DH Department of Health

SECOND EDITION UPDATE

Clinical Guidelines for Immunoglobulin Use

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Clinical guidelines for IMMUNOGLOBULIN USE

SECOND EDITION UPDATE

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Contents

Replacement pages

Summary table of conditions for which intravenous immunoglobulin use is appropriate

Condition	Short duration	Long duration
Primary and secondary antibody deficiency states		
Primary immunodeficiencies		🔴
Thymoma with immunodeficiency		🔴
HSCT in primary immunodeficiencies		🔴
Specific antibody deficiency		🔴
Secondary antibody deficiency (any cause)		🔵
Haematology		
Acquired red cell aplasia	🔵	
Alloimmune thrombocytopenia (foeto-maternal/neonatal)		🔴
Autoimmune haemolytic anaemia	🔵	
Coagulation factor inhibitors (alloantibodies and autoantibodies)	🔵	
Haemolytic disease of the newborn	🔴	
Haemophagocytic syndrome	🔵	
Immune thrombocytopenic purpura (acute and persistent, excluding chronic*)	🔴	
Post-transfusion purpura	🔵	
Neurology		
Chronic inflammatory demyelinating polyradiculoneuropathy**	🔴	🔵
Guillain-Barré syndrome	🔴	
Inflammatory myopathies		🔵
Myasthenia gravis (including Lambert-Eaton myasthenic syndrome)	🔵	
Multifocal motor neuropathy		🔵
Paraprotein-associated demyelinating neuropathy (IgM, IgG or IgA)	🔴	🔵
Rasmussen syndrome		🔵
Stiff person syndrome		🔵

continued

* Chronic immune thrombocytopenic purpura is a grey indication
** The disease should be life-threatening to allow database entry as red

Summary table of conditions for which intravenous immunoglobulin use is appropriate continued

Condition	Short duration	Long duration
Others		
Autoimmune congenital heart block	●	
Autoimmune uveitis	●	
Immunobullous diseases		●
Kawasaki disease	●	
Necrotising (PVL-associated) staphylococcal sepsis	●	
Severe or recurrent Clostridium difficile colitis	●	
Staphylococcal or streptococcal toxic shock syndrome	●	
Toxic epidermal necrolysis, Stevens Johnson syndrome	●	
Transplantation (solid organ)	●	

EXECUTIVE SUMMARY

The Clinical Guidelines for Immunoglobulin Use were implemented in 2008. The Guidelines were developed utilising an evidence review and extensive consultations with clinicians and other stakeholders. This update fulfils the commitment made in the Second Edition to undertake a biennial review from 2009. The Second Edition Guidelines remain in place and this update should be used in conjunction with the Second Edition.

This update did not review all of the Second Edition Guidelines content, but limited its focus 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.

Selection criteria for appropriate use of immunoglobulin

The Guidelines did not provide explicit selection criteria for the appropriate use of immunoglobulin. Review of data in the National Immunoglobulin Database showed a considerable volume of immunoglobulin was used in patients for whom no specific diagnosis was provided. Clearly, this was less than optimal and caused concern among commissioners. This update provides criteria that should be fulfilled if immunoglobulin is to be used, including particular disease characteristics, disease severity and any requirement for other treatments to have been demonstrably unsuccessful before immunoglobulin is considered. This reflects the approach taken by the National Blood Authority in Australia in defining appropriate prescribing of immunoglobulin.

Efficacy outcomes to assess treatment success

The Guidelines did not include efficacy tracking of immunoglobulin treatment, although Immunoglobulin Assessment Panels (IAP) were encouraged to request parameters by which efficacy could be assessed. This update provides efficacy outcomes to be measured in all indications (except primary immunodeficiencies), and it is expected that all Grey indications will have efficacy parameters defined and monitored on a case by case basis. Efficacy outcomes are expected to play an important role in the IAP decision-making process for patients in whom continuation of immunoglobulin treatment is requested beyond the short- and long-term durations defined in this update. This change reflects the wider change of focus in the NHS to patient outcomes, as presented in The NHS Outcomes Framework.

Modification of existing indications and inclusion of new indications

Changes to existing indications required proponents to submit new evidence to the Update Working Group for review. However, allocation of diseases to Red, Blue or Grey did not solely depend on the level of evidence presented, but included expert clinical advice and the availability of effective alternative therapies or treatment approaches. The British Transplantation Society made a strong case to change certain defined transplant cases to Blue, despite limited high-quality evidence for some of the clinical scenarios and the Update Working Group accepted the Society's view. For complex regional pain syndrome, although randomised evidence from a small study showed benefit, this was regarded by the Update Working Group as an emerging indication for refractory cases; a number of important questions concerning optimal treatment doses and duration of treatment remain unanswered. Therefore, this disease has been added to the Grey list. It remains the responsibility of the local IAP to decide with the PCT (or specialised commissioning group) if treatment with immunoglobulin is appropriate on a case by case basis.

Other Grey indications have been updated and others, for which there was little or no prescribing recorded in the database, deleted. 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.

Review of Red and Blue indications identified a number of disease entities with the same underlying pathophysiology that were listed separately; these are now grouped together under single disease headings.

Commissioning of immunoglobulin

Ensuring immunoglobulin prescribing is consistent with the evidence-base and restricted to those patients for whom there are no alternative treatments and for those most likely to benefit is the central aim of these guidelines. But from a commissioner's viewpoint, cost-effectiveness and affordability play an important role in their discussions with IAPs regarding prescribing. The commissioning aspects of this guideline update are included in a separate document and this should be reviewed to understand the requirements of commissioners around immunoglobulin prescribing, in particular regarding National Immunoglobulin Database entry and treatment duration.

INTRODUCTION

This update of the Department of Health's (DH) immunoglobulin guidelines fulfils the commitment made in the Second Edition to undertake a biennial review from 2009. This review was informed by changes in the clinical evidence base for immunoglobulin, the findings of the National Immunoglobulin Database (Reference number ROCR/OR/0221), and a change of focus in the NHS to patient outcomes, as presented in The NHS Outcomes Framework. The DH has consulted widely in this review and the changes have been discussed at length with clinicians and commissioners involved in the demand management of immunoglobulin.

Insights from the National Immunoglobulin Database

The DH's Demand Management Programme for Immunoglobulin was a key output from the 2006 review that assessed the opportunities available to secure the supply of immunoglobulin. The review recommended two complementary work streams, one based on securing supply and the other giving structure to the process of fulfilling demand (the Demand Management Programme). The Demand Management Programme was fully launched in late May 2008, when DH published the Second Edition of 'Clinical Guidelines for Immunoglobulin Use' and the 'Demand Management Plan for Immunoglobulin Use' (Gateway reference 10012 and 10013). The National Immunoglobulin Database was launched on 2nd June 2008. These documents and the National Immunoglobulin Database are accessible through the immunoglobulin website www.ivig.org.uk.

The first data review from the National Immunoglobulin Database, published in January 2010, contained data on immunoglobulin prescribing in 5119 patients, and offered a unique, detailed view of prescribing practice of immunoglobulin in England as well as providing, for the first time, a baseline of immunoglobulin use. This 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. The review also identified a number of issues regarding the Demand Management Programme, which are addressed in this guideline update.

Changes to the colour-coded prioritisation employed in the Demand Management Programme

Automatic assignment of Red and Blue prioritisation

The Demand Management Programme introduced colour coding to reflect the prioritisation of immunoglobulin treatment

in times of shortage, based on the availability of alternative treatments and strength of clinical evidence. The database review showed many cases for which diseases were mis-assigned to an incorrect prioritisation. In particular, there were many cases of mis-assignment of diseases to Red and Blue.

'Red' indicates conditions for which treatment is considered the highest priority because of a risk to life without treatment. The intention remains that Trusts will protect supply for these high-priority diseases in times of immunoglobulin shortage, particularly for patients with primary immunodeficiencies. To ensure accurate prioritisation assignment, the database will now automatically assign the colour coding upon patient entry on the basis of patient characteristics.

The Immunoglobulin Assessment Panels (IAP) at Trusts should continue to manage local demand for immunoglobulin; in times of shortage, local panels should continue to identify Red indications as those of most clinical need.

The database will automatically assign diseases to 'Blue', but prescribing of immunoglobulin in Blue indications will continue to require prior approval of the IAP.

Grey indications

'Grey' indications are those diseases for which the evidence is weak, in many cases because the disease is rare. Approval from both the local IAP and the Primary Care Trust (PCT) (or specialised commissioning group) is required for immunoglobulin treatment. As previously specified in the Demand Management Plan for Immunoglobulin Use, treatment should be considered on a case-by-case basis, and prioritised against other competing demands for immunoglobulin, especially in times of shortage.

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; it remains the responsibility of the local IAP to decide with the PCT (or specialised commissioning group) if treatment with immunoglobulin is appropriate on a case-by case basis.

Reclassification of diseases

1. Grey to Blue

The database review identified two of the top 10 immunoglobulin-using indications as Grey (secondary antibody deficiencies and antibody-mediated rejection following solid organ transplantation). In many Trusts, commissioners have permitted pre-approval of immunoglobulin use for these indications despite the limited evidence base. Therefore, these indications were reviewed in detail and the evidence base was reassessed.

Secondary antibody deficiencies were identified by a number of stakeholders as a key area for revision. In the previous edition, they were listed under immunosuppressive pharmacotherapy, and separately under some of the haematological malignancies such as CLL, without listing other mature B-cell malignancies such as non-Hodgkin's lymphoma. These have been revised into a single indication. The outcome of this review is that use of immunoglobulin for these indications is appropriate and is now listed as Blue (see replacement page 30).

Antibody-mediated rejection following solid organ transplantation and antibody-incompatible transplantation were reviewed, and a single grouping of 'Transplantation (solid organ)' has been introduced and listed as Blue.

Acquired von Willebrand disease has now been included with acquired haemophilia, in the general disease grouping of 'Coagulation factor inhibitors', which is listed under appropriate use of immunoglobulin. Immunoglobulin use carries selection criteria, including that these rare and severe bleeding disorders are managed in a comprehensive care centre for haemophilia.

Polymyositis and Inclusion body myositis have now been grouped with dermatomyositis under the general disease grouping of inflammatory myopathies, with strict selection criteria.

Post-transfusion hyperhaemolysis has now been grouped under the more general heading of haemolytic anaemia.

SLE with secondary immunocytopenias should be considered under the relevant immune cytopenia.

2. Blue to Red

Specific antibody deficiency, as a recognised primary antibody deficiency disorder, has been reclassified as a Red indication (for those cases where immunoglobulin replacement therapy is required).

Haemolytic disease of the newborn has been updated to reflect recommendations in NICE clinical guideline 98 on neonatal jaundice [1].

Introduction of specific selection and outcome criteria in the Demand Management Programme

Selection criteria

The database review also raised an important issue over patient diagnosis – a considerable volume of immunoglobulin was used in patients in which there was no specific diagnosis listed (13% of total recorded immunoglobulin use). Clearly, this was less than optimal and caused concern among commissioners. In addition, this showed that improvements were required before the database was sufficiently robust to be able to link to payments by use.

Further feedback from commissioners indicated widespread approval of the system used in Australia, with each indication for immunoglobulin carrying specific selection criteria for use, in particular, the need to use immunoglobulin as second- or third-line treatment in diseases for which there are a number of alternative treatment options. This approach, with selection criteria for each approved indication for immunoglobulin, has now been adopted in this guideline update. The need to employ selection criteria before prescribing will largely remove the need for panel decisions on prescribing, reducing the burden on IAPs and increasing focus on assessing patient outcome.

Efficacy outcomes

The database was not successful in the capture of data regarding the efficacy of immunoglobulin. Panels were encouraged to request up to three parameters by which efficacy could be determined in each patient [e.g., platelet count in patients with immune thrombocytopenic purpura (ITP)]. The purpose of this exercise was both to obtain preliminary data about efficacy in various conditions (fully accepting that lack of diagnostic criteria and other issues would make this a very crude analysis) and to provide feedback to individual Panels about the quality of their decision making. For example, if Panels repeatedly approved indications prioritised as Grey by the Demand Management Programme and the treatment was largely ineffective, review of these findings would improve IAP decision making.

The decision has been taken to introduce efficacy outcomes for most indications. Monitoring of efficacy outcomes by commissioners may result in withholding payments to Trusts if efficacy outcomes have not been recorded in the database. Efficacy outcomes are expected to play an important role in the decision-making process of IAPs in cases in which continuation of immunoglobulin treatment is requested beyond the short- and long-term durations defined in the next section.

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. IAPs and commissioners together will make decisions on treatment extensions.

Short-term treatment Three prescribed doses of up to 2 g/kg, given at appropriate clinical intervals	≤3 months The treatment episode ends at 3 months. The National Immunoglobulin Database will record treatment re-initiation as a new treatment episode based on a new panel decision. It is expected that the IAP decision will be influenced by the outcome measures recorded on the database.
Long-term treatment	≥3 months Treatment reviews should be conducted annually. The National Immunoglobulin Database will record treatment re-initiation as a new treatment episode based on a new panel decision. It is expected that the IAP decision will be influenced by the outcome measures recorded on the database.*

*The primary immunodeficiencies are exempt from funding termination at 1 year.

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

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. 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. This would also save significant quantities of immunoglobulin.

The First Edition of these guidelines included a recommendation to use ideal-body-weight-adjusted dosing, based on the dosing regimen used at a leading London neurology centre (see below); however, this was removed in the Second Edition. There is a very limited evidence base, which is too weak to allow firm recommendation, but there are some reports supporting this approach. The calculation included in the First Edition guidelines to determine ideal

body weight-adjusted dose is given below (no maximum applies):

Calculate ideal body weight (IBW) (kg):

IBW for males =
50 + [2.3 x (height in inches - 60)]

IBW for female =
45.5 + [2.3 x (height in inches - 60)]

Calculate dose-determining weight (DDW) (kg):

DDW =
IBW + 0.4 [actual body weight (kg) – IBW]

Use DDW for calculating the IVIg dose required

An online calculator for calculating the dose-determining weight is available at:
http://www.transfusionontario.org/dose/

Western Australia pilot study

A pilot study to reduce the immunoglobulin dose in obese patients was conducted in Western Australia. Thirty over-weight patients were administered immunoglobulin using the above equations taken from the UK First Edition guidelines. No reduction in efficacy was seen after initial dose in this cohort. This provides some evidence that using the lowest effective immunoglobulin dose in eligible patients is an effective means to minimise side-effects, as well as reducing the use of this scarce resource.

Hospital Corporation of America

Hospital Corporation of America, one of the largest providers of healthcare services in the United States, requires that all doses of IVIg are based on ideal body weight and are rounded to the nearest whole vial size (except neonates), based on the same formula specified in the First Edition of the DH guidelines.

The Ohio State University Medical Centre, Columbus, Ohio

The Ohio State University Medical Centre routinely uses ideal-body-weight-adjusted dosing of immunoglobulin in obese patients. They are confident that this is a practical and cost-effective method that accounts for the increased distribution into extra body fluids in patients with obesity, without accounting for the increase in adipose tissue. They recommend calculating adjusted body weight from IBW (see above IBW equation taken from UK First Edition guidelines) using the following equation: adjusted body weight (kg) = IBW + 0.5 [actual body weight (kg) - IBW].

This adjusted body weight is used if a patient has a body mass index (BMI) of ≥30 kg/m^2 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.

Recommendation

For patients with BMI ≥30 kg/m² or if actual weight >20% more than IBW, prescribers should consider using adjusted-body-weight dosing of immunoglobulin.

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 are provided in the table below. Immunoglobulin should be administered according to the manufacturers' recommendations.

The table below gives the infusion rates, and the infusion time at maximum infusion rate of 1 g/kg dose in a 70 kg person.

Product	Infusion rates		Infusion time of 70 g in minutes at max. rate
	Initial	Maximum	
Baxter Kiovig	0.5 mL/kg/h for 30 mins	6 mL/kg/h (8 ml/kg/h in PID)	100
BPL Gammaplex	0.01–0.02 mL/kg/min for 15 mins	0.04–0.08 mL/kg/min	250
BPL Vigam	0.01–0.02 mL/kg/min for 30 mins	0.04 mL/kg/min (max. 3mL/min)	500
Biotest Intratect	1.4 mL/kg/h for 30 mins	1.9 mL/kg/h	640
CSL Privigen	0.3 mL/kg/h	4.8 mL/kg/h (7.2 mL/kg/h in PID)	125
Grifols Flebogamma 5	0.01–0.02 mL/kg/min for 30 mins	0.1 mL/kg/min	200
Grifols Flebogamma 10	0.01 mL/kg/min for 30 mins	0.08 mL/kg/min	125
Octapharma Octagam 5	1 mL/kg/h for 30 mins	5 mL/kg/h	241
Octapharma Octagam 10	0.01–0.02 ml/kg/min for 30 mins	0.12 ml/kg/min	83

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. Seventy-four patients with primary immune deficiency disease received an average SCIg dose of 32 g/month split into an average of three times per week. Volume per site ranged from 3 to 20 mL, typically administered over 5–20 min. Mean serum IgG levels did not differ significantly compared with those receiving infusion and only two patients discontinued therapy because of an adverse event [4].

Recent evidence suggests that individualising the dosage based on measured serum IgG levels and the clinical response is preferable to using mean pharmacokinetic parameters [5]. Findings from the Oxford Self Infusion at Home Programme for CIDP and MMN also suggest that the dose of immunoglobulin and the serum IgG trough level are individual to each patient [2].

Recommendation

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

Table. *Subcutaneous immunoglobulin products licensed in the UK*

CSL Vivaglobin
Baxter Subcuvia
Octapharma Gammanorm
BPL Subgam

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SUMMARY TABLES

PRIMARY AND SECONDARY ANTIBODY DEFICIENCY STATES					
Condition	**S**	**L**	**Selection criteria**	**Outcomes for review**	**Dosing**
Primary immunodeficiencies (associated with significant antibody defects)		🔴	A specific PID diagnosis must be established by a clinical immunologist	Outcome measures are not required	Initiate at 0.4–0.6 g/kg/month; dose requirements may increase and should be based on clinical outcome
Thymoma with immunodeficiency		🔴	Profound B cell depletion and/or significant antibody deficiency	Outcome measures are not required	Initiate at 0.4–0.6 g/kg/month; dose requirements may increase and should be based on clinical outcome
HSCT in primary immunodeficiencies		🔴	PID patients undergoing HSCT	Outcome measures are not required	Initiate at 0.4–0.6 g/kg/month; dose requirements may increase and should be based on clinical outcome
Specific antibody deficiency		🔴	Approval by a clinical immunologist, AND Severe, persistent, opportunistic or recurrent bacterial infections despite continuous oral antibiotic therapy for 3 months, AND Documented failure of serum antibody response to unconjugated pneumococcal or other polysaccharide vaccine challenge	Outcome measures are not required	Initiate at 0.4–0.6 g/kg/month; dose requirements may increase and should be based on clinical outcome
Secondary antibody deficiency (any cause)		🔵	Underlying cause of hypogammaglobulinaemia cannot be reversed or reversal is contraindicated; OR Hypogammaglobulinaemia associated with NHL, CLL, MM or other relevant B-cell malignancy confirmed by haematologist; AND – Recurrent or severe bacterial infection despite continuous oral antibiotic therapy for 3 months – IgG <5 g/L (excluding paraprotein) – Documented failure of serum antibody response to unconjugated pneumococcal or other polysaccharide vaccine challenge	Reduction in number of infections and days in hospital*	0.4 g/kg/month modified to achieve an IgG trough level of at least the lower limit of the age-specific serum IgG reference range

*Database parameters will include entry of number of infections and days in hospital pre-treatment and 6 monthly thereafter

HAEMATOLOGY					
Condition	**S**	**L**	**Selection criteria**	**Outcomes for review**	**Dosing**
Acquired red cell aplasia	●		Patients with parvovirus B19 infection confirmed by PCR; AND failure of other therapies (corticosteroid and at least one other immunosuppressive therapy) In cases of foetal hydrops, if it is likely to be associated with parvovirus B19 infection	Correction of anaemia	2 g/kg in two to five divided doses; repeated on relapse and for a second relapse.
Alloimmune thrombocytopenia (foeto-maternal/neonatal)		●	Clinical suspicion in antenatal or neonatal setting based on clinical and laboratory features: Thrombocytopenia or spontaneous haemorrhage in the foetus; OR Thrombocytopenia with or without haemorrhage in the neonate; OR Unexplained foetal death in a previous pregnancy and the presence of maternal platelet-specific allo-antibodies that are known or suspected to cause this condition (most commonly HPA-1a or HPA-5b)	Increment in (neonatal) platelet count Successful outcome of pregnancy	Maternal: 1 g/kg weekly throughout pregnancy Neonatal: 1 g/kg; occasionally >1 dose required if thrombocytopenia persists
Autoimmune haemolytic anaemia (including Evans syndrome and post-transfusion hyper-haemolysis)	●		Symptomatic or severe anaemia (Hb <6 g/dL, except patients with co-morbidities) or thrombocytopenia (Evans syndrome, platelets <20x10^9/L) refractory to conventional therapy with corticosteroids (or steroids contra-indicated); OR Temporising measure prior to splenectomy	Correction of anaemia/ thrombocytopenia	Up to 2 g/kg as a single or divided dose

continued

Haematology continued

Condition	S	L	Selection criteria	Outcomes for review	Dosing
Coagulation factor inhibitors* (alloantibodies and autoantibodies) **IVIg should only be prescribed in a comprehensive care centre for haemophilia in these severe bleeding disorders**	●		**Acquired haemophilia** Life or limb-threatening haemorrhage AND failure to respond to other treatments; **Autoimmune von Willebrand syndrome** Life or limb-threatening haemorrhage AND failure to respond to other treatments OR prior to invasive procedures	Fall in relevant inhibitor levels Rise in relevant factor levels	Initial therapy: either 0.4 g/kg for 5 days or 1 g/kg for 2 days
Haemolytic disease of the newborn	●		As adjunct to continuous multiple phototherapy in cases of Rhesus haemolytic disease or ABO haemolytic disease (see NICE guideline 98)	Record bilirubin Record gestational age Avoidance of exchange transfusion	0.5 g/kg over 4 hours
Haemophagocytic syndrome	●		Diagnosis by consultant haematologist based on bone marrow biopsy AND Pancytopenia	Correction of pancytopenia Survival	Up to 2 g/kg as a single or divided dose
Immune thrombocytopenic purpura – acute	●		If corticosteroids are contraindicated or more rapid response required; If no response to corticosteroids and other treatments contraindicated; Prior to surgery to achieve a safe platelet count; In children (<16 years) for emergency or prior to procedure likely to induce bleeding	Resolution of bleeding Increment in platelet count	Use 1 g/kg (0.8–1 for children) as a single infusion, to be repeated at later date if platelet count has not responded
Immune thrombocytopenic purpura – persistent	●		For symptomatic cases unresponsive to all other treatments, IVIg is appropriate only for emergency management, e.g. potentially life-threatening haemorrhage and/or bleeding into a critical area	Resolution of bleeding Increment in platelet count	Use 1 g/kg (0.8–1 for children) as a single infusion, to be repeated at later date if platelet count has not responded
Post-transfusion purpura	●		Sudden severe thrombocytopenia 5–10 days post-transfusion of blood products; AND Active bleeding (typically occurs in Caucasian HPA-1a-negative females previously exposed to HPA-1a antigen in pregnancy or transfusion)	Resolution of bleeding Increment in platelet count	2 g/kg in divided doses over 2–5 consecutive days

NEUROLOGY					
Condition	**S**	**L**	**Selection criteria**	**Outcomes for review**	**Dosing**
Chronic Inflammatory Demyelinating Polyradiculoneuropathy	●	●	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	Improvement in any of the following prespecified measures (record 3 of 5) • MRC score (7 pairs of muscles in upper and lower limb scored 0–5, maximum 70) • INCAT sensory sum score • The ONLS • Up and go 10-m walk (in secs) • Other validated disability measure	2 doses of IVIg (2 g/kg given over several days) 6 weeks apart; restarted at relapse and repeated using the 'time to relapse' as the interval between courses (i.e. if a patient relapses after 6 weeks, 2 g/kg is given over several days every 6 weeks)
Guillain-Barré syndrome (includes Bickerstaff's brain stem encephalitis)	●		Diagnosis of GBS (or variant) in hospital; AND Significant disability (Hughes Grade 4); OR Disease progression	Record the disability grade at diagnosis	2 g/kg usually 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
Inflammatory myopathies Dermatomyositis (DM), Polymyositis (PM) Inclusion body myositis (IBM)		●	Diagnosis of myositis by a neurologist, rheumatologist, or immunologist of: Patients with PM or DM who have significant muscle weakness; OR Dysphagia and have not responded to corticosteroids and other immunosuppressive agents; OR Patients with IBM who have dysphagia affecting nutrition **(NOT patients with rapidly progressive IBM)**	1. Improvement in functional scores (ADLs) or quantitative muscle scores OR Medical Research Council (MRC) muscle assessment; OR up and go 10-m walk (in secs) 2. Stabilisation of disease as defined by stable ADLs or quantitative muscle scores OR MRC muscle assessment OR up and go 10-m walk after previous evidence of deterioration in one of these scores	2 doses of IVIg (2 g/kg given over several days) 6 weeks apart; restarted at relapse and repeated using the 'time to relapse' as the interval between courses

continued

Neurology continued

Condition	S	L	Selection criteria	Outcomes for review	Dosing
Myasthenia gravis [includes Lambert-Eaton myasthenic syndrome (LEMS)]	●		Diagnosis of MG or LEMS by a neurologist; OR Acute exacerbation (myasthenic crisis); OR Other immunosuppressive treatments are ineffective/ inappropriate; OR Weakness requires hospital admission; OR Prior to surgery and/or thymectomy	Improvement in fatigability and weakness using any pre-specified measure: • Forward arm abduction time (up to 5 min) • Quantitative Myasthenia Gravis Score (Duke) • Respiratory function, e.g. forced vital capacity • Variation of a myasthenic muscular score	2 g/kg given over 2–5 days
Multifocal motor neuropathy		●	Diagnosis by a neurologist of multifocal motor neuropathy with or without persistent conduction block; AND Significant functional impairment inhibiting normal daily activities	Improvement in pre-specified measures: • Power score from 10 pre-defined pairs of muscles including six most affected muscles neuro-physiologically • The ONLS • Up and go 10-m walk (in secs) • Other validated disability measure	2 doses of IVIg (2 g/kg given over several days) 6 weeks apart; restarted at relapse and repeated using the 'time to relapse' as the interval between courses (often may be 4 weeks, but doses required may be less than CIDP)
Paraprotein-associated demyelinating neuropathy (IgM, IgG or IgA)	●	●	Diagnosis by a neurologist AND Significant functional impairment inhibiting normal daily activities; AND Other therapies have failed, are contraindicated or undesirable	Improvement in any of the following pre-specified measures (record 3 of 5): • MRC score (7 pairs of muscles in upper and lower limb scored 0–5, maximum 70) • INCAT sensory sum score • The ONLS • Up and go 10-m walk (in secs) • Other validated disability measure	2 doses of IVIg (2 g/kg given over several days) 6 weeks apart; restarted at relapse and repeated using the 'time to relapse' as the interval between courses

continued

Neurology continued

Condition	S	L	Selection criteria	Outcomes for review	Dosing
Rasmussen syndrome		●	When other therapies (such as steroids) have failed	Reduction in seizure frequency Improvement in cognitive state	2 doses of IVIg (2 g/kg given over several days) 6 weeks apart; restarted at relapse and repeated using the 'time to relapse' as the interval between courses
Stiff person syndrome		●	Demonstration of auto-antibodies to GAD-65 or GAD-67	Reduction in stiffness Up and go 10-m walk (in secs) Number of spasms per day	2 doses of IVIg (2 g/kg given over several days) 6 weeks apart; restarted at relapse and repeated using the 'time to relapse' as the interval between courses

OTHER

Condition	S	L	Selection criteria	Outcomes for review	Dosing
Autoimmune congenital heart block (anti-Ro) OR Paediatric myocarditis	●		IVIg therapy can be 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	Improvement in the degree of heart block at birth	0.4 g/kg every 3 weeks for a total of 5 treatments from weeks 12 through 24 of gestation
Autoimmune uveitis	●		When sight is threatened	Improvement in sight	1.5 g/kg/month for 3 months

continued

Other continued

Condition	S	L	Selection criteria	Outcomes for review	Dosing
Immunobullous diseases		●	Severely affected AND Conventional corticosteroid treatment with adjuvant agents has failed or is inappropriate	Reduction in recurrence of disease/relapse Dose reduction/discontinue other therapy Improved quality of life Resolution of blisters/healing affected skin Resolution of pruritis	2 g/kg over 2–5 days
Kawasaki disease	●		Clinical diagnosis of Kawasaki disease by a paediatrician or immunologist	Resolution of fever	2 g/kg single dose, given over 10–12 hours, in conjunction with high-dose aspirin; a second dose may be given if no response, or if relapse within 48h
Necrotising (PVL-associated) staphylococcal sepsis	●		Diagnosis of streptococcal or staphylococcal TSS, preferably with isolation of organism; AND Failure to achieve rapid improvement with antibiotic therapy and other supportive measures AND Life-threatening	Improvement of FBC, ALK, CPK Reduction in hospital inpatient stay Survival (yes/no)	2g/kg as a single dose
Severe or recurrent *Clostridium difficile* colitis	●		Severe cases (WCC >15, acute rising creatinine and/or signs/symptoms of colitis) not responding to oral vancomycin 125 mg qds, high-dosage oral vancomycin +/- iv metronidazole 500 mg tds is recommended; the addition of oral rifampicin (300 mg bd) or IVIg may be considered. If multiple **recurrences**, especially if evidence of malnutrition, wasting etc., consider IVIg	Any significant clearance of *C. diff.* Duration of hospital in-patient stay	0.4 g/kg, one dose, and consider repeating

continued

Other continued

Condition	S	L	Selection criteria	Outcomes for review	Dosing
Staphylococcal or streptococcal toxic shock syndrome	●		Diagnosis of streptococcal or staphylococcal TSS, preferably with isolation of organism; AND Failure to achieve rapid improvement with antibiotic therapy and other supportive measures; AND Life-threatening	Improvement of FBC, ALK, CPK Reduction in hospital inpatient stay Survival (yes/no)	2 g/kg as a single dose
Toxic epidermal necrolysis, Stevens Johnson syndrome	●		Diagnosis by a dermatologist; AND Involved body surface area >10%; AND When other treatments are contraindicated; OR The condition is life-threatening	Resolution of the disease	2 g/kg, preferably as a single dose, or divided over 3 consecutive days
Transplantation (solid organ)	●		**Antibody Incompatible Transplant (AIT)** Patients in whom renal, heart or lung transplant is prevented because of antibodies **Antibody Mediated Rejection (AMR)** Patients experiencing steroid resistant rejection or where other therapies are contraindicated after renal, heart and/or lung transplant **Viral pneumonitis** Patients experiencing viral pneumonitis following heart and/or lung transplant (viruses to include HSV, VZV, CMV, RSV, but *excluding* influenza virus)	**AIT and AMR*** Renal Type of renal transplant HLA class DSA Rejection episodes Patient survival Graft survival Renal function = eGFR (MDRD) Cardiothoracic DSA Patient survival Length of ITU and hospital stay Graft function (heart = ejection fraction; lung = spirometry) **Viral pneumonitis*** Cardiothoracic Virus type Reversal of radiological infiltrates Length of hospital stay Survival	**AIT** Up to 2 g/kg to be repeated as per DSA, in renal desensitisation at 0.1 g/kg for 8–12 doses **AMR** Up to 2 g/kg to be repeated for 2–3 doses **Viral pneumonitis** 0.5 g/kg for 5 days

*These parameters will be reviewed after one year, at which time specific outcome criteria will be formulated.

SUMMARY OF GREY INDICATIONS

Grey indications are those diseases for which the evidence is weak, in many cases because the disease is rare. Approval from both the local IAP and the PCT is required for immunoglobulin treatment. In cases of 'unlisted' diseases, those not listed in the guidelines are to be considered as Grey. Even if the disease is unlisted, the diagnosis and locally agreed efficacy criteria are to be recorded in the database.

Immune-mediated disorders with limited evidence of immunoglobulin efficacy	Presumed immune-mediated disorders with little or no evidence of efficacy
Acute disseminated encephalomyelitis (if high-dose steroids have failed)	Acquired red cell aplasia NOT due to parvovirus B19
Autoimmune encephalitis (including NMDA and VGKC antibodies, among others)	Acute idiopathic dysautonomia
Catastrophic antiphospholipid syndrome	Aplastic anaemia/pancytopenia
Cerebral infarction with antiphospholipid antibodies	Atopic dermatitis/eczema
Chronic ITP	Autoimmune neutropenia
Complex regional pain syndrome	Chronic facial pain
CNS vasculitis	Diabetic proximal neuropathy
Intractable childhood epilepsy	Haemolytic uraemic syndrome
Neuromyotonia	PANDAS
Opsoclonus Myoclonus	Paraneoplastic disorders that are known not to be B- or T-cell mediated
Post-exposure prophylaxis for viral or pathogenic infection if intramuscular injection is contraindicated, or treatment when hyper-immune immunoglobulins are unavailable	POEMS
Pyoderma gangrenosum	SLE without secondary immunocytopenias (including juvenile)
Systemic juvenile idiopathic arthritis	
Systemic vasculitides and ANCA disorders	
Urticaria (severe, intractable)	

Removed from Grey:

- Secondary antibody deficiencies (now Blue)
- Acquired vWd (now Blue)
- Post-transfusion hyperhaemolysis (now with haemolytic anaemia)
- Graft versus host disease (delete)
- SLE with secondary immunocytopenias (included in the relevant cytopenias)
- Infection following BMT or HSCT (included in Blue)
- Polymyositis (now Blue)
- Transplantation indications (now Blue)

INDICATIONS FOR WHICH IVIG 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)
- Sepsis in the intensive care unit not related to specific toxins or C. difficile
- Asthma
- Graves' ophthalmopathy
- IVF failure
- Recurrent spontaneous pregnancy loss

Next section contains the replacement pages of Second Edition

IMMUNOLOGY

Primary immunodeficiency disorders (associated with significant antibody defects)

Antibody deficiencies may arise as primary disorders with a known or suspected genetic basis or secondary to a variety of other diseases, drugs and environmental or iatrogenic factors. They may occur in isolation or in association with defects in other effector components of the immune system (combined defects). Significant primary antibody deficiencies collectively account for the majority of primary immunodeficiency syndromes encountered in clinical practice [1,2]. The hallmark clinical presentation is recurrent or persistent bacterial infection, but these disorders are also associated with a heterogeneous variety of other infectious and non-infectious complications and with a high incidence of chronic, structural tissue damage, particularly in the respiratory tract. Clinical recognition of primary antibody deficiency is frequently delayed with consequent acute and chronic ill health, diminished quality of life, and decreased life expectancy. Primary antibody deficiency can present at any age.

Taken together, the primary antibody deficiency disorders account for at least half of all primary immunodeficiency syndromes. For some conditions, internationally-agreed diagnostic criteria have been established [3], but in other disorders formal case-definition criteria are lacking. The evidence base for current practice in the recognition, diagnosis and management of antibody deficiency has recently been reviewed [4]. Disorders which generally require immunoglobulin replacement as a central component of their management are presented below.

Diagnosis, particularly of primary deficiencies, is frequently delayed or overlooked [1,5]. Many patients present with established structural tissue damage, especially in the lungs, which is essentially irreversible even with optimal treatment. Diagnostic aims are to a) identify, or exclude, significant antibody deficiency, b) differentiate primary from secondary disease and c) delineate, where possible, a precise diagnosis.

Common	Less common
Common variable immunodeficiency group (CVID)	Germinal centre class switch recombination defects ('Hyper-IgM syndromes')
X-linked agammaglobulinaemia	Other primary antibody deficiency (XLA) (including unclassifiable disorders)
	Combined immunodeficiencies (including severe combined immunodeficiency (SCID) and unclassifiable disorders)

The goals of management are to prevent complications or retard their progression, optimise quality of life, working capacity and life expectancy and, in children, ensure optimal growth and development [6].

Replacement therapy with polyclonal human normal immunoglobulin is the cornerstone of management for significant primary antibody deficiency disorders. No viable alternatives exist to this essential, basic component of treatment, particularly in the context of severe, persistent or recurrent bacterial infections. ***For most patients, replacement therapy is a lifelong requirement***. Existing formulations replace deficient IgG only and are given by either intravenous or subcutaneous infusion in a hospital setting or, increasingly, within domestically-based programmes. Subcutaneous and intravenous preparations are therapeutically equivalent [7]. All preparations carry risks of adverse, infusion-related reactions and both real (hepatitis C) and theoretical (vCJD) risks of transmissible disease. Replacement therapy increases life expectancy and reduces the frequency and severity of infections, antibiotic usage and hospital admissions [4]; however, patients remain susceptible to sporadic breakthrough infections [8]. Optimal dosing and target levels for IgG are not known but higher doses are more effective than low-dose regimens in reducing infection rates and risk of chronic tissue damage. However, even apparently adequate treatment may fail to completely retard progression of established disease complications such as bronchiectasis [9].

Replacement therapy is frequently targeted at achieving a sustained or pre-infusion trough serum IgG level within the normal range (6–16 g/L). There is evidence that improved outcomes, particularly in respect of respiratory infection, are associated with higher serum IgG levels up to at least 10 g/L [10]. Dosage should generally be initiated at 0.4–0.6 g/kg/month, but individual patients may require higher doses in the long term. The goal of therapy in individual cases should be to improve clinical outcome rather than achieve a minimum target level of serum IgG [11]. Dose requirements are commonly increased in the context of secondary structural tissue damage (especially in the respiratory tract) or co-existent chronic inflammatory conditions. Risk assessments for ongoing therapy with immunoglobulin should be carried out regularly (including the need to continue with active treatment).

Recommendation

Replacement immunoglobulin therapy in patients with significant, symptomatic primary defects of antibody production or function should be tailored to individual patient outcomes with the minimum aim of maintaining serum IgG levels within the age-related normal range (grade B recommendation, level IIb evidence).

Other Specific Disorders

Thymoma with immunodeficiency (Good's Syndrome)

Good's syndrome is a complex CVID-like condition where thymoma is found in association with profound B cell lymphopenia and quantitative or functional antibody deficiency. Infection frequencies correlate better with numerical B-cell depletion than with hypogammaglobulinemia. Thymectomy rarely results in normalisation of immunoglobulin levels and the syndrome may therefore constitute, and be classified as, a primary rather than secondary defect and, in respect of any antibody deficiency, be treated as for other primary antibody defects [2,12].

Recommendation

Immunoglobulin replacement is recommended for patients with thymoma associated with profound B-cell depletion and/or significant antibody deficiency (grade C recommendation, level III evidence).

Combined immunodeficiencies requiring haemopoietic stem cell transplantation

In this group of disorders, including Severe Combined Immunodeficiency and occurring predominantly in children, immunoglobulin therapy is required as a central measure to protect against infection and should be implemented as soon as possible after the diagnosis is established. Pre-existing infection in the high-risk situation of a combined primary immunodeficiency reduces the chances of a successful outcome from a haemopoietic stem cell transplant. Treatment with immunoglobulin should be continued following transplantation until reconstitution of B cells and antibody production has been achieved. In some cases, prolonged immunoglobulin replacement therapy is required.

Recommendation

Immunoglobulin replacement therapy should be considered an important adjunct to haemopoietic stem cell transplantation in the management of some primary immunodeficiency disorders. Duration of treatment should be based on individual reconstitution of B-cell function post-transplantation (grade C recommendation, level III evidence).

Specific antibody deficiency

Specific antibody deficiency is characterised by an inability to mount adequate humoral responses to polysaccharide antigens, with otherwise normal immunoglobulins [13]. Robust case definition is currently hampered by a lack of consensus on *in-vitro* diagnostic criteria. Consequently, uniform recommendations for treatment are yet to be developed. Most cases appear to have a relatively mild clinical phenotype (encompassing mainly respiratory infections) which

can be managed with prophylactic antibiotics and acute treatment of breakthrough infections. Immunoglobulin replacement is reserved for those cases where prophylactic antibiotics fail to control either the frequency or severity of breakthrough infections.

Recommendation

Immunoglobulin replacement therapy is recommended in specific antibody deficiency in cases of failure of prophylactic antibiotic treatment where severe, persistent, opportunistic or recurrent breakthrough infections are encountered (grade C recommendation, level III evidence).

Transient hypogammaglobulinaemia of infancy

Hypogammaglobulinaemia in young children is often transient, reflecting delayed maturation of the immune system. In the majority of such children, immunoglobulin levels normalise by the age of around 4 years, but in a minority this can be delayed until 11 or 12 years of age. Most of these children are affected by frequent, minor infections, which can be managed with early, acute antibiotic usage or antibiotic prophylaxis [14]. However, in a small minority, infections are more severe and cannot be controlled or prevented with antibiotics alone. In such circumstances, immunoglobulin replacement is required until normalisation of endogenous antibody production.

Recommendation

Immunoglobulin replacement therapy may be required in a proportion of infants with prolonged physiological delay of native immunoglobulin production. Where required, the planned duration of therapy should be defined prior to initiation of active treatment (grade C recommendation, level III evidence).

Secondary antibody deficiency

Secondary antibody defects are found in a wide range of circumstances (in association with drugs, malignant disease, chronic infections, protein-losing states, systemic inflammatory diseases, trauma and iatrogenic factors such as splenectomy).

Infections associated with low measured antibody levels appear to be relatively uncommon in secondary deficiencies, with the exceptions of hypogammaglobulinaemia linked with haematological malignant disease, occasional cases of drug-associated deficiency and rare cases of nephrotic syndrome [15]. Dosage and treatment duration are important factors in drug-associated deficiencies. The deficit may, or may not, be reversible on cessation of therapy.

The selection criteria for IVIg to treat hypogammaglobulinaemia linked with haematological malignancy includes the requirement to document failure of serum antibody response to

unconjugated pneumococcal or other polysaccharide vaccine challenge. Although this may sound onerous from a practical point of view, the intention is simply to ensure that a patient's response to polysaccharide vaccination is included as a component of the evaluation for IVIg therapy. For example, if a patient received pneumococcal polysaccharide vaccine 3 months previously and their specific antibody levels are low, it would seem reasonable to prescribe immunoglobulin. However, if the patient was vaccinated many years previously, it would be reasonable to vaccinate again and assess the functional antibody response before immunoglobulin was prescribed.

Recommendation

Immunoglobulin replacement therapy is recommended in secondary antibody deficiency if the underlying cause of hypogammaglobulinaemia cannot be reversed or reversal is contraindicated, or is associated with B-cell malignancy where severe infections with encapsulated bacteria are persistent despite prophylactic antibiotic therapy (grade C recommendation, level III evidence).

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Update for page 32, replace 'Acquired haemophilia'

HAEMATOLOGY

Coagulation factor inhibitors

Case series and case reports suggest that patients with antibodies to clotting factors who do not respond to immunosuppression might benefit from high-dose IVIg [1–5]. In acquired von Willebrand syndrome, an international registry series reported that one-third of the 63 patients treated with high-dose immunoglobulin had a good response [6]. The underlying diagnoses of the responders were lymphoproliferative disorders, solid tumours and autoimmune diseases. IVIg efficacy seems to improve when used in combination with immunosuppressive agents.

In those with life- or limb-threatening haemorrhage, who have not responded to other treatments [corticosteroids or other immunosuppressive agents such as cyclophosphamide, factor VIII inhibitor-bypassing activity (FEIBA), recombinant factor VIIa, rituximab], IVIg may be an appropriate treatment in conjunction with other immunosuppressive therapy and factor replacement.

Recommendation

IVIg treatment in these severe bleeding disorders should only be undertaken in a comprehensive care centre for haemophilia.

IVIg is only recommended for patients with acquired haemophilia with life or limb-threatening haemorrhage who have not responded to other treatments (grade C recommendation, level III evidence).

IVIg is only recommended for patients with acquired von Willebrand syndrome with life or limb-threatening haemorrhage who have not responded to other treatments, or prior to invasive procedures (grade B recommendation, level IIa evidence).

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Update for page 34

Haemolytic disease of the foetus and newborn (isoimmune haemolytic jaundice in neonates)

The severity of haemolytic disease of the foetus and newborn (HDN) varies. The aim of therapy is to avoid bilirubin encephalopathy, which causes kernicterus and has devastating effects. Kernicterus is associated with 10% mortality and 70% long-term morbidity (choreo-athetoid, cerebral palsy, hearing impairment) [53].

Two systematic reviews demonstrated that IVIg significantly reduced the need for exchange transfusion in neonates with HDN [54,55]. As exchange transfusion is associated with morbidity and mortality [56], IVIg is an option for patients with HDN and worsening hyperbilirubinaemia (as defined in NICE guideline 98) despite intensive phototherapy.

Recommendation

Use immunoglobulin (0.5 g/kg over 4 hours) as an adjunct to continuous multiple phototherapy in cases of Rhesus haemolytic disease or ABO haemolytic disease (see NICE guideline 98)(grade B recommendation, level III evidence).

Update for page 35

Immune thrombocytopenic purpura (ITP)

ITP is classified by duration into newly diagnosed, persistent (3–12 months duration) and chronic (≥12 months duration) [1]. If treatment is required for ITP, it should be tailored to the individual patient, taking into account the presence and severity of bleeding, co-morbidities predisposing to bleeding, potential interactions that may cause bleeding, ITP medications that may cause a bleeding risk, patients expectations, as well as the rapidity of desired platelet count rise and possible side-effects. Recent guidelines from the American Society of Hematology emphasise that the goal of treatment (in children, or in adults) is to achieve a platelet count that is associated with adequate haemostasis, rather than a "normal" platelet count [2]. An extensive review of the treatment options for ITP is provided by the recent International Consensus Report [3].

Children

ITP in children is usually a benign disorder that requires no active management other than careful explanation and counselling. This is because serious bleeding is rare, and about 80% of children with ITP will recover spontaneously within 6–8 weeks [4]. Children with no bleeding or mild bleeding (defined as skin manifestations, such as bruising and petechiae only) should be managed with observation alone regardless of platelet count.

Recommendation

IVIg is only recommended in children with moderate-to-severe symptomatic ITP (e.g. overt mucosal bleeding, or suspected internal bleeding), or prior to procedures likely to induce bleeding (grade A recommendation, level Ib evidence).

Adults

The ability of IVIg to increase platelet counts in ITP in adults is well supported [5–8]. When high-dose IVIg was compared with systemic corticosteroids in randomised multicentre trials, it provided a clinically relevant advantage [5,8].

In pregnancy, there is no evidence that any particular platelet threshold is 'safe' either in the ante- or peri-partum period; patients with platelet counts of 20–30 x10^9/L or higher do not routinely require treatment. Treatment may be required for symptomatic patients or patients requiring a procedure. Nearing delivery, patients may need higher platelet counts to allow procedures (e.g. epidural anaesthesia with platelet counts of at least 75 x10^9/L suggested by obstetric anaesthetists; haematologists believe a platelet count of 50 x10^9/L is adequate to allow Caesarean section).

Recommendation

Prior to surgery, IVIg is appropriate if unresponsive to steroids [platelet count will depend on surgery type: minor, >50 x10^9/L; major, >80 x10^9/L; critical (CNS/spinal), >100 x10^9/L] (grade C recommendation, level 4 evidence).

In pregnancy, IVIg is appropriate for patients unresponsive to steroids or for whom there are contraindications to steroids or significant side effects (grade B recommendation, level 2b evidence).

Acute (newly diagnosed) ITP

IVIg is appropriate in symptomatic ITP when steroids are contraindicated or a more rapid response is desirable, e.g. potentially life-threatening haemorrhage and/or bleeding into a critical area (grade B recommendation, level 2b evidence).

IVIg is appropriate in symptomatic ITP that is unresponsive to steroids and when other treatments, e.g. splenectomy or immuno-suppression, are considered inappropriate, aiming to keep patients symptom free. In such patients, the goal is to achieve platelet counts >30 x10^9/L (grade B recommendation, level 2c evidence).

Persistent ITP

For symptomatic cases unresponsive to all other treatments, IVIg is appropriate only for emergency management, e.g. potentially life-threatening haemorrhage and/or bleeding into a critical area (grade B recommendation, level 2b evidence).

There is no evidence to guide a sequence of treatments for patients who have recurrent or persistent thrombocytopenia associated with bleeding after an initial treatment course with corticosteroids or IVIg.

Use 1 g/kg (0.8–1 for children) as a single infusion, to be repeated at later date if platelet count has not responded.

Chronic ITP

Lifelong treatment with IVIg should be considered as exceptional and alternative approaches (splenectomy) and treatments (such as rituximab, thrombopoietin receptor agonists) should be considered.

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Update for page 41

NEUROLOGY

The efficacy of IVIg in the management of patients with specific autoimmune-mediated neuromuscular diseases has been established in controlled clinical trials. However, clinicians need to consider the expected benefit of IVIg compared with that of alternative therapies as well as issues of safety and cost.

IVIg is often prescribed where plasma exchange may have similar efficacy. IVIg is more readily available in most medical centres and placement of an indwelling venous catheter is not necessary, while plasma exchange is not universally available, requires specially trained personnel and may have greater side effects in certain situations, such as in Guillain-Barré syndrome (GBS) with autonomic involvement. In the past, the cost of IVIg was roughly equivalent to that of plasma exchange, but it is now significantly higher.

Assessing outcome with immunoglobulin treatment

Assessing valid, responsive and straightforward outcomes in neuromuscular disease is the target of considerable research interest. Suggested research outcomes for trials of neuromuscular disease have been published previously [1]. A current trial to refine these, emphasise and encourage patient involvement and include relevant responsive disability measures is underway (see http://www.perinoms.org). Outcomes have been suggested in this guideline update to reflect both impairment and disability as far as possible. Not all patients will respond to medication in the same way, and improvement or deterioration may be measurable in one or a number of domains. Improvements should be demonstrable in impairment measures or relevant disability measures and be quantifiable, reproducible and pre-specified.

Chronic inflammatory demyelinating polyradiculoneuropathy

The efficacy of immunoglobulin has been demonstrated in the short term in a number of studies [2] The ICE trial demonstrated the short- and the sustained long-term benefit of IVIg in patients with ongoing disease [3].

IVIg should be given to maintain the patient's strength as near normal as possible without relapses, by the empirical titration downwards of the dose at an individualised dose interval (see summary table). In CIDP, this is most frequently about 6 weeks, but for some patients it may be longer and for MMNCB may be significantly shorter. At 1 year, if the patient is stable on IVIg, reasonable attempts should be made to reduce the dose, either by increasing the dose interval or by using a reduced dose.

There is evidence to indicate that patients with CIDP treated with steroids or IVIg may remit from their condition, at a rate of about 40% in the first year [4,5]. Attempts to reduce, suspend or withdraw IVIg on a yearly basis would be appropriate for those patients demonstrating little or no fluctuation.

Randomised controlled trials of drugs to turn off CIDP or other inflammatory neuropathies are warranted. A planned study [the Rituximab vs IVIG in CIDP Efficacy (RICE) Study] will look for evidence of a 'biological' pharmaceutical substitute for IVIg. This may have substantial health economic benefits in terms of hospital and resource saving, and patient quality of life and earning-potential improvement.

Recommendation

IVIg is recommended for CIDP in cases of significant impairment inhibiting normal daily activities (grade A recommendation, level Ia evidence); the choice of corticosteroids, plasma exchange or IVIg should be individualised.

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Update for 'Dermatomyositis' page 42

Inflammatory myopathies

The idiopathic inflammatory myopathies, known collectively as myositis, can be characterized clinically by weakness and low endurance of skeletal muscle, and histopathologically by the presence of inflammatory cells in muscle tissue [1]. Differences in clinical and histopathological findings define separate subtypes, most often classified as polymyositis, dermatomyositis and sporadic inclusion body myositis [1]. Few controlled trials have been reported and treatment recommendations are based mostly on clinical experience and open-label trials [2].

An open-label study suggested efficacy in polymyositis [3], and controlled and open-label studies show that IVIg is effective in dermatomyositis [3,4]. A Cochrane Database systematic review identified one RCT using IVIg in adult-onset dermatomyositis showing a significant improvement in strength over 3 months when used in combination with conventional immunosuppressive agents [4], and a case series showing that it lead to improvement of refractory juvenile dermatomyositis as add-on therapy [5,6]. The use of IVIg in long-term treatment (>3 months) has not been studied. There is no evidence of efficacy of immunoglobulin in inclusion body myositis.

IVIg may be used where other treatment options have failed or are inappropriate, or in aggressive disease requiring hospitalisation with involvement of the respiratory and bulbar musculature. Alternative therapies include corticosteroids, other immunosuppressive agents and plasma exchange.

Recommendation

IVIg is appropriate in patients with resistant or aggressive disease (grade B recommendation, level IIb evidence).

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Update for page 65

TRANSPLANTATION

Antibody Incompatible Transplant (AIT)

One randomised, double blind, placebo-controlled clinical trial of more than 100 patients showed that IVIg was superior to placebo in reducing anti-HLA antibody levels and improving transplantation rates in highly sensitised patients [1]. More recently, 76 HLA-sensitized patients who met strict sensitization criteria received kidney transplants after desensitization using IVIg 2 g/kg (days 1 and 30) and rituximab (1 g, day 15). The study found significant benefits in reduction of anti-HLA antibodies allowing improved rates of transplantation, including the use of deceased donors, with acceptable antibody-mediated rejection and survival rates at 24 months [2].

Recommendation

Patients in whom renal, heart or lung transplant is prevented because of antibodies can receive IVIg.

Antibody-Mediated Rejection (AMR)

Antibody-mediated rejection (AMR) of solid organ transplants leads to inevitable failure of the transplanted organ if it is not reversed, and there are no reports of spontaneous recovery from AMR. Encouraging results, including those from RCTs, showed some benefit from plasma exchange followed by IVIg in patients with AMR kidney rejection and those with steroid-resistant rejection [3-6], although the number of patients randomised was not large. However, economic analyses suggest that IVIg might be financially advantageous [7].

Recently, a study compared IVIg, plasmapheresis and rituximab in 24 patients with AMR; 12 were treated with high-dose IVIg alone, and 12 with a combination of IVIg/plasmapheresis/rituximab. Three-year allograft survival was 50% in the IVIG alone and 91.7% in combination treatment group [8].

Recommendation

Patients experiencing steroid resistant rejection or where other therapies are contraindicated after renal, heart and/or lung transplant can receive IVIg.

Viral pneumonitis

Treatment of CMV-pneumonitis with high-dose IVIg [9,10], or high-titre anti-CMV polyclonal IVIg (CMV-IVIg) [11], has been reported in several small series of immunodeficient patients. The combination of high-dose IVIg and ganciclovir improved survival; whereas, either treatment alone did not [9]. Similarly, CMV-IVIg plus ganciclovir resulted in better survival than would be expected from other treatment regimens [11].

A small, single-centre report of heart and lung transplant patients reported resolution of infection without sequelae in four patients with severe disseminated varicella-zoster virus infection in whom treatment with the combination of intravenous acyclovir was employed [12].

Recommendation

Patients experiencing viral pneumonitis following heart and/or lung transplant (viruses to include HSV, VZV, CMV, RSV, but *excluding* influenza virus) can receive IVIg.

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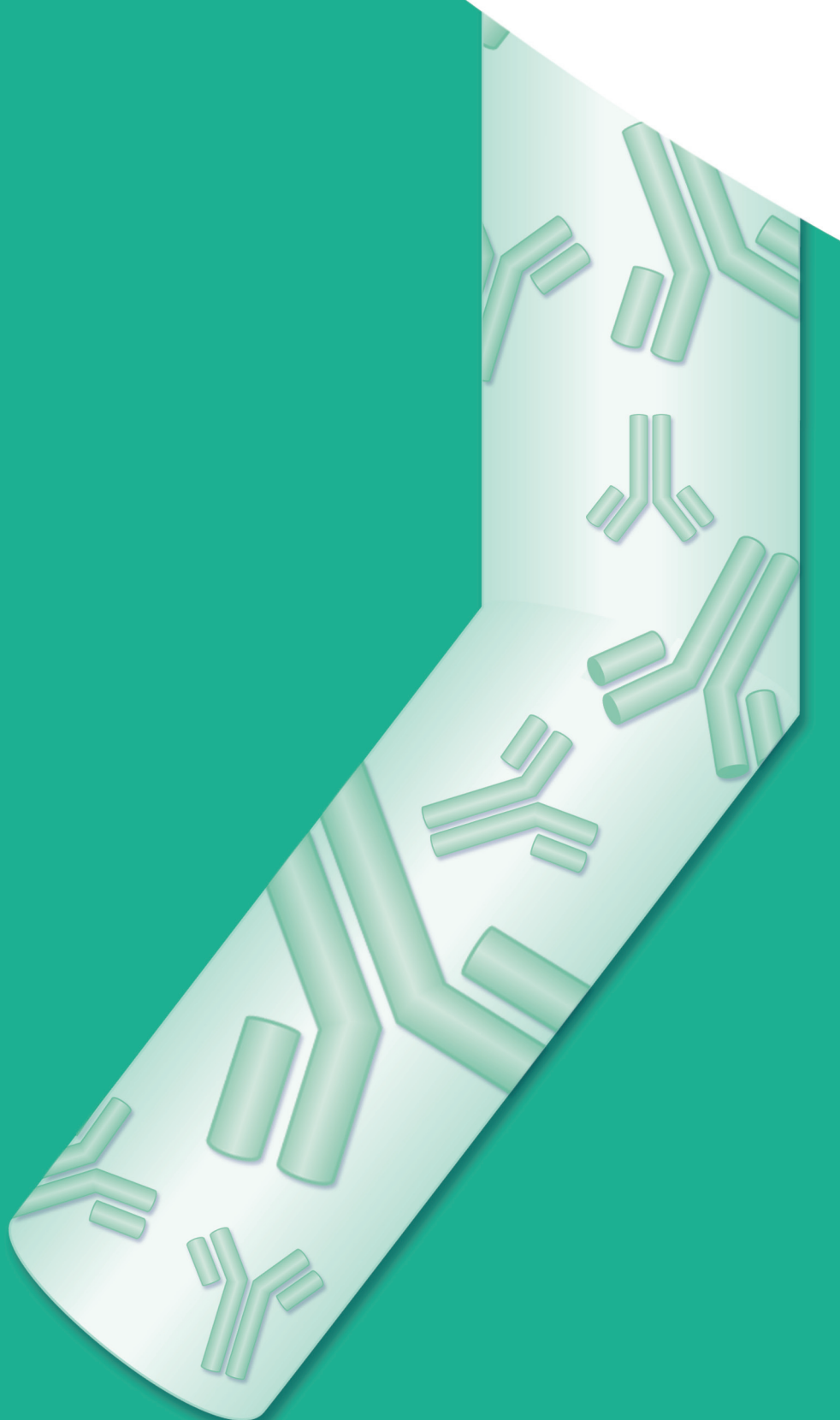

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