

Developed for  
Scotland using



SECOND EDITION UPDATE

# Clinical Guidelines for

# Immunoglobulin Use

March 2012

# Clinical guidelines for

## IMMUNOGLOBULIN USE

### 2<sup>nd</sup> EDITION UPDATE SCOTLAND

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**SUMMARY TABLE OF CONDITIONS FOR WHICH INTRAVENOUS IMMUNOGLOBULIN USE IS APPROPRIATE**

Condition	Short duration	Long duration
<b>Primary and secondary antibody deficiency states</b>		
Primary immunodeficiencies		●
Thymoma with immunodeficiency		●
HSCT in primary immunodeficiencies		●
Specific antibody deficiency		●
Secondary antibody deficiency (any cause)		●
<b>Haematology</b>		
Acquired red cell aplasia	●	
Alloimmune thrombocytopaenia (foeto-maternal/neonatal)		●
Autoimmune haemolytic anaemia	●	
Coagulation factor inhibitors (alloantibodies and autoantibodies)	●	
Haemolytic disease of the newborn	●	
Haemophagocytic syndrome	●	
Immune thrombocytopaenic purpura (acute and persistent, excluding chronic*)	●	
Post-transfusion purpura	●	
<b>Neurology</b>		
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		●
<b>Others</b>		
Autoimmune congenital heart block	●	
Autoimmune uveitis	●	
Immunobullous diseases		●
Kawasaki disease	●	
Necrotising (PVL-associated) staphylococcal sepsis	●	
Severe or recurrent <i>Clostridium difficile</i> colitis	●	
Staphylococcal or streptococcal toxic shock syndrome	●	
Toxic epidermal necrolysis, Stevens Johnson syndrome	●	
Transplantation (solid organ)	●	

\*Chronic immune thrombocytopenic purpura is a grey indication

\*\*The disease should be life-threatening to allow database entry as red

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## **EXECUTIVE SUMMARY**

The 2<sup>nd</sup> edition of the DoH Clinical Guidelines for Immunoglobulin Use were implemented in England in 2008 and introduced in amended form in Scotland in October 2009. These Guidelines were developed utilising an evidence review and extensive consultations with clinicians and other stakeholders. This update of the guidelines performed in 2011 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 the appropriate use of immunoglobulin***

The Second Edition of the Guideline did not provide explicit selection criteria for the appropriate use of immunoglobulin. This 2011 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.

### ***Efficacy outcomes to assess treatment success***

The 2011 update also provides efficacy outcomes that can 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. Such efficacy outcomes are expected to play an important role in the decision-making process for patients in whom continuation of immunoglobulin treatment is required beyond the short- and long-term durations defined in the 2011 update.

### ***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 chronic 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 local prescribing bodies to decide if treatment with immunoglobulin is appropriate on a case by case basis.

Other Grey indications have been updated and some, for which there was little or no prescribing recorded in the database, deleted. Grey indications are now listed in a table 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. Where 2008 recommendations have been substantially updated, or where conditions are now considered together, readers are referred from 2008 information to the updated recommendations in the appropriate text or tables.

## **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 IgG suitable for intravenous use (IVIg) were developed. With the ability to administer large quantities of immunoglobulin intravenously, IVIg 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 IVIg to the NHS, due to a global supply shortage and issues specific to the UK. It is important to note that IVIg is now the most widely used plasma component, and as usage continues to grow, is considered the primary driving force for plasma procurement. IVIg 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 illnesses in addition to immune deficiencies.

IVIg 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 IVIg, 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 IVIg given to pregnant women can lead to acute fetal compromise. In the 1980s and 1990s, cases of hepatitis C transmission were reported with IVIg. 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 IVIg is used to describe mean pooled normal human immunoglobulin. Depending on volume required, it can be

administered intravenously or subcutaneously. In this document, IVIg does not cover hyperimmune immunoglobulins. However, in certain cases, IVIg may be used where the appropriate hyperimmune immunoglobulin is not available.

### ***Objectives of IVIg 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 IVIg across all indications, based on available evidence and expert opinion.

### ***Demand management of IVIg***

Immunoglobulin remains the only treatment option for patients with primary immunodeficiencies and, in certain cases, is life saving. 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 IVIg 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 IVIg 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. Part of the remit was to provide suggestions for alternative treatments to IVIg and, where possible, alternatives are included. Graded recommendations are not provided for alternatives; to avoid any sense of a hierarchy of alternative treatments, these are listed in alphabetical order.

## ***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.org.uk](http://www.ivig.org.uk). A review of 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 in England 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.

### ***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 directors 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.

### ***The UK national Immunoglobulin database in Scotland***

Access to the UK National Immunoglobulin database has now been provided for those prescribing immunoglobulin in Scotland. It is anticipated that this database will be employed to record all prescriptions for pooled normal human immunoglobulin in a similar manner to the current method of use in England. 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.

## ***DEVELOPMENT METHODS***

The aims and processes for this guideline were prospectively developed and agreed by the Guideline Development Group to provide consensus guidelines for IVIg prescribing (appendix 1). Briefly, a systematic review of the literature was not deemed feasible in the short time-frame available. Rather, 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 IVIg supplemented, where necessary, by relevant Cochrane reviews

## **Search strategy**

An electronic database (PubMed) was searched using the terms '(guidelin\* OR statement OR recommendatio\*) AND (in- travenous OR IV) AND (immunoglobuli\* OR gammaglobuli\* OR gamma-globuli\*)' for papers published between January 1999 and November 2006. Bibliographies of certain journal articles were hand searched to locate additional inclusions, and websites of societies mentioned in abstracts were used to find other relevant or more recent guidelines. An electronic search of the internet (using Google) was also performed.

Relevance of articles identified was assessed using a hierarchical approach based on title, abstract and then review of the published paper. Only papers that included formal recommendations for the use of IVIg were included. Irrelevant manuscripts were discarded.

Formal guideline recommendations for IVIg were extracted, including any descriptions of the level and grade of evidence, and the system used to determine the evidence level and grade. A summary document identifying the indications assessed and comparing the recommendations contained in the identified guidelines was drafted. A series of telephone conferences were used to review areas of disagreement between guidelines and achieve consensus. Four members of the Guidelines Development Group were designated as the lead for their pre-defined groups of indications and their decision was final on areas of uncertainty.

## **Evidence levels and grades of recommendations**

A summary of the evidence presented for each indication was prepared. This document was reviewed by each member of the Guidelines Development Group independently and a telephone conference was used to review areas of disagreement between guidelines and to achieve consensus. A summary document was formulated and presented to the main Expert Working Group and to a small number of external experts for review and comment.

The members of the Expert Working Group are given in appendix 2. Evidence presented in the summary document was assessed and graded according to the in strength of supporting evidence based on the US Department of Health and Human Services Agency for Healthcare Policy and Research (AHPCR) system (documented appendix 3).

Generally, for off-label indications, there were few randomised trials and many of the recommendations made in guidelines were based on expert opinion. Where there is insufficient evidence for a recommendation, these have been listed as grey indications. If alternative treatments are appropriate, suggestions are made that reflect clinical practice, although the evidence in favour of these has not been assessed.

## **Guideline update in 2008**

To ensure widespread, effective and transparent consultation on the content of these guidelines, the DH decided to formalise the review process in 2008. Interested bodies registered as Stakeholders (see appendix 4 for list) and provided comments on the document. All comments were then reviewed by the IVIg Expert Group and appropriate changes made to the guidelines. Stakeholder comments and the Expert Group response were published on the website ([www.intravenousimmunoglobulin.org](http://www.intravenousimmunoglobulin.org)) in mid-May 2008. The second version of the IVIg guidelines was published by DH on May 30th 2008.

## **Guideline update in 2011**

The 2011 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 UK 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.

## Prioritisation of treatment recommendations

As part of IVIg 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 IVIg 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 IVIg 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.

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.

## Changes in the classification of diseases from 2008 to the 2011 update

### 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). 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.

*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 immunocytopaenias* should be considered under the relevant immune cytopaenia.

## 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 in England**

### *Selection criteria*

The UK database review of 2010 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.

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 local decisions on prescribing, which will increase the focus on assessing patient outcome.

### *Efficacy outcomes*

The database was not successful in the capture of data regarding the efficacy of immunoglobulin. Local panels involved in immunoglobulin approval 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 such 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 local decision making.

## **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 long-term IVIg.

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.

## 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 ( $\leq 3$  months) and long-term ( $\geq 3$  months) treatment needs. The definitions of duration of treatment are included in the table below.

Short term treatment	$\leq 3$ months  The treatment episode ends at 3 months  The national database will record re-initiation as a new treatment episode
Long term treatment	$\geq 3$ 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

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 =  $50 + [2.3 \times (\text{height in inches} - 60)]$

IBW for female =  $45.5 + [2.3 \times (\text{height in inches} - 60)]$

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

DDW =  $IBW + 0.4 [\text{actual body weight (kg)} - IBW]$

**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/?searchresult=1&sstring=%E0>

*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) =  $IBW + 0.5 [\text{actual body weight (kg)} - IBW]$ .

This adjusted body weight is used if a patient has a body mass index (BMI) of  $\geq 30 \text{ kg/m}^2$  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  $\geq 30 \text{ kg/m}^2$  or if actual weight >20% more than IBW, prescribers should consider using adjusted-body-weight dosing of immunoglobulin.

**Recommendations for pharmacists: individual patient doses**

To minimize the amount of IVIg used in individual treatments, rounding down IVIg dose to the nearest whole vial (adults) is recommended. Where the dose would be less than one vial in children, IVIg 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 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

### Future research

A feature of this guideline is the predominance of low-grade recommendations and low-level evidence in many indications for which IVIg is prescribed. Clearly, there is a need for further research. Potential research questions are listed in appendix 5.

## 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	●		<p>Patients with parvovirus B19 infection confirmed by PCR; AND failure of other therapies (corticosteroid and at least one other immunosuppressive therapy)</p> <p>In cases of foetal hydrops, if it is likely to be associated with parvovirus B19 infection</p>	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)		●	<p>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)</p>	<p>Increment in (neonatal) platelet count</p> <p>Successful outcome of pregnancy</p>	<p>Maternal: 1 g/kg weekly throughout pregnancy</p> <p>Neonatal: 1 g/kg; occasionally &gt;1 dose required if thrombocytopenia persists.</p>	
Autoimmune haemolytic anaemia (including Evans syndrome and post-transfusion hyperhaemolysis)	●		<p>Symptomatic or severe anaemia (Hb &lt;6 g/dL, except patients with co-morbidities) or thrombocytopenia (Evans syndrome, platelets &lt;20x10<sup>9</sup>/L ) refractory to conventional therapy with corticosteroids (or steroids contra-indicated); OR Temporising measure prior to splenectomy</p>	Correction of anaemia/ thrombocytopenia	Up to 2 g/kg as a single or divided dose.	
<p>Coagulation factor inhibitors* (alloantibodies and autoantibodies)</p> <p><b>IVIg should only be prescribed in a comprehensive care centre for haemophilia in these severe bleeding disorders</b></p>	●		<p><b>Acquired haemophilia</b> Life or limb-threatening haemorrhage AND failure to respond to other treatments;</p> <p><b>Autoimmune von Willebrand syndrome</b> Life or limb-threatening haemorrhage AND failure to respond to other treatments OR prior to invasive procedures</p>	<p>Fall in relevant inhibitor levels</p> <p>Rise in relevant factor levels</p>	Initial therapy: either 0.4 g/kg for 5 days or 1 g/kg for 2 days	
Haemolytic disease of the newborn	●		<p>As adjunct to continuous multiple phototherapy in cases of Rhesus haemolytic disease or ABO haemolytic disease (see NICE guideline 98)</p>	<p>Record bilirubin</p> <p>Record gestational age</p> <p>Avoidance of exchange transfusion</p>	0.5 g/kg over 4 hours	
Haemophagocytic syndrome	●		<p>Diagnosis by consultant haematologist based on bone marrow biopsy AND Pancytopenia</p>	<p>Correction of pancytopenia</p> <p>Survival</p>	Up to 2 g/kg as a single or divided dose	

Immune thrombocytopaenic 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 thrombocytopaenic 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 thrombocytopaenia 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 pre-specified measures (record 3 of 5) <ul style="list-style-type: none"> <li>• MRC score (7 pairs of muscles in upper and lower limb scored 0–5, maximum 70)</li> <li>• INCAT sensory sum score</li> <li>• The ONLS</li> <li>• Up and go 10-m walk (in secs)</li> <li>• Other validated disability measure</li> </ul>	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 ( <b>NOT patients with rapidly progressive IBM</b> )	<ol style="list-style-type: none"> <li>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)</li> <li>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</li> </ol>	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
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: <ul style="list-style-type: none"> <li>• Forward arm abduction time (up to 5 min)</li> <li>• Quantitative Myasthenia Gravis Score (Duke)</li> <li>• Respiratory function, e.g. forced vital capacity</li> <li>• Variation of a myasthenic muscular score</li> </ul>	2 g/kg given over 2–5 days
Multifocal motor neuropathy		●	Diagnosis by a neurologist of multifocal motor neuropathy with or	Improvement in pre-specified measures:	2 doses of IVIg (2 g/kg given over

			without persistent conduction block; AND Significant functional impairment inhibiting normal daily activities	<ul style="list-style-type: none"> <li>Power score from 10 pre-defined pairs of muscles including six most affected muscles neuro-physiologically</li> <li>The ONLS</li> <li>Up and go 10-m walk (in secs)</li> <li>Other validated disability measure</li> </ul>	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): <ul style="list-style-type: none"> <li>MRC score (7 pairs of muscles in upper and lower limb scored 0–5, maximum 70)</li> <li>INCAT sensory sum score</li> <li>The ONLS</li> <li>Up and go 10-m walk (in secs)</li> <li>Other validated disability measure</li> </ul>	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
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	
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 <i>Clostridium difficile</i> colitis	●		<b>Severe</b> 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 <b>recurrences</b> , especially if evidence of malnutrition, wasting etc., consider IVIg	Any significant clearance of <i>C. diff.</i> Duration of hospital inpatient stay	0.4 g/kg, one dose, and consider repeating	
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)	●		<b>Antibody Incompatible Transplant (AIT)</b> Patients in whom renal, heart or lung transplant is prevented because of antibodies	<b>AIT and AMR*</b> Renal Type of renal transplant HLA class DSA Rejection episodes Patient survival	<b>AIT</b> Up to 2 g/kg to be repeated as per DSA, in renal desensitisation at 0.1 g/kg for 8–12 doses	



		<p><b>Antibody Mediated Rejection (AMR)</b> Patients experiencing steroid resistant rejection or where other therapies are contraindicated after renal, heart and/or lung transplant</p> <p><b>Viral pneumonitis</b> Patients experiencing viral pneumonitis following heart and/or lung transplant (viruses to include HSV, VZV, CMV, RSV, but <i>excluding</i> influenza virus)</p>	<p>Graft survival Renal function = eGFR (MDRD) Cardiothoracic DSA Patient survival Length of ITU and hospital stay Graft function (heart = ejection fraction; lung = spirometry) <b>Viral pneumonitis*</b> Cardiothoracic Virus type Reversal of radiological infiltrates Length of hospital stay Survival</p>	<p><b>AMR</b> Up to 2 g/kg to be repeated for 2–3 doses</p> <p><b>Viral pneumonitis</b> 0.5 g/kg for 5 days</p>
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## SUMMARY OF GREY INDICATIONS

Grey indications are those diseases for which the evidence is weak, in many cases because the disease is rare. 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 should be recorded in the database.

<b>Immune-mediated disorders with limited evidence of immunoglobulin efficacy</b>	<b>Presumed immune-mediated disorders with little or no evidence of efficacy</b>
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
Chronic 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 2008 GREY CLASSIFICATION IN THE 2011 UPDATE

- Secondary antibody deficiencies (now Blue)
- Acquired vWd (now Blue)
- Post-transfusion hyperhaemolysis (now with haemolytic anaemia)
- Graft versus host disease (delete)
- SLE with secondary immunocytopaenias (included in the relevant cytopaenias)
- 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

## 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 (6,7). 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 (8), 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 (9). 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 (6,10). 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 (XLA)	Other primary antibody deficiency (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 (11).

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 (12). 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 (9); however, patients remain susceptible to sporadic breakthrough infections (13). 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 (14).

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 (15). 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 (16). 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).

## 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 lymphopaenia and quantitative or functional antibody deficiency. Infection frequencies correlate better with numerical B-cell depletion than with hypogammaglobulinaemia. 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 (7,17).

#### 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 (18). 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 (19). 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 (20). 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).



## HAEMATOLOGY

### Acquired red cell aplasia

In acquired red cell aplasia due to parvovirus B19, an uncontrolled trial and case reports show that IVIg may be useful when corticosteroid therapy fails (21-27).

In patients with parvovirus B19 infection confirmed by polymerase chain reaction (PCR) with no other cause for persistent red cell aplasia, a bone marrow consistent with persistent red cell aplasia, a chronic immunodeficient state (e.g., HIV, haematological malignancy), clinically significant or transfusion dependent anaemia and failure of corticosteroid

Therapy, IVIg is appropriate, repeated on relapse; maintenance therapy is appropriate for a second relapse.

#### Recommendation

IVIg is recommended for patients with red cell aplasia due to parvovirus B19 (grade C recommendation, level III evidence).

### Adult HIV-associated thrombocytopaenia

One randomised crossover study showed that all patients responded to IVIg therapy (28) and one non-randomised study demonstrated response to low dose IVIg (29). In thrombocytopaenic patients with significant bleeding and failure of anti-D(Rh) 0 in Rh(D)-positive patients, IVIg may be used. The use of corticosteroids is controversial; alternative therapies include anti-D(Rh) and tailored antiretroviral therapy.

Fetal hydrops may be caused by red cell aplasia. However, there may not be time to prove either red cell aplasia or a cause of parvovirus B19, although the mother may be known to have parvovirus B19. IVIg may be appropriate in these infants.

#### Recommendation

IVIg is an option for HIV-positive patients with thrombocytopaenia and significant bleeding in whom other treatments have failed or are inappropriate (grade A recommendation, level Ib evidence).

## Alloimmune thrombocytopenia

### Fetal

Alloimmune thrombocytopenia is a serious fetal disorder resulting from platelet-antigen incompatibility between the mother and fetus and is identified in mothers who have already delivered a child with neonatal alloimmune thrombocytopenia (NAIT). There is a significant risk of intrauterine death as a result of intrauterine platelet transfusion (30). A large case series on the antenatal use of IVIg (31) and a retrospective analysis of prospectively collected pregnancy data suggest that IVIg increases the live-birth rate (32). Administration of IVIg with or without a corticosteroid has become routine first-line therapy in this setting.

### Neonatal

Case series with a sound biological basis and supported by anecdotal experience demonstrate the efficacy of IVIg in newborns with severe thrombocytopenia due to NAIT (33-35). The rise in platelet count is, however, delayed and selected HPA-1a-negative, 5b-negative platelets will lead to an immediate increment in most cases. Unmatched platelets may also be immediately effective in a significant proportion of cases if HPA-1a negative, 5b-negative platelets are not available sufficiently rapidly (36). IVIg, at an initial dose of 1 g/kg (37), might provide benefit in newborns when platelets are not available or not advisable.

### Recommendation

IVIg is recommended as first-line therapy for fetal alloimmune thrombocytopenia (grade C recommendation, level III evidence).

IVIg is only recommended for NAIT if other treatments fail or are not available or appropriate (grade C recommendation, level III evidence).

## 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 (38-42). 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 (43). 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).

## *Autoimmune haemolytic anaemia*

Although there are many anecdotal reports of the benefit of IVIg in autoimmune haemolytic anaemia (44-46) , its use should be considered only when corticosteroids have failed as first-line therapy (47). In patients with clinically significant direct antiglobulin test-positive haemolysis, failure of or contraindication for conventional therapy, some indication of better response with pre-treatment haemoglobin in the 6–7 g/dL range and hepatosplenomegaly, IVIg may be used, always in combination with other therapies. Further therapeutic options include other immunosuppressive agents, rituximab and splenectomy.

### *Recommendation*

IVIg is only recommended in patients with autoimmune haemolytic anaemia when corticosteroids have failed (grade C recommendation, level III evidence).

## *Autoimmune thrombocytopaenia*

See idiopathic thrombocytopaenic purpura (ITP).

### *Evans' syndrome*

(In 2011 update - now included with AIHA- see Table p20)

Case series and case reports show that IVIg is useful in Evans' syndrome, mainly as part of combination immunosuppressive therapy in conjunction with corticosteroids and cyto-toxic drugs such as cyclophosphamide (47-56). Given the rarity of Evans' syndrome, IVIg may be used as part of combination immunosuppressive therapy. Alternative therapies include corticosteroids and other immunosuppressive agents.

### *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)(57).

Two systematic reviews demonstrated that IVIg significantly reduced the need for exchange transfusion in neonates with HDN (58,59). As exchange transfusion is associated with morbidity and mortality (60), 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).

### *Haemophagocytic lymphohistiocytosis/haemophagocytic syndrome*

In case series and case reports, IVIg has been used successfully to treat virus-associated haemophagocytic syndrome (HPS), in combination with other therapy (high-dose corticosteroids, antivirals or immunomodulatory therapies) (61-64). IVIg is recommended in patients with haemophagocytic lymphohistiocytosis (HLH)/HPS as part of supportive therapy, which includes antibiotic and antimycotic prophylaxis, with the addition of an antiviral if there is persistent viral infection. Supportive therapy is provided with both initial and continuation therapy (65).

#### **Recommendation**

IVIg is recommended as part of supportive therapy for patients with acute HLH/HPS (grade C recommendation, level III evidence).

## **Immune thrombocytopenic purpura (ITP)**

ITP is classified by duration into newly diagnosed, persistent (3–12 months duration) and chronic ( $\geq 12$  months duration) (66). 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 (67). An extensive review of the treatment options for ITP is provided by the recent International Consensus Report (68).

### **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 (69). 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 (70-73) When high-dose IVIg was compared with systemic corticosteroids in randomised multicentre trials, it provided a clinically relevant advantage (70, 73).

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  $\times 10^9/L$  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  $\times 10^9/L$  suggested by obstetric anaesthetists; haematologists believe a platelet count of 50  $\times 10^9/L$  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,  $>50 \times 10^9/L$ ; major,  $>80 \times 10^9/L$ ; critical (CNS/spinal),  $>100 \times 10^9/L$ ] (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 immunosuppression, are considered inappropriate, aiming to keep patients symptom free. In such patients, the goal is to achieve platelet counts  $>30 \times 10^9/L$  (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 thrombocytopaenia 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.

## **Post transfusion purpura**

A few case reports show that combination therapy with corticosteroids and IVIg provides benefit in post transfusion purpura (74-79), but no controlled studies have been conducted. However, given the potential life-threatening nature of the disease, its rarity and the lack of evidence of any other effective treatment, IVIg is recommended therapy in patients with decreased platelets 2–14 days post-transfusion and bleeding (almost always in Caucasian HPA-1a-negative females previously exposed to HPA-1a antigen in pregnancy or transfusion). Alternative therapies include corticosteroids and plasma exchange.

### **Recommendation**

IVIg is recommended therapy in patients with post transfusion purpura with decreased platelets 2–14 days post-transfusion and bleeding (grade C recommendation, level III evidence).

### **Grey indications**

There is insufficient evidence on which to base recommendations regarding the use of IVIg in the following conditions, which are either rare or have a poor evidence base. Please refer to the Demand Management Plan for advice on how to request IVIg treatment in these disorders.

### **Acquired red cell aplasia**

The available case reports using IVIg in acquired red cell aplasia due to causes other than parvovirus B19 do not support its use in this setting (80-85). Treatment should involve corticosteroids or other immunosuppressive agents.

### **Aplastic anaemia/pancytopenia**

The evidence for the use of IVIg in aplastic anaemia, from case reports, is conflicting (86,87). Antithymocyte globulin/antilymphocyte globulin and ciclosporin A are the treatment of choice.

### **Autoimmune neutropenia**

Several small series of patients with autoimmune neutropenia treated with IVIg have described clinical responses (44, 88-90). Anecdotal reports also suggest utility in post-bone marrow transplantation (BMT) neutropenia, which might be autoimmune in nature (49, 50, 91). It is unclear whether IVIg offers any advantage over corticosteroid therapy or other immunosuppressive agents.

### **Haemolytic uraemic syndrome**

Case reports and case series provide conflicting evidence on IVIg in haemolytic uraemic syndrome (92-96). Supportive care is the treatment of choice for the majority (usually diarrhoea-associated disease); plasma exchange is preferred to IVIg.

### **Post-exposure prophylaxis for viral infection where intramuscular injection is contraindicated, or treatment when hyperimmune immunoglobulins are unavailable**

Rarely, IVIg may be used instead of intramuscular immunoglobulin when post-exposure prophylaxis against specified viruses (e.g., measles, varicella zoster, tetanus) is recommended but where intramuscular injection of hyperimmune globulin is contraindicated (e.g., severe thrombocytopenia or bleeding disorder). In addition, it may be used to treat viral infections if the appropriate hyperimmune immunoglobulin is not available.

### ***Post-transfusion hyperhaemolysis (usually in patients with sickle cell disease)***

(In 2011 update - now blue indication included  
with AIHA- see Table p20)

Post-transfusion hyperhaemolysis, an atypical and severe form of delayed haemolytic transfusion reaction in which there is destruction of both donor and autologous red cells, has been described mainly, though not exclusively, in sickle cell disease. IVIg has been used successfully in combination with corticosteroids (97, 98).

### ***POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, skin changes)***

There are no controlled trials on the treatment of neuropathy in POEMS. There is no evidence that IVIg, plasma exchange or other immunosuppressive agents are effective when used alone (99). Possible treatments include local radiation or surgery, and melphalan with or without corticosteroids and autologous bone marrow transplantation may be considered.

### ***Systemic lupus erythematosus with secondary immunocytopenias***

For treatment recommendations for secondary immunocytopaenias, see the recommendations for the relevant cytopaenia in this section (e.g., for autoimmune haemolytic anaemia, see page 35; for autoimmune thrombocytopaenia, see page 35; for Evans' syndrome, see page 20) or other sections (for catastrophic antiphospholipid syndrome (CAPS), see page 57).



## 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 (100). 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 (101) The ICE trial demonstrated the short- and the sustained long-term benefit of IVIg in patients with ongoing disease (102).

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 (103, 104). 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.

## 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 (105). Differences in clinical and histopathological findings define separate subtypes, most often classified as polymyositis, dermatomyositis and sporadic inclusion body myositis (105). Few controlled trials have been reported and treatment recommendations are based mostly on clinical experience and open-label trials (106).

An open-label study suggested efficacy in polymyositis (107), and controlled and open-label studies show that IVIg is effective in dermatomyositis (107, 108). 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 (108), and a case series showing that it lead to improvement of refractory juvenile dermatomyositis as add-on therapy (109, 110). 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).

## Guillain-Barré syndrome

A Cochrane systematic review of RCTs found six that compared IVIg with plasma exchange in GBS (111). A meta-analysis of five trials involving 536, mostly adult, participants who were unable to walk unaided and had been ill for less than 2 weeks, showed that IVIg had an equivalent effect to plasma exchange with better tolerability. Limited evidence indicates that IVIg is also beneficial in children.

### Recommendation

IVIg is recommended for GBS with significant disability (grade A recommendation, level Ia evidence); plasma exchange is an alternative. Treatment should be started as soon as possible, preferably in the first 2 weeks of illness.

## Lambert Eaton myasthenic syndrome

(In 2011 update - now included with Myasthenia Gravis- current guidance - see Table p22)

A Cochrane systematic review identified limited evidence from RCTs showing that either 3,4-diaminopyridine or IVIg improved muscle strength scores and compound muscle action potential amplitudes in patients with Lambert Eaton myasthenic syndrome (LEMS) (112). IVIg led to initial clinical improvement in one randomised, double-blind, placebo-controlled crossover trial (113). Case reports and uncontrolled trials report similar response and lack of serious adverse effects (114-116). Initial therapies include 3,4-diaminopyridine with or without pyridostigmine, immunosuppressive agent(s) and plasma exchange.

Candidates for IVIg treatment are those with severe weakness not responsive to anticholinesterases and 3,4-diaminopyridine.

## Multifocal motor neuropathy

Several randomised, double-blind, placebo controlled, crossover clinical trials show that IVIg effectively treats multifocal motor neuropathy (MMN) (117-121). A follow-up study demonstrated that IVIg has long-term benefit for muscle strength and upper limb disability (122). MMN is unresponsive to plasma exchange and might be exacerbated by both corticosteroids and plasma exchange. IVIg is currently the safest treatment, and can be combined with other immunosuppressive agents, although the efficacy of all other immunosuppressive agents is unproven (123, 124). If initial treatment is effective, a downward titration of the dosage should be considered for repeated courses, tailored to individual needs.

### Recommendation

IVIg is recommended for MMN patients who require treatment (grade A recommendation, level Ia evidence).

## Myasthenia gravis

(In 2011 update – for updated recommendations- see Table p22)

A recent randomised, placebo-controlled, masked study conducted in patients with worsening weakness showed that 2 g/kg of IVIg resulted in a clinically meaningful improvement in QMG Score for Disease Severity at day 14 that persisted at day 28 (125). In exacerbations of myasthenia gravis, a systematic review (126) of two available trials concluded that IVIg gave comparable benefit to plasma exchange in myasthenia gravis, with better tolerability (127, 128), although a third randomised placebo-controlled study failed to demonstrate a significant effect after 6 weeks (129). In

observational studies, IVIg appeared beneficial in myasthenic crises (130), juvenile myasthenia (131) and in preparing myasthenic patients for surgery (132, 133). In one randomised trial, the effect of 1 g/kg was not significantly different from 2 g/kg (134).

The Cochrane systematic review concluded that there is insufficient evidence to determine whether IVIg is efficacious in chronic myasthenia (126).

IVIg is recommended for patients with autoimmune myasthenia gravis with myasthenic crisis, where corticosteroid therapy with other immunosuppressive agent has failed or is inappropriate, or there is weakness requiring hospital admission. Plasma exchange is an alternative.

### Recommendation

IVIg is recommended only for myasthenia gravis sufficiently severe to require hospitalisation. Plasma exchange is an alternative (grade B recommendation, level Ia evidence).

## **Paraprotein-associated demyelinating neuropathy**

### **IgG- or IgA-associated paraproteinaemic demyelinating neuropathy**

Patients with CIDP-like neuropathy should be treated as for CIDP (135).

In rigorously controlled randomised trials of CIDP, IVIg improved CIDP disability within 2–6 weeks compared with placebo. The efficacy of IVIg was similar to that of plasma exchange and prednisolone (136-140). A Cochrane systematic review found no significant difference in efficacy between IVIg and plasma exchange or IVIg and corticosteroids (141).

Patients with CIDP-like neuropathy may receive IVIg. Repeated courses should be titrated to individual needs. Alternative therapies include corticosteroids and plasma exchange.

#### **Recommendation**

IVIg is recommended for CIDP-like neuropathy (grade A recommendation, level Ia evidence); the choice of corticosteroids, plasma exchange or IVIg should be individualised.

## **IgM-associated paraproteinaemic demyelinating neuropathy**

There have been two randomised trials of IVIg in IgM paraprotein-associated demyelinating neuropathy (142). Both were crossover trials in which IVIg was compared with placebo. In the first, two of 11 patients showed significant increases in strength and one other showed improvement in sensation (143). The second trial included 22 patients. After 4 weeks, 10 of these had improved after IVIg and four after placebo and the mean improvement in disability after IVIg was greater than after placebo (144). This condition is often mild and does not routinely require treatment.

IVIg may be considered in patients with significant disability due to IgM-associated paraproteinaemic demyelinating neuropathy. Alternative treatments include corticosteroids and plasma exchange.

#### **Recommendation**

IVIg may only be considered in patients with significant disability due to IgM-associated paraproteinaemic demyelinating neuropathy (grade A recommendation, level Ib evidence).

## **Rasmussen syndrome**

There are encouraging reports of IVIg for the treatment of Rasmussen syndrome (145-147).

### **Recommendation**

IVIg may be considered for Rasmussen syndrome when all other treatment options have failed (grade B recommendation, level IIb evidence).

## **Stiff person syndrome**

(2011 update – updated recommendations -

see Table p23)

One randomised crossover trial suggests that IVIg is probably beneficial in stiff person syndrome (148). If corticosteroids, plasma exchange and symptomatic treatments do not work, IVIg may be considered.

### **Recommendation**

IVIg is recommended for stiff person syndrome where other therapies have failed (grade A recommendation, level Ib evidence).

## **Grey indications**

There is insufficient evidence on which to base recommendations regarding the use of IVIg in the following conditions, which are either rare or have a poor evidence base.

Please refer to the Demand Management Plan for advice on how to request IVIg treatment in these disorders.

## **Acute disseminated encephalomyelitis**

Anecdotal evidence suggests that IVIg might provide benefit in acute disseminated encephalomyelitis (149), particularly in patients who have failed to respond to high dose corticosteroids (150).

## **Acute idiopathic dysautonomia**

Although case reports and series suggest that IVIg might provide benefit in acute idiopathic dysautonomia (151-154), there is insufficient evidence for a recommendation. Symptomatic treatment is important, which may include plasma exchange.

## **Autoimmune diabetic proximal neuropathy**

This condition usually improves spontaneously so it is difficult to judge reports of improvement in strength and functioning with IVIg (155, 156). There is no proven treatment for this condition, but alternative treatments tried have included corticosteroids, other immunosuppressive agents and plasma exchange.

### ***Bickerstaff's brainstem encephalitis***

(In 2011 update - now red indication included with Guillain-Barré- see Table p22)

A variant of GBS, Bickerstaff's brainstem encephalitis is associated with upper motor neuron signs and disturbance of consciousness. A Cochrane review identified no randomised or non-randomised prospective controlled trials of immunotherapy (157). Corticosteroids or plasma exchange may be considered.

### ***Cerebral infarction with antiphospholipid antibodies***

There are anecdotal reports of improvement following IVIg (159), but the data are insufficient for a recommendation. Anticoagulant agents or antiplatelet therapy may be considered.

### ***CNS vasculitis***

Single-blind RCTs support using IVIg in non-neurological aspects of small-vessel vasculitis and in renal lupus, and there is an unsubstantiated recommendation to use IVIg in antiphospholipid syndrome, but IVIg cannot be advocated for routine use in isolated neurological manifestations of such conditions without reliable

Data (159). Disorders such as Hashimoto's encephalopathy and giant cell arteritis usually respond to conventional treatments (160). Appropriate therapy includes corticosteroids and other immunosuppressive agents.

### ***Intractable childhood epilepsy***

Most available evidence for a benefit for IVIg in intractable childhood epilepsy (Lennox-Gastaut syndrome, West syndrome, early myoclonic encephalopathy, Landau-Kleffner syndrome) comes from uncontrolled open series or case reports (161-164). Two randomised placebo-controlled trials in Lennox-Gastaut syndrome provide conflicting results (165, 166). There is a paucity of reliable studies demonstrating substantial benefit in these syndromes. Combination antiepileptic therapy is appropriate.

### ***Neuromyotonia***

A single case study suggests that IVIg can be beneficial in neuromyotonia (167). Recommended treatments include carbamazepine, lamotrigine, phenytoin or sodium valproate, alone or in combination; corticosteroids with other immunosuppressive agents; and plasma exchange.

### ***PANDAS (paediatric autoimmune neuropsychiatric disorders associated with streptococcal infection)***

Only one case–control study shows benefit from plasma exchange and IVIg (single dose) in PANDAS (168). There are no established treatments for this condition.

### ***Paraneoplastic disorders***

There are no randomized trials in paraneoplastic encephalomyelitis, limbic encephalitis, cerebellar degeneration, peripheral neuropathy or opsoclonus myoclonus because of the rarity of these syndromes. Case reports and small series provide conflicting results. Such anecdotal reports are impossible to interpret since paraneoplastic disorders may stabilize or improve spontaneously. IVIg has been of little benefit, except possibly in opsoclonusmyoclonus.

### ***POEMS***

There are no controlled trials on the treatment of neuropathy in POEMS. There is no evidence that IVIg, plasma exchange or other immunosuppressive agents are effective when used alone (99). Possible treatments include local radiation or surgery, and melphalan with or without corticosteroids, and autologous bone marrow transplantation may be considered.

### ***Polymyositis***

(In 2011 update - now included with Inflammatory Myopathies- see page 48)

### ***Potassium channel antibody-associated, non-neoplastic limbic encephalitis***

There are no RCTs in potassium channel antibody-associated, non-neoplastic limbic encephalitis, but case series suggest that a variety of immunomodulatory interventions, including IVIg, plasma exchange and corticosteroids, give encouraging results (169, 170).

### ***Vasculitic neuropathy***

Individual case reports provide insufficient information on which to recommend IVIg (171-173). Alternative therapy is corticosteroids and other immunosuppressive agent.

## DERMATOLOGY

### 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 (105). Differences in clinical and histopathological findings define separate subtypes, most often classified as polymyositis, dermatomyositis and sporadic inclusion body myositis (105). Few controlled trials have been reported and treatment recommendations are based mostly on clinical experience and open-label trials (106).

An open-label study suggested efficacy in polymyositis (17), and controlled and open-label studies show that IVIg is effective in dermatomyositis (107, 109). 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 (108), and a case series showing that it lead to improvement of refractory juvenile dermatomyositis as add-on therapy (109, 110). 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).

### Immunobullous diseases

Immunobullous diseases vary in clinical presentation and have different histopathological and immunological features. They are often associated with significant morbidity and some can even cause mortality, if left untreated.

In open uncontrolled trials, IVIg as a last resort for the treatment of bullous pemphigoid showed some benefit (174-177). IVIg therapy was also found to provide therapeutic benefit for both pemphigus foliaceus (178) and pemphigus vulgaris (179, 180). Other autoimmune blistering diseases reported to benefit from IVIg therapy are epidermolysis bullosa acquisita and linear IgA disease (181). All the publications related to the subject are prospective open-label studies or case reports. Controlled studies in these rare conditions are unlikely. If corticosteroids, plasma exchange and other immunosuppressive agents (mycophenolate, ciclosporin and azathioprine) fail or are inappropriate in patients with severe disease in this category of disorders, IVIg therapy may be considered.

#### Recommendation

IVIg is an effective treatment in severely affected patients when combined conventional corticosteroid treatment with adjuvant agents has failed or is inappropriate (grade C, level III evidence).



## **Toxic epidermal necrolysis and Stevens-Johnson syndrome**

Toxic epidermal necrolysis and Stevens-Johnson syndrome are potentially fatal disorders. Early administration of high-dose IVIg helps to resolve the disease and reduce fatality, as shown by sporadic case reports and prospective and retrospective multicentre studies (182). Although there are conflicting reports (183), most evidence supports the use of high-dose IVIg as an early therapeutic intervention given the risk of mortality (184). IVIg is appropriate in toxic epidermal necrolysis or Stevens-Johnson syndrome in patients with contraindications to corticosteroid or immunosuppressive therapy, or those in whom the condition is life-threatening.

### **Recommendation**

IVIg is recommended in toxic epidermal necrolysis and Stevens-Johnson syndrome when other treatments are contraindicated, or when the condition is life-threatening (grade B recommendation, level IIa evidence).

### **Grey indications**

There is insufficient evidence on which to base recommendations regarding the use of IVIg in the following conditions, which are

either rare or have a poor evidence base. Please refer to the Demand Management Plan for advice on how to request IVIg treatment in these disorders.

### **Atopic dermatitis/Eczema**

IVIg treatment has been tried in patients with atopic dermatitis who fail standard therapeutic regimens in small, open, uncontrolled trials (185-187). A single small, randomised, evaluator-blinded trial (n=10) did not support the routine use of IVIg in patients with atopic dermatitis (188). Topical corticosteroids are appropriate therapy.

Three small studies using IVIg in eczema did not show pronounced effectiveness (185, 188, 189). However, some patients were resistant not only to topical treatments, but also to systemic corticosteroids and/or azathioprine (185, 189). IVIg was associated with hypertension, haematuria, transient increase in serum creatinine and serum sickness-like reaction (189).

Ciclosporin is recommended as first choice for patients with atopic eczema refractory to conventional treatment (190), followed by azathioprine. Although frequently used in clinical practice, systemic corticosteroids have not been assessed adequately in studies. Published data do not support the use of IVIg.

### ***Pyoderma gangrenosum***

Most of the six cases reported received adjunctive high-dose IVIg and responded over several weeks where other therapies had failed (191-196). Improvement in the setting of hypogammaglobulinaemia has also been described with replacement IVIg (197, 198). Treatment with IVIg may be considered in selected cases of severe pyoderma gangrenosum that has failed to respond to all other therapies, particularly where a vital organ or structure is threatened, and in patients for whom immuno-suppressants are inappropriate.

### ***Urticaria***

Urticaria, commonly known as hives, affects about a fifth of people at some stage of life. Both acute and chronic urticaria are caused by the release of histamine from mast cells. One-third of patients with chronic urticaria (lasting more than 6 weeks) appear to have an autoimmune disease (199-201).

In a report of five patients presenting with chronic urticaria as the first sign of COVID, there was amelioration of the urticaria with IVIg (202). Ten patients with severe, autoimmune chronic urticaria, poorly responsive to conventional treatment, were treated with IVIg 0.4 g/kg per day for 5 days. Clinical benefit was noted in 9 patients, with 3 in prolonged complete remissions (3 years follow-up), 2 with temporary complete remissions, and improved symptoms in 4 patients (203). However, similar benefit was not found in a case report of 3 patients with severe chronic urticaria (204). In a single case report of an autologous serum test-negative patient treated with low-dose IVIg, the urticaria improved (205). In an open trial of delayed pressure urticaria, one-third of enrolled patients achieved remission, another third experienced some benefit and the last third did not respond (206). Current data are insufficient to recommend the routine administration of IVIg in patients with urticaria. Recommended treatments include antihistamines, H<sub>2</sub>-antagonists, tricyclic antidepressants, corticosteroid and ciclosporin.

## PAEDIATRICS

### *Alloimmune thrombocytopenia*

Case series with a sound biological basis and supported by anecdotal experience demonstrate the efficacy of IVIg in newborns with severe thrombocytopenia due to NAIT (33-35). The rise in platelet count is, however, delayed and selected HPA-1a-negative, 5b-negative platelets will lead to an immediate increment in most cases. Unmatched platelets may also be immediately effective in a significant proportion of cases if HPA-1a negative, 5b-negative platelets are not available sufficiently rapidly (36). IVIg, at an initial dose of 1 g/kg (37), might provide benefit in newborns when platelets are not available or not advisable.

#### *Recommendation*

IVIg is only recommended for NAIT if other treatments fail or are not available or appropriate (grade C recommendation, level III evidence).

### *Fetal hydrops*

Fetal hydrops may be caused by red cell aplasia. Studies in adults show that IVIg may be useful in acquired red cell aplasia due to parvovirus B19 (21-27). However, there may not be time to prove either red cell aplasia or a cause of parvovirus B19, although the mother may be known to have parvovirus B19. Given the need for urgent treatment in fetal hydrops, IVIg may be used in patients with fetal hydrops that may be related to parvovirus B19 infection.

#### *Recommendation*

IVIg is recommended for patients with fetal hydrops that may be related to parvovirus B19 infection (grade D recommendation, level IV evidence)

## *Haemolytic disease of the fetus and newborn (isoimmune haemolytic jaundice in neonates)*

The severity of 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) (57).

Two systematic reviews demonstrated that IVIg significantly reduced the need for exchange transfusion in neonates with HDN (58, 59). As exchange transfusion is associated with morbidity and mortality (60), IVIg is an option for patients with HDN and worsening hyperbilirubinaemia (defined in appropriate guidelines) despite intensive phototherapy.

### *Recommendation*

IVIg may be used in selected cases of HDN with worsening hyperbilirubinaemia (grade B recommendation, level III evidence).

## *Idiopathic thrombocytopenic purpura (<16 years)*

(In 2011 update – See ITP- p37)

ITP in children is uncommon and 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 (69). Initially, children should receive no treatment, but be observed only; if treatment is required, this should be anti-D(Rh), high-dose oral or parenteral corticosteroids, or rituximab. IVIg should only be given for emergency treatment of serious bleeding or in children undergoing procedures likely to induce blood loss.

### *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).

## *Kawasaki disease*

Kawasaki disease is a systemic vasculitis of unknown cause, occurring primarily in young children; children of Japanese and Korean origin are at highest risk.

There is convincing evidence for the use of IVIg in Kawasaki disease from meta-analyses and prospective, multicentre trials. A meta-analysis of RCTs supported the use of a single 2-g/kg dose of IVIg; this regimen resulted in a significant decrease in new coronary artery abnormalities 30 days after diagnosis (207). There were no distinctions among different IVIg products. Another meta-analysis (n>3400 patients) demonstrated that a single high dose of IVIg was superior to other IVIg regimens in preventing coronary aneurysms (158).

Patients should receive a single 2-g/kg dose as soon as the diagnosis is established (5–10 days after start of fever), in conjunction with high-dose aspirin. Some patients require a second dose if there is no response to the first dose or a relapse within 48 hours. If a second dose fails to elicit a response, high-dose pulsed corticosteroids are the next line of treatment.

### *Recommendation*

IVIg in conjunction with aspirin is the treatment of choice for Kawasaki disease (grade A recommendation, level Ia evidence).

## *Toxin-related infection in paediatric intensive care*

Although toxin-related infections are relatively uncommon in children, they are associated with mortality. There is little data specific to children (208), but experimental studies show that it can neutralise superantigen toxins and opsonise bacteria not otherwise adequately cleared by antibiotics or surgery alone (209-211). Studies in adults suggest that IVIg may be useful in patients with toxin-related infection when other treatment options have been explored (212-217). IVIg may be considered for children with severe toxin-related infection and failure to improve despite best standard care. Activated protein C is not an appropriate alternative in children.

### *Recommendation*

IVIg is recommended in children with severe toxin-related infections that fail to improve despite best standard care (grade C recommendation, level III evidence).

## Paediatric rheumatology

### Kawasaki disease

Kawasaki disease is a systemic vasculitis of unknown cause, occurring primarily in young children; children of Japanese and Korean origin are at highest risk.

There is convincing evidence for the use of IVIg in Kawasaki disease from meta-analyses and prospective, multicentre trials. A meta-analysis of RCTs supported the use of a single 2-g/kg dose of IVIg; this regimen resulted in a significant decrease in new coronary artery abnormalities 30 days after diagnosis (207). There were no distinctions among different IVIg products. Another meta-analysis (n>3400 patients) demonstrated that a single high dose of IVIg was superior to other IVIg regimens in preventing coronary aneurysms (158).

Patients should receive a single 2-g/kg dose as soon as the diagnosis is established (5–10 days after start of fever), in conjunction with high-dose aspirin. Some patients require a second dose if there is no response to the first dose or a relapse within 48 hours. If a second dose fails to elicit a response, high-dose pulsed corticosteroids are the next line of treatment.

#### Recommendation

IVIg in conjunction with aspirin is the treatment of choice for Kawasaki disease (grade A recommendation, level Ia evidence).

### Juvenile dermatomyositis

A number of case studies that provide some evidence for the effectiveness of IVIg in paediatric practice (107,218-222). In all cases, patients reported improved muscle strength and skin changes if IVIg was used early in the course. Alternative therapies include corticosteroids, other immunosuppressive agents and plasma exchange.

#### Recommendation

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

### **Grey indications**

There is insufficient evidence on which to base recommendations regarding the use of IVIg in the following conditions, which are either rare or have a poor evidence base. Please refer to the Demand Management Plan for advice on how to request IVIg treatment in these disorders.

### **Intractable childhood epilepsy**

Most available evidence for a benefit for IVIg in intractable childhood epilepsy (Lennox-Gastaut syndrome, West syndrome, early myoclonic encephalopathy, Landau-Kleffner syndrome) comes from uncontrolled open series or case reports (161-164). Two randomised placebo-controlled trials in Lennox-Gastaut syndrome provide conflicting results (165-166). There is a paucity of reliable studies demonstrating substantial benefit in these syndromes. Combination antiepileptic therapy is appropriate.

### **Juvenile systemic lupus erythematosus**

There are no randomised studies to support the use of IVIg to treat juvenile systemic lupus erythematosus (SLE). Conventional therapy includes anti-malarials, corticosteroids and immunosuppressive agents. Rituximab and mycophenolate mofetil may have a role in treatment when conventional therapies have failed. In cases of SLE-associated life-threatening sepsis, SLE-associated severe cytopenias, SLE-associated immune deficiency and SLE-associated CAPS, IVIg may be used according to the recommendations for these conditions.

### **Other systemic vasculitides**

In one open-label trial, IVIg induced remission in 15 of 16 systemic vasculitis patients, which was sustained in eight but only transient in seven (224). In a randomised, placebo-controlled trial investigating the efficacy of a single course of IVIg (total dose 2 g/kg) in previously treated patients with ANCA-associated systemic vasculitis

with persistent disease activity in whom there was an intention to escalate therapy, 17 patients received IVIg and 17 received placebo. A single course of IVIg reduced disease activity, but this effect was not maintained beyond 3 months (225). The role of IVIg in systemic sclerosis-scleroderma (226) remains unclear. Immunosuppression is the preferred treatment.

### **PANDAS**

Only one case-control study shows benefit from plasma exchange and IVIg (single dose) in PANDAS (168). There are no established treatments for this condition.

### **Systemic juvenile idiopathic arthritis**

The role of IVIg in systemic juvenile idiopathic arthritis (sJIA) is controversial (227). In an open-label study of 27 patients with sJIA, IVIg was associated with a significant reduction in systemic symptoms and a steroid-sparing effect. IVIg may have a role in management, but immunosuppression is the preferred treatment (228).

## RHEUMATOLOGY

### Adult rheumatology

#### **Dermatomyositis**

(In 2011 update - now included as Inflammatory myopathies- for updated guidance see p42)

Controlled and open-label studies show that IVIg is effective in dermatomyositis (107, 108, 229, 230). A Cochrane systematic review (110) identified one RCT using IVIg in adult-onset disease showing a significant improvement in strength over 3 months (230) and a case series showing that it leads to improvement of refractory juvenile dermatomyositis as add-on therapy (109). The use of IVIg in long-term treatment (>3 months) has not been studied.

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 dermatomyositis or aggressive disease (grade B recommendation, level IIa evidence).

### Paediatric rheumatology

#### **Kawasaki disease**

Kawasaki disease is a systemic vasculitis of unknown cause, occurring primarily in young children; children of Japanese and Korean origin are at highest risk.

There is convincing evidence for the use of IVIg in Kawasaki disease from meta-analyses and prospective, multicentre trials. A meta-analysis of RCTs supported the use of a single

2-g/kg dose of IVIg; this regimen resulted in a significant decrease in new coronary artery abnormalities 30 days after diagnosis (207). There were no distinctions among different IVIg products. Another meta-analysis (n>3400 patients) demonstrated that a single high dose of IVIg was superior to other IVIg regimens in preventing coronary aneurysms (158).

Patients should receive a single 2-g/kg dose as soon as the diagnosis is established (5–10 days after start of fever), in conjunction with high-dose aspirin. Some patients require a second dose if there is no response to the first dose or a relapse within 48 hours. If a second dose fails to elicit a response, high dose pulsed corticosteroids are the next line of treatment.

#### **Recommendation**

IVIg in conjunction with aspirin is the treatment of choice for Kawasaki disease (grade A recommendation, level Ia evidence).



## **Juvenile dermatomyositis**

A number of case studies that provide some evidence for the effectiveness of IVIg in paediatric practice (109, 218-222). In all cases, patients reported improved muscle strength and skin changes if IVIg was used early in the course. Alternative therapies include corticosteroids, other immunosuppressive agents and plasma exchange.

### **Recommendation**

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

### **Grey indications**

There is insufficient evidence on which to base recommendations regarding the use of IVIg in the following conditions, which are either rare or have a poor evidence base. Please refer to the Demand Management Plan for advice on how to request IVIg treatment in these disorders.

## **Catastrophic antiphospholipid syndrome**

CAPS is an often fatal disorder characterised by multiple rapidly progressive arterial and venous thrombotic events. Immunosuppression, especially with cyclophosphamide, increases the risk of a fatal outcome. A large registry-based study suggests plasma exchange or IVIg together with intensive anticoagulation and supportive therapy may be beneficial (231).

## **Juvenile systemic lupus erythematosus**

There are no randomised studies to support the use of IVIg to treat juvenile SLE.

Conventional therapy includes anti-malarials, corticosteroids and immunosuppressive agents. Rituximab and mycophenolate mofetil may have a role in treatment when conventional therapies have failed. In cases of SLE-associated life-threatening sepsis, SLE-associated severe cytopenias, SLE-associated immune deficiency and SLE-associated CAPS, IVIg may be used according to the recommendations for these conditions.

## **Polymyositis**

(In 2011 update - now included in Inflammatory Myopathies- see p42)

## **Systemic juvenile idiopathic arthritis**

The role of IVIg in sJIA is controversial (227). In an open-label study of 27 patients with sJIA, IVIg was associated with a significant reduction in systemic symptoms and a steroid-sparing effect. IVIg may have a role in management, but immunosuppression is the preferred treatment (228).

### ***Systemic lupus erythematosus***

In a small (n=59) retrospective study, IVIg resulted in a transient improvement in 65% of patients with SLE (232). Various case reports have shown that high-dose IVIg is associated with disease resolution in patients with SLE affecting specific organs including the kidneys (233, 234), myocardium (235), nerves (236), bone marrow (237) and multiple organs (238). However, the potential thromboembolic effects of IVIg and reports of azotemia suggest caution in using IVIg in this setting. Immunosuppression is the preferred treatment.

### ***Systemic lupus erythematosus with secondary immunocytopaenias***

For treatment recommendations for auto-immune cytopaenias associated with SLE, see the relevant entry (e.g., for autoimmune haemolytic anaemia, see page 35; for thrombocytopaenia, see page 35; for Evans' syndrome, see table p20).

### ***Systemic vasculitides and ANCA disorders***

In one open-label trial, IVIg induced remission in 15 of 16 systemic vasculitis patients, which was sustained in eight but only transient in seven (224). In a randomised, placebo-controlled trial investigating the efficacy of a single course of IVIg (total dose 2 g/kg) in previously treated patients with ANCA-associated systemic vasculitis with persistent disease activity in whom there was an intention to escalate therapy, 17 patients received IVIg and 17 received placebo. A single course of IVIg reduced disease activity, but this effect was not maintained beyond 3 months (225). The role of IVIg in systemic sclerosis-scleroderma (226) remains unclear. Immunosuppression is the preferred treatment.

## INFECTIOUS DISEASES

### *Severe invasive group A streptococcal disease*

Numerous case reports, one retrospective case control study and one RCT have suggested that IVIg confers benefit in severe invasive group A streptococcal disease (212, 213). Experimental studies support its use due to its ability to neutralise superantigen toxins and opsonise bacteria not otherwise adequately cleared by antibiotics or surgery alone (210-211). Although the results of the RCT did not reach significance due to shortfalls in recruitment, mortality was lower in the IVIg than placebo group (1/10 vs 4/11) and measures of organ failure improved in the IVIg group (213). IVIg may be added to adequate toxin-neutralising antimicrobials, source control and sepsis management when these approaches have failed to elicit a response.

#### *Recommendation*

IVIg is only recommended for severe invasive group A streptococcal disease if other approaches have failed (grade C recommendation, level III evidence).

### *Staphylococcal toxic shock syndrome*

Superantigen toxins produced by certain strains of *Staphylococcus aureus* pose a particular hazard to non-immune younger patients. Expert opinion supports the use of IVIg in staphylococcal toxic shock syndrome (TSS), provided all other therapies have been explored (214). The use of IVIg was highlighted in children with TSS subsequent to a small burn in a recent practice guideline (208). IVIg may be used for TSS resulting from an infection refractory to several hours of aggressive therapy, in the presence of an undrainable focus, or where there is persistent oliguria with pulmonary oedema. It should be used in addition to adequate toxin-neutralising antimicrobials, source control and sepsis management.

#### *Recommendation*

IVIg is recommended for staphylococcal TSS when other therapies have failed (grade C recommendation, level III evidence).

### ***Necrotising (PVL-associated) staphylococcal sepsis***

Panton Valentine leukocidin (PVL) is associated with severe necrotising staphylococcal lung infection, with attendant mortality of 75%. Case reports suggest that IVIg provides benefit in severe cases of necrotising PVL-associated staphylococcal pneumonia (215-217). IVIg may be considered for necrotising infections due to PVL-positive *S. aureus*, in addition to intensive care support, high-dose antibiotic therapy and source control, when other therapeutic options have failed to elicit a response.

#### ***Recommendation***

IVIg is recommended for necrotising PVL-associated staphylococcal sepsis when all other treatments have failed (grade C recommendation, level III evidence).

### ***Severe or recurrent *Clostridium difficile* colitis***

Limited clinical studies support the use of IVIg for patients with fulminant *C. difficile* colitis who are too ill to undergo surgery, as an adjuvant to standard antimicrobial agents (239, 240). In addition, a small case series has shown that IVIg may be useful in multiple recurrent *C. difficile*-associated diarrhoea (241). IVIg may be considered for severe or multiple recurrent *C. difficile* when other treatment options have failed, and should be used in conjunction with appropriate antibiotic therapy.

#### ***Recommendation***

IVIg is only recommended for severe or multiple recurrent *C. difficile* colitis when all other treatments have failed or are inappropriate (grade C recommendation, level III evidence).

### ***Grey indications***

There is insufficient evidence on which to base recommendations regarding the use of IVIg in the following condition, which is either rare or has a poor evidence base. Please refer to the Demand Management Plan for advice on how to request IVIg treatment in these disorders.

### ***Post-exposure prophylaxis for viral infection where intramuscular injection is contraindicated, or treatment when hyperimmune immunoglobulins are unavailable***

Rarely, IVIg may be used instead of intramuscular immunoglobulin when post-exposure prophylaxis against specified viruses (e.g., measles, varicella zoster, tetanus) is recommended, but where intramuscular injection of hyperimmune globulin is contraindicated (e.g., severe thrombocytopenia or bleeding disorder). In addition, it may be used to treat viral infections where the appropriate hyperimmune immunoglobulin is not available.

## 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 (242). 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 (243).

#### 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 (244-247), although the number of patients randomised was not large. However, economic analyses suggest that IVIg might be financially advantageous (248).

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

(249).

#### 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 (250, 251), or high-titre anti-CMV polyclonal IVIg (CMV-IVIg) (252), 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 (250). Similarly, CMV-IVIg plus ganciclovir resulted in better survival than would be expected from other treatment regimens (252).

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 (253).

#### 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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## **DISCLAIMER**

Although the advice and information contained in these guidelines is believed to be true and accurate at the time of going to press, neither the authors nor the publishers can accept any legal responsibility for any errors or omissions that may have been made.

## **EQUALITY IMPACT ASSESSMENT**

An initial equality impact screening considered the possible impact of these new immunoglobulin guidelines on people according to their age, disability, race, religion and beliefs, gender and sexual orientation. The screening revealed there was no need for an Equality Impact Assessment (EIA) for these immunoglobulin guidelines. It was therefore decided that no EIA would be made in relation to the strategy now recommended.

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## APPENDIX 1

### Use of intravenous immunoglobulin in human disease

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#### IVIg Expert Working Group (1<sup>st</sup> & 2008 edition)

#### Guideline Development Group Objectives

#### Background

Over the past 20 years, administration of IVIg has become an important therapy in clinical medicine. Although IVIg was originally developed as an antibody replacement therapy, a number of other clinical benefits of IVIg treatment have been demonstrated. Some of these new indications are based on strong clinical evidence, but a number of proposed uses are based on relatively little data or anecdotal reports. Because the supply of currently available IVIg preparations is limited, and demand is expected to exceed supply in the near future, there is a pressing need to develop cross-specialty guidelines to ensure appropriate, evidence based usage of IVIg.

#### Aims

- The remit for this Guideline subgroup of the Expert Working Group was prospectively defined at a meeting at the Department of Health on October 9th, 2006.

- The overall objective of the guideline is to provide recommendations for the rational prescribing of IVIg. This will not include an assessment of cost-effectiveness, but will be based on clinical need.
- The guidelines will identify, where possible, alternative treatments to IVIg and describe their relative efficacy (if appropriate).
- The guidelines will be cross-specialty and will provide a clear description of the patients to whom the guideline is meant to apply.

#### Guideline development

This guideline will be derived from a consensus of expert opinion and will not be based on an independent assessment of the evidence base. Rather, this guideline will be based on an independent assessment of current, up-to-date guidelines on IVIg use.

There will be multidisciplinary participation in the guideline development.

The Guideline Development Group includes experts from the four principal medical specialties that commonly prescribe

**IVIg (immunology, neurology, haematology and haemato-oncology). The Guideline Development Group members are:**

- Dr. Drew Provan (Haematology, Chair)
- Dr Phil Wood (Immunology)
- Dr J.B. Winer (Neurology)
- Dr Tim Nokes (Haematology)
- Dr Samir Agrawal (Haemato-oncology)

**The guideline development will be based on:**

- Systematic review of the literature to identify evidence-based IVIg guidelines
- Documentation and summary of areas of agreement / disagreement between guidelines
- Drafting of summary recommendations for IVIg usage
- Drafting of summary recommendations for alternatives to IVIg usage

It is acknowledged that this approach to guideline development is not as rigorous as undertaking an independent, systematic assessment of the clinical evidence base.

However, given that high-quality guidelines, such as those of the Association of British Neurologists, are available that reflects the clinical evidence base, and given the urgency of the need for cross-specialty guidelines for IVIg, this approach of systematic guideline review has been suggested by the Department of Health as the best approach.

**Process**

Guidelines will be identified by a systematic review.

Irrelevant manuscripts will be discarded and the guideline recommendations extracted. A summary document will be drafted. A telephone conference will be used to achieve consensus and review areas of disagreement between guidelines. Action to be taken to resolve disagreement / discrepancy will be decided and following further communication / telephone conference a consensus statement from the Guidelines Development Group will be produced for presentation to the main Expert Working Group.

## APPENDIX 2

### IVIg Expert Working Group (1<sup>st</sup> & 2008 edition)

Catherine Howell*	Transfusion Liaison Nurse Manager	National Blood Service
Dr Alison Jones	Immunologist	Great Ormond Street Hospital NHS Trust
Dr Michael Lunn	Neurologist	University College London Hospitals NHS Trust
Dr Mary Reilly	Neurologist	University College London Hospitals NHS Trust
Dr Helen Chapel	Immunologist – PID	Oxford Radcliffe Hospitals NHS Trust
Dr Samir Agrawal	Haemato-oncologist	Barts and the London NHS Trust
Dr Tim Nokes	Haematologist	Plymouth Hospitals NHS Trust
Dr John Winer	Neurologist	University Hospital Birmingham NHS Foundation Trust
Dr Philip Wood	Immunologist	Leeds Teaching Hospitals NHS Trust
Dr Drew Provan	Haematologist	Barts and the London NHS Trust
Evelyn Frank	Pharmacist	University College London Hospitals NHS Trust
Prof Richard Hughes	Neurologist	Kings College Hospitals NHS Trust
Dr Denise O’Shaughnessy	Haematologist	Department of Health Blood Policy Unit
Prof Carrock Sewell	Immunologist	North Lincolnshire and Goole NHS Trust
Dr Khaled El-Ghariani	Plasmapheresis	National Blood Service
Peter Sharrott*	Pharmacist	PMSG
Kevan Wind*	Pharmacist	PMSG

\*Only in year 1.

## APPENDIX 3

### Classification of evidence levels

- 
- Ia** Evidence obtained from meta-analysis of randomised controlled trials.
- 
- Ib** Evidence obtained from at least one randomised controlled trial.
- 
- IIa** Evidence obtained from at least one well-designed controlled study without randomisation. **IIb**  
Evidence obtained from at least one other type of well-designed quasi- experimental study. **III**
- 
- Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies and case studies.
- 
- IV** Evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities.
- 

### Classification of grades of recommendations

- 
- A.** Requires at least one randomised controlled trial as part of a body of literature of overall good quality and consistency addressing specific recommendation. (Evidence levels Ia, Ib).
- 
- B.** Requires the availability of well conducted clinical studies but no randomised clinical trials on the topic of recommendation. (Evidence levels IIa, IIb).
- 
- C.** Requires evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities. Indicates an absence of directly applicable clinical studies of good quality. (Evidence levels III, IV).
-

## APPENDIX 4

### *Stakeholders in Guideline review process (1<sup>st</sup> & 2008 edition)*

1. **Charles Hay**, UK Haemophilia Centre Doctors' Organisation
2. **Christopher Hughan**, Primary Immunodeficiency Association
3. **Christopher Watson**, British Transplantation Society
4. **Debra Anderson**, GBS Support Group
5. **Edward Freestone**, Commissioner
6. **Gavin Cleary**, British Society for Paediatric and Adolescent Rheumatology
7. **Greg Williams**, British Burn Association
8. **Hazel Bell**, British Association of Dermatologists
9. **Helen Booth**, Royal College of Paediatrics and Child Health
10. **John Grainger**, ITP Support Association
11. **Karen Reeves**, Association of British Neurologists
12. **Katy Lewis**, British Society of Rheumatology
13. **Marina Morgan**, Association of Clinical Pathologists
14. **Marina Morgan**, Association of Medical Microbiologists
15. **Matthew Thalanany**, Commissioner
16. **Patrick Carrington**, Royal College of Pathology
17. **Patrick Carrington**, British Society for Haematology
18. **Paul East**, Baxter
19. **Paula Blackmore**, Grifols
20. **Peter Macnaughton**, Intensive Care Society
21. **Philip Wood**, UK Primary Immunodeficiency Network
22. **Richard Smith**, Royal College of Ophthalmologists
23. **Robert Fox**, Royal College of Obstetricians and Gynaecologists
24. **Ruth Gottstein**, British Association of Perinatal Medicine
25. **shiranee sriskandan**, British Infection Society
26. **simon Land**, Royal College of Physicians
27. **Sue Davidson**, Kawasaki Syndrome Support Group
28. **Suresh Chandran**, Commissioner
29. **Tracey Guise**, British Society for Antimicrobial Chemotherapy



## APPENDIX 5

### *Suggested research areas (2008 edition)*

Many indications that use immunoglobulin have very little evidence for use and therapy is often prescribed based on anecdotal evidence. This list of suggested research projects has been provided during the review process. However, it should be noted that this list is not exhaustive.

Use of immunoglobulin as a last resort or in exceptional circumstances should be developed into case series where possible. Such sequential collections of rare cases would be valuable. All such cases will be included in the database.

#### **Immunology**

1. Optimal dosing for primary immunodeficiency disorders and rational management of specific antibody deficiency. Need to agree outcome criteria to design a good study.

#### **Haematology**

2. Dosage and length of use study for **autoimmune haemolytic anaemia**.
3. Comparative head to head study with Rituximab in **autoimmune haemolytic anaemia**.
4. International Neonatal Immunotherapy Study (INIS): an ongoing, prospective, randomised, placebo-controlled trial in a target population of 5000 neonates, which is designed to provide definitive evidence on the role of IVIg in neonatal sepsis

#### **Neurology**

5. Effectiveness of additional doses of IVIg for **Guillain-Barré syndrome**, with stratification to show long-term cost-effectiveness in terms of reduced disability.
6. Efficacy of IVIg for mild (ambulant) **Guillain-Barré syndrome**.
7. Efficacy of combination therapy of IVIg with immunosuppressants for **Chronic Inflammatory Demyelinating Polyradiculoneuropathy**, with stratification to try to identify the 20% who benefit from IVIg and to show cost-effectiveness in terms of reduced disability.
8. Efficacy of immunosuppressants to treat and reduce the need for IVIg for multifocal Motor Neuropathy.
9. Comparative head to head study with Rituximab in MMN, with stratification to try to identify the 60% who benefit from IVIg and to show cost-effectiveness in terms of reduced disability.
10. Effectiveness of subcutaneous immunoglobulin as a more convenient and less expensive replacement for IVIg in patients with **Multifocal Motor Neuropathy** and **Chronic Inflammatory Demyelinating Polyradiculoneuropathy** who are dependent on IVIg.

11. Efficacy data collection in the new **rare autoantibody mediated diseases** e.g. stiff man syndrome, limbic encephalitis, etc; study to determine predictive factors for response to IVIg
12. Efficacy of IVIg for **Miller fisher syndrome**.
13. Efficacy of IVIg for **autoimmune diabetic proximal neuropathy**.
14. Efficacy of IVIg for **Potassium channel antibody-associated, non-neoplastic limbic encephalitis**.
15. Efficacy of IVIg for **rasmussen syndrome**.

#### **Dermatology**

16. Use of IVIg as a steroid sparing agent in pemphigoid and epidermolysis bullosa acquisita.
17. Study to determine predictive factors for response to IVIg in pemphigoid.
18. Head to head study with Rituximab in bullous skin diseases.

#### **Paediatrics**

19. The International Neonatal Immunotherapy Study (INIS), a prospective, randomised, placebo controlled trial in a target population of 5000 neonates, is designed to provide definitive evidence on the role of IVIg in **neonatal sepsis** – this study is ongoing in Liverpool.

#### **Rheumatology**

20. **systemic lupus erythematosus**: Dr Maria Cuadrado recently submitted abstract to Am College of Rheumatology (will review next year).
21. **Dermatomyositis** – study to determine predictive factors for response to IVIg.

#### **Infectious diseases**

22. There is a need for adequately powered high quality RCTs to assess the impact of IVIg in severe sepsis in the general ICU.
23. Use of IVIgs in the management of severe *C. difficile* colitis.

#### **Transplantation**

24. The relative value of low dose and high dose IVIg in **antibody incompatible transplantation** should be better defined.
25. Previous studies of AiT in deceased donor transplantation have produced overall graft survival rates inferior to those in transplantation performed in the absence of DSA. Efforts should be made either to refine the current treatments available, or to introduce novel treatments that allow deceased donor transplantation to be performed with a success rate similar to that of otherwise uncomplicated transplantation. This may include randomised studies on the use of IVIg and Rituximab.

