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THIRD EDITION UPDATE

Clinical Guidelines for Immunoglobulin Use

MARCH 2021

This latest guidance has been agreed by the NPPEAG following consultation with Scottish National Specialty groups and is based on the guidance from the NHS Commissioning group on behalf of DoH England

Contents

EXECUTIVE SUMMARY

The 3rd edition of the Scottish Guidance on the appropriate use of Immunoglobulin has been endorsed by the National Plasma Product Expert Advisory group following consultation and approvals from Scottish National Specialty groups. These recommendations and guidance were agreed by the NHS Commissioning group on behalf of the Department of Health in England. These Guidelines were developed utilising an evidence review and extensive consultations with clinicians and other stakeholders. This update of the guidelines was limited to three key areas: defining selection criteria for appropriate use; efficacy outcomes to assess treatment success; and reassignment of existing indications /inclusion of new indications in the Specialties of Hematology, Immunology and Neurology. Other specialty areas will be the focus of update over the coming months and will be added to this guidance when available. Until this is concluded Immunoglobulin should be prescribed in these specialties for the conditions outlined in the second edition.

Efficacy outcomes to assess treatment success

Scottish patients have been included in the National Immunoglobulin database since 2013. The input of efficacy outcomes of such treatments has not previously been required. **Grey** indications will have efficacy parameters defined and monitored on a case by case basis. Such efficacy outcomes are expected to play an important role in future decision-making process.

INTRODUCTION

Immunoglobulin preparations were first used therapeutically in the 1950s as Immunoglobulin replacement therapy for primary immunodeficiency disorders. It was not until technological advances in the fractionation of plasma about 30 years ago that monomeric suspensions of Immunoglobulin suitable for intravenous use were developed. With the ability to administer large quantities of Immunoglobulin intravenously, Immunoglobulin has now become an important treatment option in a number of clinical indications beyond primary immunodeficiency, including autoimmune and acute inflammatory conditions, and off-label prescribing has crossed over into almost every medical specialty.

For some time, there has been concern over availability of Immunoglobulin to the NHS, due to a global supply shortage and issues specific to the UK. It is important to note that Immunoglobulin is now the most widely used plasma component, and usage continues to grow. Immunoglobulin supply shortage is compounded by an ever increasing demand for Immunoglobulin because of a number of factors, including the emergence of new therapeutic indications, widespread off-label use and an indefinite duration of use in some indications, particularly for the treatment of some neurological and Haematology illnesses in addition to immune deficiencies.

Immunoglobulin can be an expensive therapeutic choice in disease states where other interventions may be indicated. Even if there are data that support the potential efficacy of Immunoglobulin, its use should still be carefully considered, not only because of

supply issues, but because of potential and often individual risks. For example, anaphylactoid reactions to Immunoglobulin given to pregnant women can lead to acute fetal compromise. In the 1980s and 1990s, cases of hepatitis C transmission were reported with Immunoglobulin. Since the standardization of viral inactivation steps and the introduction of second- and third-generation screening of donors, there have been no transmissions, but there is no place for complacency because of the possibility of unknown as well as novel viruses and other infectious agents; therefore vigilance is required.

In this guideline, the term Immunoglobulin is used to describe mean pooled normal human Immunoglobulin. Depending on volume required, it can be administered intravenously or subcutaneously. In this document, Immunoglobulin does not cover hyperimmune immunoglobulins. However, in certain cases, Immunoglobulin may be used where the appropriate hyperimmune Immunoglobulin is not available.

Objectives of Immunoglobulin national clinical guidelines

The overall objective of this guideline is distinct from other disease-specific guidelines, which seek to provide recommendations on how best to manage a single disease. The goal of this guideline is to ensure best practice in the use of Immunoglobulin across all indications, based on available evidence and expert opinion.

Demand management of Immunoglobulin

Immunoglobulin remains the only treatment option for patients with primary immunodeficiencies and, in certain cases, is lifesaving. Shortages must never jeopardize supply for these patients and this factor must be given primary consideration. Children should also be a therapy priority in shortage situations. As a consequence, to deliver best use of Immunoglobulin requires a second factor to be considered: prioritisation of indications. These guidelines employ a colour-coded classification of Immunoglobulin indications, according to prioritisation.

Although some of the new indications for Immunoglobulin are based on strong clinical evidence, a number of uses are based on relatively sparse data or anecdotal reports. This may be due to lack of trial data or the low prevalence of a particular disease preventing appropriate randomised controlled trials (RCTs). In other indications, immunoglobulin is used despite evidence that it is not efficacious. This guideline provides recommendations on Immunoglobulin use which reflects the evidence base. Where available these guidelines provide suggestions for alternative treatments to Immunoglobulin and these alternatives are included.

The UK National Immunoglobulin Database

The UK National Immunoglobulin Database was launched on 2nd June 2008 and is accessible through the Immunoglobulin website www.ivig.nhs.uk. Scottish patients have been included in this database since 2013. The Database was a major step forward in establishing the Demand Management

Programme and, in particular, gave insights into the appropriate use of this treatment across all indications. Generally, the data demonstrated appropriate and controlled prescribing of Immunoglobulin for a wide range of conditions, most of which was evidence based. Data on trends of use from both a Scottish and UK-wide context will be available from the database to inform those involved in local prescribing as well as those concerned with national purchasing and demand management of Immunoglobulin in Scotland.

Demand management in Scotland

In Scotland the responsibility for implementing a demand management plan is through the National Plasma Product Expert Advisory Group (NPPEAG). This multidisciplinary group was formed in January 2009 at the request of NHS Scotland Chief Executives' group. This was seen as a crucial part of the future management and financing of plasma products, and part of the remit of this group was to prepare national clinical guidelines and to formulate a Management Plan for times of shortage. The group has a membership including specialist clinical users of therapeutic immunoglobulin, pharmacists, finance director and a representative from SGHD.

The aim of this plan is to ensure that in times of shortage

- Immunoglobulin is available for all essential infusions to patients, equally in Scotland.
- The most clinically appropriate cases receive the supply

The NPPEAG chair/deputy will be alerted by the plasma product stockholder when there is a batch failure or if the stockholding of a particular product falls to 2 months or less. The NPPEAG will then decide if the NHS Boards require to be informed using such information as length of possible shortage and, knowledge of stock replenishment or alternative product availability.

If they are to be alerted then the Chief Executive and Director of Pharmacy will be informed in each NHS board. The stockholding for primary immunodeficiency (PID) patients will be ring-fenced.

If notified of shortage, individual Boards will ensure Red indications only will be issued without any further ratification. PID patient requests should be filled from the ring fenced supply in the national stock. The Board should put in place a mechanism by which any request for treatment of Blue indications will be considered. Where clinically achievable, those on long term therapy may have lengthening of the interval between treatments for Blue indications agreed for treatment. This may be of particular use where batch failure of a single product arises and may ensure the patient is not transferred to another product. Alternative treatments including plasma exchange should be considered where appropriate and indicated.

DEVELOPMENT METHODS

Given the availability of high-quality single-specialty and single- disease guidelines that provide recommendations based on systematic reviews of the literature, the decision was taken by the Guideline Development Group to base these guidelines on published evidence- based guidelines for Immunoglobulin supplemented, where necessary, by relevant Cochrane reviews

Prioritisation of treatment recommendations

As part of Immunoglobulin demand management, a classification of Immunoglobulin indications according to prioritisation has been introduced. Colour coding is now superimposed on the guideline recommendations. The details of how the colours relate to the use of Immunoglobulin are described in the Demand Management Plan.

In brief:

Red indications

Red signifies a disease for which treatment is considered the highest priority because of a risk to life without treatment. The intention remains that supply should be protected for these high-priority diseases in times of immunoglobulin shortage, particularly for patients with primary immunodeficiencies.

Blue indications

Blue indicates a disease for which there is a reasonable evidence base, but where other treatment options are available. The use of Immunoglobulin in these indications should be modified in times of shortage.

Grey indications

'Grey' indications are those diseases for which the evidence is weak, in many cases because the disease is rare. Treatment should be considered on a case-by-case basis, and prioritised against other competing demands for Immunoglobulin, especially in times of shortage. All NHS Boards in Scotland should put in place a process to ensure scrutiny of the use of product for Grey indications. All patients receiving Immunoglobulin for a Grey Indication should have their outcomes recorded in the National Database.

It is not possible or desirable to list every disease that could potentially be prescribed Immunoglobulin. In cases of 'unlisted' diseases, it is important to restate that those not listed in the guidelines are to be considered as Grey. The database review showed a considerable volume of Immunoglobulin prescribed without a specific diagnosis being provided. Even if the disease is unlisted, the diagnosis and agreed efficacy criteria are to be recorded in the database.

Grey indications are now listed as immune-mediated disorders with limited evidence of Immunoglobulin efficacy, or presumed immune- mediated disorders with little or no evidence of efficacy. It is accepted that the lack of an evidence base may reflect the rarity of these diseases.

IMMUNOGLOBULIN PREPARATIONS AND LICENSED INDICATIONS

Immunoglobulin is a sterile preparation of concentrated antibodies (immune globulins) recovered from pooled human plasma of healthy donors. A number of Immunoglobulin preparations are currently licensed in the UK.

Recommendations

Pharmacists and prescribers will continue the policy of brand consistency for patients on life-long-term Immunoglobulin.

All patients must undergo an annual efficacy review in line with Good Clinical Practice. The outcome of an annual review must be entered into a National Immunoglobulin Database

Specific requirements

Some patients, particularly those with antibody deficiency encompassing very low endogenous IgA levels, can (rarely) experience anaphylactic reactions to Immunoglobulin. If this form of reaction is confirmed by an immunologist, then low IgA-containing products must be used. Appropriate immunoglobulin products are available

Care should be taken when prescribing Immunoglobulin in those at risk of renal insufficiency, as there is a risk of deterioration in renal function. Although the mechanism for this is not fully understood, low or non-sucrose containing Immunoglobulin products are preferred for such patients.

All moderate or severe adverse reactions to Immunoglobulin should be recorded in the Immunoglobulin Database. Definitions of these reactions can be found on the NPPEAG website www.nppeag.scot.nhs.uk.

Definitions of duration of Immunoglobulin treatment

The definitions of short-term and long-term treatment durations are refined in this update, with each approved indication for Immunoglobulin now approved on the basis of short-term (≤3 months) and long-term (≥3 months) treatment needs. The definitions of duration of treatment are included in the table below.

Short term treatment	≤3 months The treatment episode ends at 3 months The national database will record re-initiation as a new treatment episode
Long term treatment	>3 months Treatment reviews should be conducted annually

Recommended dosing of Immunoglobulin

The Second Edition of the Clinical Guidelines did not provide specific dosing recommendations; it is widely accepted that the standard immunomodulatory dose of 2 g/kg is usually divided into five daily infusions of 0.4 g/kg, although some physicians prefer to use two daily doses of 1 g/kg each. The database infusion records were incomplete and, therefore, it was not possible to fully interpret the data and decipher the dosing that had been used. This update to the guidelines now provides specific dosing recommendations for each of the conditions for which prescribing is regarded as appropriate. Immunoglobulin users are expected to record the dosing employed in the national database.

An ongoing issue for diseases that require long-term Immunoglobulin treatment is that once responsiveness to Intravenous Immunoglobulin (IVIg) is proven 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 (2).

The study also indicated that the precise dose and infusion interval to keep each patient asymptomatic was not predictable, but the authors suggested a rough guide: patients in whom responses last <6 weeks may need 1 g/kg infusions once every 3 weeks; those patients with responses lasting 6–8 weeks need approximately 0.5 g/kg infusions every 3 weeks; and those patients with longer-lasting responses can be given 0.25 g/kg infusions every 3 weeks.

Recommendation

In patients on long-term immunomodulatory doses, reasonable attempts should be made to reduce the dose, by increasing the dose interval or by using reduced dose, or both.

Ideal body weight-adjusted dosing of Immunoglobulin

For patients with BMI ≥30 kg/m^2 or if actual weight >20% more than IBW, prescribers should consider using adjusted-body-weight dosing of immunoglobulin.

There is considerable interest in the use of ideal body weight-adjusted dosing of Immunoglobulin, based on the view that drugs with a narrow therapeutic index are usually dose-adjusted by surface area or another formula to allow for the poorly perfused excess adipose tissue. This adjusted body weight is used if a patient has a body mass index (BMI) of ≥30 kg/m2 or if the patient's actual weight is more than 20% over IBW. If calculated doses fall between vial sizes then they are rounded to the nearest whole vial size available. The rounded dose should be within 10% of the calculated dose.

The concept of using biological agents at their lowest effective dose is logical and may also contribute to minimisation of side-effects, some of which may be dose related and as such is endorsed by NPPEAG.

Use dosing weight (DW) for calculating the Immunoglobulin dose required for obese or overweight patients

Dosing weight (DW) is an adjusted body weight for obese or overweight patients

An online calculator for calculating the dosing weight and ideal body weight is available at: https://ivig.transfusionontario.org/dose/

Calculate ideal body weight (IBW) (kg):
IBW for males = 50kg + (2.3 x (each inch > 5 feet)
IBW for female = 45.5kg + (2.3 x (each inch > 5 feet)

Calculate dosing weight (DW) (kg):
DW = IBW + [0.4 x (actual – IBW)] *exception: If Actual < IBW, then Dosing Weight = Actual*

Recommendations for pharmacists: individual patient doses

To minimize the amount of Immunoglobulin used in individual treatments, rounding down Immunoglobulin dose to the nearest whole vial (adults) is recommended. Where the dose would be less than one vial in children, Immunoglobulin dose should be rounded up to a whole vial of the most appropriate size.

Infusion rates for intravenous Immunoglobulin

Initial intravenous infusion rates are low, and if well tolerated, the rate of administration may be increased, as specified in the products' Summary of Product Characteristics (SPC). For certain products, the SPC indicates that if the higher rate is tolerated, the rate may be further increased in primary immunodeficiency (PID) patients to the maximum infusion rate. Higher infusion rates may lead to improved convenience for patients and may reduce nursing time and the need for hospital resources. Infusion rates for each of the licensed Immunoglobulins available in Scotland can be found in their manufacturers recommendations in their SPC

Subcutaneous administration

Subcutaneous immunoglobulin (SCIg) as replacement therapy for primary immune deficiency disease and as immunomodulatory therapy for some autoimmune diseases, including peripheral neuropathies, can be a safe, effective and convenient alternative to intravenous therapy. Subcutaneous administration can offer advantages that may be important for many patients (3).

Although SCIg is typically administered weekly by infusion pump, administration by a rapid push technique may provide a greater degree of convenience, and recent evidence suggests it is a safe and effective method. Guidance on the use of Rapid push techniques is available on the NPPEAG website.

> ***Recommendation***
>
> Prescribers should consider the comparative advantages of intravenous and subcutaneous administration for individual patients requiring Immunoglobulin treatment where this is clinically appropriate.

IMMUNOLOGY

RIMARY AND SECONDARY ANTIBODY DEFICIENCY STATES							
Indications	S	L	Selection criteria	Exclusion criteria	Position of Immunoglobulin, taking into account alternative therapies	Recommended dose	Clinical outcomes
Primary immunodeficiencies associated with significant antibody defects (excluding specific antibody deficiency)		🔴	A specific PID diagnosis must be established by a clinical immunologist.	No	Only definitive treatment for antibody deficiency.	Initiate at 0.4-0.6 g/kg/month; dose requirement may increase and should be based on clinical outcome.	Trough IgG Reduction in: - No of infections - Treatment courses of antibiotics - Days in hospital.
Thymoma with immunodeficiency		🔴	Profound B cell depletion and/or significant antibody deficiency.	No	Only definitive treatment for antibody deficiency.	Initiate at 0.4-0.6 g/kg/month; dose requirement may increase and should be based on clinical outcome.	Trough IgG Reduction in: - No of infections - Treatment courses of antibiotics - Days in hospital.
HSCT in primary immunodeficiencies		🔴	PID patients undergoing HSCT.	No	Only definitive treatment for antibody deficiency.	Initiate at 0.4-0.6 g/kg/month; dose requirement may increase and should be based on clinical outcome. Assess/Monitor B cell reconstitution as decision parameter for cessation/continuation of treatment.	Trough IgG +/- specific antibody levels/responses.
Specific antibody deficiency		🔴	- Diagnosis by a clinical immunologist - Severe, persistent, opportunistic or recurrent bacterial infections despite continuous prophylactic oral antibiotic therapy for 6 months	No (but see comments in next column)	Many patients with specific antibody deficiency will achieve adequate protection from bacterial infections with prolonged antibiotic prophylaxis. Immunoglobulin is	Initiate trial at 0.4-0.6g/kg/month for a period of 6-12 months.	Reduction in: - No of infections - Treatment courses of antibiotics - Days in hospital.

RIMARY AND SECONDARY ANTIBODY DEFICIENCY STATES							
Indications	S	L	Selection criteria	Exclusion criteria	Position of Immunoglobulin, taking into account alternative therapies	Recommended dose	Clinical outcomes
			- Documented failure of serum antibody responses to unconjugated pneumococcal or other polysaccharide vaccine challenge.		reserved for those patients in whom antibiotic prophylaxis has proved to be ineffective.	Long term maintenance treatment should be based on clear and recorded evidence of benefit from trial therapy period. Dose requirements may increase and should be based on clinical outcome.	Database recording of decision point parameters such as infection frequency, acute antibiotic usage and days in hospital pre-treatment and 6 monthly thereafter may be useful.
Secondary antibody deficiency			- Underlying cause(s) of hypogammaglobulinaemia cannot be reversed or reversal is contraindicated. **OR** - Hypogammaglobulinaemia associated with a) NHL, CLL, MM or other relevant B cell malignancy confirmed by haematologist or b) drugs and other therapies targeted at B cells and plasma cells (rituximab, anti-CD19/20 agents, daratumumab etc.) or c) haematological malignancy post-HSCT*. **AND** 1) Recurrent or severe bacterial infection despite continuous oral prophylactic antibiotic therapy for 6 months 2) Serum IgG <4 g/L (excluding paraprotein) 3) Documented failure of serum antibody response to unconjugated pneumococcal or other polysaccharide vaccine challenge. NOTES - It is recognised that vaccine challenge may be of limited value in patients with very low serum IgG (<3 g/L). In these	No (but see comments in next column)	Many patients with secondary antibody deficiency will achieve adequate protection from bacterial infections with prolonged antibiotic prophylaxis. Immunoglobulin is reserved for those patients in whom antibiotic prophylaxis has proved to be ineffective. Since infection susceptibility in patients with haematological malignancies is frequently multifactorial, the reduction in overall burden of infections with long term immunoglobulin replacement may be variable. For this reason, annual reviews of treatment are recommended. In patients with a significantly seasonal preponderance of infections it may be appropriate to consider temporary cessation of immunoglobulin over the summer months.	0.4-0.6 g/kg/month, modified to achieve an IgG trough level of at least the lower limit of the age-related serum IgG reference range.	Reduction in: - No of infections - Treatment courses of antibiotics - Days in hospital. Database recording of decision point parameters such as infection frequency, acute antibiotic usage and days in hospital pre-treatment and 6 monthly thereafter may be useful.

RIMARY AND SECONDARY ANTIBODY DEFICIENCY STATES							
Indications	S	L	Selection criteria	Exclusion criteria	Position of Immunoglobulin, taking into account alternative therapies	Recommended dose	Clinical outcomes
			circumstances vaccine challenge may be omitted if it is considered to be clinically inappropriate - It is acknowledged that not all of the above criteria will need to be (or be able to be) fulfilled in some individual patient circumstances - In developing hypogammaglobulinaemia associated with Chimeric Antigen Receptor-T cell (CAR-T) therapy targeted against B cell antigens the prophylactic use of immunoglobulin in the absence of a burden of severe infections and vaccine challenge data may be appropriate*.				

HAEMATOLOGY

Indications	S	L	Selection criteria	Exclusion criteria	Position of immunoglobulin, taking into account alternative therapies	Recommended dose	Clinical outcomes
Alloimmune thrombocytopenia (foetal-maternal/neonatal) (FMAIT NAIT):/			Prevention or treatment of foetal thrombocytopenia or haemorrhage: Clinical suspicion of FMAIT in the antenatal setting based on clinical and laboratory features: Unexplained previous foetal death, haemorrhage, hydrocephalus or thrombocytopenia or known affected sibling, AND the presence of maternal platelet-specific alloantibodies directed against current paternal antigens (most commonly HPA-1a or HPA-5b).	No	Immunoglobulin is the primary treatment and sometimes combined with steroids First line treatment is with HPA-1a/5b – negative platelets which covers 95% of HPA incompatibilities responsible for NAIT. Platelet transfusion is effective immediately. In contrast, Immunoglobulin is a second line treatment and works in approximately 75% of cases.	Maternal: 0.5 -1g/kg weekly throughout pregnancy. Dose and stage of gestation at which to start treatment to be tailored to individual risk profile primarily based on the history of NAIT in earlier pregnancies. Patients with a low-risk obstetric history should be	Successful outcome of pregnancy i.e. no severe haemorrhage such as intracranial haemorrhage Platelet count above 50x109 /L at time of delivery Increment in neonatal platelet count

Indications	S	L	Selection criteria	Exclusion criteria	Position of immunoglobulin, taking into account alternative therapies	Recommended dose	Clinical outcomes
			Prevention or treatment of neonatal thrombocytopenia or haemorrhage: 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		It has a delayed effect over 24 – 48 hours. Immunoglobulin may be of value if there is prolonged thrombocytopenia with the aim of minimising the need for platelet transfusions.	commenced on 0.5.g/kg (Winkelhorst D et al. Fetal and neonatal alloimmune thrombocytopenia:evidence based antenatal and postnatal management strategies. Exp Rev Hematol 2017;10:729-737) Neonatal: 1g/kg; a 2nd dose may be required if thrombocytopenia persists	
Haemolytic disease of the newborn			Adjunct to continuous multiple phototherapy in cases of Rhesus haemolytic disease, or ABO haemolytic disease: • Rising bilirubin despite intensive phototherapy • Prevention of foetal haemolytic disease in women with a previous history of this and confirmed red cell antibodies to current paternal or foetal antigens, to delay the need for intrauterine transfusion	No	Immunoglobulin is an adjunct to phototherapy	0.5kg/kg over 4 hours	

Indications	S	L	Selection criteria	Exclusion criteria	Position of immunoglobulin, taking into account alternative therapies	Recommended dose	Clinical outcomes
Immune Thrombocytopenic Purpura (ITP)	●	●	Immunoglobulin generally used in only 3 situations in ITP:- 1) Life-threatening bleeding 2) Where an immediate increase in platelet count is required e.g. before emergency surgery or other procedure (see table for target platelet counts) 3) Where the patient is refractory to all other treatment to maintain the platelet count at a level to prevent haemorrhage. It may need to be given every 2-3 weeks during a period where other second line treatments are being tried. ITP in pregnancy: Maintenance treatment with Ig may be required antenatally to maintain platelets above 20x109/l and/or to increase platelets to over 50 x109/l for delivery in women with symptomatic persistent or chronic ITP where other treatments have failed. *There is controversy regarding the target platelet count for epidural anaesthesia (Provan et al. Blood 2010;115:168-186). There are no data to support a minimum platelet count and each case must be carefully considered. In the absence of bruising, bleeding history, and anticoagulation and if the INR, APTT and fibrinogen levels are normal, a small consensus of obstetric anaesthetists agree no changes to normal practice are needed until the platelet count drops below 50.	No	Thrombopoietin mimetics may be useful substitutes in some patients	Adults: 1g/kg as a single infusion. A 2nd dose may be required after 24 – 48 hours, if severe or life-threatening bleeding: e.g. Intracranial bleed or pulmonary haemorrhage Otherwise, if a haemostatically adequate platelet count is not achieved a 2nd dose (1g/kg) may be considered at day 5 to 7 Children: 0.8 – 1g/kg as a single infusion. A 2nd dose may be required after 24 – 48 hours, if severe or life-threatening bleeding, such as an intracranial bleed or pulmonary haemorrhage. Otherwise, if a haemostatically adequate platelet count is not achieved a 2nd dose (1g/kg) may be considered at day 5 to 7	Increase in platelet count Resolution of bleeding Number of bleeding complications

Indications	S	L	Selection criteria	Exclusion criteria	Position of immunoglobulin, taking into account alternative therapies	Recommended dose	Clinical outcomes
Acquired red cell aplasia associated with chronic parvovirus B19 infection	●	●	Parvovirus B19 infection: • Parvovirus B19 infection confirmed by PCR, AND • Evidence of high viral load, usually above 109 IU/ml In cases of foetal hydrops: • Likely to be associated with parvovirus B19	Infection other than parvovirus B19	Immunoglobulin is an adjunct to transfusion. Chronic parvovirus infection generally occurs on a background of immunosuppressive therapy, primary or HIV-related immunodeficiency and may resolve with a reduction in immunosuppression. Acute parvovirus infection associated with transient aplastic crisis requires urgent transfusion rather than Immunoglobulin.	1 – 1.2g/kg in divided doses. This may be repeated on relapse and for a 2nd relapse	Rise in haemoglobin Transfusion independence Reticulocyte count
Autoimmune haemolytic anaemia (AHA, including Evans syndrome)	●	●	AHA, including Evans syndrome: • Symptomatic or severe anaemia, except in patients with co-morbidities), AND • Refractory to conventional treatment with corticosteroids, OR • Corticosteroids contra-indicated, OR • As a temporising measure prior to splenectomy AHA in Pregnancy: Pregnant women with warm AHA refractory to corticosteroids OR with evidence of fetal anaemia Neonates of mothers with AHA who have evidence of haemolysis and rising bilirubin despite intensive phototherapy	NO	Immunoglobulin is reserved for patients unresponsive to steroids or where steroids are contra-indicated.	1-2g/kg in two to five divided doses. This may be repeated on relapse and for a 2nd relapse	Rise in haemoglobin Transfusion independence Reduction in haemolysis markers (bilirubin, lactate dehydrogenase)

Indications	S	L	Selection criteria	Exclusion criteria	Position of immunoglobulin, taking into account alternative therapies	Recommended dose	Clinical outcomes
Post-transfusion hyperhaemolysis **Prevention of haemolysis in patients with a history of transfusion-associated hyperhaemolysis** **Prevention of delayed haemolytic transfusion reaction**	●	●	Treatment of acute post-transfusion hyperhaemolysis: • Symptomatic or severe anaemia (Hb <6g/dL, with evidence of on-going intravascular haemolysis due to a delayed haemolytic transfusion/hyperhaemolysis). It is recognised that some patients with an Hb > 6 g/dl may require treatment. Patients who have had previous delayed haemolytic transfusion reactions/post-transfusion hyperhaemolysis or who have single or multiple allo-antibodies AND who may require a blood transfusion	No	In combination with steroids, Immunoglobulin is used as first-line treatment.	2g/kg (usually over two days) given with IV methylprednisolone 1-2g/kg over two or five days given with steroids 1 – 2 g/kg over 2 to 5 days, given with IV methylprednisolone	Rise in haemoglobin Transfusion Independence Reduction in haemolysis markers (bilirubin, lactate dehydrogenase) No haemolysis Maintenance of post-transfusion Hb at 1 – 3 weeks Avoidance of need for repeated transfusion
Coagulation factor inhibitors* (alloantibodies and autoantibodies)	●	●	Acquired von Willebrand disease (VWD): • Life- or limb-threatening haemorrhage, AND • Failure to respond to other treatments, AND/OR • Prior to invasive procedure • Treatment directed by the haemophilia centre at which the patient is registered	Acquired VWD associated with IgM monoclonal gammopathy	Immunoglobulin is a therapeutic option in acquired VWD, particularly in cases associated with a IgG monoclonal gammopathy alongside other therapies – plasmapheresis, desmopressin, VWF-containing concentrates and recombinant Factor VII.	Either 0.4g/kg for five days or 1g/Kg for two days	Rise of factor level Resolution of bleeding Number of bleeding episodes
Haemophagocytic syndrome	●	●	Diagnosis by consultant haematologist based on bone marrow biopsy, AND /OR Pancytopenia, AND Non-response to conventional treatment (e.g. corticosteroids, immunosuppressive agents, chemotherapy), OR Conventional treatment is contra-indicated or inappropriate	No		2g/kg in two to five divided doses. This may be repeated on relapse and for a 2nd relapse	Improvement of cytopenias Survival Improvement of HLH markers – Ferritin/soluble CD25

Indications	S	L	Selection criteria	Exclusion criteria	Position of immunoglobulin, taking into account alternative therapies	Recommended dose	Clinical outcomes
Post-transfusion purpura			• Sudden severe thrombocytopenia 5 to 10 days post-transfusion of blood products, AND • Active bleeding (typically occurs in Caucasian HPA-1a antigen negative females previously exposed to HPA-1a antigen in pregnancy or transfusion)	No	There are now very few cases in UK following the implementation of universal leucocyte-reduction of blood components in 1999	1 - 2g/kg in divided doses over two to five days	Increase in platelet count Resolution of bleeding Number of bleeding complications

NEUROLOGY

Indication	**S**	**L**	**Eligibility criteria:**	**Exclusion criteria:**	**Position of immunoglobulin, taking into account alternative therapies:**	**Recommended dose:**	**Outcome measures to be recorded on the national database:**
CIDP (including IgG or IgA associated paraprotein associated demyelinating neuropathy)			Probable or definite diagnosis of CIDP by a neurologist according to the EFNS/International Peripheral Nerve Society Guidelines; AND Significant functional impairment inhibiting normal daily activities. All patients should have an initial documented assessment after induction dosing and a further assessment after 2-3 doses to demonstrate meaningful functional improvement. Annual withdrawal/clinical reviews should be performed to document on-going need.	No specific exclusion criteria but see general comments regarding prothrombotic risks of Immunoglobulin.	Immunoglobulin should not always be considered first line treatment for CIDP, although it may be where steroids are contra-indicated and plasma exchange is not available. Where steroids, Immunoglobulin and plasma exchange are all available Immunoglobulin 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	An initiation regimen of 2g/kg over 5 days, then review at week 2, 4, 6 & 8. If required, repeat 2g/kg and reassess at week 2, 4, 6 & 8. If positive responder, give 1g/kg every 4 weeks in the first instance. Review dose and frequency regularly and consider dose reduction and/or extending dosing interval.	Efficacy outcomes should be used to measure response after the chosen initial regimen and thereafter when assessing for dose optimisation.

Indication	S	L	Eligibility criteria:	Exclusion criteria:	Position of immunoglobulin, taking into account alternative therapies:	Recommended dose:	Outcome measures to be recorded on the national database:
					consideration should be given to the early use of steroids or plasma exchange in other circumstances.		
Guillain-Barre syndrome (GBS) (includes Bickerstaff's brain stem encephalitis and other GBS variants)	🔴	⚫	Diagnosis of GBS (or variant) in hospital, AND Significant disability (Hughes Grade 4); OR Disease progression towards intubation and ventilation OR mEGRIS score ≥ 3 OR Poor prognosis mEGOS ≥ 4	Patients with mild and/or non-progressive disease not requiring intubation.	Patients with Miller-Fisher Syndrome do not usually require Immunoglobulin and unless associated with GBS overlap with weakness will recover normally.	2g/kg given over 5 days (shorter time frame not recommended because of potential fluid overload and autonomic problems); Second dose may be considered at 14 days for non-responsive or late deteriorating patients **NB: Immunoglobulin dosing beyond 4 weeks is unlikely to have clinical benefit.**	
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	Immunoglobulin is seldom significantly effective and response should be reviewed at least every 6 months if there is initial functional improvement. Alternative underlying haematological diagnoses should be considered which may direct treatment, or other	An initiation regimen of 2g/kg over 5 days, then review at week 2, 4, 6 & 8. If required, repeat 2g/kg and reassess at week 2, 4, 6 & 8. If positive	Efficacy outcomes should be used to measure response after the chosen initial regimen and thereafter when assessing for dose optimization.

Indication	S	L	Eligibility criteria:	Exclusion criteria:	Position of immunoglobulin, taking into account alternative therapies:	Recommended dose:	Outcome measures to be recorded on the national database:
					therapies such as single agent rituximab (or biosimilars) should be considered.	responder, give 1g/kg every 4 weeks in the first instance. Review dose and frequency regularly and consider dose reduction and/or extending dosing interval.	
Inflammatory Myopathies Dermatomyositis (DM) Polymyositis (PM)			• Diagnosis of myositis by a neurologist, rheumatologist, dermatologist or immunologist of DM or PM AND EITHER: • Patients with PM or DM who have significant muscle weakness; OR • Dysphagia and have not responded to corticosteroids and other immunosuppressive agents; • ORDM with refractory skin involvement.	No specific exclusion criteria but see general comments regarding prothrombotic risks of Immunoglobulin.	Where progression is not rapid and in the absence of contra-indications, steroids should be considered first Immunoglobulin is seldom effective in isolation and is best used as an adjunct to immunosuppressive therapy. Maintenance treatment with Immunoglobulin for a prolonged period (usually less than 12 months) may be required in a small minority of patients with inflammatory myositis, as a third line treatment after consideration of 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	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.	Clinically meaningful improvement in three pre- defined measures from the list below: DM: functional/disability scores (ADLs): • semi-quantitative muscle scores (MRC sumscore) • other quantitative muscle strength (e.g. MMT8) • up and go 10-m walk (in secs) • CDASI • FVC • HAQ

Indication	S	L	Eligibility criteria:	Exclusion criteria:	Position of immunoglobulin, taking into account alternative therapies:	Recommended dose:	Outcome measures to be recorded on the national database:
					be attempted at least annually to establish on-going need for treatment In patients with refractory disease associated with myositis-specific antibodies, rituximab is often considered; with Immunoglobulin being considered as a third line treatment.		PM: 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) • HAQ • FVC Efficacy outcomes should be recorded after the initiation course and regularly reassessed and recorded thereafter.
Myasthenia Gravis (MG), includes Lambert-Eaton Myasthenic Syndrome (LEMs)			Diagnosis of MG or LEMS by a neurologist AND EITHER; Acute exacerbation (myasthenic crisis); OR Weakness requires hospital admission; OR Prior to surgery and/or thymectomy	No specific exclusion criteria but see general comments regarding prothrombotic risks of Immunoglobulin.	All patients requiring urgent in patient treatment should receive plasma exchange first if available, including considering transfer to an appropriate neuroscience centre. Immunoglobulin could follow plasma exchange if required. Where plasma exchange is not available, Immunoglobulin may be appropriate.	For first presentation or significant relapse, give 2g/kg over 5 days or use plasma exchange where available. For patients requiring cyclical Immunoglobulin, give 1g/kg initially and titrate according to	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)

Indication	S	L	Eligibility criteria:	Exclusion criteria:	Position of immunoglobulin, taking into account alternative therapies:	Recommended dose:	Outcome measures to be recorded on the national database:
					In rare circumstances where a patient has failed all standard treatments (including steroids and immunosuppression) and where authorised by a specialist in MG from a centre with a specialist neuromuscular service, maintenance therapy may be considered. A rituximab biosimilar agent is likely to be an equally effective alternative therapy.	response. Patients with life threatening disease (ITU with respiratory and/ or bulbar failure) should receive 2g/kg. Refer to dose optimisation section for maintenance.	• Quantitative Myasthenia Gravis Score (Duke) • Respiratory function, e.g. forced vital capacity • Variation of another myasthenic muscular score • Dysphagia score • Dysarthria 1-50 counting Diplopia or ptosis measurement.
Multifocal Motor Neuropathy (MMN)			Diagnosis by a neurologist of multifocal motor neuropathy with or without persistent conduction block; AND Significant functional impairment inhibiting normal daily activities	No specific exclusion criteria but see general comments regarding prothrombotic risks of Immunoglobulin.	No alternative treatments known.	An initiation regimen of 2g/kg over 5 days, then review at week 2, 4, 6 & 8. If required, repeat 2g/kg and reassess at week 2, 4, 6 & 8. If positive responder, give 1g/kg every 4 weeks in the first instance. Review dose and frequency regularly and consider dose	Improvement in 3 pre- specified measures from the below list: • MRC score • Power score from 7 pre-defined pairs of muscles including 4 most affected muscle groups neuro-physiologically • RODS for MMN • Hand dynamometry

Indication	S	L	Eligibility criteria:	Exclusion criteria:	Position of immunoglobulin, taking into account alternative therapies:	Recommended dose:	Outcome measures to be recorded on the national database:
						reduction and/or extending dosing interval.	• ONLS10-m walk (in secs)Any other validated MMN disability measure
Rasmussen's Encephalitis			When other therapies (such as steroids) have failed.	No specific exclusion criteria but see general comments regarding pro-thrombotic risks of Immunoglobulin.	Immunoglobulin is reserved for patients unresponsive to steroids and other therapies.	2g/kg given over 2-5 days and repeated monthly for three months for initial trial.	Seizure frequency with expected reduction of 30% to continue therapy.
Stiff person syndrome (SPS) or variant			Diagnosis of SPS or a variant (stiff limb, PERM, etc) by a consultant neurologist Supportive criteria: Demonstration of auto-antibodies to GAD, Glycine receptor, DPPX, amphyphysin, gephyrin or other stiff person associated antibodies AND/OR Continuous motor unit activity at rest on EMG testing in paraspinal or affected limb musculature	No specific exclusion criteria but see general comments regarding prothrombotic risks of Immunoglobulin.	Consider plasma exchange as initial treatment. Rituximab is likely to be equally effective but is not commissioned for this indication.	An initiation regimen of a maximum 4g/kg divided into at least two courses of 1-2g/kg each, and given over a 4 to 8 week period, with assessment at the end of the period. Regimens to establish response might include: 2g/kg given over 2 to 5 days and repeated after 6 weeks (Fig 1 Lunn	Report on at least two of the measures below: • Reduction in stiffness • Up and go 10-m walk (in secs) • BRIT score • Number of spasms per day Validated measure of functional abilities

Indication	S	L	Eligibility criteria:	Exclusion criteria:	Position of immunoglobulin, taking into account alternative therapies:	Recommended dose:	Outcome measures to be recorded on the national database:
						et al J Peripheral Nerv Syst 2016;21:33-37) 2g/kg initially followed by 1g/kg after 3 weeks and a further 1g/kg 3 weeks later (Hughes et al Expert Rev Neurother 2009;9:789-95) For maintenance dose optimisation see general note below. If no significant measurable and functionally meaningful improved in abilities had been achieved after 3 doses Immunoglobulin should be stopped.	