple dental extraction >30 Complex dental extraction >50 Regional dental block >30 Minor surgery >50 Major surgery >80					2nd dose for subsequent relapse (<3 months) or dosing while establishing 2nd agent **Class II indication** Long-term dosing as sole agent **Class IV indication**

	Major neurosurgery | >100 PLT units x 10^9 per litre. **ITP in pregnancy:** Maintenance treatment with Ig may be required antenatally to maintain platelets to maintain platelets above 20x 10^9/L and/or to increase platelets to over 50x10^9/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[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, 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 x 10^9/L.					

Thrombosis and thrombocytopenia following Covid-19 vaccination (VITT) **SHORT TERM**	Confirmed or probably diagnosis of VITT made by a haematologist conforming to the up-to-date guidance from the Expert Haematology Panel – see British Society for Haematology website for details. Also see NICE NG200 [17] Acute thrombosis or new onset thrombocytopenia within 28 days of receiving Covid-19 vaccination Also follow Expert Haematologist Panel advice, including investigation of: - FBC: check PLT - Coagulation screen: check fibrinogen and D dimer It is crucial that the online **yellow card** is completed and this will trigger a request from MHRA for further details. https://coronavirus-yellowcard.mhra.gov.uk/	If >28 days from vaccination, seek advice from EOEIAP If isolated thrombo-cytopenia or thrombosis: • Reduced PLT count without thrombosis with D dimer at or near normal and normal fibrinogen. •Thrombosis with normal PLT and D dimer.	**AVOID** platelet transfusion **AVOID** heparin **AVOID** thrombopoeitin receptor antagonists unless specifically authorised through the haematology MDT **CONSIDER** corticosteroid and **ANTICOAGULATE** with non-heparin based therapy either therapeutically or prophylactically (if no overt thrombosis but thrombocytopenia with raised D dimer) based on advice from the local specialist haemostasis team. Irrespective of degree of thrombocytopenia, **IVIG treatment is urgent** and the most likely to influence the disease process. A repeat course of IVIg may be required depending on the clinical course.	**Adults and children:** 0.8g/kg as a single infusion over 1-2 days; total dose not exceeding 1g/kg. EOEIAP: Use DDW for dosing. A 2nd infusion may be required (e.g. after 24-48 hours) depending on the clinical course.	Increase in platelet count Resolution of bleeding Number of bleeding complications Survival	Consultant haematologist may approve 1st dose. The use of a 2nd dose should be discussed with the EOEIAP before treatment. **Out of hours** Permitted for first acute treatment **Repeat courses** require EOEIAP application **First dose:** **Class I indication** **Subsequent dose(s):** **Class II indication**

Post-transfusion hyperhaemolysis **SHORT TERM**	**Treatment of acute post-transfusion hyperhaemolysis:** Symptomatic or severe anaemia (Hb <60g/L, with evidence of ongoing intravascular haemolysis due to a delayed haemolytic transfusion / hyperhaemolysis). It is recognised that some patients with an Hb >60g/L may require treatment.	None	In combination with steroids, Ig is used as first-line treatment.	2g/kg over 2-5 days (usually over two days) given with IV methylprednisolone **EOEIAP:** Use DDW for dosing.	Rise in haemoglobin Reduction in haemolysis markers (bilirubin, lactate dehydrogenase) Transfusion independence No haemolysis Maintenance of post-transfusion Hb and 1-3 weeks Avoidance of need for repeated transfusion	Consultant may approve – for treatment of acute episodes **Out of hours** Yes **Treatment - Class I indication**
Prevention of haemolysis in patients with a history of transfusion-associated hyperhaemolysis **Prevention of delayed haemolytic transfusion reaction** **SHORT TERM**	Symptomatic or severe anaemia (Hb <60g/L, with evidence of ongoing intravascular haemolysis due to a delayed haemolytic transfusion / hyperhaemolysis). It is recognised that some patients with an Hb >60g/L may require treatment. **Prevention of haemolysis in those with a history of transfusion-associated hyperhaemolysis / haemolytic transfusion reaction:**	See position for Ig therapy	Eculizumab is commissioned as a 2nd line treatment where 1st line has failed; Rituximab is recommended as a 3rd line treatment [18]	1-2g/kg over two to five days given with steroids (usually IV methylprednisolone)		Apply to EOEIAP – for prevention unless emergency **Out of hours** Yes **Prevention - Class I indication**

	Patients who have had previously delayed haemolytic transfusion reactions / post-transfusion hyperhaemolysis or who have single or multiple allo-antibodies AND who may require a blood transfusion.					
Post-transfusion purpura **SHORT TERM**	• 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)	None	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. EOEIAP: Use DDW for dosing.	Increase in platelet count Resolution of bleeding Reduction in number of bleeding complications	Haematology consultant may approve **Out of hours** Yes **Class I indication**

Indication	Selection criteria	Exclusion criteria	Position of immunoglobulin, taking into account alternative therapies	Recommended dose	Clinical outcomes	Prior panel approval required
Neurology indications						
Acute idiopathic/autoimmune dysautonomia/ganglionopathy	• Acute onset autonomic failure with presence of ganglionic (alpha-3) 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 **EOEIAP:** Use DDW for dosing.	• Postural BP drop reduction with improved activities of daily living • Increase in time to significant postural BP drop • Reduction numbers of syncopal and pre-syncopal episodes • Reduced oral dryness score • Reduced diarrhoea and constipation frequency	**Apply to EOEIAP** **Out of hours** No **Class II indication**
Autoimmune encephalitides (AIE) (antibody associated) **OR** **Autoimmune encephalitides (no known antibody defined)**	<u>Antibody associated:</u> • Non-infective encephalitis, with or without underlying teratoma or malignancy with known encephalitis associated antibody (e.g. LGI1, Caspr2, NMDAR, GAD GlycineR, DPPX, AMPA,	Infective encephalitis or other non-inflammatory cause of encephalopathy or seizures	Search for underlying malignancy and treat as appropriate Prednisolone (or methylprednisolone) is first line, with or without Plasma	2g/kg over 5 days initially repeated at 3 to 6 weeks. Repeat course 3 times if necessary. If repeated	AIE outcomes for all types (except Ab titre where antibody is undefined) • Antibody titre (if relevant and measurable)	Apply to EOEIAP **Out of hours** No **Class III indication**

	GABAb and others) • Functional disability caused by seizures, encephalopathy, stiffness, cognitive dysfunction or other relevant neurological sequelae <u>No known antibody defined:</u> • Non-infective encephalitis, with or without underlying teratoma or malignancy **without** known encephalitis associated antibody • Functional disability caused by seizures, encephalopathy, stiffness, cognitive dysfunction or other relevant neurological sequelae • Evidence of inflammatory CNS disorder including active CSF, EEG defined seizures, MRI changes consistent with AIE in the absence of infection.		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-19 study is available [19]. Consider recruitment for eligible patients.	courses are required, consider institution of alternative longer-term strategy immediately **EOEIAP:** Use DDW for dosing.	• Modified Rankin Score • Reduction in seizure frequency or severity • Improvement on one or more validated tests of memory or executive tasks • Resolution of MR signal change (where present) • Resolution of hyponatraemia where present	
Chronic inflammatory demyelinating polyradiculopathy (CIDP) - including IgG or IgA associated paraprotein associated demyelinating neuropathy	• Probable or definite diagnosis of CIDP by a neurologist according to the EAN/International Peripheral Nerve Society criteria; **AND** • Significant functional	No specific exclusion criteria but see general comments regarding prothrombotic	IVIG should not always be considered first line treatment for CIDP, although it may be where steroids are contra-indicated and plasma	An initial regimen of a maximum 4g/kg divided into at least two courses of 1-2g/kg each, and given over a 4 to	Efficacy outcomes should be used to measure response after the chosen initial regimen and therefore when assessing for dose	Short-term initiation treatment to assess Ig responsiveness **Neurology consultant**

	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 continuing need.	risks of Ig	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.	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[19] • 2g/kg initially followed by 1g/kg after 3 weeks and a further 1g/kg 3 weeks later[20] For maintenance dose optimisation see general note below. EOEIAP: Use DDW for dosing.	optimisation. Clinically meaningful improvement in any three of the following pre-specified 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 • Inflammation RODS score • 10-m walk (in seconds) • Berg Balance scale • Other validated disability score	**may approve with retrospective application to EOEIAP** Long-term treatment following initial assessment period **Apply to EOEIAP** **Out of hours** No **Class II indication**
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**	Patients with mild and/or non-progressive disease not requiring	Patients with Miller-Fisher Syndrome do not usually require IVIg and, unless associated with GBS overlap with	2g/kg given over **5 days** - Administration over a shorter time frame not recommended	None	Neurology consultant may approve first course. **Out of hours**

	• Disease progression toward intubation and ventilation **OR** • mEGRIS score ≥3 **OR** Poor prognosis mEGROS ≥4	intubation.	weakness, will recover normally. Plasma exchange is equally efficacious as IVIg in GBS and should be preferentially considered where it is clinically appropriate and easily accessible.	because of fluid overload with associated autonomic problems, and protein overload with pro-coagulation risks; EOEIAP: Use DDW for dosing. IVIg is unlikely to be effective if given more than 4 weeks after the onset of symptoms. Second doses of IVIg are rarely effective and may be associated with harm[21]. Plasma exchange may be considered if deterioration following clear improvement after the first dose.		Permitted unless mild / non-progressive **Class I indication** 2nd dose: **Class II indication** Apply to EOEIAP

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 an 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 neuropathy in adults in line with NHS England policy[23]	An initial 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[19] • 2g/kg initially followed by 1g/kg after 3 weeks and a further 1g/kg 3 weeks later[20] For maintenance dose adjustment see general note below. EOEIAP: Use DDW for dosing.	Efficacy outcomes should be used to measure response after the chosen initial regimen and therefore when assessing for the 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 • Inflammation RODS score • 10-m walk (in seconds) • Berg Balance scale • Other validated disability score	Apply to EOEIAP **Out of hours** No **Class II indication**

Inflammatory myopathies Including Dermatomyositis (DM) Juvenile dermatomyositis (JDM) Polymyositis (PM) Other inflammatory myopathies*	• Diagnosis of myositis by a neurologist, rheumatologist, dermatologist or immunologist **AND EITHER** • Patients who have significant muscle weakness **OR** • Dysphagia and has not responded to corticosteroid and other immuno-suppressive 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.** In adult patients (and post-pubescent children through NHS England and NHS Improvement Medicines for Children policy[24]) with refractory disease associated with myositis-specific antibodies, **rituximab** (or biosimilar) has been approved as a second-line treatment by NHS England[25]. **Abatacept** is recommended in refractory idiopathic inflammatory myopathies (adults and children aged 2 and over) as a third-line treatment by NHS England[26]. IVIg is fourth-line	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 sum score) • other quantitative muscle strength (e.g. MMT8) • up and go 10-m walk (in secs) • CDASI • FVC • CHAQ (to include the childhood score) **PM and other inflammatory myopathies** functional / disability scores (ADLs): • semi-quantitative muscle scores (MRC sum score) • other quantitative muscle strength (e.g. MMT8) • up and go 10-m	Apply to EOEIAP **Out of hours** No **Class II indication**

			treatment. 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 <12 months) may be required in a small minority of patients with inflammatory myositis, as third line treatment after consideration of **rituximab** (see comments under position of immunoglobulin). In such cases, every effort should be made to establish the minimum clinically effective dose by either reduction of dose or lengthening the intervals between infusions. Attempt cessation at least annually.	Cessation trials should be attempted at least annually to establish ongoing need for treatment. EOEIAP: Use DDW for dosing.	walk (in secs) • HAQ • FVC **For juvenile dermato-myositis (JDM):** • MMT-8 • CMAS score • CK for baseline and assess how a patient has improved after each infusion or at least 3 infusions • PGALs in used to assess how a patient has improved after each infusion or at least after 3 infusions. **Efficacy outcomes should be recorded after the initiation course and regularly reassessed and recorded thereafter.**	

Multifocal Motor Neuropathy (MMN)	• Diagnosis by a neurologist of MMN 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 initial 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[19] • 2g/kg initially followed by 1g/kg after 3 weeks and a further 1g/kg 3 weeks later[20] Refer to dose optimisation section below for maintenance dosing; **If no significant measurable and**	Clinically meaningful improvement in three pre-defined measures from the list below; • 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 **Neurology consultant may approve** Long-term treatment **Apply to EOEIAP** **Out of hours** No **Class II indication**

				functionally meaningful improvement in abilities has been achieved after 3 doses, IVIg should be stopped. EOEIAP: Use DDW for dosing.		
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 – for instance, deteriorated mobility, unable to walk unaided; **OR** Prior to surgery and/or thymectomy	No specific exclusion criteria but see general comments regarding prothrombotic risks of IVIg	All patients requiring urgent inpatient 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 patients has failed all standard treatments (including steroids and	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 (e.g. over 2-5 days). Patients with life-threatening disease (e.g. in intensive care) with respiratory	Clinically meaningful 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 (FVC) • Variation of	Myasthenic crisis – **Consultant may approve** **Class I if myasthenic crisis** Long-term treatment **Apply to EOEIAP** **Out of hours** If crisis; Respiratory or bulbar failure Otherwise **Class II indication**

			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 and has been approved by NHS England[27] for this group of patients with resistant myasthenia.	and/or bulbar failure) should receive 2g/kg over 2-5 days. **Refer to dose optimisation section for maintenance.** EOEIAP: Use DDW for dosing.	another myasthenic muscular score • Dysphasia score • Dysarthria 1-50 counting • Diplopia or ptosis measurement	
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. <u>Immunomodulation</u>: • 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 EOEIAP: Use DDW for dosing.	Clinically meaningful improvement in • Timed up and go walk • Functional measure: e.g. Myotonia Behaviour Scale (MBS), Rivermead Mobility Index, or Brief Pain Inventory • Neurophysiological myotonia assessment	Apply to EOEIAP **Out of hours** No **Class II indication**

Non-MS CNS inflammatory disease covering the clinical phenotype of Aquaporin-4 antibodies (AQP4 ab) disease, Neuromyelitis Optica Spectrum Disorder (NMOSD), Acute Disseminated Encephalomyelitis (ADEM) (with or without encephalopathy, including brainstem attacks), Myelin Oligodendrocyte Antibody Disease (MOGAD) disease, Transverse Myelitis (TM) and Optic Neuritis (ON)						
	All sub-types, refer also to Further Information section below for information on attack and relapse clarification					
Non-MS CNS inflammatory disease **Acute Disease: Short term use**	• Acute disease attack* not responding to IV methylprednisolone (5g-7g or equivalent in children) and PLEX. When PLEX is not available or delayed or contra-indicated, IVIG can be used before PLEX (see exclusions) • Consider patient transfer to specialist centre with PLEX availability AND • Evidence of ongoing inflammation AND • Within 6 weeks unless evidence of active inflammation	Mild relapses without: new neurological signs OR reduced activities of daily living OR other inflammatory disease diagnoses (e.g. MS Sarcoid, Behçet's etc.)	Refractory to IV methylprednisolone OR PLEX not available or contraindicated OR refractory to PLEX in cases of severe disability and ongoing inflammation (usually within 6 weeks)	2g/kg over 2-5 days EOEIAP: Use DDW for dosing.	To be determined by disease features including 3 of: • Modified Rankin score • 10m walk • 9-hole peg test • Validated neuropsychometric testing • Improvement of other relevant validated scale • Objective relevant imaging improvement If ON - clinical improvement of visual acuity. If TM – clinically meaningful improvement in either 1. EDMUS **OR** 2. ASIA	Apply to EOEIAP **Out of hours** No **Class II indication** Class I if preceding weekend or bank holiday and panel decision may take >24 hours.

Non-MS CNS inflammatory disease **<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 mycophenolate / rituximab / azathioprine / methotrexate) OR serious side effects with prednisolone (adequate dose and length of time)	Pseudo relapse 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 regular steroid and IVIg at 1g/kg) Annual reviews for dose optimisation EOEIAP: Use DDW for dosing.	Suppression of further relapses* Treatment Failure – defined as objective evidence of true relapse* on treatment	Apply to EOEIAP **Out of hours** No **Class II indication**
Non-MS CNS inflammatory disease **<u>Chronic relapse prevention:</u>** **AQP4 NMOSD (Aquaporin 4 Neuromyelitis Optica Spectrum Disorder)**	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) PLUS immunosuppressant (azathioprine / rituximab / mycophenolate / methotrexate / ciclosporin or tacrolimus / PLEX or new RCT treatment if available)	Pseudo relapse	As per selection criteria	1g/kg monthly for first year; if relapse despite regular steroid and IVIg at 1g/kg, titrate up to 2g/kg Review annually EOEIAP: Use DDW for dosing.	Suppression of further relapses* Treatment Failure – defined as objective evidence of true relapse* on treatment	Apply to EOEIAP **Out of hours** No **Class II indication**

Non-MS CNS inflammatory disease **<u>Chronic relapse prevention:</u>** **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 dose and time) PLUS immunosuppressant (azathioprine / rituximab / mycophenolate / methotrexate / ciclosporin or tacrolimus / PLEX or new RCT treatment if available)	Pseudo relapse OR Other inflammatory disease diagnoses (e.g. MS Sarcoid, Behçet's etc.)	As per selection criteria	1g/kg over 2 days then monthly for first year Review at one year try reducing interval /dose with alternative options EOEIAP: Use DDW for dosing.	Suppression of further relapses* Failure – defined as objective evidence of true relapse* on treatment	Apply to EOEIAP **Out of hours** No **Class II indication**
<u>Further information</u> **Non-MS CNS inflammatory disease**	*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.					
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 / 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 EOEIAP: Use DDW for dosing.	• Improvement in OMS score	Apply to EOEIAP **Out of hours** No **Class II indication**

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. EOEIAP: Use DDW for dosing.	• Modified Rankin Scale • 10m walk • Any validated relevant disability measure appropriate to the condition	Apply to EOEIAP **Out of hours** No **Class II indication**
Rasmussen's Encephalitis	When other therapies (such as steroids) have failed.	No specific exclusion criteria but see general comments regarding prothrombotic risks of IVIg	Ig is reserved for patients unresponsive to steroids and other therapies.	2g/kg divided over two to five days, and repeated monthly for three months for initial trial. EOEIAP: Use DDW for dosing.	Seizure frequency with expected reduction of 30% to continue therapy.	Apply to EOEIAP **Out of hours** No **Class II indication**
Stiff person syndrome (SPS) or variant	Diagnosis of SPS or a variant (stiff limb, PERM, etc.) by a consultant neurologist	No specific exclusion criteria but see general	Consider **plasma exchange** as initial treatment. Rituximab is likely to	An initiation regimen of a maximum 4g/kg divided into at	Clinically meaningful improvement in at least two of the measures below:	Apply to EOEIAP **Out of hours**

	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	comments regarding prothrombotic risks of IVIg	be equally effective but is not commissioned for this indication.	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[19] 2g/kg initially followed by 1g/kg after 3 weeks and a further 1g/kg 3 weeks later[20] If no significant measurable and functionally meaningful improved in abilities had been achieved after 3 doses IVIG should be stopped	• Reduction in stiffness • Up and go 10-m walk (in secs) • BRIT score • Number of spasms per day • Validated measure of functional disabilities	No **Class II indication**

				EOEIAP: Use DDW for dosing.		
Immune effector cell-associated neurotoxicity syndrome (ICANS)	Grade 3 or 4 (see reference below for criteria) or refractory to standard care.	Patient must be reviewed by a neurologist and CAR-T specialist	Most centres are using corticosteroids as first-line therapy for isolated ICANS, with tocilizumab plus corticosteroids given for ICANS that develops concurrently with CRS, although therapy remains largely empirical and there are no clinical trial data yet comparing the various approaches. Different corticosteroids are used depending on institutional standards, although dexamethasone use is most common because it has excellent CNS penetration and improves the integrity of the blood–brain barrier. High pulse-dose	2g/kg Repeat as necessary with specialist advice EOEIAP: Use DDW for dosing. Submit IFR to NHSE	Seizure resolution Improved ADL Resolution of cerebral oedema Improved level of consciousness Improved dysphasia, tremor, headache or disorientation.	Apply to EOEIAP **Out of hours** No **Class IV indication**

			methylprednisolone is used in the more severe cases of ICANS based on experience with fulminant neuroinflammatory disorders. Immunoglobulin should be reserved for cases that are more severe (higher grade) or refractory to standard care.			

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[28].

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[19]. 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[29] 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 continuing need for treatment[30].

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.

ICANS grading criteria available here

Indication	Selection criteria	Exclusion criteria	Position of immunoglobulin, taking into account alternative therapies	Recommended dose	Clinical outcomes	Prior panel approval required
Infectious Disease indications						
Hepatitis A	Immunoglobulin is recommended in addition to hepatitis A vaccine for contacts of hepatitis A who are less able to respond to vaccine, ie. • those aged 60 or over, **OR** • those with immunosuppression and those with a CD4 count <200 cell per microliter, **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. Use of commercial stock should be recorded in the National Immunoglobulin Database. UKHSA immunoglobulin stocks are issued nationally and distributed locally. Hospitals should keep records of all instances of use of UKHSA-provided stocks (e.g. in patient records).	**Use commercial stock for any patient treated in hospital.** **UKHSA-provided SCIG for community-based treatment; available from nearest UKHSA depot (HPA team to advise).** Use **IVIG** preferentially for hospital patients, in particular if thrombo-cytopaenic. **Hospital treatment:** Commercial stock of IVIG (as per local formulary) <10 years – 500mg >10 years – 1000mg If IV cannulation impractical, consider **SCIG via IM route:**	Outcome measures not routinely recorded on surveillance database.	Permission required from UKHSA health protection team* Notification of treatment to EOEIAP only if commercial stock used. Find local protection team here: https://www.gov.uk/health-protection-team **Out of hours** Permitted with ID consultant approval only if pressing need – e.g. treating at

				<10 years – 500mg >10 years – 1000mg Given with vaccine in those at high risk, within 2 weeks of exposure in those less able to respond to vaccination and those at risk of severe complications. 1st line – equivalent dose of **Cutaquig 16.5%** by IM route 2nd line – equivalent dose of **Hizentra 20%** by IM route **Community treatment:** UKHSA-provided **Subgam**. <10 years – 500mg >10 years – 1000mg For those exposure 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		risk contacts who will not be available later **Class I indication** **Use UKHSA provided stock only for patients treated in the community.**

				infection), ***See notes at the end of this section***		
Measles (immunosuppressed individuals) **Further info:** Think measles	Immunosuppressed individuals (Group A and Group B based on the level of immunosuppression[31]) who have had a significant exposure to measles and are known to be susceptible (based on vaccine history and/or IgG testing). Advice is available at: National measles guidelines - https://www.gov.uk/government/publications/national-measles-guidelines All patients are to be reviewed in the context of the additional detail contained in the UKHSA guideline. HNIg is assumed to contain at least 80 IU/g, with 11 IU/Kg required to provide protection from measles.	Patients who are known to be measles IgG positive following immunosuppressive treatment are unlikely to require IVIG. **Group A** patients who have Hx of measles infection or vaccination are unlikely to require IVIG.	Eligibility is stratified by Group A and Group B risk groups as defined on pages 27-31 of the National Measles Guideline 2024. Immunoglobulin is mainstay management for PEP in: • Pregnant contacts • Infant contacts below 6 months • Group B contacts who are not already receiving IVIG replacement therapy • Immunosuppressed contacts Contacts already receiving Ig replacement therapy do not require additional IVIG if last dose of Ig within previous 3 weeks (IVIG) or previous week (SCIG).	**Use commercial IVIG stock all patients.** • 0.15g/kg IVIG (to provide 11 IU/kg of measles antibody) within 6 days of exposure – though ideally within 72 hours. 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. EOEIAP: Use DDW for dosing in adults, ABW in infants or booking weight in pregnancy.	Prevention of measles	Permission required from UKHSA health protection team Notification of treatment to EOEIAP **Out of hours** With UKHSA approval **Class I indication** **Use hospital stocks** Find local protection team here: https://www.gov.uk/health-protection-team

Dosing of IVIG in immunosuppressed individuals following a significant exposure to measles:

Weight (Kg)	Dose (g)	Weight (Kg)	Dose (g)
<20	2.5g	71-90	12.5g
20-35	5g	91-105	15g
36-54	7.5g	106-116	17.5g
55-70	10g	116-133	20g

- IVIG is available in 2.5g, 5g, 10g and 20g vial sizes.

Measles (pregnant women and infants) **Further info:** Think measles	Pregnant women who have been identified as susceptible based on vaccine history and/or antibody testing who have had a significant exposure to measles. Neonates born to mothers who develop a measles rash 6 days before to 6 days after delivery. Infants under 9 months of age with a significant exposure to measles. Advice is available at: National measles guidelines - https://www.gov.uk/government/publications/national-measles-guidelines All patients are to be reviewed in the context of the additional detail contained in	See eligibility criteria	For pregnant patients and infants who are immunosuppressed contacts, immunoglobulin is mainstay management. 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 Use of commercial stock should be recorded in the National Immunoglobulin Database. UKHSA immunoglobulin stocks are issued	**Use commercial stock for any patient treated in hospital.** **UKHSA-provided SCIG for community-based treatment; available from nearest UKHSA depot (HPA team to advise).** Use **IVIG** preferentially for hospital patients, in particular if thrombo-cytopaenic. • Pregnant women: approximately 3000mg (round up to 5g if using IVIG) • Infants 100mg/kg up to a maximum of 1000mg.	Prevention of measles.	Permission required from UKHSA health protection team* Notification of treatment to EOEIAP only if commercial stock used. Find local protection team here: https://www.gov.uk/health-protection-team **Out of hours** Give in working hours if possible within 72 hour window

	the UKHSA guideline. Further advice in viral illness in pregnancy: Guidance on the investigation, diagnosis and management of viral illness (plus syphilis), or exposure to viral rash illness , in pregnancy.		nationally and distributed locally. Hospitals should keep records of all instances of use of UKHSA-provided stocks (e.g. in patient records).	**Hospital treatment:** Commercial stock of IVIG (as per local formulary) If IV cannulation impractical, consider **SCIG via IM route:** 1st line – **Cutaquig 16.5%** • 3g ≈ 20ml of 16.5% in pregnancy • 0.6ml/kg up to 1g for infants 2nd line – **Hizentra 20%** • 3g ≈ 15ml of 20% in pregnancy • 0.5ml/kg up to 1g for infants **Community treatment:** UKHSA-provided **Subgam**. **Subgam 16% w/v** of which >95% is IgG. For dosing purposes: • 3g ≈ 20ml of 16.5% in pregnancy • ~0.6ml/kg up to 1g for infants		**Class I indication** **Use UKHSA provided stock only for patients treated in the community.**

				For other brands and dosing, liaise with EOEIAP or UKHSA directly. ***See notes at the end of this section***		
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. Use of commercial stock should be recorded in the National Immunoglobulin Database. UKHSA immunoglobulin stocks are issued nationally and distributed locally. Hospitals should keep records of all instances of use of UKHSA-provided stocks (e.g. in patient records).	**Use commercial stock for any patient treated in hospital.** **UKHSA-provided SCIG for community-based treatment; available from nearest UKHSA depot (HPA team to advise).** • <1 year: 250mg • 1 – 2 years: 500mg • >3 years: 750mg Use **IVIG** preferentially for hospital patients, in particular if thrombo-cytopaenic. **Hospital treatment:** Commercial stock of IVIG (as per local formulary) If IV cannulation impractical, consider	Either: • Prevention of infection OR • Resolution of infection	Permission required from UKHSA health protection team* Notification of treatment to EOEIAP only if commercial stock used. Find local protection team here: https://www.gov.uk/health-protection-team **Out of hours** With UKHSA approval **Class I indication** **Use UKHSA**

				SCIG via IM route: 1st line – equivalent dose of **Cutaquig 16.5%** by IM route 2nd line – equivalent dose of **Hizentra 20%** by IM route **Community treatment:** UKHSA-provided **Subgam**. Equivalent dose of Subgam 16% by IM route. 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		**provided stock only for patients treated in the community.**

				on two consecutive occasions. ***See notes at the end of this section***		
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 **OR** • 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[32] Faecal microbiota transplantation is approved by NICE for patients with recurrent CDI unresponsive to antibiotics and is likely to be an effective alternative[33].	0.4 g/kg IVIG, one dose, and consider repeating once EOEIAP: Use DDW for dosing.	• Clearance of C. diff. • Duration of hospital in-patient stay	Apply to EOEIAP [or ID consultant where delay could be detrimental] **Out of hours** No **Class II indication**
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** • Failure to achieve rapid	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	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 1g/kg. Should there be	• Improvement of FBC, ALK, CPK,and acute phase markers • Reduction in hospital inpatient stay • Survival	Consultant may approve Ideally, prior approval is recommende d but if this is not possible,

	improvement with antibiotic therapy and other supportive measures, **AND** • Life-threatening		**streptococcal TSS**, it should be noted that 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[34]. 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[35]. Based on the results of this meta-analysis,	no evidence of improvement at 24 hours, a further 1g/kg may be considered. EOEIAP: Use DDW for dosing.		treatment should proceed, and retrospective approval should be sought. **Out of hours** Permitted **Class I indication**

			the use of IVIg as adjunctive therapy is supported by Stevens DL[36].			
Tetanus prone injury **(IM-TIg or SCIg via IM route)**	Tetanus specific immunoglobulin (TIG) has limited stock and is recommended for susceptible individuals sustaining high risk tetanus prone injuries as defined in guidance[37] (**https://www.gov.uk/government/publications/tetanus-advice-for-health-professionals**)	See eligibility criteria	• Thorough cleaning of wound is essential, including debridement of devitalised tissue if necessary • Immunoglobulin for Prophylaxis • Booster of tetanus-containing vaccine for long term protection Use of commercial stock should be recorded in the National Immunoglobulin Database.	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. 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 in commercial immunoglobulin products, the dose of HNIg required to achieve the recommended dose of 250IU anti-tetanus Ig is approximately 1g.	Prevention of tetanus infection	Consultant may approve **Out of hours** Permitted with ID consultant approval **Class I indication**

				Hospital treatment: Commercial stock of SCIG via IM route (as per local formulary) **SCIG via IM route:** • 250IU TIg ≈ 1000mg • 500IU Tig ≈ 2000mg 1st line – equivalent dose of **Cutaquig 16.5%** by IM route 2nd line – equivalent dose of **Hizentra 20%** by IM route Doses for other brands are contained in the table at the end of this section. 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).		

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 IU for individuals > 50kg See table below* If TIg is not available, or the patient cannot tolerate the volume of TIg IM, the EOEIAP recommend (where available): **Flebogamma DIF 5%:** 20g IV stat ≈ 5,000IU TIg 40g IV stat ≈ 10,000IU TIg Other IVIG brands have published anti-tetanus activity. Testing varies by company with either standard ranges or batch-specific results. See further information at the end of this table.	Resolution of tetanus infection	Consultant may approve **Out of hours** Permitted with ID consultant approval **Class I indication**
Varicella zoster (VZ)	Individuals for whom intra-muscular injections are contra-indicated (e.g. those with bleeding disorders) and thus cannot receive prophylaxis with VZIG	Mildly immunocompromised whose level of immunosup	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	Prevention of chicken pox infection Prevention of severe chicken pox	Permission required from UKHSA. Notification of treatment to EOEIAP.

	Ig 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 have been in place since August 2018 with VZIG currently being advised for women exposed in first 20 weeks of pregnancy and neonates. It is not clear how long these restrictions will be in place and when VZIG supplies will return to expected levels. Advice is available at:	pression does not meet the criteria for either Group A or Group B do not require VZIG e.g. children on doses of predniso-lone less than 2mg/kg/day, patients on doses of metho-trexate 25mg/week or less . A further dose of IVIg is not required if a new exposure occurs within 3 weeks of admin-istration of VZIG or IVIG		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 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* EOEIAP: Use DDW for dosing.		Find local protection team here: https://www.gov.uk/health-protection-team **Out of hours** No **Class II indication**

	https://www.gov.uk/government/publications/varicella-zoster-immunoglobulin					
Viral pneumonitis following HSCT or solid organ transplant	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 disseminated disease. For guidance on treatment of patients with significant exposure to chicken pox or herpes zoster, please see the use of Ig in Varicella zoster (above). **RSV, HPIV** – **patients with lower respiratory tract infections**. In RSV, Ig would be used as an adjunct to ribavirin. **RSV, HPIV, patients with RSV and HPIV upper respiratory tract infections post-HSCT**, consider Ig in the presence of some or all of the following risk factors[38]: • Older age • GvHD • Lymphopaenia <0.2 x 10^9/L • Neutropenia • Mismatched /	1-2g/kg IVIG in divided doses EOEIAP: Use DDW for dosing.	• Radiological improvement • Length of stay in hospital • Survival	Apply to EOEIAP **Out of hours** No **Class II indication**

			unrelated donor • Immediate aftermath of HSCT (<1 month)			

* Please note SPC currently indicates subcutaneous route of administration only (although previously indicate both SC and IM routes), UKHSA 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)**	
	Individuals less than 50kg	Individuals ≥50kg
Gammaplex 5%, Intratect 5%, Flebogamma DIF 5%, Vigam 5%	400ml	800ml
Gamunex 10%, Intratect 10%, Octagam 10%, Panzyga 10%, Privigen 10%,	200ml	400ml

Indications	**IM-TIG**	**Subgam 16%**	**Cuvitru 20%**	**Gammanorm 16.5%**
For most uses	250 IU	6.25ml	4.5ml	5ml
If more than 24 hours have elapsed or there is risk of heavy contamination or following burns	500 IU	12.5ml	9ml	10ml

NHS Trusts should sources supplies of immunoglobulin for the management of tetanus-prone wounds directly from the manufacturer.

Further information on the use of immunoglobulins in the Management of Suspected Tetanus Cases and on the Assessment and Management of Tetanus-prone Wounds is available in the Public Health England guidelines;

- https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/820628/Tetanus_information_for_health_professionals_2019.pdf

UK Health Security Agency (UKHSA) supply stocks of Subgam for the treatment of hepatitis A, measles, rubella† and polio to NHS Trusts. This stock is free of charge to the end user Trust and supplies must be maintained by each organisation through UKHSA channels. Where UKHSA stocks are not available, Subgam may be provided through normal routes and if used in line with the measures described in this guideline, NHS England will reimburse Trusts for this use. This mechanism is however secondary to the established route of supply through UK Health Security Agency.

†Treatment of rubella is not contained in this guideline. The UK Health Security Agency guidelines can be found at the following website:
https://www.gov.uk/government/publications/immunoglobulin-when-to-use
National measles guidelines October 2023 (publishing.service.gov.uk)
PHE National Polio Guidelines - Local and regional services (publishing.service.gov.uk)

Where Subgam stock from the UKHSA is not available (or not available in a timely manner) or where intravenous immunoglobulin is indicated **and** where there is written instruction from UKHSA or local Health Protection Team (HPT), it is permissible to use commercial stocks of immunoglobulin (human normal) for infection prophylaxis after a significant exposure to measles, hepatitis A, rubella, varicella zoster or polio. Specific clinical approval from the sub-regional IAP is not required for these indications in addition to UKHSA or HPT written instruction.

- GPs are not permitted to prescribe or direct the supply of immunoglobulins.

Cases requiring intramuscular administration of immunoglobulin should use UKHSA provided stock of Subgam where available. Where this is not available, or not available in a timely manner, hospitals should consider purchasing a suitable alternative to store in pharmacy in case of need, or enter into a mutual aid agreement with a local hospital that does hold stock. It is important to note

that manufacturers have different recommendations for the use of 'subcutaneous' immunoglobulins given by the intramuscular route.

Product	Concentration	License in relation to IM use
Cutaquig	16.5% w/v	It must "not be administered intramuscularly in case of severe thrombocytopenia and in other disorders of haemostasis" [4.3]
Cuvitru	20% w/v	"Cuvitru must not be given intravascularly or intramuscularly" [4.3]
Gammanorm	16.5% w/v	*Not commercially available*
Hizentra	20% w/v	For subcutaneous use only [4.2]
Subgam	16% w/v	"Subgam must not be administered intramuscularly in cases of severe thrombocytopenia and in other disorders of haemostasis" [4.3]
Xembify	20% w/v	Licensed for subcutaneous infusion only. Not currently in the NHS Framework for supply (Dec 2023).

***SmPC checked 20th Dec 2023**

In the absence of Subgam and Gammanorm, the next preferred commercial immunoglobulin for intramuscular administration is Cutaquig (Octapharma) followed by Hizentra (vials or PFS). In the East of England, stocks of Cutaquig are held for this purpose at Cambridge University Hospitals and mutual aid can be arranged for EOE panel affiliated Trusts through Pharmacy Procurement, the pharmacy immunoglobulin team (add-tr.iap-eastofengland@nhs.net) or the on-call pharmacist out of hours.

In cases requiring intravenous immunoglobulin, local commercial stock should be used.

Relevant anti-toxin titres for Cutaquig are published in Gupta S, Kobayashi RH, Litzman J *et al*. Subcutaneous immunoglobulin 16.5% for the treatment of pediatric patients with primary antibody immunodeficiency. *Expert Review of Clinical Immunology* 2023; 19(1): 7-17 [https://doi.org/10.1080/1744666X.2023.2144836] and are republished below.

Antibody titres for subcutaneous immunoglobulin 16.5% (Cutaquig) from 8 batches:

Antibody	**Units**	**Mean ± SD**
Hepatitis **A virus**	IU/mL	26.7 ± 6.6
Hepatitis **A virus surface antigen**	IU/mL of IgG	70.9 ± 17.2
Parvovirus B19	IU/mL	547 ± 35.1
Poliovirus	Relative to NIH176	1.1 ± 0.6
Measles virus	Relative to NIH176	0.8 ± 0.2
Diphtheria virus	IU/mL	16.5 ± 4.8
Rubella virus	IU/mL	694 ± 131
Tetanus toxin	IU/mL	48.5 ± 14.5
Varicella zoster virus	mIU/mL	19,100 ± 8955

Indication	Selection criteria	Exclusion criteria	Position of immunoglobulin, taking into account alternative therapies	Recommended dose	Clinical outcomes	Prior panel approval required
Use of immunoglobulin in other indications						
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 **OR** • Affected neonates 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. For further information please refer to the NHS England Clinical Commissioning Policy: Maternal intravenous immunoglobulin (IVIg) for the prevention of alloimmune fetal and neonatal haemochromatosis[38].	**Maternal dose**: 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. **Neonatal dose:** 1g/kg ± repeat. The need for repeat doses, which may exceptionally be required, should be based on clinical need and local policy. **EOEIAP:** The weight used to calculate the dose will be the mother's weight at booking.	• Fetal loss (including gestation) • Gestation at delivery • Neonatal outcomes	Apply to EOEIAP Consultant obstetrician may request following input from a liver unit specialist. **Out of hours** No **Class II indication** For further information please see; NHSE Clinical Commissioning Policy: Maternal intravenous immunoglobulin (IVIg) for the prevention of allo-immune fetal and neonatal haemochromatosis

				Use IBW for neonates.		
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. EOEIAP: Use DDW for dosing.	• Improvement in Birmingham Vasculitis Activity Score (BVAS) • Fall in inflammatory markers • Improvement in organ function	Apply to EOEIAP **Out of hours** No **Class III indication**
(Prevention of) Autoimmune congenital heart block (anti-Ro) **SHORT TERM**	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** • Maternal anti-Ro and/or anti-La antibodies are present. More recent evidence has cast doubt on the beneficial effects of IVIg, with hydroxychloroquine being	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, or there is uncertainty regarding its efficacy. At a dose of 0.4 g/kg every 3 weeks administered from weeks 12 through to	Two infusions of 1g/kg/day, the first at 14 weeks and the second at 18 weeks of gestation EOEIAP: Use mother's weight at booking for dosing.	• Improvement in the degree of heart block at birth	Apply to EOEIAP **Out of hours** No **Class II indication**

	regarded as first line therapy – see comments under position of Immunoglobulin		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.			
Autoimmune uveitis **SHORT TERM**	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[40]).	1.0 - 1.5 g/kg/month – two to three infusions given 6 – 8 weeks apart to assess benefit EOEIAP: Use DDW for dosing.	• Improvement or stabilisation in visual acuity • Imaging endpoints • Electrodiagnostic studies	Apply to EOEIAP **Out of hours** No **Class III indication**
Capillary Leak Syndrome (Clarkson disease)	Diagnosis of monoclonal gammopathy-associated capillary leak syndrome by a consultant immunologist.	Exclude secondary capillary leak syndrome	This is an extremely rare condition with fewer than 250 cases reported since the 1960s. IVIG is considered first-line	Initially 2g/kg over 3-5 days, repeated every 6-8 weeks to assess benefit. Aim to reduce dosing	• Reduction in frequency of acute flares • Reduction in severity of acute flares	Apply to EOEIAP **Out of hours** No

	Acutely: • Hypovolaemia • Interstitial oedema • Haemoconcentration (HCT or Hb exceeding normal values for age / gender, or >20% of the last patient reference value). • Monoclonal gammopathy Diagnosis relies on recurrent acute flares associated with monoclonal gammopathy (>85% of patients).	or hypo-proteinaemia.	preventative treatment with a strong indication for improved survival. Alternative therapies include **thalidomide** (50-100mg daily PO), **terbutaline** (15mg-25mg daily PO), **theophylline** (400mg-1600mg daily PO; monitor levels). None have a strong evidence base, though IVIG and terbutaline appear to have the best evidence of a positive effect on survival at this time [36].	interval as able without relapse. Use DDW for dosing. Cases to be reviewed at regional EOEIAP meetings at least annually.	• Survival	**Class IV Indication** Additional funding approval required.
Catastrophic antiphospholipid syndrome (CAPS) **SHORT TERM**	Diagnosis of definite or probable CAPS: • Thromboses in 3 or more organs, systems and/ or tissues • Development of manifestations simultaneously in less than a week • Histological evidence of microthrombosis (small vessel occlusion) in at least one organ or tissue • Laboratory confirmation of the presence of antiphospholipid	Chronic recurrent thrombo-sis due to other causes Thrombo-sis associated with stable anti-phospho-lipid syndrome in the	Steroids, anticoagulant 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. IVIg may be less suitable	2g/kg over 4-5 days	• Survival • Clinical improvement • Prevention of permanent organ dysfunction • Reduction in anti-phospholipid antibody levels	Apply to EOEIAP **Out of hours** No **Class III indication** **In life-threatening disease ONLY:** Apply to EOEIAP If PLEX unavailable & patient cannot be transferred

	antibodies (lupus anticoagulant and / or anticardiolipin antibodies with Anti-β2GPI of IgG or IgM isotype as a co-factor) **Definite** CAPS: all 4 criteria **Probable** CAPS: • All 4 criteria, except only two organs, systems or tissues involved. • All 4 criteria, except unable to confirm antiphospholipid antibody persistence owing to new diagnosis. • Development of a third event in >1 week but < 1 month despite anticoagulation. • Absence of histological confirmation of small vessel occlusion.	context of other disorders	in elderly patients and patients with renal insufficiency owing to an increased risk of adverse renal effects.			to a centre offering PLEX or thrombocyto-paenia prevents PLEX **AND** if panel decision is not communicated on same day as application, Trusts may commence treatment over 5 days **pending panel decision**. Pharmacy supply sufficient IVIG to last until next working day while panel decision pending.
Immunobullous diseases	• Severely affected **AND** • Conventional corticosteroid treatment with adjuvant	See comments under position of	IVIg is reserved as adjunctive therapy for patients with severe disease refractory to conventional	1-2g/kg over 2-5 days. There may be a need for maintenance therapy in exceptional patients unresponsive or	• Reduction in recurrence of disease/relapse • Dose reduction / discontinuation of	Apply to EOEIAP **Out of hours** No

	immunosuppressive agents has failed or is inappropriate	Ig	immunosuppressive therapy. **Rituximab** is increasingly supplanting IVIg as the preferred treatment for resistant disease and is approved by NHS England[41]. In such patients it is listed as a 3rd line treatment alongside IVIg. However, rituximab should be favoured over IVIG, given the stronger evidence base supporting its use.	intolerant of rituximab. In such cases every attempt should be made to define the minimum effective dose of Ig by undertaking periodic dose reduction and /or lengthening the intervals between treatments.	other immunosuppressive therapy • Improved quality of life • Resolution of blisters / healing of affected skin • Resolution of pruritis	**Class III indication**
Kawasaki disease **SHORT TERM** **Paediatric Inflammatory Multisystem Syndrome** temporally associated with Covid-19 (**PIMS-TS**) **SHORT TERM**	Clinical diagnosis in a <u>paediatric patient</u> by a paediatrician, paediatric infectious disease consultant or paediatric immunologist of: • Kawasaki disease (fulfilling full or partial criteria for Kawasaki disease) **OR** • PIMS-TS Clinical diagnosis in an <u>adult</u> of PIMS-TS (also known as MIS-A or AIMS-TS) by a	None	**Kawasaki** IVIg in combination with anti-inflammatory doses of aspirin is the treatment of choice Consider steroids as first-line therapy while reserving IVIg for those cases where there is difficulty in distinguishing Kawasaki disease from MIS-C. In practice, this is	2g/kg single dose, in conjunction with high dose aspirin, a second dose may be given if no response, or if relapse within 48 hours.	• Resolution of fever • Improvement in acute phase markers	Consultant may approve **Out of hours** Permitted **Class I indication**

	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 PIMS [Royal College of Paediatrics and Child Health guideline 'Paediatric multisystem inflammatory syndrome temporally associated with Covid-19']. https://www.rcpch.ac.uk More recent data suggests that steroids should be first-line therapy, especially for children 6 years or over without symptoms of Kawasaki disease – see comments under position of immunoglobulin.		particularly challenging in children under 6 years in whom IVIg may need to be considered as first-line therapy. IVIg was originally recommended as a first-line treatment for MIS-C based on its clinical similarities to Kawasaki disease. New data from an international observational cohort of 2009 patients with MIS-C from 39 countries randomised to receive IVIg alone (n=680), IVIg plus steroids (n= 698) and steroids alone (n=487) suggests that initial treatment with steroids was a safe and effective alternative to IVIg or combined therapy. There were no significant differences between treatment arms for primary outcomes – need for ventilation, inotropic support or death. In addition, the occurrence and			

			resolution of coronary artery aneurysms did not differ significantly between the groups.			
Toxic epidermal necrolysis, Stevens Johnson Syndrome **Indication excluded from NHS England commissioning guidance (from Aug 2021)** **SHORT TERM (if approved)**	Diagnosis by a dermatologist or consultant in a specialist burns unit; **AND** Involved body surface area >10% **AND** When other treatments are contraindicated **AND** The condition is life-threatening	Mild / moderate disease or any level amenable to supportive care ± steroid / ciclosporin See general comments regarding prothrom-botic risks of IVIg	No therapy with unequivocal benefit for SJS/TEN exists[35]. The immunological basis has led to the use of immunomodulation; the best studied of which are IVIg, corticosteroid and ciclosporin. In meta-analysis, there is no robust evidence that IVIg improves overall survival vs. supportive care alone, nor is there a benefit demonstrated (with or without corticosteroid) that IVIg improves ocular, oral or urogenital outcomes versus corticosteroid alone[35].	2g/kg, usually divided as 1g/kg over 2 days. EOEIAP: Use DDW for dosing.	Resolution of the disease Survival	Apply to EOEIAP (<u>no treatment</u> without panel approval) **Out of hours** No **Class IV indication**
Transplant (solid organ)	**Antibody Incompatible Transplant (AIT)** Patients in whom renal, heart	See comments under	While IVIg is included in many protocols, there is a paucity of high-quality	Renal transplant blood group incompatible transplant (renal	AIT and AMR: <u>Renal:</u>	Apply to EOEIAP **Out of hours**

SHORT TERM	liver or lung transplant is prevented because of antibodies. Blood group incompatibility renal transplant only.	position of Ig See comments under position of Ig	evidence to support its use. A systemic review of AMR in kidney transplant recipients categorised the evidence supporting IVIg as 'very low'[42]. Where IVIg is used in combination with PLEX, any beneficial effects of Ig are likely 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.	desensitisation): 100mg/kg IVIG for 8 - 12 doses. AIT: Up to 2 g/kg to be repeated as per DSA;	• Type of renal transplant • HLA class DSA (where available) • Rejection episodes • Patient survival • Graft survival • Renal function = eGFR (MDRD) <u>Cardiothoracic:</u> • DSA • Length of ITU and hospital stay Resolution / improvement in objective measures of graft dysfunction: **Renal transplant** If DSA levels remain high or graft dysfunction persists, then a further transplant biopsy is indicated. **Liver transplant** Liver function Clotting indices **Lung transplant** Spirometry	No **Class II indication**
	Antibody Mediated Rejection (AMR) Patients experiencing steroid resistant rejection or where other therapies are contra-indicated after renal, heart, liver and/or lung transplant. **e.g. Renal transplant** Especially in the known presence of donor reactive anti-HLA antibody (DSA) pre-transplantation. Diagnosis based on: - Graft dysfunction		Following a significant positive DSA finding in HLA-antibody screening, commence plasma exchange where available for this indication (min. 5 sessions in 7 days) with pulsed IV corticosteroid (given after PLEX on days of PLEX. Then refer to "recommended dose" in these guidelines for immunoglobulins.	Renal transplant: If DSA levels have fallen following 5th course of PLEX therapy, commence 2g/kg over 4-5 days. If DSA levels remain high, continue PLEX on alternative days followed on the same day as PLEX by 10g of IVIG or 100mg/kg IVIG (whichever is the greater). Round up to the nearest 5g.		

	(oliguria, rise in serum creatinine) - Rising DSA level - High level of association with T-Cell mediated rejection			EOEIAP: Use DDW for dosing.	**Heart transplant** Ejection fraction	

14 IFR applications

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 Class III and IV indications via the MDSAS database and provide SRIAPs and commissioners with data relating to use in uncommissioned, unlisted indications and indications with less evidence.

- **See main body for Class I to III indications.**
- **See paragraph 12 for a list of Class IV and V indications.**

15 Class I, Class II, Class III (commissioned, lower ranking), Class IV (unlisted / formerly listed) and Class V (automatically rejected) indications

NHS England classify indications as commissioned or not commissioned. Commissioned indications are further classified into those which require panel approval before treatment, and those with Group Prior Approval (GPA) which can commence without panel approval (Class I indications).

- Class I treatment must be notified to panel for tracking, audit, billing and retrospective review of eligibility.
- Class II indications require **prospective panel authorisation**. This may be given by a single panel member who is specialist in the condition to be treated.
- Class III indications require **prospective panel consensus**. This is given where there are three of more panel members in support of the treatment with no panel member who objects.
- Class IV indications are those which are not listed in the guidelines including new clinical entities, or those which have formerly been listed in the clinical guidelines (NHSE commissioning guideline or DH clinical guideline). Class IV indications require **prospective panel consensus** and **funding approval.**

No Class II to IV indication treatment may commence without approval from the East of England Immunoglobulin Assessment Panel (EOEIAP). www.cuh.nhs.uk

- Only electronic applications are accepted by the EOEIAP. Class III and IV indications must have presumed immune-mediated disorders with some evidence of efficacy or a presumed mechanism immune-mediation.
- Class I, II and III indications are funded as a commissioned treatment provided treatment is approved by the EOEIAP and used with the stipulation of the clinical approval.
- Class IV indications require IFR submission following clinical panel approval (if granted). that indication. The EOEIAP will advise following a request for treatment.

Class IV – Not routinely commissioned indications / indications that are no longer routinely commissioned (those with limited or no evidence for efficacy).
Acquired red call aplasia NOT due to parvovirus B19
Acute disseminated encephalomyelitis (if high dose steroids have failed)
Acute idiopathic dysautonomia
Aplastic anaemia / pancytopenia
Atopic dermatitis / eczema
Autoimmune neutropenia
Cerebral infarction with antiphospholipid antibodies
Chronic facial pain
Chronic ITP (as monotherapy)
Chronic regional pain syndrome
Diabetic proximal neuropathy
Haemolytic uraemic syndrome
Intractable childhood epilepsy
PANDAS
Paraneoplastic disorders that are known not to be B-cell or T-cell mediated
POEMS
Pyoderma gangrenosum
SLE without secondary immunocytopenias (including juvenile)

Systemic juvenile idiopathic arthritis
Toxic Epidermal Necrolysis (TEN) or Stevens Johnson Syndrome (SJS)
Urticaria (severe, intractable)
ANY INDICATION NOT LISTED BY NAME IN THIS DOCUMENT is considered to be CLASS IV

All indications that are not recommended are **Class V indications** which are **automatically rejected** by the EOEIAP.

Indications for which immunoglobulin therapy is not recommended

- Immunodeficiency secondary to paediatric HIV infection
- Autologous BMT
- Adrenoleukodystrophy
- Alzheimer's disease
- Amyotrophic lateral sclerosis
- Chronic fatigue syndrome
- Critical illness neuropathy
- Multiple sclerosis
- Rheumatoid arthritis
- Neonatal sepsis (prevention or treatment)
    - East of England panel have recommended IgM-enriched immunoglobulin as part of a service evaluation for this indication, to tightly defined criteria for overwhelming neonatal sepsis. Use must be within this context and be approved by the EOE panel.
- Sepsis in the intensive care unit not related to specific toxins or C. difficile
- Asthma
- Graves' ophthalmopathy
- IVF failure
- Recurrent spontaneous pregnancy loss

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18 Associated documents

The Immunoglobulin Policy and Procedure

The Immunoglobulin Treatment Authorisation Form (Immunomodulation)

The Immunoglobulin Treatment Authorisation Form (Immunodeficiency)

Equality and diversity statement

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Document management

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Appendix 1:

List of guideline amendments by date:

May 2024 Version 6.02	**New:** • **Improved clarity of processes for IEI/PID patient management.**
April 2024 Version 6.01	**New:** • **Amended in line with the publication of updated national commissioning policy**
Apr 2024 Version 5.13	**New:** • **Updated advice on antibody-incompatible transplant and antibody mediated rejection (of a transplant)** • **Updated advice for use of commercial vs. UKHSA supplied immunoglobulin in post-exposure prophylaxis (viral).**
Mar 2024 Version 5.12	**New:** • **Link to UKHSA viral illness in pregnancy.** • **Dosing advice for neonates after maternal exposure to measles.**
Feb 2024 Version 5.11	**New:** • **Updated dosing advice following exposure to measles.**
Feb 2024 Version 5.10	**New:** • **Updated link to the revised National Measles Guideline**
Jan 2024 Version 5.9	**New:** • **Update to unify units used for Hb (g/L)**
Dec 2023 Version 5.8	**New:** • **Update on the use of HNIg in viral exposure**
Oct 2023 Version 5.7	**New:** • **Updated advice on the management of catastrophic antiphospholipid syndrome published**
Sept 2023 Version 5.6	**Minor edit**
July 2022 Version 5.5	**New:** • **Updated with NICE CG information in ITP** • **Immunobullous diseases update** • **Addition of autoimmune neutropenia to Class IV**
June 2022 Version 5.4	**Review of document:** **New:** • **Revised Class I information** • **Information including re: place of Ig therapy for chronic ITP** • **Clarification re: dosing in children** • **References reviewed and corrected, DOI hyperlinks** • **Autoimmune encephalitis with known or without known antibody information combined**
Feb 2022	**Further update reflecting NHS England revised commissioning**
July 2021	**Further update on classification structure.** **Indications are classified as Class I to V as before:**

	• **Class IIIa becomes Class III** • **Class IIIb joins unlisted indications in Class IV** • **References to Red, Blue, Grey and Black are removed.** **Updated advice re: IFR applications**
June 2021	**Updates in line with revised NHSE commissioning guidelines:** **New:** • Secondary antibody deficiency – CAR-T specific information • Acute idiopathic / autoimmune dysautonomia / ganglionopathy • Opsoclonus myoclonus • Paraneoplastic neurological syndromes • Neuromyotonia • Non-MS CNS inflammatory syndromes **Revised:** • Coagulation factor antibodies • Autoimmune encephalitis • GBS outcome criteria • Inflammatory myopathies • Catastrophic antiphospholipid syndrome • Severe or recurrent Clostridium difficile colitis • Immunobullous diseases • Autoimmune uveitis • ANCA associated systemic vasculitides • Antibody incompatible transplant / Antibody mediated rejection • Class IV indications
Apr 2021	**Thrombosis and Thrombocytopenia following Covid-19 vaccination** Preliminary advice in line with MHRA and NHSE guidance covering an emerging and commissioned indication for IVIG. Consult in line with the Expert Haematology Panel (working in conjunction with the MHRA) advice from March 2021 and will be reviewed as new information comes to light. **Measles exposure**: Update to reflect UKHSA guidance
Dec 2020	**Haemophagocytic syndrome:** update to clinical treatment and monitoring criteria
Dec 2020	**Toxic epidermal necrolysis:** update to permit regional burns unit to commence treatment
Oct 2020	**Toxic epidermal necrolysis:** Change to OOH permissions for TEN
Oct 2020	**General document:** Modification to document title
Aug 2020	**Tetanus treatment and prophylaxis:** Revised “recommended dose” information for NAIT / Foeto-maternal alloimmune thrombocytopenia, in line with revised
Aug 2020	**Foeto-maternal alloimmune thrombocytopenia / NAIT:** Revised recommended dose information.
Aug 2020	**Commissioning status for former GREY / Class III indications:** Clinical approval from a Sub-Regional Immunoglobulin Assessment Panel is now sufficient to commence treatment for all former grey / Class III indications. All “little to no evidence for efficacy” indications now therefore become Class IIIb. Class IV indications are now any indication which is not listed in national commissioning documents