

SECOND EDITION

**Clinical
Guidelines
for**

**Immunoglobulin
Use**

May 2008

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Clinical guidelines for IMMUNOGLOBULIN USE

SECOND EDITION

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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. In the UK, the major supplier of immunoglobulin, Bio Products Laboratories (BPL), is required to buy plasma from the USA due to the risk of vCJD in the UK. This has significantly increased production costs. Plasma was previously sourced within the UK as a by-product of voluntary blood donations. The

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; vigilance is required.

In this document, 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.

Department of Health demand management initiative for IVIg

In 2006, the Department of Health (DH) initiated a review to assess the opportunities available to secure the supply of immunoglobulin in the UK and to develop a more evidence-based approach to IVIg use. The review recommended two complementary work streams, which were agreed by the DH and initiated in late 2006. These were:

- 1. New procurement arrangements** for immunoglobulin products, with improved levels of commitment from purchasers and suppliers to ensure adequate supply.
- 2. A National Demand Management Programme** to provide guidance on the appropriate use of immunoglobulin products.

The Demand Management Programme is a three-part initiative that consists of:

- A.** National Clinical Guidelines for the appropriate use of IVIg
- B.** Demand Management Plan
- C.** National Immunoglobulin Database (Reference No. ROCR/OR/0221)

Objectives of IVIg National Clinical Guidelines

There was a clear need to provide guidance on appropriate use of IVIg and a framework for the promotion of evidence-based clinical practice to help improve consistency in patient care.

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.

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.

Demand management of IVIg

In addition, because the supply of IVIg is limited, and demand is expected to continue to exceed supply in the medium term, there is a pressing need to introduce a process to rationalize demand, as well as increasing supply, to ensure that an appropriate supply–demand balance is attained. In particular, 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 introduce a classification of immunoglobulin indications according to prioritisation. They have been created in synchrony with the Demand Management Plan. These two documents should be reviewed and understood in conjunction with each other.

National Immunoglobulin Database (Reference No. ROCR/OR/0221)

To complement demand management, support long-term planning and provide data on the use of immunoglobulin in rare disorders, an immunoglobulin treatment

database has been initiated, which will be activated in June 2008. The database will monitor immunoglobulin use, help Trusts to predict future use and improve consistency in prescribing in keeping with Good Clinical Practice (see www.intravenousimmunoglobulin.org for further information).

The Demand Management Programme was launched in November 2007. The DH issued a ‘Dear Colleague’ letter highlighting the launch of the Demand Management Plan, the National Clinical Guidelines and confirming that the National Immunoglobulin Database would be launched in June 2008.

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, given the enormous undertaking to consider the evidence for IVIg in every single treatment indication through a systematic review of the literature, this approach 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 (*intravenous* 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 strength of supporting evidence based on the US Department of Health and Human Services Agency for Healthcare Policy and Research (AHPACR) system (documented in appendix 3).

Table 1: Clinical guideline recommendations

Yes	Immunoglobulin use is recommended in all cases
No	Immunoglobulin use is not recommended
Selected	Immunoglobulin use is recommended for this indication in some cases. Selection may relate to disease severity or likelihood of response.

Table 2: Short- and long-term treatment

Short-term	Short-term treatment in serious or potentially life-threatening conditions and/or consisting of a single course of treatment, which may comprise a number of doses up to a maximum of three. A single dose is defined as the appropriate dosage for the disease indication, usually in g/kg, which may be fractionated and delivered over 1–5 days
Long-term	Medium- to long-term treatment, which is one or more courses of IVIg where further courses may be anticipated from the diagnosis before the initiation of treatment or decided upon following response to a single trial course

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 (see page 12). If alternative

treatments are appropriate, suggestions are made that reflect clinical practice, although the evidence in favour of these has not been assessed. The definitions of the recommendations within the clinical guidelines are shown in table 1 and definitions of short- and long-term treatment are given in table 2.

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) in mid-May 2008. This second version of the IVIg guidelines was published by DH on May 30th 2008.

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 signifies a disease for which treatment is considered the highest priority because of a risk to life without treatment. 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 are those for which the evidence base is weak, in many cases because the disease is rare; IVIg treatment should be considered on a case-by-case basis, prioritised against other competing demands.

Patients addressed by this guideline; patient communications, support and views

This guideline is aimed at all those who treat, or who consider treating, patients using IVIg. IVIg is life saving for certain patients, particularly those with primary immunodeficiencies, and these guidelines provide the basis for prioritisation of usage. Prioritisation of indications for IVIg is described in detail in the *Demand Management Plan for Immunoglobulin Use*. A patient communication programme was seen as vital to ensure that patients understand that their IVIg supply is not threatened and for others to appreciate the need for more evidence-based use. A patient leaflet highlighting the need to control IVIg usage, the value of considering alternative therapies to IVIg because of some of the risks associated with IVIg and the value of the Demand Management Plan in securing provision to those most in need is available. This can be accessed at: www.intravenousimmunoglobulin.org. Patient organisations have formed an important part of the consultation process for these guidelines.

Procedure for updating the guideline

These clinical guidelines will be reviewed and updated on a regular and defined basis. The central goal of the Demand Management Programme is to ensure appropriate provision of IVIg, and not to deny IVIg to patients who would experience clinical benefit. Given the uniquely broad nature of this guideline, it was expected that the first iteration would be controversial, particularly when reviewed in conjunction with the *Demand Management Plan for Immunoglobulin Use*. Therefore, in the first 2 years, the intention was to review and update this document on an annual basis, followed by biennial review from 2009.

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.

Immunoglobulin preparations and licensed indications

Immunoglobulin is a sterile preparation of concentrated antibodies (immune globulins) recovered from pooled human plasma of healthy donors. Immunoglobulin preparations currently licensed in the UK are shown in table 3.

Table 3. Summary of licensed UK immunoglobulins from summary of product characteristics (SPC) [<http://emc.medicines.org.uk>]

Product	Form	Vial sizes	Company, date of last revision of SPC text	Source of plasma
Flebogamma 5%	50 g/L solution (5%) for IV administration	0.5 g, 2.5 g, 5 g, 10 g	Grifols UK, August 2000	USA
Gammagard SD I-V	Powder for reconstitution to 5% or 10% solution for IV administration	0.5 g, 2.5 g, 5 g, 10 g	Baxter, June 1999	Europe and North America

continued ➔

➔ Summary of licensed UK immunoglobulins from summary of product characteristics (SPC) continued

Product	Form	Vial sizes	Company, date of last revision of SPC text	Source of plasma
Octagam	50 mg/mL (5%) solution for IV infusion	2.5 g, 5 g, 10 g	Octapharma, April 2004	Germany, USA, Sweden, Austria and Switzerland
Sandoglobulin powder* / Sandoglobulin NF liquid	Powder for solution for IV infusion/120 mg/mL solution for IV infusion	1 g, 3 g, 6 g, 12 g/6 g, 12 g)	CSL Behring, January 2004/ April 2008	USA and Europe
Vigam	5 g/100 mL (5%) freeze-dried powder for reconstitution (Vigam-S) or liquid (Vigam Liquid) for IV administration	2.5 g, 5 g (both forms), 10 g (Vigam Liquid)	Bio Products Laboratory, February 2003	USA
Intratect	50 g/L solution for infusion	1 g, 2.5 g, 5 g, 10 g	Biotest Pharma	USA, Germany, Austria, Belgium
Kiovig	100 mg/mL solution for infusion	1 g, 2.5 g, 5 g, 10 g, 20 g	Baxter, January 2006	Europe and North America
Subgam	140–180 mg/mL solution for subcutaneous or intramuscular injection	0.25 g, 0.75 g, 1.5 g	Bio Products Laboratory	USA
Subcuvia	160 mg/mL (16%) solution for subcutaneous or intramuscular administration	5 mL, 10 mL	Baxter, June 2003	Europe and North America
Vivaglobulin	160mg/mL solution for injection for subcutaneous injection	0.48 g, 1.6 g	CSL Behring, April 2008	USA and Europe

* To be discontinued

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.

Recommendation

Pharmacists and prescribers are recommended to “round down” the dose to the nearest whole vial in an effort to conserve drug volumes.

Although the standard immunomodulatory dose for adults is 2 g/kg (set empirically), it is administered in various regimens to address issues of complications and patient convenience, and may be reduced for some

conditions and in paediatrics. The 2-g/kg dose is frequently divided into five daily infusions of 0.4 g/kg, although some clinicians prefer to divide it into two daily doses of 1 g/kg each. In general, the 2-day infusion is not associated with more adverse reactions than the 5-day infusion. The 2-day dosage schedule may prevent rapid deterioration in patients with acute conditions and minimise disruption in those with chronic conditions. The replacement dose for patients with immunodeficiencies is different from the immunomodulatory dose and is tailored to an individual patient. Generally, these guidelines do not provide specific dosing recommendations.

Long-term users

Although the active ingredient in IVIg—purified immunoglobulin—is the same from brand to brand, there are considerable differences in the manufacturing processes used. This results in individual products that cannot be used interchangeably.

Furthermore, there are differences in buffers, stabilisers and diluents employed, which can have diverse effects in individual patients. The policy of maintaining the same brand of IVIg for long-term therapy is recommended for safety reasons.

As part of a review of disease management and treatment options, all patients receiving long-term IVIg should be reviewed annually to assess their disease activity and determine the best therapeutic option. This review should be seen as part of normal clinical practice.

Recommendation

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 the National Immunoglobulin Database.

SUMMARY TABLES

<i>Summary of recommendations</i>				
Condition	Recommend?		Recommendation/ Evidence grade	Alternatives
	Short-term	Long-term		
Immunology				
Primary immunodeficiencies	SELECTED	YES	B, IIb	None
Impaired specific antibody production	NO	SELECTED	C, III	Antibiotics (therapeutic & prophylactic), meticulous hygiene
Kawasaki disease	YES	NO	A, Ia	None
Haematology				
Acquired red cell aplasia due to parvovirus B19	SELECTED	NO	C, III	Corticosteroids, other immunosuppressive agent
Adult HIV-associated thrombocytopenia	SELECTED	NO	A, Ib	Anti-D(Rh ₀), tailored antiretroviral therapy
Alloimmune thrombocytopenia – fetal therapy (treatment to the mother)	YES	NO	C, III	Corticosteroids
Alloimmune thrombocytopenia – neonatal therapy	SELECTED	NO	C, III	HPA-1a-negative and HPA-5b-negative or specific HPA-compatible platelets
continued ➡				

➔ *Haematology continued*

Condition	Recommend?		Recommendation/ Evidence grade	Alternatives
	Short-term	Long-term		
Autoimmune (acquired) haemophilia	SELECTED	NO	C, III	Corticosteroids, FEIBA, other immunosuppressive agents, recombinant factor VIIa, rituximab
Autoimmune haemolytic anaemia	SELECTED	NO	C, III	Corticosteroids, other immunosuppressive agent, rituximab, splenectomy
Autoimmune thrombocytopenia (see ITP)	SELECTED	NO	A, Ia	
Evans' syndrome	SELECTED	NO	C, III	Corticosteroids, other immunosuppressive agent
Haemolytic disease of the fetus and newborn (isoimmune haemolytic jaundice in neonates)	SELECTED	NO	C, III	Phototherapy
Haemophagocytic lymphohistiocytosis/ haemophagocytic syndrome	SELECTED	NO	C, III	Corticosteroids + immunomodulation + antimicrobial agents
Idiopathic thrombocytopenic purpura – paediatric (<16 years)	SELECTED	NO	A, Ib	Anti-D(Rh ₀), corticosteroids, other immunosuppressive agent, rituximab
Idiopathic thrombocytopenic purpura – adult	SELECTED	NO	A, Ia	Anti-D(Rh ₀), corticosteroids, other immunosuppressive agent, rituximab, splenectomy

continued ➔

➔ *Haematology continued*

Condition	Recommend?		Recommendation/ Evidence grade	Alternatives
	Short-term	Long-term		
Post transfusion purpura	SELECTED	NO	C, III	Corticosteroids, plasma exchange
Haemato-oncology				
Low serum IgG levels following HSCT for malignancy	YES	SELECTED	B, IIb	None
Chronic lymphocytic leukaemia	NO	SELECTED	A, Ib	Prophylactic antibiotic
Haemophagocytic lymphohistiocytosis/haemophagocytic syndrome	SELECTED	NO	C, III	Corticosteroids + immunomodulation + antimicrobial agents
Multiple myeloma	NO	SELECTED	A, Ib	Antibiotics (therapeutic/prophylactic), immunisation
Neurology				
Chronic inflammatory demyelinating polyradiculoneuropathy	SELECTED	SELECTED	A, Ia	Corticosteroids, other immunosuppressive agent, plasma exchange
Dermatomyositis	SELECTED	SELECTED	B, IIa	Corticosteroids, other immunosuppressive agent, plasma exchange
Guillain-Barré syndrome	SELECTED	NO	A, Ia	Plasma exchange
Lambert Eaton myasthenic syndrome	SELECTED	SELECTED	A, Ib	3,4-DAP ± pyridostigmine, other immunosuppressive agent, plasma exchange

continued ➔

➡ *Neurology continued*

Condition	Recommend?		Recommendation/ Evidence grade	Alternatives
	Short-term	Long-term		
Multifocal motor neuropathy	SELECTED	SELECTED	A, Ia	No proven alternative
Myasthenia gravis	SELECTED	SELECTED	B, Ia	Corticosteroids, other immunosuppressive agent, plasma exchange
Paraprotein-associated demyelinating neuropathy (IgG or IgA)	SELECTED	SELECTED	A, Ia	Corticosteroids, plasma exchange
Paraprotein-associated demyelinating neuropathy (IgM)	NO	SELECTED	A, Ib	Corticosteroids, plasma exchange
Rasmussen syndrome	NO	SELECTED	B, IIb	Combination antiepileptic therapy
Stiff person syndrome	NO	SELECTED	A, Ib	Corticosteroids, plasma exchange, symptomatic therapy
Dermatology				
Dermatomyositis	SELECTED	SELECTED	B, IIa	Corticosteroids, other immunosuppressive agent, plasma exchange
Immunobullous diseases	SELECTED	SELECTED	C, III	Corticosteroids, other immunosuppressive agents, plasma exchange
Toxic epidermal necrolysis, Steven's Johnson syndrome	YES	SELECTED	B, IIa	Corticosteroids, other immunosuppressive agent

continued ➡

➔ continued

Condition	Recommend?		Recommendation/ Evidence grade	Alternatives
	Short-term	Long-term		
Paediatrics				
Alloimmune thrombocytopenia – neonatal therapy	SELECTED	NO	C, III	HPA-1a-negative and HPA-5b-negative or specific HPA-compatible platelets
Fetal hydrops	SELECTED	NO	D, IV	None
Haemolytic disease of the fetus and newborn (isoimmune haemolytic jaundice in neonates)	SELECTED	NO	C, III	Phototherapy
Idiopathic thrombocytopenic purpura (< 16 years)	SELECTED	NO	A, Ia	Anti-D(Rh ₀), corticosteroids, other immunosuppressive agent, rituximab
Toxin-related infection in paediatric intensive care	SELECTED	NO	C, III	Antibiotics
Paediatric rheumatology				
Kawasaki disease	YES	NO	A, Ia	None
Juvenile dermatomyositis	SELECTED	SELECTED	B, IIa	Corticosteroids, other immunosuppressive agent, plasma exchange
Adult rheumatology				
Dermatomyositis	SELECTED	SELECTED	B, IIa	Corticosteroids, other immunosuppressive agent, plasma exchange

continued ➔

➡ continued				
Condition	Recommend?		Recommendation/ Evidence grade	Alternatives
	Short-term	Long-term		
Infectious diseases				
Severe invasive group A streptococcal disease	SELECTED	NO	B, Ib	Activated protein C, antibiotics
Staphylococcal toxic shock syndrome	SELECTED	NO	C, III	Antibiotics
Necrotising (PVL-associated) staphylococcal sepsis	SELECTED	NO	C, III	Activated protein C, antibiotics
Severe or recurrent <i>Clostridium difficile</i> colitis	SELECTED	NO	C, III	Antibiotics, colectomy
Transplantation				
CMV-induced pneumonitis following transplantation	YES	NO	A, Ib	Ganciclovir

FEIBA=Factor VIII inhibitor-bypassing activity; ITP=idiopathic thrombocytopenia; HSCT=haematopoietic stem cell transplant; DAP=diaminopyridine.

Red signifies a disease for which treatment is considered the highest priority because of a risk to life without treatment. Blue indicates a disease for which there is a reasonable evidence base but where other treatment options are available; the use of immunoglobulin in these indications should be modified in times of shortage.

Summary of grey indications		
Condition	Evidence grade	Alternatives
Immunology		
Secondary antibody deficiencies		Prophylactic antibiotics
Haematology		
Acquired red cell aplasia NOT due to parvovirus B19	III	Corticosteroids, other immunosuppressive agent
Acquired von Willebrand disease	III	Corticosteroids, desmopressin, factor VIII/vWF, other immunosuppressive agent, plasma exchange
Aplastic anaemia/pancytopenia	III	Antithymocyte globulin/ antilymphocyte globulin, ciclosporin A
Autoimmune neutropenia	III	Corticosteroids, other immunosuppressive agent
Haemolytic uraemic syndrome	III	Supportive care, plasma exchange
Post-exposure prophylaxis for viral infection if intramuscular injection is contraindicated, or treatment when hyperimmune immunoglobulins are unavailable	IV	None
Post-transfusion hyperhaemolysis (usually in patients with sickle cell disease)	IV	Corticosteroids
Systemic lupus erythematosus with secondary immunocytopenias	III	As relevant cytopenia
Haemato-oncology		
Graft versus host disease following allogeneic BMT or HSCT	Ib	Immunosuppressive agent(s)
Infection following allogeneic BMT or HSCT	Ia	Antibiotics, ganciclovir
continued ➔		

➡ <i>Haemato-oncology</i> continued		
Condition	Evidence grade	Alternatives
POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, skin changes)	III	Autologous BMT, local radiation, melphalan ± corticosteroids, surgery
Neurology		
Acute disseminated encephalomyelitis	III	Corticosteroids, plasma exchange
Acute idiopathic dysautonomia	III	Plasma exchange, symptomatic treatment
Autoimmune diabetic proximal neuropathy	III	No proven treatment but could include corticosteroids, other immunosuppressive agent, plasma exchange
Bickerstaff's brain stem encephalitis	III	Corticosteroids, plasma exchange
Cerebral infarction with antiphospholipid antibodies	III	Anticoagulants, antiplatelet therapy
CNS vasculitis	IIb	Corticosteroids, other immunosuppressive agent
Intractable childhood epilepsy	III	Combination antiepileptic therapy
Neuromyotonia	III	Corticosteroids with other immunosuppressive agent, plasma exchange, symptomatic treatment
PANDAS (paediatric autoimmune neuropsychiatric disorders associated with streptococcal infection)	III	None established
Paraneoplastic disorders	III	Corticosteroids, other immunosuppressive agent
POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, skin changes)	III	Autologous BMT, local radiation, melphalan ± corticosteroids, surgery
continued ➡		

➡ <i>Neurology continued</i>		
Condition	Evidence grade	Alternatives
Polymyositis	III	Corticosteroids, other immunosuppressive agent, plasma exchange
Potassium channel antibody-associated, non-limbic encephalitis	III	Corticosteroids, plasma exchange
Vasculitic neuropathy	III	Corticosteroids, other immunosuppressive agent
Dermatology		
Atopic dermatitis/eczema	Ila	Topical corticosteroids, other immunosuppressive agent
Pyoderma gangrenosum	III	Immunosuppressive agent(s)
Urticaria	Ib	Antihistamines, corticosteroids, ciclosporin, H ₂ - antagonists, tricyclic antidepressants
Paediatrics		
Intractable childhood epilepsy	III	Combination antiepileptic therapy
PANDAS (paediatric autoimmune neuropsychiatric disorders associated with streptococcal infection)	III	None established
Paediatric rheumatology		
Juvenile systemic lupus erythematosus	III	Anti-malarials, corticosteroids, other immunosuppressive agent
Other systemic vasculitides	III	Immunosuppressive agent(s)
Systemic juvenile idiopathic arthritis	III	Immunosuppressive agent(s)
Adult rheumatology		
Catastrophic antiphospholipid syndrome supportive therapy	III	Anticoagulant, plasma exchange
continued ➡		

➡ <i>Adult rheumatology continued</i>		
Condition	Evidence grade	Alternatives
Polymyositis	III	Corticosteroids, other immunosuppressive agent, plasma exchange
Systemic lupus erythematosus	III	Immunosuppressive agent(s)
Systemic lupus erythematosus with secondary immunocytopenias	III	As relevant cytopenia
Systemic vasculitides and ANCA disorders	III	Immunosuppressive agent(s)
Infectious diseases		
Post-exposure prophylaxis for viral infection if intramuscular injection is contraindicated, or treatment when hyperimmune immunoglobulins are unavailable	IV	None
Transplantation		
Antibody incompatible transplantation	Ib	None
Treatment of acute antibody-mediated rejection following solid organ transplantation	Ib	Corticosteroids, plasma exchange, rituximab, cytotoxic anti-T-cell antibodies, polyclonal antithymocyte globulin

BMT=bone marrow transplant; HSCT=haematopoietic stem cell transplant; ANCA=antineutrophil cytoplasmic antibody.

Grey indications are those for which the evidence base is weak, in many cases because the disease is rare. IVIg treatment should be considered on a case by case basis, prioritised against other competing demands.

Indications for which IVIg is not recommended

The prescription of IVIg is not appropriate for the following conditions. These are described as 'Black' indications in the *Demand Management Plan for Immunoglobulin Use*.

Specialty	Indication
Immunology	Immunodeficiency secondary to paediatric HIV infection
Haemato-oncology	Autologous BMT
Neurology	Adrenoleukodystrophy Alzheimer's disease Amyotrophic lateral sclerosis Chronic fatigue syndrome Critical illness neuropathy Inclusion body myositis Multiple sclerosis
Rheumatology	Inclusion body myositis Rheumatoid arthritis
Infectious diseases	Neonatal sepsis (prevention or treatment) Sepsis in the intensive care unit not related to specific toxins or <i>Clostridium difficile</i>
Other	Asthma Autoimmune uveitis Graves' ophthalmology IVF failure Recurrent spontaneous pregnancy loss

IMMUNOLOGY

Primary immunodeficiencies

Not requiring bone marrow transplant

Primary immunodeficiencies include antibody and combined T- and B-cell defects resulting in antibody failure. Patients in whom significant failure of antibody responses are demonstrated and who suffer from recurrent/severe/persistent infections are treated with immunoglobulin replacement therapy.

Severe humoral immune deficiency requires IVIg for patient survival. Controlled studies and retrospective surveys show that IVIg reduces acute and chronic infections [1–3]. In children, retrospective analyses suggest the number and severity of infectious complications is inversely correlated with IVIg dose [3,4].

In hyper-IgM syndromes, two large series have shown that patients receiving intramuscular immunoglobulin therapy experience reduced risk of meningitis and pneumonia [5,6]. In patients with common variable immunodeficiency disorders (CVIDs), IVIg substantially reduced acute illnesses and antibiotic use compared with before IVIg treatment [7]. Other studies have shown a reduction in pneumonia [8] and progression of lung disease [9].

Small open-label and case-report studies suggest that IVIg may have benefit in hyper IgE syndrome [10,11].

In Wiskott-Aldrich syndrome, a small study suggests that IVIg may reduce the risk of infection and increase platelet counts [12].

There is no alternative therapy to immunoglobulin as the central component of management for severe antibody deficiency. IVIg is appropriate in patients with reduced levels of serum IgG with low levels of IgA and/or IgM and a clinical history of bacterial infections. Where appropriate, a demonstrated inability to produce antibody normally following test immunisation is required to justify the use of IVIg. Dosage should start at 0.4–0.6 g/kg/month with titration to maintain trough IgG in the normal range. Higher trough levels may improve pulmonary outcome [13]. Individual patients may require higher doses.

Subcutaneous immunoglobulin is therapeutically equivalent to IV therapy [14,15] and may be considered as first line. It can be given if the patient has poor veins, adverse reactions to IV products or for patient preference.

Patients with partial antibody deficiency and mild to moderate symptoms may not require regular IVIg therapy. In particular, patients with IgA or IgG subclass deficiency can often be managed without IVIg. Patients with impaired specific antibody production and severe infections may benefit from IVIg, although preventative measures, combined with the appropriate antibiotic treatment, can give satisfactory control.

Haemopoetic stem cell transplant for primary immunodeficiencies

Pre-existing infection in patients with primary immunodeficiencies reduces the chances of a successful outcome of a haemopoetic stem cell transplant (HSCT). Measures to protect against infection in this high-risk group should be implemented immediately once a diagnosis of severe combined immune deficiency (SCID) is made. This treatment should include IVIg. Treatment with IVIg continues after the transplant until reconstitution of B cells and antibody production has been achieved.

Recommendation

For patients with severe antibody deficiency, trough IgG levels should be maintained within the normal range using IVIg as prophylaxis against infections (grade B recommendation, level IIb evidence).

IVIg therapy is recommended in specific antibody deficiency in cases of failure of prophylactic antibiotic treatment and/or where recurrent or severe bacterial infections are encountered (grade C recommendation, level III evidence).

Low serum IgG levels following HSCT

Patients with non-functioning B cells following HSCT for malignancy should be treated as if they were agammaglobulinaemic [16]. IVIg may be titrated to maintain trough IgG in the normal range.

Recommendation

IVIg is recommended for patients with low serum IgG levels following HSCT (grade B recommendation, level IIb evidence).

Low serum IgG levels due to absent B cells in thymoma

Patients with absent circulating B cells in association with benign or malignant thymoma should be treated as if they were agammaglobulinaemic, as infections can be life-threatening. IVIg may be titrated to maintain trough IgG in the normal range.

Recommendation

IVIg is recommended for patients with absent circulating B cells in association with benign or malignant thymoma (grade B recommendation, level III 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 [17]. 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 [18].

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).

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.

Secondary antibody deficiencies following drug therapies

Other causes of secondary antibody deficiencies, such as irreversible hypogammaglobulinaemia following drug therapies, may be treated with IVIg if recurrent or severe infections are a clinical problem that is unresponsive to prophylactic antibiotics.

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 [19–25].

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.

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

Adult HIV-associated thrombocytopenia

One randomised crossover study showed that all patients responded to IVIg therapy [26] and one non-randomised study demonstrated response to low-dose IVIg [27]. In thrombocytopenic patients with significant bleeding and failure of anti-D(Rh₀) in Rh(D)-positive patients, IVIg may be used. The use of corticosteroids is controversial; alternative therapies include anti-D(Rh₀) and tailored antiretroviral therapy.

Recommendation

IVIg is an option for HIV-positive patients with thrombocytopenia 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 [28]. A large case series on the antenatal use of IVIg [29] and a retrospective analysis of prospectively collected pregnancy data suggest that IVIg increases the live-birth rate [30]. 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 [31–33]. 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 [34]. IVIg, at an initial

dose of 1 g/kg [35], 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).

Acquired haemophilia

Case series and case reports suggest that patients with antibodies to two clotting factors who do not respond to immunosuppression might benefit from high-dose IVIg [36–39]. 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 used in conjunction with other immunosuppressive therapy and factor replacement.

Recommendation

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

Autoimmune haemolytic anaemia

Although there are many anecdotal reports of the benefit of IVIg in autoimmune haemolytic anaemia [40–42], its use should be considered only when corticosteroids have failed as first-line therapy [43]. 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 thrombocytopenia

See idiopathic thrombocytopenic purpura (ITP).

Evans' syndrome

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 cytotoxic drugs such as cyclophosphamide [43–52]. Given the rarity of Evans' syndrome, IVIg may be used as part of combination immunosuppressive therapy. Alternative therapies include corticosteroids and other immunosuppressive agents.

Recommendation

Given the rarity of Evans' syndrome, IVIg may be used as part of combination immunosuppressive therapy in conjunction with corticosteroids and cytotoxic drugs (grade C recommendation, level III evidence).

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

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

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

Recommendation

IVIg may be used in selected cases of HDN with worsening hyperbilirubinaemia (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) [57–60]. 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 [61].

Recommendation

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

Idiopathic thrombocytopenic purpura

Paediatric (<16 years)

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 [62]. Initially, children should receive no treatment, but only be observed; if treatment is required, this should be anti-D(Rh₀), 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 ITP for emergency treatment or prior to procedures likely to induce bleeding (grade A recommendation, level Ib evidence).

Adult

The ability of IVIg to increase platelet counts in ITP in adults is well supported [63–66]. When high-dose IVIg was compared with systemic corticosteroids in randomised multicentre trials, it provided a clinically relevant advantage [63,66].

IVIg is recommended in patients with persistent or potentially life-threatening haemorrhage and a low platelet count, with a peripheral smear and a history not suggestive of any other cause of thrombocytopenia. It is also appropriate for bleeding

unresponsive to corticosteroid treatment and/or anti-D(Rh₀), or if these therapies are inappropriate. Alternative therapies include anti-D(Rh₀), azathioprine, oral corticosteroids, ciclosporin and rituximab.

In emergencies, platelet transfusion provides most rapid elevation of platelet count, but the benefit of the transfusion is short lived. IVIg, IV corticosteroids or another IV immunosuppressive agent (cyclophosphamide or vincristine) can be used where there is less urgency. In second-line therapy (post-splenectomy), danazol, immunosuppressive agent(s) and vinca alkaloids are worth considering.

There are no published comparative trials of corticosteroids and IVIg in pregnancy [62] and few data to distinguish the management of pregnant women from that of non-pregnant patients [67]. Corticosteroids are the standard treatment in pregnant women, although if therapy is likely to be prolonged, or if there is no response to corticosteroids or their use is inappropriate, IVIg may be considered.

Recommendation

IVIg is an important and useful treatment modality in adults with severe ITP and low platelet count (grade A recommendation, level Ia evidence).

Post transfusion purpura

A few case reports show that combination therapy with corticosteroids and IVIg provides benefit in post transfusion purpura [68–73], 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 [74–79]. Treatment should involve corticosteroids or other immunosuppressive agents.

Acquired von Willebrand disease

Despite the reporting of 200 cases of acquired von Willebrand disease since 1968, no retrospective or randomised prospective studies of treatment are available and no approach to treatment is reliably effective in most patients [80].

Aplastic anaemia/pancytopenia

The evidence for the use of IVIg in aplastic anaemia, from case reports, is conflicting [81,82]. 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 [40,83–85]. Anecdotal reports also suggest utility in post-bone marrow transplantation (BMT) neutropenia, which might be autoimmune in nature [45,46,86]. 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 [87–91]. 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)

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 [92,93].

Systemic lupus erythematosus with secondary immunocytopenias

For treatment recommendations for secondary immunocytopenias, see the recommendations for the relevant cytopenia in this section (e.g., for autoimmune haemolytic anaemia, see page 33; for autoimmune thrombocytopenia, see page 33; for Evans' syndrome, see page 33) or other sections (for catastrophic antiphospholipid syndrome (CAPS), see page 60).

HAEMATO-ONCOLOGY

These guidelines assume the standard use of prophylactic anti-bacterial, -viral and -fungal medications according to the chemo-immunotherapy a patient is undergoing. There is no good evidence for the efficacy of IVIg in reducing viral or fungal infections in the clinical settings discussed in this section.

Low serum IgG levels following HSCT

Patients with non-functioning B cells following HSCT for malignancy should be treated as if they were agammaglobulinaemic [18]. IVIg may be titrated to maintain trough IgG in the normal range.

Recommendation

IVIg is recommended for patients with low serum IgG levels following HSCT (grade B recommendation, level IIb evidence).

Chronic lymphocytic leukaemia

IVIg is probably beneficial in reducing the number of bacterial infections in patients with chronic lymphocytic leukaemia (CLL), with most reported cases using IVIg in those with serum IgG levels <5 g/L who had experienced significant infections [94–96].

IVIg may be used in patients with reduced IgG levels and failure to respond to immunisation and where antibiotic prophylaxis is ineffective. All patients should be reviewed after 1 year and, if the numbers of infectious episodes and days in hospital have not decreased, IVIg should be discontinued.

Recommendation

IVIg is probably beneficial for reducing infections in CLL patients with associated low serum IgG levels despite antibiotic prophylaxis with an antibiotic appropriate to the type of infection and previous organism(s) isolated (grade A recommendation, level Ib evidence).

Haemophagocytic lymphohistiocytosis/haemophagocytic syndrome

In case series and case reports, IVIg has been used successfully to treat virus-associated HPS, in combination with other therapy (high-dose corticosteroids, antivirals or immunomodulatory therapies) [57–60]. IVIg is recommended in patients with HLH/HPS as part of supportive therapy, which includes antibiotic and antimycotic prophylaxis, and an antiviral if there is persistent viral infection. Supportive therapy is provided with both initial and continuation therapy [61].

Recommendation

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

Multiple myeloma

For multiple myeloma patients in plateau phase with suppressed IgG and recurrent infections, a multicentre RCT showed that IVIg reduces serious bacterial infections [97]. Such patients may receive IVIg for 6–12 months. Where IVIg is not indicated or not available, alternative therapies include antibiotics (prophylaxis or therapy) and immunisation.

Recommendation

IVIg is probably beneficial for multiple myeloma patients in plateau phase only with recurrent infections (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.

Graft versus host disease following allogeneic BMT or HSCT

In a randomised placebo-controlled trial in patients receiving HLA-identical sibling marrow, there was no benefit with IVIg in infection incidence, interstitial pneumonia, graft versus host disease (GVHD), transplantation-related mortality or overall survival, but an increased risk of severe veno-occlusive disease [98]. Immunosuppressive therapy should be used to prevent GVHD.

Infection following allogeneic BMT or HSCT

Two large meta-analyses reach divergent conclusions on the efficacy of IVIg in preventing infection following allogeneic BMT [99,100]. None of the trials reviewed were placebo controlled and most were carried out before effective treatment for cytomegalovirus (CMV) was available. Treatments to prevent or treat infections include antibiotics and ganciclovir.

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 [101]. Possible treatments include local radiation or surgery, and melphalan with or without corticosteroids and autologous bone marrow transplantation may be considered.

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 and 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, IVIg cost was roughly equivalent to that of plasma exchange, but it is now significantly higher.

Chronic inflammatory demyelinating polyradiculoneuropathy

In rigorously controlled randomised trials in chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), IVIg improved disability within 2–6 weeks compared with placebo. The efficacy of IVIg was similar to that of plasma exchange and prednisolone [102–106]. A Cochrane systematic review found no significant difference in efficacy between IVIg and plasma exchange or IVIg and corticosteroids [107]. A recent large study has shown that chromatography-purified IVIg is effective in both short- and long-term treatment of CIDP [108].

Patients with a probable or definite diagnosis of CIDP according to the International Peripheral Nerve Society Guidelines [109] may receive IVIg. Repeated courses should be titrated to individual needs. Alternative therapies include corticosteroids and plasma exchange.

Recommendation

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

Dermatomyositis

Controlled and open-label studies show that IVIg is effective in dermatomyositis [110–112]. A Cochrane systematic review [113] identified one RCT using IVIg in adult-onset disease showing a significant improvement in strength over 3 months [110] and a case series showing that it leads to improvement of refractory juvenile dermatomyositis as add-on therapy [112]. 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).

Guillain-Barré syndrome

A Cochrane systematic review of RCTs found six that compared IVIg with plasma exchange in GBS [114]. 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

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) [115]. IVIg led to initial clinical improvement in one randomised, double-blind, placebo-controlled crossover trial [116]. Case reports and uncontrolled trials report similar response and lack of serious adverse effects [117–119]. 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.

Recommendation

IVIg should be considered for LEMS if other treatments have failed or are inappropriate (grade A recommendation, level Ib evidence).

Multifocal motor neuropathy

Several randomised, double-blind, placebo-controlled, crossover clinical trials show that IVIg effectively treats multifocal motor neuropathy (MMN) [120–124]. A follow-up study demonstrated that IVIg has long-term benefit for muscle strength and upper limb disability [125]. 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 [126,127]. 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

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 [128]. In exacerbations of myasthenia gravis, a systematic review [129] of two available trials concluded that IVIg gave comparable benefit to plasma exchange in myasthenia gravis, with better tolerability [130,131], although a third randomised placebo-controlled study failed to demonstrate a significant effect after 6 weeks [132]. In observational studies, IVIg appeared beneficial in myasthenic crises [133], juvenile myasthenia [134] and in preparing myasthenic patients for surgery [135,136]. In one randomised trial, the effect of 1 g/kg was not significantly different from 2 g/kg

[137]. The Cochrane systematic review concluded that there is insufficient evidence to determine whether IVIg is efficacious in chronic myasthenia [129].

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 [138].

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 [102–106]. A Cochrane systematic review found no significant difference in efficacy between IVIg and plasma exchange or IVIg and corticosteroids [107].

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 [139]. 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 [140]. 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 [141]. 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 [142–144].

Recommendation

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

Stiff person syndrome

One randomised crossover trial suggests that IVIg is probably beneficial in stiff person syndrome [145]. 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 [146], particularly in patients who have failed to respond to high-dose corticosteroids [147].

Acute idiopathic dysautonomia

Although case reports and series suggest that IVIg might provide benefit in acute idiopathic dysautonomia [148–151], 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 [152,153]. 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

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 [154], but there have been published cases reports using IVIg [155]. Corticosteroids or plasma exchange may be considered.

Cerebral infarction with antiphospholipid antibodies

There are anecdotal reports of improvement following IVIg [18], 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 [156]. Disorders such as Hashimoto's encephalopathy and giant cell arteritis usually respond to conventional treatments [157]. 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 [158–161]. Two randomised placebo-controlled trials in Lennox-Gastaut syndrome provide conflicting results [162,163]. 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 [164]. 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 [165]. There are no established treatments for this condition.

Paraneoplastic disorders

There are no randomised 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 opsoclonus myoclonus [18].

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 [101]. Possible treatments include local radiation or surgery, and melphalan with or without corticosteroids, and autologous bone marrow transplantation may be considered.

Polymyositis

There are no controlled trials in polymyositis [157]. Appropriate treatments include corticosteroids, other immunosuppressive agents and plasma exchange.

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 [166,167].

Vasculitic neuropathy

Individual case reports provide insufficient information on which to recommend IVIg [168–170]. Alternative therapy is corticosteroids and other immunosuppressive agent.

DERMATOLOGY

Dermatomyositis

Controlled and open-label studies show that IVIg is effective in dermatomyositis [110–112]. A Cochrane systematic review [113] identified one RCT using IVIg in adult-onset disease showing a significant improvement in strength over 3 months [110] and a case series showing that it leads to improvement of refractory juvenile dermatomyositis as add-on therapy [112]. 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).

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 [171–174]. IVIg therapy was also found to provide therapeutic benefit for both pemphigus foliaceus [175] and pemphigus vulgaris [176,177]. Other autoimmune blistering diseases reported to benefit from IVIg therapy are epidermolysis bullosa acquisita and linear IgA disease [178]. 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 [179]. Although there are conflicting reports [180], most evidence supports the use of high-dose IVIg as an early therapeutic intervention given the risk of mortality [181]. 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 [182–184]. A single small, randomised, evaluator-blinded trial ($n=10$) did not support the routine use of IVIg in patients with atopic dermatitis [185]. Topical corticosteroids are appropriate therapy.

Three small studies using IVIg in eczema did not show pronounced effectiveness [186–188]. However, some patients were resistant not only to topical treatments, but also to systemic corticosteroids and/or azathioprine [186,187]. IVIg was associated with hypertension, haematuria, transient increase in serum creatinine and serum sickness-like reaction [186].

Ciclosporin is recommended as first choice for patients with atopic eczema refractory to conventional treatment [189], 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 [190–195]. Improvement in the setting of hypogammaglobulinaemia has also been described with replacement IVIg [196,197]. 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 immunosuppressants 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 [198–200].

In a report of five patients presenting with chronic urticaria as the first sign of CVID, there was amelioration of the urticaria with IVIg [201]. 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 [202]. However, similar benefit was not found in a case report of 3 patients with severe chronic urticaria [203]. In a single case report of an autologous serum test-negative patient treated with low-dose IVIg, the urticaria improved [204]. 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 [205]. Current data are insufficient to recommend the routine administration of IVIg in patients with urticaria. Recommended treatments include antihistamines, H₂- 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 [31–33]. 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 [34]. IVIg, at an initial dose of 1 g/kg [35], 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 [19–25]. 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) [53].

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

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 [62]. Initially, children should receive no treatment, but be observed only; if treatment is required, this should be anti-D(Rh₀), 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 ITP for emergency treatment 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 [1]. 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 [2].

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 [206], but experimental studies show that it can neutralise superantigen toxins and opsonise bacteria not otherwise adequately cleared by antibiotics or surgery alone [207–209]. Studies in adults suggest that IVIg may be useful in patients with toxin-related infection when other treatment options have been explored [18,210–215]. 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 [1]. 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 [2].

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 [111,216–220] have been reviewed in detail [221]. 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 [158–161]. Two randomised placebo-controlled trials in Lennox-Gastaut syndrome provide conflicting results [162,163]. 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 [222]. 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 [223]. The role of IVIg in systemic sclerosis-scleroderma [224] remains unclear. Immunosuppression is the preferred treatment.

PANDAS

Only one case–control study shows benefit from plasma exchange and IVIg (single dose) in PANDAS [165]. There are no established treatments for this condition.

Systemic juvenile idiopathic arthritis

The role of IVIg in systemic juvenile idiopathic arthritis (sJIA) is controversial [225]. 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 [226].

RHEUMATOLOGY

Adult rheumatology

Dermatomyositis

Controlled and open-label studies show that IVIg is effective in dermatomyositis [110–112]. A Cochrane systematic review [113] identified one RCT using IVIg in adult-onset disease showing a significant improvement in strength over 3 months [110] and a case series showing that it leads to improvement of refractory juvenile dermatomyositis as add-on therapy [112]. 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 [1]. 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 [2].

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 [112,216–220] have been reviewed in detail [221]. 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 [227].

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

There are no controlled trials in polymyositis [157]. Appropriate treatments include corticosteroids, other immunosuppressive agents and plasma exchange.

Systemic juvenile idiopathic arthritis

The role of IVIg in sJIA is controversial [225]. 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 [226].

Systemic lupus erythematosus

In a small ($n=59$) retrospective study, IVIg resulted in a transient improvement in 65% of patients with SLE [228]. Various case reports have shown that high-dose IVIg is associated with disease resolution in patients with SLE affecting specific organs including the kidneys [229,230], myocardium [231], nerves [232], bone marrow [233] and multiple organs [234]. 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 immunocytopenias

For treatment recommendations for autoimmune cytopenias associated with SLE, see the relevant entry (e.g., for autoimmune haemolytic anaemia, see page 33; for thrombocytopenia, see page 33; for Evans' syndrome, see page 33; for CAPS see page 60).

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 [222]. 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 [223]. The role of IVIg in systemic sclerosis-scleroderma [224] 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 [210,211]. 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 [207–209]. 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 [211]. 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 [18,212]. The use of IVIg was highlighted in children with TSS subsequent to a small burn in a recent practice guideline [206]. 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 [213–215]. 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 [235,236]. In addition, a small case series has shown that IVIg may be useful in multiple recurrent *C. difficile*-associated diarrhoea [237]. 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

CMV-induced pneumonitis following transplantation

Treatment of CMV-pneumonitis with high-dose IVIg [238,239] or high-titre anti-CMV polyclonal IVIg (CMV-IVIg) [240] 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 [238]. Similarly, CMV-IVIg plus ganciclovir resulted in better survival than would be expected from other treatment regimens [240].

In confirmed CMV-pneumonitis, IVIg may be used in conjunction with ganciclovir.

Recommendation

IVIg in conjunction with ganciclovir is the treatment of choice for CMV-induced pneumonitis (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.

Antibody incompatible transplantation

One randomised 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 [241].

Treatment of acute antibody-mediated rejection and steroid-resistant rejection following solid organ transplantation

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 [242–245], although the number of patients randomised was not large. However, economic analyses suggest that IVIg might be financially advantageous [246].

AMR may sometimes be reversed with the use of steroids, plasma exchange, rituximab or cytotoxic anti-T-cell antibodies (muromonab-CD3 [OKT3]) or polyclonal preparations such as antithymocyte globulin, but there are issues with all of these alternatives [247,248].

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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

IVIg Expert Working Group

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

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. **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

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 IVIg as 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 the 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.

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