Standing Council on Health

Criteria for the clinical use of **intravenous immunoglobulin** in Australia

Second Edition
July 2012

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Disclaimer: Important information about this document

This document is not a clinical practice guideline. It intends only to provide information about criteria for accessing intravenous immunoglobulin funded under the National Blood Arrangements. Any advice relating to other forms of treatment relevant to the conditions in *The Criteria for the clinical use of intravenous immunoglobulin in Australia (the Criteria)* have not been subject to a systematic review and should not be relied upon to guide treatment.

Patients and doctors should not use this document as a substitute for expert medical guidance and advice. The relevance and appropriateness of information in this document depends, amongst other things, on an accurate diagnosis, the severity of the condition being properly ascertained, the individual response to diagnostic tests and therapies, and other relevant circumstances in each case.

The Criteria was first published in 2007 after a systematic review that was completed in mid-2006. Another systematic review, of a limited number of indications, was then undertaken in 2010-11 to update *the Criteria*. This review resulted in the addition of a small number of indications, removal of a small number of indications and a rewording of a limited number of indications.

Inclusion of indications in *the Criteria* is based where possible upon systematic review of the evidence. In the absence of published evidence, information and access criteria are based on clinical advice provided to the development group by clinical colleges, clinical societies and individual experts.

Each person involved in developing this document, and their employer where they are involved as an employee, or the organisation they represent where they are involved in a representative capacity, expressly disclaims and accepts no responsibility for any consequences arising from relying upon the information or recommendations contained herein.

This document was prepared under the auspices of the Jurisdictional Blood Committee for and on behalf of the Standing Council on Health (formerly the Australian Health Ministers' Conference).

The Jurisdictional Blood Committee would like to acknowledge and thank those who contributed to the compilation of the first and second editions of the document. In particular, we would like to thank the members of the original IVIg Working Party and the National IVIg Criteria Review Working Group.

We would also like to thank all individuals and organisations that provided submissions to the 2010–11 Criteria Review. Principal clinical advisers were Associate Professor John Gibson, Associate Professor Andrew Kornberg and Associate Professor Sean Riminton. Clinical representatives from; the Australian Society of Clinical Immunology and Allergy, the Australian & New Zealand Association of Neurology, the Haematology Society of Australia and New Zealand and the Australian Red Cross Blood Service Transfusion Medicine Team also contributed to this review. Many other clinical experts gave generously of their time and expertise. All contributions are gratefully acknowledged.

It is intended that this document will be updated periodically.

This document and its updates will be available on the National Blood Authority website at www.nba.gov.au.

This document may be cited as Jurisdictional Blood Committee, for and on behalf of the Australian Health Ministers' Conference. *Criteria for the clinical use of intravenous immunoglobulin in Australia. Second Edition*. Canberra: Commonwealth of Australia, 2012.

ISBN 978-0-9872519-0-9

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Foreword

Foreword

This document is to assist clinicians and transfusion medicine professionals identify the conditions and circumstances for which the use of intravenous immunoglobulin (IVIg) is able to be accessed under the National Blood Arrangements. IVIg is a precious biological product and, as such, its use should be consistent with the evidence base and prescribed for the treatment of patients who are likely to benefit from IVIg therapy and for whom there are no safe and effective alternative treatments. The growth in demand for IVIg prompted action by Australian governments to ensure it is reserved for use in those patients with the greatest need.

There is not an exact alignment between Therapeutic Goods Administration registered indications and the indications listed in *the Criteria*. Where safe and effective alternative therapies are available, the alternative product should be used in preference to IVIg.

In addition, IVIg is used to treat a growing number of diseases where immunomodulation or immunoglobulin replacement therapy is of benefit but the treatment indication does not have regulatory approval. Some of these uses of IVIg have a foundation in the medical literature and others are supported by clinical consensus but have a less conclusive basis in evidence.

The Criteria is based on evidence identified through systematic reviews of the literature and the opinions of clinical experts. In conjunction with government policy, this publication may be used to identify those conditions and circumstances for which IVIg products can be accessed under the National Blood Agreement (see Appendix A).

The development of *the Criteria* was based on the following key principles:

- Where safe, effective and affordable alternative therapies exist, these are considered preferable to IVIg.
- When IVIg is used, the lowest dose for the shortest duration required to achieve the desired outcome should be chosen.
- For ongoing therapy, the achievement of measurable clinical outcomes is a requirement and IVIg should not be continued in patients with no demonstrable clinical benefit.

Structure of this document

This document provides background information on the supply, manufacture, and use of IVIg in Australia, and criteria for its appropriate use.

Chapter 1 deals with the governance of the Australian blood sector and the roles and responsibilities of the various organisations. It discusses the availability of IVIg and two mechanisms through which it can be accessed by clinicians.

Chapter 2 looks broadly at the safety and quality aspects of production, the role of the Therapeutic Goods Administration (TGA) and the obligations of manufacturers and suppliers.

Chapter 3 describes national and international trends in demand for IVIg.

Chapter 4 outlines the process used to develop this document and establish *the Criteria*.

Chapters 5 to 8 list the conditions considered for IVIg therapy during the compilation of this document.

Chapter 5 lists conditions for which IVIg in select patients has a well-established therapeutic role.

Chapter 6 lists conditions for which the therapeutic role of IVIg is emerging. Chapters 5 and 6 also list the clinical criteria used to identify the subsets of patients who benefit from IVIg therapy.

Chapter 7 lists conditions that rarely, if ever, would require IVIg use.

Chapter 8 lists conditions for which the use of IVIg therapy is not supported at this time, either because there are preferred alternative therapies, or there is evidence of no benefit, or because there is insufficient evidence or clinical support.

Maintaining the currency of this document

Governments recognise the need for the conditions identified and the criteria for the clinical use of IVIg to be regularly reviewed to take account of the evolving processes of disease diagnosis, treatment and outcome evaluation.

In concert with its development, the National Blood Authority (NBA) has been charged by the Jurisdictional Blood Committee (JBC) with the responsibility of developing plans for the implementation of this document. These plans include reviewing the current governance and authorisation arrangements.

This document was prepared with the following assistance.

National IVIg Criteria Review Working Group

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Individuals making submissions and many other clinical experts gave generously of their time and expertise. All contributions are gratefully acknowledged.

Further information

For information regarding the *Criteria for the clinical use of intravenous immunoglobulin in Australia*, please visit www.nba.gov.au or contact:

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Executive summary

Intravenous immunoglobulin (IVIg) is a fractionated blood product made from pooled human plasma. It is registered for use in Australia for the treatment of a number of diseases where immunoglobulin replacement or immune modulation therapy is indicated. IVIg is used to treat a growing number of unregistered indications where there is some evidence for its utility. IVIg is a lifesaving therapy in appropriately selected patients and clinical circumstances.

Access to intravenous immunoglobulin in Australia

Since the 1980s, the demand for IVIg has greatly increased, both internationally and in Australia. In the late 1990s, worldwide shortages prompted action by Australian governments to ensure that IVIg was available for those patients most in need. Since that time, strategies to ensure supply have included:

- rationalising the use of IVIg by specifying conditions and limiting IVIg access under the National Blood Arrangements to those patients meeting the specified condition and eligibility criteria;
- increasing the manufacture of IVIg in Australia; and
- importing IVIg from overseas.

The average annual growth of IVIg use per capita in Australia from 2004–05 to 2010–11 was 14.18% per annum and the growth from 2009–10 to 2010–11 financial year was 9.46%. In 2010–11, the National Blood Authority spent, on behalf of Australian governments, $149 million on IVIg products. These are the product costs only and do not include costs associated with the collection of plasma for fractionation. The continual significant annual growth in IVIg use, the relatively high cost of IVIg products and the potential for supply shortages have maintained the focus of Australian governments on ensuring use remains consistent with

an evidence-based approach and that IVIg is able to be accessed under the National Blood Arrangements for those patients with the greatest clinical need.

The *Criteria for the clinical use of intravenous immunoglobulin in Australia* describes current arrangements for access to IVIg funded under the National Blood Arrangements and the conditions for its use. It has been developed to assist clinicians and medical professionals identify the conditions and circumstances for which the use of IVIg is appropriate and funded.

Production and safety

For more than a decade, the local production of IVIg has fallen short of national consumption and overseas-sourced products have been used to supplement the Australian-made product. No plasma product, whether locally manufactured or imported from overseas, can be used in Australia unless the product has been assessed and approved by the Therapeutic Goods Administration (TGA). The TGA regulates the safety, quality, and efficacy of all IVIg products. The IVIg products funded in Australia under the National Blood Arrangements are available on the NBA website at www.nba.gov.au.

Rationale for developing criteria for intravenous immunoglobulin use

Before the adoption of the first edition of *the Criteria*, the management and use of IVIg in Australia was based upon the recommendations of a 2000 review conducted by the Blood and Blood Products Committee of the Australian Health Ministers' Advisory Council. A recommendation of this review was that conditions for access to IVIg therapy undergo regular review to ensure that the therapeutic use of IVIg is kept current. These criteria were developed in response to that recommendation.

The term 'criteria for use' was chosen specifically to indicate a more directive framework to describe the circumstances, based on evidence and clinical experience, under which the clinical use of IVIg is considered appropriate to be funded in Australia.

Conditions considered for IVIg therapy

The *Criteria for the clinical use of intravenous immunoglobulin in Australia (the Criteria*) was first published in 2007 after a systematic review that was completed in mid-2006. In accordance with government commitments, the Jurisdictional Blood Committee (JBC) initiated a review of *the Criteria* in 2010. The review was limited to proposals to modify an entry or reassign the location (chapter) of an existing condition or to remove or add a condition to *the Criteria*. This resulted in the addition of seven rare conditions, removal of two conditions and the review of a limited number of conditions.

Twenty-seven formal submissions were considered and based on the information provided and expert opinion, a systematic review of the literature between 2006 and 2010 or a consensus process using expert clinical opinion was conducted.

The *Criteria for the clinical use of intravenous immunoglobulin in Australia (second edition)* identifies:

- Twelve conditions for which IVIg has an established therapeutic role. For these conditions, its use is supported by reasonable-quality evidence and expert opinion. For a number of conditions IVIg is first-line therapy in selected patients and may be the only established treatment option: for example, as replacement therapy in primary immunodeficiency disease.
- Twenty conditions for which IVIg has an emerging therapeutic role. For these conditions, there is clinical support for IVIg use in selected patients, although the quality of evidence supporting use is variable. For many conditions, IVIg is considered only as second or third-line therapy when standard therapies have been proven to be ineffective, become intolerable, or are contraindicated. Many of these conditions are rare and as a result, the evidence of benefit is often patchy and inconclusive. Other conditions are more prevalent, yet the evidence of benefit is either conflicting or uncertain, requiring more research, or the use of IVIg represents a relatively new direction in their

management and evidence of benefit is still emerging. For these conditions, the collection of effectiveness data is of particular importance.

- Twenty-nine conditions for which IVIg is used in exceptional circumstances only. These conditions rarely, if ever, require IVIg use, either because there are safe and effective alternative therapies, or because the evidence of benefit does not justify use in most cases. IVIg is considered to have a therapeutic role only in exceptional circumstances, such as in urgent or life-threatening circumstances, or in circumstances in which significant morbidity would be expected and other clinically appropriate therapies have been exhausted or are contraindicated.
- Thirty-six conditions for which IVIg therapy is not supported or funded. IVIg therapy for these conditions is not supported or funded at this time, either because there is evidence of no benefit, insufficient evidence of benefit, or some evidence of benefit but preferred alternative therapies are available.

Where the therapeutic role of IVIg is well established or there is emerging evidence of a role for IVIg therapy in selected patients, a structured proforma is provided. The proforma details the diagnostic parameters and criteria that need to be met for IVIg to be accessed under the National Blood Arrangements. *The Criteria* generally refer to matters such as patient selection, particular disease characteristics, disease severity, and any requirement for other treatments to have been demonstrated as unsuccessful before IVIg is considered.

The national implementation of *the Criteria* facilitates access and use of IVIg in a manner consistent with the evidence base, for the treatment of patients who are likely to benefit, and for whom there are no safe and effective alternative treatments.

1

Introduction

1. Introduction

Intravenous immunoglobulin (IVIg) is a fractionated blood product made from pooled human plasma. IVIg is increasingly important in replacement therapy and as an immunomodulatory agent in autoimmune disease. It is the market driver for the plasma industry in the developed world with an increasing demand internationally. The continued growth in IVIg demand in Australia makes its supply and management a high priority in both the government and clinical settings alike. Governments will continue to develop and refine mechanisms for monitoring the use of IVIg.

National Blood Agreement

The National Blood Agreement[1] sets out the primary and secondary policy objectives of all Australian governments in relation to the Australian blood sector. The Australian Government, and state and territory governments, signed the agreement in 2003 and, in so doing, agreed to implement a coordinated national approach to policy setting, governance and management of the Australian blood sector, including administrative and financial arrangements.

Under the agreement, blood products are provided at no direct cost to patients. The blood sector is funded by the Australian Government (63%) and by the states and territories (37%), with the funding provided by each state and territory determined by the quantity of product provided to each particular state and territory.

The National Blood Agreement's primary policy objectives are:

a. to provide an adequate, safe, secure and affordable supply of blood products, blood-related products and blood-related services in Australia; and

1 National Blood Authority 2003, *National blood agreement between the Commonwealth of Australia and the states and territories*, Australian Government, Canberra. Available from: http://www.nba.gov.au/policy/agreement.html

b. to promote safe, high-quality management and use of blood products, blood-related products and blood-related services in Australia.

A supporting principle is that blood and blood-related products can be accessed by patients at no direct cost, provided such use is in accordance with clinical need and appropriate clinical practice.

In December 2007, Australian Health Ministers agreed to fund the conditions identified in Chapters 5, 6 and 7 of *the Criteria* under the National Blood Agreement, as outlined in the Funding Policy Statement (Appendix A). IVIg funded under the National Blood Agreement is not available for use to treat conditions identified in Chapter 8. This funding policy was confirmed during the approval of this second edition.

For conditions **not** described in Chapters 5, 6 or 7, Approved Recipients may obtain IVIg via the Jurisdictional Direct Order component of the IVIg Standing Offer arrangements (see page 22).

Governance arrangements for the supply and management of blood products in Australia

SCoH and AHMAC

The Standing Council on Health (SCoH) formerly the Australian Health Ministers' Conference (AHMC) is the ultimate decision-maker responsible for the oversight and management of the Australian blood sector. AHMC's responsibilities include national policy and financial decisions in relation to the supply of blood and blood products, and the determination of which products and services can be bought with public funds. It has oversight of the implementation of the National Blood Agreement and is supported in its roles by the Australian Health Ministers' Advisory Council (AHMAC). In November 2010, AHMC endorsed the *Statement on national stewardship expectations for the supply of blood and blood products*. The statement was developed to address the lack of specific accountability obligations, other than general safety and quality issues mandated by other agencies,

on health providers such as laboratories and clinics and other institutions that receive blood and blood products for dispensing to patients.

The Statement contains a concise description of responsible, sustainable and appropriate use of blood and blood products relevant to handling, storage, administration, usage and capacity to report inventory and can be found at Appendix B.

Clinical, Technical and Ethical Principal Committee

The role of the Clinical, Technical and Ethical Principal Committee (CTEPC) is to provide advice to AHMAC on clinical, technical and medico-legal issues that affect the formulation of health care policy or delivery of health care services across multiple jurisdictions. Among other things, CTEPC provides advice on options for the ongoing coordination of clinical and technical services that are managed on a national basis.

Jurisdictional Blood Committee

The Jurisdictional Blood Committee (JBC) is a sub-committee of CTEPC established to implement a coordinated national approach to policy setting and management of the blood sector. The JBC has representation from the Australian Government, and each state and territory government. It provides recommendations to the AHMC on policy relating to the blood sector.

National Blood Authority

The National Blood Authority (NBA) was established in 2003. It manages contracts with suppliers of blood and blood products to ensure that the supply of products meets the needs of the Australian public. Together, the *National Blood Authority Act 2003* and the National Blood Agreement form the foundations of the current arrangements within the blood sector and underpin the functions of the NBA.

Therapeutic Goods Administration

All blood, blood components and plasma derivatives supplied in Australia are regulated under the *Therapeutics Goods Act 1989* by the Therapeutic Goods Administration (TGA). The TGA is responsible for enforcing standards within the blood sector to ensure blood products meet appropriate safety, quality and efficacy requirements. It also registers individual products for specific indications.

The TGA undertakes a comprehensive assessment of the safety, quality and efficacy of all domestic and imported plasma products before they can be registered on the Australian Register of Therapeutic Goods and approved for supply in the Australian market. The TGA licenses (manufacturers in Australia) or certifies (manufacturers located overseas) the facilities where plasma products are manufactured against standards of Good Manufacturing Practice (GMP). Audits are conducted to ensure ongoing compliance with GMP.

Australian Red Cross Blood Service

The Australian Red Cross Blood Service (the Blood Service) is responsible for the collection, processing and distribution of blood and blood components sourced from Australian voluntary non-remunerated donors. All plasma collected by the Blood Service for the manufacture of IVIg is sent to CSL Biotherapies Australia for fractionation. The Blood Service Transfusion Medicine Team currently issues IVIg based on *the Criteria*.

Availability of intravenous immunoglobulin in Australia

The availability of IVIg in Australia relative to clinical need and demand has been reviewed repeatedly since at least the early 1990s. Three approaches have been used to ensure that IVIg is available for the patients who need it most:

- aligning the use of IVIg with conditions for which there is evidence of benefit;

- increasing the manufacture of IVIg in Australia; and
- importing IVIg from overseas suppliers.

a) Aligning IVIg use with conditions for which there is evidence of benefit

Despite much published clinical research on IVIg, evidence for its efficacy and effectiveness in the treatment of many different conditions remains uncertain. This is due to:

- the difficulty of conducting rigorous evaluative studies of treatments for rare and complex medical conditions that are often accompanied by equally complex co-morbidities;
- the difficulty of evaluating outcomes where IVIg is used as a treatment of last resort (as is sometimes the case) after other therapies have failed; and
- a lack of monitoring data from all parts of the world on the use and outcomes of IVIg therapy.

Given the variable extent and quality of evidence for IVIg use, successive reviews and guidelines since 1992 have recommended that conditions should be categorised according to the quality of the available evidence and whether IVIg treatment was considered beneficial.

b) Increasing the manufacture of IVIg in Australia

Australia has a long-standing commitment to a policy of self-sufficiency in the production and supply of blood and plasma products. This position was endorsed by the 2000 *Review of the use and supply of intravenous immunoglobulins in Australia*[2], the 2001 *Review of the Australian Blood Banking and Plasma Product*

2 Blood and Blood Products Committee 2000, *Review of the use and supply of intravenous immunoglobulins in Australia. A report by the Blood and Blood Products Committee* (prepared under the auspice of the Australian Health Ministers' Advisory Council, Canberra), Blood and Blood Products Committee, Canberra.

Sector[3] and the 2006 *Review of Australia's Plasma Fractionation Arrangements*[4].

Domestically produced IVIg is made exclusively by CSL Biotherapies Australia. It is manufactured from plasma collected around Australia from voluntary non-remunerated donors by the Blood Service. The collection of plasma and the manufacture of domestic IVIg have increased in response to increasing demand for plasma products (see Figures 2 and 3).

c) Importing IVIg from overseas suppliers

In 2004, the JBC agreed to supplement the Australian made product with IVIg sourced from overseas.

Intravenous Immunoglobulin Standing Offer

The IVIg Standing Offer is an arrangement for the contingent supply of imported IVIg. Under this arrangement, imported IVIg is used to supplement the domestic IVIg supply. The NBA has Standing Offer arrangements and details are available on the NBA website at www.nba.gov.au.

The IVIg Standing Offer can be accessed through two mechanisms:

- the National Blood Supply component, whereby imported IVIg supplements domestic IVIg for uses under the National Blood Agreement and is supplied at no direct cost to patients; and
- the Jurisdictional Direct Order component, whereby imported IVIg is available to Approved Recipients.

3 A report to the Commonwealth Minister for Health and Aged Care by a committee chaired by the Rt. Hon Sir Ninian Stephen. Review of the Australian Blood Banking and Plasma Product Sector [Online]. 2001 [cited 7 Dec 2007]. Available from www.nba.gov.au/policy/pdf/report.pdf

4 Flood, P, Wills, P, Lawler, P, et al 2006, *Review of Australia's plasma fractionation arrangements*, Australian Government, Canberra. Available from: http://www.health.gov.au/internet/main/publishing.nsf/Content/0938448E0E296AC0CA25723A001F6FD2/$File/plasma_FINAL%20as%20at%2030%20November%202006.pdf

National Blood Supply component

Under the National Blood Supply component, imported IVIg is used to supplement domestically produced IVIg. This is to ensure supply meets demand. To optimise shelf life and continuity of patient care, imported IVIg is issued when there are still reserves of domestically produced product through an allocation model under the management of the Transfusion Medicine Services at the Blood Service.

Jurisdictional Direct Order component

Under the Jurisdictional Direct Order (JDO) component, imported IVIg is available to Approved Recipients. The JDO component operates as follows:

a. Approved Recipients are entities such as hospitals that wish to purchase IVIg. Each state and territory health department will have nominated these entities to suppliers.

b. If an entity is unsure whether it is an Approved Recipient under the JDO component of the Standing Offer it should contact the relevant state or territory health department to clarify this and ensure it is nominated as an Approved Recipient to each supplier.

c. Approved Recipients place orders for imported IVIg directly with the supplier.

d. Purchases from this component of the Standing Offer are paid for in full by the Approved Recipient.

e. Upon placement of the order, a contract is established directly between the supplier and the Approved Recipient for the supply of the IVIg product.

Further details about the IVIg Standing Offer, information on the products available under the Standing Offer, and the contact details of suppliers and each state and territory health department are available on the NBA website at www.nba.gov.au.

2

Production of normal immunoglobulins

2. Production of normal immunoglobulins

Pooled human plasma is the starting point for the manufacture of intravenous immunoglobulin (IVIg). Plasma is obtained either by separation of whole blood or by plasmapheresis. Plasmapheresis is a process whereby only plasma is collected at the time of donation and the cellular components of blood are returned to the donor. The procedure is more time consuming for the donor. However, it does enable larger quantities of plasma to be collected more frequently from each donor.

Plasma fractionation

The plasma component of blood contains a large number of proteins, each of which performs a different role. Work conducted in the late 1930s by Dr Edwin Cohn and associates at Harvard University established a process by which the major proteins within plasma could be selectively precipitated using variations in the concentration of ethanol, salt, temperature and pH. This process, known as the Cohn Process, is a method used for the fractionation of plasma and most manufacturers use the Cohn Process or variations of it.

There have been a number of alternative processes developed for the fractionation of plasma, but only one of these has been implemented on an industrial scale. This is the chromatographic process developed by John Curling and associates in Sweden in the late 1970s. The process relies on the separation of plasma proteins based on their size and charge rather than their solubility. The CSL Biotherapies Australia plant in Australia uses a combined Cohn and chromatographic process to separate plasma fractions.

Of critical importance in the manufacture of plasma products over the past 20 years has been the incorporation of procedures that either eliminate or destroy viral pathogens. All licensed manufacturers have incorporated viral reduction procedures into their manufacturing processes and have completed studies that confirm that the possibility of a viral transmission to a patient

using these products is exceptionally small. When combined with donor screening and plasma quarantining procedures now in place in all developed countries, these manufacturing procedures result in a close to zero risk of viral transmission to the recipients of plasma products.

Product safety and regulation

The Therapeutic Goods Administration (TGA) is the Australian Government body responsible for ensuring the quality, safety, and efficacy of therapeutic products manufactured and/or supplied in Australia.

A sponsor company that wishes to supply an immunoglobulin product in Australia must apply to the TGA to have its product included in the Australian Register of Therapeutic Goods (ARTG). The sponsoring company is required to support its application with detailed information relating to:

- the chemistry, standards of manufacture and quality control of the product[5];
- any preclinical in vitro tests and animal studies conducted on the product[6]; and
- clinical data derived from studies conducted in humans[7].

5 The required information includes data about the starting plasma for fractionation (donor selection, donation testing and plasma storage), the manufacturing process (including infectious disease removal and inactivation steps, and consistency of manufacture), quality control tests (in-process and final product tests) and the stability of the final product.

6 Issues that are commonly assessed through in vitro and animal data are acute and repeated dose toxicity (using doses higher than those intended for humans), carcinogenicity, genotoxicity, mutagenicity and reproductive toxicity. These issues must be considered for any excipients contained in the product as well as for the active ingredients.

7 Clinical data in an application for an IVIg product typically includes results of pharmacokinetic studies as well as clinical efficacy and safety studies conducted in the patient populations for whom the sponsor company is seeking approval. If the product has been supplied in foreign markets, the sponsor is also required to submit any post-marketing safety information such as spontaneously reported adverse reactions or safety data from the published literature. There is no requirement that separate clinical trials be conducted in Australian patients.

In terms of the type and extent of data required from companies, the TGA has aligned its data requirements with those of the European regulatory authority, the European Medicines Agency (EMA).

If the sponsoring company's application is accepted, the supporting information is evaluated to determine whether the quality, safety and efficacy of the product have been demonstrated. On completion of the evaluations the application is considered by the Advisory Committee on Prescription Medicines (ACPM), an independent advisory committee composed mainly of practising specialist clinicians drawn from outside the TGA. The ACPM provides the TGA with expert advice on any issues that have arisen during the evaluation process. Once an IVIg product is registered, the sponsor company has marketing approval to supply the product in Australia. The product's registration imposes certain restrictions and conditions on supply. For example, each IVIg product is approved for certain indications and dosage regimens based on the clinical data provided to the TGA. Sponsor companies are not permitted to promote their IVIg products for indications and at dosages not approved by the TGA. The registration also sets out specifications for the quality of the product. Any product supplied in Australia must comply with these specifications.

The TGA requires the sponsor company to submit updated post-marketing safety data at regular intervals for the first three years after registration. After this period, the sponsor is required to keep the TGA informed of any significant safety issues that arise with the product. The TGA also collects information from health care professionals on adverse reactions occurring in Australia through the Adverse Drug Reactions Advisory Committee reporting scheme.

Many of the indications for which IVIg products are used in Australia have not been approved by the TGA, as sponsor companies have not provided data to support registration. Use of a product for an unapproved indication is commonly referred to as 'off-label use'. Although 'off-label' use is a clinician's prerogative, the TGA encourages sponsor companies to seek formal approval

of their products for such indications. To facilitate approval, the TGA will accept applications based upon published literature. In addition, under its Orphan Drug Program, the TGA is able to waive normal evaluation fees for products intended to treat rare diseases. The registration of IVIg products for currently unapproved indications is an issue to be resolved by sponsors in association with the TGA and is beyond the scope of this document.

Virus and prion removal

In the past, all plasma derivatives have been implicated in the transmission of infectious blood-borne pathogens. The risk has decreased considerably over the past 20 years due to increased regulatory oversight.

The TGA assesses all IVIg products available in Australia for transmissible disease risk. Measures undertaken to reduce risk include ensuring plasma quality by screening and excluding high-risk donors, testing of plasma for viral markers, and viral inactivation and removal steps during the manufacturing process. Viral inactivation and removal steps during the manufacturing process are the most significant in reducing the risk of viral transmission in these products.

Different manufacturers use different viral inactivation and removal processes. The fractionation processes (cold ethanol and chromatography) are themselves efficient at removing viruses from plasma. Additional viral inactivation steps such as pasteurisation (heating in aqueous solution at 60°C for 10 hours), solvent or detergent and low pH incubation, and filtration are used to kill and remove both enveloped viruses, such as HIV and hepatitis B and C viruses, and the non-enveloped virus, hepatitis A. The TGA requires a minimum of two viral reduction steps in the manufacturing process.

The TGA uses international best-practice guidelines and the advice of the Transmissible Spongiform Encephalopathies Advisory Committee (TSEAC) in minimising prion transmission risk in plasma products on the Australian market. Each plasma

derivative on the market is carefully assessed for this risk, irrespective of its source. All overseas-derived products approved for the Australian market by the TGA have a prion and viral safety profile that is at least equivalent to that of the Australian product.

To date, no known recipient of a plasma derivative has developed a transmissible spongiform encephalopathy although prion transmission was detected at autopsy in one haemophilia patient who died of unrelated causes. While prions cannot be inactivated by processes used to inactivate viruses, they can be removed through the manufacturing process, although each such purification step has to be validated to ensure prion removal. In general, alcohol precipitation results in the clearance of prions away from therapeutic proteins and into waste fractions. Similarly, chromatographic separation tends to purify therapeutic fractions separately from prions.

Intravenous immunoglobulin products in Australia

Several intravenous immunoglobulin products are currently registered on the ARTG and are available for use in Australia.

While all products are assessed by the TGA against the same criteria, each manufacturer's IVIg preparation is a unique product carrying its own specific evidence-based indications and safety profile.

Information on individual products should be obtained from the TGA or the manufacturer.

3

Intravenous immunoglobulin supply and demand

3. Intravenous immunoglobulin supply and demand

Since the 1980s, intravenous immunoglobulin (IVIg) has been used to treat an increasing number of conditions. Consequently, the demand for IVIg has greatly increased both internationally and in Australia.

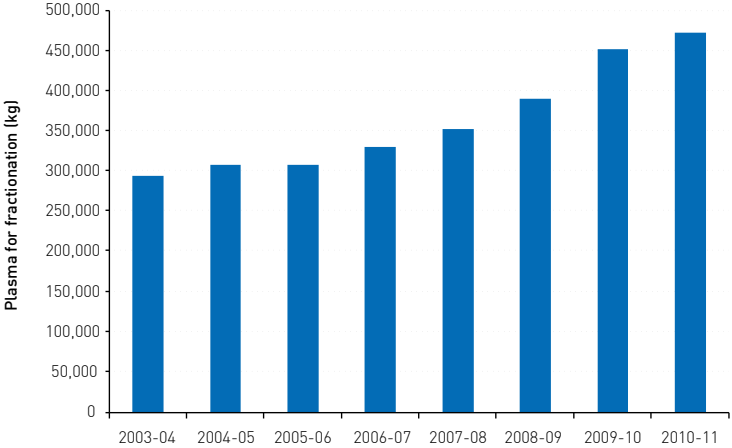
International

Despite fluctuations in demand, the overall worldwide supply of IVIg has increased steadily.

Domestic

The supply of domestically manufactured IVIg is largely determined by the volume of domestic plasma available for fractionation. The Australian Red Cross Blood Service (the Blood Service) collects plasma from Australian voluntary donors on behalf of all Australian governments. The total amount of plasma collected by the Blood Service over the period from 2003–04 to 2010–11 and sent to CSL Biotherapies Australia for fractionation is shown in Figure 1. CSL Biotherapies Australia is the exclusive manufacturer of IVIg in Australia. All locally produced IVIg is used within Australia.

Figure 1 Plasma sent to CSL Biotherapies Australia for fractionation

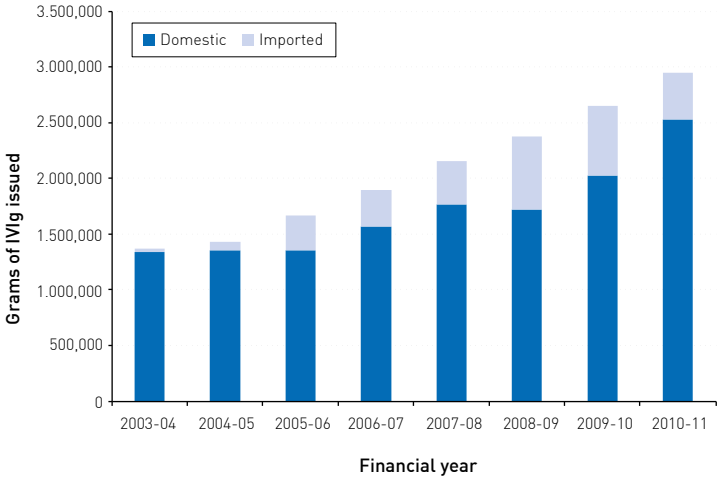


Source: National Blood Authority data on file

The shortages of IVIg that occurred in the late 1990s stimulated a review of the use of IVIg in Australia by the then Blood and Blood Products Committee of the Australian Health Ministers' Advisory Council (AHMAC). This review made a number of recommendations relating to the use, distribution and supply targets of IVIg. Clinical guidelines were revised and conditions classified into three groups based on evidence of patient benefit. The report also recommended that the supply of IVIg should be increased through a combination of increasing the amount of plasma collected and enabling the importation of alternative IVIg products. Acting on this, and with the agreement of all governments, the National Blood Authority (NBA) negotiated a standing offer for imported IVIg. This has resulted in imported product being available to meet the supply plans of all jurisdictions and the clinical needs of patients on a more secure basis and at a greatly reduced price compared to previous arrangements.

Demand for IVIg has experienced double digit growth between 2006–07 to 2009–10. The annual percentage growth in total grams issued is shown below in Figure 2.

Figure 2 IVIg grams issued in Australia



Source: National Blood Authority data on file

Cost of IVIg products

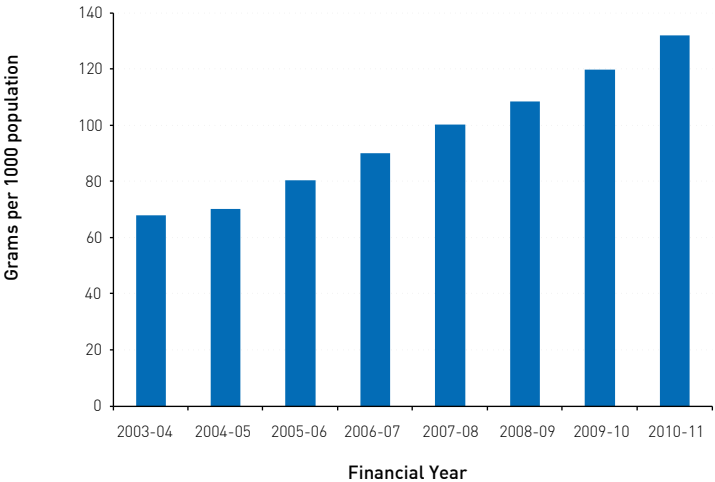
The cost to Australian governments of providing patients with fresh blood products, plasma products and recombinant alternatives in 2010–11 was $967 million. Approximately $149 million of this was spent on IVIg (86% for domestically produced product and 14% for imported product). These are the product costs only and do not include costs associated with the collection of plasma for fractionation.

World trends

Factors that affect the quantities of plasma products required and produced vary with time, but include changes in clinical indications and demographics, the introduction of alternative therapeutics, changes in actual and perceived risks of blood products and modifications to manufacturing processes.

The average annual per capita growth rate for IVIg issued in Australia in the following years before *the Criteria* was 14% and 10% after *the Criteria*. The amount of IVIg issued per 1000 head of population is illustrated in Figure 3.

Figure 3 Australian IVIg issued in g/1000 head of population



Source: National Blood Authority data on file

In considering the supply and demand of IVIg in Australia over the next decade, considerable effort has been undertaken to analyse both the Australian and international trends presented above.

There is no international consensus on expected growth rates, but the following factors are generally considered important in predicting future growth:

- availability and cost of plasma;
- costs of products and national reimbursement policies;
- development of products that are easier to use;
- development of products that can be administered by other routes (e.g. subcutaneous);
- promotion by the industry;
- availability of clinical studies supporting/not supporting use;
- identification of conditions where a benefit of IVIg is proven or inferred;
- clinical guidelines and authorisation processes; and
- demographics, including the growth of a number of treatable conditions in an ageing population.

How these factors may play out in Australia is difficult to predict with any certainty.

IVIg demand management

A formal review and evaluation of alternative therapies to IVIg has not been undertaken and, as such, specific guidance on the relative efficacy and place in therapy of IVIg in relation to other therapies for each indication cannot be provided.

However, when developing individual treatment plans for patients, clinicians are asked to consider the comparative efficacy, risks and costs associated with IVIg and alternative therapies. Furthermore, clinicians are asked to consider suitable adjuvant therapies that may reduce individual patient requirement for IVIg. These clinical considerations will assist in curtailing the growth in demand for IVIg. For some conditions, the priority of the use of IVIg has been reduced in favour of alternative therapies and is now considered exceptional practice (e.g. the treatment of acute leukaemia in children and HIV in children).

4

Development and maintenance of *the Criteria*

4. Development and maintenance of *the Criteria*

The purpose of *the Criteria* is to assist clinicians and transfusion medicine professionals identify the conditions and circumstances for which the use of intravenous immunoglobulin (IVIg) is clinically appropriate and able to be accessed under the National Blood Arrangements.

Development of first edition

In response to concerns that the AHMAC 2000 guidelines were in need of review, consultation about the development of criteria for IVIg use began in May 2004.

After a workshop was conducted in 2004 to gather information about the changes in the use of IVIg, the following activities, which led to the first edition of *the Criteria* being approved by Australian Health Minister's in December 2007, were undertaken:

- In 2004 and 2005, systematic literature reviews of the efficacy and risks of IVIg treatment were undertaken.
- In August 2005, a discussion paper about the development of the new guidelines was circulated for comment, which resulted in a report outlining proposed options for the development of criteria for use.
- Based on the evidence, a clinical proforma and exposure draft of *the Criteria* were developed and reviewed by sub-groups of clinical experts in the disciplines of neurology, haematology and immunology before being circulated to the clinical community for comment.
- In late 2006, a clinical workshop was conducted to seek input into the proposed proforma and content.
- Finally, *the Criteria* were revised based on the outcomes of workshop, additional information, and expert opinion for approval by health ministers in December 2007.

Further details of the arrangements and process for developing the first edition of *the Criteria* is provided at Appendix C.

2008 clarification process

As part of the process to implement the new *Criteria*, the National Blood Authority (NBA) established a clarification process in November 2008. A consultation group, comprising senior clinical advisers, IVIg Authorisers, clinical representatives from all jurisdictions and a Jurisdictional Blood Committee (JBC) representative, was consulted on specific queries that arose in relation to interpretation of *the Criteria*.

A Resolution Group, comprising the senior clinical advisers from the consultation group, and a JBC representative, was established to consider the input of the wider consultation group and to determine resolutions. The Criteria Resolution Group's consideration of the queries and comments resulted in some amendments to specific indications in *the Criteria*. The revisions were published on the NBA's website (www.nba.gov.au) in February 2009.

Where agreement could not be reached on how to address the clarification matters, they were forwarded to the next formal review process. Any indications that were judged new indications were not considered as part of the clarification process.

2010–11 Criteria Review

In accordance with government commitments, JBC initiated a review of *the Criteria* in 2010. The 2010–11 Criteria Review was based on the following principles:

- safe, effective and affordable alternative therapies are preferable to IVIg;
- the lowest dose of IVIg for the shortest period should be prescribed to achieve the desired clinical outcome; and
- measurable clinical outcomes must be achieved for IVIg therapy to continue.

The focus of the 2010–11 Criteria Review was limited to proposals for any of the following:

- chapter reassignment of existing conditions;
- modifications to existing conditions;
- removal of existing conditions; or
- inclusion of new conditions.

In addition to providing evidence to support a proposal submitted to the review, each proposal also had to demonstrate international parity.

A National IVIg Criteria Review Working Group (NICRWG) was established to oversee the 2010–11 Criteria Review process. The NICRWG comprised of representatives from both clinical and government sectors and individual experts who were engaged in the initial review.

The 2010–11 Criteria Review was undertaken using a rigorous and comprehensive process consisting of the following steps:

- formal submission process;
- review of submissions;
- systematic review process;
- development of revised wording;
- consensus process;
- public consultation; and
- finalisation and approval.

Throughout this process, experts from other clinical speciality areas were consulted for advice as required. Where possible, these individuals were sourced through relevant societies and colleges. Further details of the arrangements and process for developing the second edition of *the Criteria* is provided at Appendix C.

Assessment of evidence

During the development of the first edition of the Criteria and the 2010–11 Criteria Review, an assessment of the level of evidence was conducted.

The reviews followed the methods described in the National Health and Medical Research Council (NHMRC) handbook, *How to review the evidence: systematic review and assessment of the scientific literature* (NHMRC 2000)[8] and the *Evidence-based practice workbook* published by BMJ Books (Glasziou et al 2007)[9]. Reviews were restricted to studies published since 2004 (the date of the last major systematic literature review conducted on the indications for IVIg use), and aimed to:

- identify and critically appraise the scientific literature regarding the efficacy and risks of IVIg therapy;
- analyse scientific publications (including existing guidelines) that identify the key therapeutic issues in IVIg therapy; and
- include studies comparing IVIg with other treatments, including immunoglobulin administered by other routes, when such other treatments have been studied in comparison with intravenous administration.

Biotext Pty Ltd was engaged by the NBA to undertake the systematic review. Biotext Pty Ltd worked closely with the NICRWG to develop review questions based on the 'PICO' method (population, intervention, comparator and outcome) for each condition included in the review.

Where appropriate, an evidence statement was developed for each clinical question using the NHMRC Evidence Statement

8 National Health and Medical Research Council, 2000, *Handbook: How to review the evidence: systematic review and assessment of the scientific literature,* NHMRC, Canberra.

9 Glasziou P, Mar CD, Salisbury J, 2007, *Evidence-based practice workbook: bridging the gap between health care*, 2nd ed, Wiley-Blackwell, Massachusetts.

Form as described in *Additional levels of evidence and grades for recommendations for guideline developers* (NHMRC 2008).[10]

An evidence report was prepared for each systematic review undertaken. The evidence reports included specific details of the review methods and search terms used for that particular condition.

As this was a partial review of the Criteria, and to ensure consistency in any revised edition, each evidence report includes an assessment of the alignment of the literature against the categories previously used in the Criteria, outlined in Table 1. As many of the systematically reviewed conditions are rare and there is limited published clinical evidence, this approach also assisted in the consensus process.

Table 1 Level of evidence categories

Category	Studies	Evidence
1	High-quality randomised controlled trials (RCTs)	Clear evidence of benefit
2a	Some RCTs and/or case studies	Evidence of probable benefit – more research needed
2b	Some RCTs and/or case studies	Evidence of no probable benefit – more research needed
2c	High-quality RCTs with conflicting results	Conflicting evidence of benefit
3	High-quality RCTs	Clear evidence of no benefit
4a	Small case studies only	Insufficient data
4b	No included studies	—

10 www.nhmrc.gov.au/guidelines/consult/consultations/add_levels_grades_dev_guidelines2.htm

Condition proforma

The clinical criteria are contained within condition proforma and have been set out to cover four major issues:

- *Indication for IVIg use* – this specifies the purpose for which IVIg treatment would be considered once the condition has been confirmed using the proposed diagnostic parameters. The indication generally refers to the prevention or management of a particular manifestation of disease.
- *Qualifying criteria* – these are the criteria that should be fulfilled if IVIg is to be used. The qualifying criteria generally refer to matters such as patient selection, particular disease characteristics, disease severity, and any requirement for other treatments to have been demonstrably unsuccessful before IVIg is considered. The qualifying criteria are additional to diagnostic criteria.
- *Exclusion criteria* – these define the circumstances in which IVIg should not be used in patients who have the specified indication.
- *Review criteria* – these are the major clinical factors that should be taken into account when reviewing the progress of a patient who is receiving IVIg. They comprise parameters that indicate the patient's response to IVIg and may be used to decide whether to:
  - continue or cease IVIg therapy;
  - or alter the dose or frequency of administration.

To establish if the patient is eligible to access IVIg funded under the National Blood Arrangements, the above clinical criteria are to be used in conjunction with:

- the diagnostic criteria that may indicate consideration of a patient for the use of IVIg therapy; and
- the category of available evidence on the effectiveness of IVIg therapy for a diagnosed condition.

Replacement and immunomodulation therapy

Most conditions considered for IVIg therapy comprise either an immunoglobulin replacement or an immunomodulatory indication. A few conditions involve both inflammatory and immunodeficiency phenomena and both indications may co-exist, or arise at different times.

Replacement therapy

In general, replacement therapy is indicated for patients who have primary or secondary immunodeficiency diseases only if they have recurrent and/or severe infections and deficient or absent antibody production.

In rare cases, recurrent infection may be related to a functional failure of the immune system to mount protective antibody responses to antigenic challenge despite normal serum total IgG. This is most often demonstrated by a lack of antibody response to polysaccharide and/or protein vaccines (i.e. antigenic challenge). Infection risk in immunodeficiency may also be related to deficits in peripheral blood subpopulations of memory B-lymphocytes defined by flow cytometry. However, serum levels of individual subclasses of IgG1–4 are relatively poorly predictive of infection risk.

Isolated IgG subclass deficiency is not sufficient to warrant IVIg therapy (see *Specific antibody deficiency*).

With very rare exceptions, replacement therapy is not indicated for patients who have laboratory evidence of immunodeficiency in the absence of clinical infections (i.e. primary prevention of infection). This is for three reasons:

- the human immune system is characterised by the redundancy of host defence mechanisms;
- laboratory tests are imperfect in their prediction of immune function; and
- primary prevention strategies would impose an unnecessarily large burden on IVIg supply.

Exceptions to this rule include the severe combined primary immunodeficiencies of childhood.

Immunomodulation therapy

IVIg can interrupt the pathological immune responses that result in a wide range of human diseases, including various diseases of the immune system, the nervous system, the blood and blood-forming organs, and the skin. The immunomodulatory effects of IVIg are likely to be exerted by several mechanisms that appear to act in concert. These mechanisms, which are not fully understood, include the following:

- neutralisation of auto-antibodies;
- inhibition of complement binding and activation;
- effects mediated by Fc receptor binding;
- enhancing clearance of pathogenic auto-antibodies via saturation of the FcRn salvage pathway;
- suppression of pathogenic cytokines;
- neutralisation of super-antigens; and
- down-regulation of T or B cell function

In general, immunomodulatory doses of IVIg are higher than replacement doses and some of the immunomodulatory actions are dose-dependent.

For each immunomodulatory indication, qualifying criteria are described and review criteria are listed. The qualifying criteria should be applied in deciding whether and how to use IVIg. The review criteria are intended as a guide to clinicians who are assessing the effectiveness of IVIg therapy in individual patients and, in many instances, facing a decision to continue or cease IVIg therapy.

Dosing

The dosing of IVIg will vary, depending on whether IVIg is for replacement therapy or immunomodulation and the individual patient's condition, clinical presentation, comorbidities, concurrent therapy and response. While there is some evidence for the use of dosing based on lean body weight, further research is required. The lowest dose for the shortest duration required to achieve the desired outcome should be chosen.

Research priorities

The systematic review of the available literature of treatment options for IVIg showed there was a paucity of high-quality studies. During the development of *the Criteria* and the 2010–11 Criteria Review, a number of gaps in knowledge and evidence were identified:

- The need to assess the efficacy of alternative approaches to determining IVIg dosing for specific conditions including lean body mass based dosing.
- The need for an improved database of agreed minimum data fields that include information on the treatment outcomes of IVIg.
- The need for a mechanism to review and analyse IVIg use for conditions with high use, high rate of growth and/or high variability in use.
- The role of subcutaneous immunoglobulin as an alternative to IVIg.

Maintenance

Governments recognise the need for the conditions identified for IVIg therapy and the clinical criteria for IVIg use to be reviewed regularly to take account of the evolving processes of disease diagnosis, treatment and outcome evaluation.

5

Conditions for which IVIg has an established therapeutic role

5. Conditions for which IVIg has an established therapeutic role

This chapter comprises conditions for which intravenous immunoglobulin (IVIg) use is well established in Australia. There is evidence from reasonable-quality studies and clinical support for IVIg therapy in selected patients. For a number of conditions, IVIg is first-line therapy and may be the only established treatment option; for example, as replacement therapy in primary immunodeficiency disease.

The information provided is not intended to be a definitive reference on any of the conditions, or to be used by clinicians for actual diagnosis or management. Expert clinical opinion about treatment regimens should always be sought. In particular, dose and schedule information is provided as a guide only. The aim in each case is to find the minimal effective dose and optimise the treatment of each individual.

Table 2 Conditions for which IVIg has an established therapeutic role as immunoglobulin-replacement therapy

Condition	Evidence level	Page
Acquired hypogammaglobulinaemia secondary to haematological malignancies (chronic lymphocytic leukaemia, multiple myeloma, non-Hodgkin lymphoma and other relevant malignancies, and post-haemopoietic stem cell transplantation)	2a	48
Primary immunodeficiency diseases with antibody deficiency	2a	55

Table 3 Conditions for which IVIg has an established therapeutic role as immunomodulation therapy

Condition	Evidence level	Page
Chronic inflammatory demyelinating polyneuropathy	1	58
Guillain–Barré syndrome	1	62
Idiopathic (autoimmune) thrombocytopenic purpura (ITP) in adults	2a	66
Inflammatory myopathies (polymyositis, dermatomyositis, inclusion body myositis)	2a	73
Kawasaki disease	1	79
Lambert–Eaton myasthenic syndrome	2a	83
Multifocal motor neuropathy	1	87
Myasthenia gravis	1	92
Neonatal haemochromatosis	2a	96
Stiff person syndrome	2a	99

Medical condition	Acquired hypogammaglobulinaemia secondary to haematological malignancies chronic lymphocytic leukaemia (CLL), multiple myeloma (MM), non-Hodgkin lymphoma (NHL) and other relevant malignancies, and post-haemopoietic stem cell transplantation (HSCT)
Indication for IVIg use	Prevention of recurrent bacterial infections due to antibody failure associated with haematological malignancies. Prevention of recurrent bacterial infections in patients undergoing HSCT for haematological malignancies.
Level of evidence	Evidence of probable benefit (Category 2a).
Description and diagnostic criteria	The manifestations of haematological malignancies can include a wide range of symptoms and physical and laboratory abnormalities in an individual patient. For diagnostic criteria, refer to the current World Health Organization classification criteria.
Justification for evidence category	One small crossover study of 12 patients with CLL or NHL reported that the number of serious bacterial infections was significantly decreased ($p = 0.001$) in the months in which patients received IgG every three weeks for one year. Serious bacterial infections showed a trend to be associated with an IgG level <6.4 g/L.

Medical condition	Acquired hypogammaglobulinaemia secondary to haematological malignancies chronic lymphocytic leukaemia (CLL), multiple myeloma (MM), non-Hodgkin lymphoma (NHL) and other relevant malignancies, and post-haemopoietic stem cell transplantation (HSCT)
Justification for evidence category continued	Three randomised controlled trials (RCTs) and one crossover trial of low–moderate quality reported a reduction in infection rates in CLL patients with hypogammaglobulinaemia after three to four-weekly administration of IVIg for one year. One placebo-controlled RCT of monthly IVIg given to 82 MM patients for one year (with 22 withdrawing due to reaction) concluded that IVIg protects against life-threatening infections and significantly reduces risk of recurrent infections. The greatest benefit was seen in individuals who had a poor response to pneumococcal vaccine. A small prospective RCT with 30 multiple myeloma patients reported a possible decrease in symptoms of chronic bronchitis. A recent systematic review and meta-analysis of patients undergoing HSCT [60 trials (›4000 patients)] reported an increased risk of veno-occlusive disease with no survival benefit particularly in studies conducted since 2000. The authors concluded that routine prophylaxis with IVIg is not supported, but suggest that its use may be considered in lymphoproliferative disorder patients with hypogammaglobulinaemia and recurrent infections, for reduction of clinically documented infections.

Medical condition	Acquired hypogammaglobulinaemia secondary to haematological malignancies chronic lymphocytic leukaemia (CLL), multiple myeloma (MM), non-Hodgkin lymphoma (NHL) and other relevant malignancies, and post-haemopoietic stem cell transplantation (HSCT)
Qualifying criteria for IVIg therapy	Diagnosis of acquired hypogammaglobulinaemia secondary to haematological malignancies or stem cell transplantation with: • Recurrent or severe bacterial infection(s) and evidence of hypogammaglobulinaemia (excluding paraprotein); OR • Hypogammaglobulinaemia with IgG ‹4 g/L (excluding paraprotein). **Note:** For data tracking purposes, the type of malignancy being treated should be recorded with each request for IVIg.
Exclusion criteria	The following conditions should not be approved under this indication: 1. HIV in children (see page 185); 2. Transplantation-related immunomodulation (solid organ transplantation; (see page 208); 3. Secondary hypogammaglobulinaemia (including iatrogenic immunodeficiency (see page 106).

Medical condition	Acquired hypogammaglobulinaemia secondary to haematological malignancies chronic lymphocytic leukaemia (CLL), multiple myeloma (MM), non-Hodgkin lymphoma (NHL) and other relevant malignancies, and post-haemopoietic stem cell transplantation (HSCT)
Review criteria for assessing the effectiveness of IVIg use	Six-monthly review to assess clinical benefit. Cessation of IVIg should be considered, at least after each 12 months of therapy, extended as required to enable cessation of therapy in September/October, with repeat clinical and/or immunological evaluation before re-commencement of therapy. Written confirmation from the treating physician that: • an annual review has been undertaken; • the patient had demonstrated clinical benefit; • a trial period of cessation of IVIg for the purpose of immunological evaluation is medically contraindicated on safety grounds. In principle, IVIg should be continued or renewed only if there is a demonstrated clinical benefit.
Dose	**Maintenance dose:** 0.4 g/kg every four weeks, modified to achieve an IgG trough level of at least the lower limit of the age-specific serum IgG reference range. **Loading dose:** One additional dose of 0.4 g/kg in the first month of therapy is permitted if the serum IgG level is <4 g/L.

Medical condition	Acquired hypogammaglobulinaemia secondary to haematological malignancies chronic lymphocytic leukaemia (CLL), multiple myeloma (MM), non-Hodgkin lymphoma (NHL) and other relevant malignancies, and post-haemopoietic stem cell transplantation (HSCT)
Dose continued	Subcutaneous administration of immunoglobulin can be considered as an alternative to IVIg. A suggested dose is 0.1 g/kg lean body mass every week modified to achieve an IgG trough level of at least the lower limit of the age-specific serum IgG reference range. **Refer to the current product information sheet for further information.** **The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.**

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Medical condition	Primary immunodeficiency diseases (PID) with antibody deficiency This excludes: 1. specific antibody deficiency (see page 110); 2. IgG subclass deficiency (not funded see page 112).
Indication for IVIg use	Management of infection related to antibody deficiency.
Level of evidence	Evidence of probable benefit (Category 2a).
Description and diagnostic criteria	PID comprise a group of more than 120 separate conditions. Many of these are manifest by failure of protective antibody production. Key diagnoses include common variable immunodeficiency (CVID), severe combined immunodeficiencies, transient hypogammaglobulinaemia of infancy, Wiskott Aldrich syndrome and X-linked agammaglobulinaemia. In certain conditions, such as Wiskott Aldrich syndrome, antibody failure may not be manifest as hypogammaglobulinaemia but functional antibody responses will be impaired. Some PID does not involve antibody failure, such as chronic granulomatous disease and deficiencies of complement components. In these cases, antibody replacement therapy is not justified.
Justification for evidence category	The Biotext (2004) review reported level 2a evidence for the use of IVIg in the treatment of common variable immunodeficiency and primary hypogammaglobulinaemia.
Qualifying criteria for IVIg therapy	In each case, a specific PID diagnosis must be established under the supervision of a specialist clinical immunologist and the diagnosis must be advised for IVIg to be approved.

Medical condition	Primary immunodeficiency diseases (PID) with antibody deficiency This excludes: 1. specific antibody deficiency (see page 110); 2. IgG subclass deficiency (not funded see page 112).
Exclusion criteria for IVIg therapy	The following conditions should not be approved under this indication: 1. Miscellaneous hypogammaglobulinaemia (see *Secondary hypogammaglobulinaemia*, page 106) 2. Specific antibody deficiency (see page 110) 3. IgG subclass deficiency (not funded; see page 112).
Review criteria for assessing the effectiveness of IVIg use	Review criteria for primary immunodeficiency diseases with antibody deficiency are not mandated. Nevertheless, the following may be of value to the clinician: • frequency of clinical episodes of infection • trough levels; and • renal function.
Dose	**Maintenance dose:** 0.4 g/kg every four weeks, modifying dose and schedule to achieve IgG trough level of at least the lower limit of the age-specific serum IgG reference range. **Loading dose:** One additional dose of 0.4 g/kg in the first month of therapy is permitted if the serum IgG level is markedly reduced. Chronic suppurative lung disease: Dosing to achieve IgG trough level of up to 9 g/L is permitted if chronic suppurative lung disease is not adequately controlled at an IgG trough level at the lower limit of the age-specific serum IgG reference range.

Medical condition	Primary immunodeficiency diseases (PID) with antibody deficiency This excludes: 1. specific antibody deficiency (see page 110); 2. IgG subclass deficiency (not funded see page 112).
Dose continued	Subcutaneous administration of immunoglobulins is a suitable alternative to IVIg in this disease. **Refer to the current product information sheet for further information.** **The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.**

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Medical condition	Chronic inflammatory demyelinating polyneuropathy (CIDP), (including IgG and IgA paraproteinaemic neuropathies)
Indication for IVIg use	First-line treatment for CIDP with treatment initiated when progression is rapid, or walking is compromised, or there is significant functional impairment.
Level of evidence	Clear evidence of benefit (Category 1).
Description and diagnostic criteria	CIDP is an acquired sensorimotor polyneuropathy characterised by a progressive or relapsing/remitting course with evidence of demyelination on electrophysiological or pathological studies and response to immunomodulating therapies. There is no specific diagnostic test, but characteristic clinical and laboratory findings help distinguish this disorder from other immune mediated neuropathic syndromes. Serum protein electrophoresis with immunofixation may be indicated to search for monoclonal gammopathy and associated conditions.
Justification for evidence category	The Biotext (2004) review found one Cochrane review of six RCTs with a total sample size of 170. The quality of the studies was low–moderate, found IVIg improved disability in the short-term, and had comparable results to treatment with plasma exchange or prednisolone. The Frommer and Madronino (2006) review found one low-quality RCT with a total sample size of 20, which demonstrated that more patients responded to immunoadsorption than IVIg, although the baseline disease duration was higher in the IVIg group. Differences were not significant.

Medical condition	Chronic inflammatory demyelinating polyneuropathy (CIDP), (including IgG and IgA paraproteinaemic neuropathies)
Qualifying criteria for IVIg therapy	1. Diagnosis of CIDP verified by a neurologist; AND 2. Significant functional impairment of activities of daily living (ADL).
Review criteria for assessing the effectiveness of IVIg use	IVIg should be used for three to six months (three to six courses) before determining whether the patient has responded. Most individuals will respond within three months unless there is significant axonal degeneration whereby a six-month course will be necessary. If there is no benefit after three to six courses, IVIg therapy should be abandoned. **Review** Regular review by a neurologist is required: frequency as determined by clinical status of patient. For stable patients on maintenance treatment, review by a neurologist is required at least annually. **Effectiveness** Clinical documentation of effectiveness is necessary for continuation of IVIg therapy. Effectiveness can be demonstrated by objective findings of either: 1. improvement in functional scores (activities of daily living — ADLs) or quantitative muscle scores or Medical Research Council (MRC) muscle assessment or neuropathy score; or 2. stabilisation of disease as defined by stable functional scores (ADLs) or quantitative muscle scores or MRC muscle assessment or neuropathy score after previous evidence of deterioration in one of these scores.

Medical condition	Chronic inflammatory demyelinating polyneuropathy (CIDP), (including IgG and IgA paraproteinaemic neuropathies)
Dose	**Induction:** 2 g/kg in 2 to 5 divided doses. **Maintenance:** 0.4–1 g/kg, 2–6 weekly. The amount per dose should be titrated to the individual's response. Aim for minimum dose to maintain optimal functional status. **Refer to the current product information sheet for further information.** **The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.**

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Medical condition	Guillain–Barré Syndrome (GBS)
Indication for IVIg use	GBS and its variants with significant disability and progression.
Level of evidence	Clear evidence of benefit (Category 1).
Description and diagnostic criteria	GBS is the commonest cause of acute flaccid paralysis in the West. The syndrome typically presents with rapidly progressive, relatively symmetrical ascending limb weakness consistent with a polyradiculoneuropathy and often with associated cranial nerve involvement. Motor signs and symptoms usually predominate over sensory signs and symptoms. Loss of tendon reflexes occurs in most cases. Major complications include respiratory failure and autonomic dysfunction. The disease is monophasic, reaching its nadir usually within two weeks, although arbitrary definition accepts a limit of four weeks. A plateau phase of variable duration follows the nadir before gradual recovery. Although recovery is generally good or complete in the majority of patients, persistent disability has been reported to occur in about 20% and death in 4 to 15% of patients. IVIg has been shown to have the same efficacy as plasma exchange. The choice is based on availability, practicality, convenience, cost, and ease or safety of administration (Asia–Pacific IVIg Advisory Group). *Investigations* There is no biological marker for GBS. It is diagnosed by clinical recognition of rapidly evolving paralysis with areflexia. Investigations include the following:

Medical condition	Guillain–Barré Syndrome (GBS)
Description and diagnostic criteria continued	• Cerebrospinal fluid (CSF) protein elevation, although the level may be normal in the first two weeks of illness. The CSF white cell count may rise transiently, but a sustained pleocytosis suggests an alternative diagnosis or association with an underlying illness (e.g. HIV). • Electrophysiological studies may show changes after the first or second week of the illness, including conduction block, conduction slowing or abnormalities in F waves.
Justification for evidence category	One systematic review of nine RCTs of moderate quality found IVIg hastened recovery in adults with GBS to the same degree as plasma exchange (Biotext 2004). One low-quality RCT with a small sample size (n=21), in which the randomisation of patients to the IVIg treatment group was skewed, was identified. Children who received IVIg treatment showed earlier signs of improvement, and disability scores were lower at four weeks than the placebo group (Frommer and Madronio 2006).
Qualifying criteria for IVIg therapy	Patients with GBS (or variant) with significant disability and disease progression. **Note:** Assessment by a neurologist is recommended, but not mandatory.

Medical condition	Guillain–Barré Syndrome (GBS)
Review criteria for assessing the effectiveness of IVIg use	Primary outcome measures: improvement in disability grade four weeks after treatment: 0. healthy 1. minor symptoms or signs of neuropathy but capable of manual work 2. able to walk without support of a stick but incapable of manual work 3. able to walk with a stick, appliance or support 4. confined to bed or chair bound 5. requiring assisted ventilation 6. dead Secondary outcome measures: 1. time until recovery of unaided walking 2. time until recovery of walking with aid 3. time until discontinuation of ventilation (for those ventilated) 4. death or disability (inability to walk without aid after 12 months) 5. treatment-related fluctuation
Dose	2 g/kg in 2 to 5 divided doses. Approximately 10% of patients relapse, which may require a second treatment with IVIg. A second dose of IVIg must only be on the advice of and after assessment by a neurologist. **Refer to the current product information sheet for further information.** **The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.**

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Medical condition	Idiopathic (autoimmune) thrombocytopenic purpura (ITP) — adult
Indication for IVIg use	**1. Refractory acute ITP *on the recommendation of a clinical haematologist*** Patients with severe thrombocytopenia (platelets ‹30x10^9/L) who have not responded to corticosteroid therapy. **2. ITP with life-threatening haemorrhage or the potential for life-threatening haemorrhage** Patients with severe thrombocytopenia (‹30x10^9/L) with clinical evidence of a haemostatic defect (e.g. mucous membrane haemorrhage) or active bleeding. **3. ITP in pregnancy** a. Platelets ‹30x10^9/L b. Impending delivery **4. Specific circumstances** a. Planned surgery b. Other concurrent risk factors for bleeding (e.g. concurrent anti-coagulant therapy) c. Severe ITP (platelets ‹30x10^9/L) where corticosteroids and immunosuppression are contraindicated d. Chronic ITP under the guidance of a clinical haematologist, as adjunctive therapy or where other therapies have failed or are not appropriate **5. HIV–associated ITP** Patients with severe ITP associated with HIV infection.
Level of evidence	Evidence of probable benefit (Category 2a).

Medical condition	Idiopathic (autoimmune) thrombocytopenic purpura (ITP) — adult
Description and diagnostic criteria	ITP is a reduction in platelet count (thrombocytopenia) resulting from shortened platelet survival due to anti-platelet antibodies. When counts are very low (<30x10^9/L), bleeding into the skin (purpura) and mucous membranes can occur. Bone marrow platelet production (megakaryopoiesis) is morphologically normal. In some cases, there is additional impairment of platelet function related to antibody binding to glycoproteins on the platelet surface. ITP is divided into chronic and acute forms. It is a common finding in patients with HIV, and while it may be found at any stage of the infection, its prevalence increases as HIV disease advances. Around 80% of adults with ITP have the chronic form of disease. The highest incidence of chronic ITP is in women aged 15–50 years, although some reports suggest increasing incidence with age. Chronic ITP may relapse and remit spontaneously and the course may be difficult to predict. If the platelet count can be maintained at a level that prevents spontaneous bleeding or bruising, the outlook is good.
Justification for evidence category	Five small prospective studies, including three randomised studies, demonstrated equivalent efficacy of IVIg in comparison to prednisone 1 mg/kg/day and high-dose dexamethasone regimen. Overall, the studies found a dose response with more rapid increment in platelet counts at scheduling ≥0.8 g/kg on day one compared with 0.4 g/kg/day for three days.

Medical condition	Idiopathic (autoimmune) thrombocytopenic purpura (ITP) — adult
Justification for evidence category continued	A small controlled study (10 patients in each arm) of HIV-positive patients with severe thrombocytopenia reported possible benefit for the restoration and maintenance of platelet count for the duration of the haemorrhagic disorder (Biotext 2004). An international consensus statement from January 2010 (Provan et al 2010) reported on new data and provided consensus-based recommendations relating to diagnosis and treatment of ITP in adults, in children, and during pregnancy. This statement concluded that few RCTs have been conducted and that multi-centre, prospective RCTs are required.
Qualifying criteria for IVIg therapy	**1. Refractory acute ITP:** a. Patients qualify for initial IVIg therapy when conventional doses of corticosteroids (0.5-2.0 mg/kg prednisolone, or equivalent) have failed to improve the platelet count or stop bleeding within a clinically appropriate time frame, as assessed by a clinical haematologist. The objective of therapy is to induce a prompt increase in the platelet count (to ›30x10^9/L) while other therapies are introduced. b. Patients qualify for continuing doses when splenectomy has failed or is contraindicated AND where therapy with at least one second-line agent has been unsuccessful in maintaining a platelet count ›30x10^9/L. With ongoing therapy, IVIg may be administered to achieve a platelet count ›30x10^9/L. Further doses may be administered in responsive patients for up to 6 months (thereafter see *Chronic refractory ITP*). The frequency and dose should be titrated to maintain a platelet count of at least 30x10^9/L. The objective of therapy is to maintain a safe platelet count while other therapeutic options are explored.

Medical condition	Idiopathic (autoimmune) thrombocytopenic purpura (ITP) — adult
Qualifying criteria for IVIg therapy continued	**2. ITP with life-threatening haemorrhage or the potential for life-threatening haemorrhage:** IVIg therapy may be given when conventional doses of corticosteroids have failed or in conjunction with steroids when a rapid response is required. **3. ITP in pregnancy:** a. Platelets ‹30x10^9/L: IVIg therapy may be used to avoid corticosteroids, immunosuppressive agents and splenectomy. Further doses titrated to maintain a platelet count ›30x10^9/L may be administered every three to four weeks throughout the pregnancy. b. Impending delivery: IVIg therapy may be used to achieve a platelet count considered safe for delivery (80–100x10^9/L). **4. Specific circumstances:** a. Planned surgery: IVIg may be used to achieve a platelet count considered safe for surgery. The safe threshold will vary with the nature of the surgery *(Recommended platelet counts for patients without concurrent risks of bleeding: minor dental work ›30x10^9/L, minor surgery ›50x10^9/L, major surgery ›80x10^9/L, major neurosurgery ›100x10^9/L.)* b. Severe ITP: IVIg may be used where corticosteroids and immunosuppression are contraindicated. c. Chronic refractory ITP unresponsive to all other available therapies: These patients may be considered for long-term maintenance therapy with IVIg, subject to regular review by a haematologist.

Medical condition	Idiopathic (autoimmune) thrombocytopenic purpura (ITP) — adult
Qualifying criteria for IVIg therapy continued	**5. HIV-associated ITP:** a. Failure of antiretroviral therapy with platelet count <30x10^9/L; OR b. Life-threatening haemorrhage secondary to thrombocytopenia.
Review criteria for assessing the effectiveness of IVIg use	• In chronic refractory ITP, six-month review assessing evidence of clinical benefit; • Resolution of bleeding; • Increment in platelet count.
Dose	**Initial therapy:** 1–2 g/kg as a single or divided dose. **Ongoing therapy:** When indicated, 1–2 g/kg in single or divided dose at 4 to 6 weekly intervals titrated to symptoms and platelet count. **Dosing above 1 g/kg per day is contraindicated for some IVIg products.** **Refer to the current product information sheet for further information.** **The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.**

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Medical condition	Inflammatory myopathies: polymyositis (PM), dermatomyositis (DM) and inclusion body myositis (IBM)
Indication for IVIg use	1. Patients with PM or DM with significant muscle weakness unresponsive to corticosteroids and other immunosuppressive agents. 2. Patients with IBM who have dysphagia affecting function. 3. Patients with rapidly progressive IBM.
Level of evidence	Evidence of probable benefit (Category 2a).
Description and diagnostic criteria	The inflammatory myopathies are a group of three discrete disorders of skeletal muscle: DM, PM and IBM. These disorders are acquired and have in common the occurrence of significant muscle weakness and the presence of an inflammatory response within the muscle. The diagnosis of DM, PM or IBM is usually made by neurologists or rheumatologists, and relies on the combination of careful clinical evaluation, an elevated creatine kinase level, electromyography and muscle biopsy.
Justification for evidence category	PM: The Biotext (2004) review included one prospective case-series study of 35 adults with chronic refractory polymyositis. IVIg may be of benefit in these patients, improve mean muscle power and allow reduction in dose of corticosteroid. Further research is needed.

Medical condition	Inflammatory myopathies: polymyositis (PM), dermatomyositis (DM) and inclusion body myositis (IBM)
Justification for evidence category continued	DM: The Biotext (2004) review included one double-blind, placebo-controlled trial considered of low quality of 15 patients with biopsy-confirmed, treatment-resistant dermatomyositis. IVIg treatment combined with prednisone led to significant improvement in muscle strength and neuromuscular symptoms of patients in the intervention group (n=8). IBM: The Biotext (2004) review included three small controlled studies, two of which had a crossover design. A total sample of 77 patients diagnosed with IBM was followed for between 4 and 12 months. The three studies showed possible slight benefit in reducing endomysial inflammation, disease progression and severity of IBM. Further research is needed. One submission reported the effectiveness of IVIg therapy for PM and DM as add-on therapy for patients who have not responded to steroids and immunosuppression (NSW IVIg User Group). A further submission confirms a role for IVIg as add-on maintenance therapy in some patients resulting in an increased chance of complete remission and reduction in corticosteroid dose. A third submission suggests that IVIg can be tried as add-on treatment for patients with PM or DM who have not responded adequately to corticosteroids and second-line immunosuppressive agents (Asia–Pacific IVIg Advisory Board 2004). Weak evidence suggests that it may benefit patients with dysphagia associated with IBM (Asia–Pacific IVIg Advisory Board 2004).

Medical condition	Inflammatory myopathies: polymyositis (PM), dermatomyositis (DM) and inclusion body myositis (IBM)
Qualifying criteria for IVIg therapy	Diagnosis made by a neurologist, rheumatologist or immunologist of: 1. Patients with PM or DM who have significant muscle weakness or dysphagia and have not responded to corticosteroids and other immunosuppressive agents; OR 2. Patients with IBM who have dysphagia affecting function; OR 3. Patients with rapidly progressive IBM.
Exclusion criteria for IVIg therapy	Expert consensus does not recommend IVIg to treat the limb weakness of IBM.
Review criteria for assessing the effectiveness of IVIg use	IVIg should be used for three to six months (three to six courses) before determining whether the patient has responded. If there is no benefit after three to six courses, IVIg therapy should be abandoned. **Review** Regular review by a neurologist, rheumatologist, or clinical immunologist is required; frequency as determined by clinical status of patient. For stable patients on maintenance treatment, review by a specialist is required at least annually.

Medical condition	Inflammatory myopathies: polymyositis (PM), dermatomyositis (DM) and inclusion body myositis (IBM)
Review criteria for assessing the effectiveness of IVIg use continued	**Effectiveness** Clinical documentation of effectiveness is necessary for continuation of IVIg therapy. Effectiveness can be demonstrated by objective findings of either: 1. Improvement in functional scores activities of daily living (ADL) or quantitative muscle scores or Medical Research Council (MRC) muscle assessment; OR 2. Stabilisation of disease as defined by stable functional scores (ADLs) or quantitative muscle scores or MRC muscle assessment after previous evidence of deterioration in one of these scores.
Dose	**Induction:** 2 g/kg in 2 to 5 divided doses. **Maintenance:** 0.4–1 g/kg, 4–6 weekly. Aim for the minimum dose to maintain optimal functional status. **Dosing above 1 g/kg per day is contraindicated for some IVIg products.** **Refer to the current product information sheet for further information.** **The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.**

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Medical condition	Kawasaki disease (mucocutaneous lymph node syndrome)
Indication for IVIg use	Early in Kawasaki disease to prevent coronary artery pathology.
Level of evidence	Clear evidence of benefit (Category 1).
Description and diagnostic criteria	Kawasaki disease is an acute, febrile, multi-system disease of children and young infants often involving the coronary arteries. Coronary artery aneurysms may occur from the second week of illness during the convalescent stage. The cause of the condition is unknown but there is evidence that the characteristic vasculitis results from an immune reaction characterised by T-cell and macrophage activation to an unknown antigen, secretion of cytokines, polyclonal B-cell hyperactivity, and the formation of autoantibodies to endothelial cells and smooth muscle cells. It is likely that in genetically susceptible individuals, one or more uncharacterised common infectious agents, possibly with super-antigen activity, may trigger the disease. **Diagnosis** A diagnosis of Kawasaki disease is generally made if fever of four or more days' duration is associated with at least four of the following changes, which often appear sequentially: • bilateral (non-purulent) conjunctival injection; • changes of the mucous membranes of the upper respiratory tract and oropharynx, including diffuse redness of pharyngeal mucosa, dry fissured lips, red fissured lips, and/or 'strawberry tongue'; • changes of the extremities, including peripheral erythema, peripheral oedema, and subsequent periungual or more generalised desquamation;

Medical condition	Kawasaki disease (mucocutaneous lymph node syndrome)
Description and diagnostic criteria continued	• polymorphous rash; • cervical lymphadenopathy. A diagnosis of Kawasaki disease may be made if fever and fewer than four of the changes listed above are present where there is strong clinical suspicion of Kawasaki disease (refer to Newburger 2004). Between 10% and 20% of cases, particularly in younger infants, present with fever and fewer than four of the listed criteria. Expert advice should be sought. Data support the use of IVIg while there is ongoing inflammation (usually taken as ongoing fever or raised acute inflammatory markers). Prognosis is worse if IVIg is used 10 days post-onset, but should be used at any time if there is evidence of inflammation. Up to 15% of patients do not respond to initial IVIg therapy. Consensus is for re-treatment with 2 g/kg of IVIg before considering steroids.
Justification for evidence category	One high-quality systematic review of 16 RCTs that showed that IVIg is of benefit in treating Kawasaki disease (Biotext 2004).
Qualifying criteria for IVIg therapy	Clinical diagnosis of Kawasaki disease by a paediatrician or immunologist.
Dose	2 g/kg in a single dose over 10–12 hours unless cardiac function necessitates the administration of a prolonged or divided treatment dose, usually once only. Re-treatment with 2 g/kg in a single dose may be given when there is ongoing inflammation.

Medical condition	Kawasaki disease (mucocutaneous lymph node syndrome)
Dose continued	**Dosing above 1 g/kg per day is contraindicated for some IVIg products.** **Refer to the current product information sheet for further information.** **The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.**

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Medical condition	Lambert–Eaton myasthenic syndrome (LEMS)
Indication for IVIg use	Short-term therapy for severely affected nonparaneoplastic LEMS patients.
Level of evidence	Evidence of probable benefit (Category 2a).
Description and diagnostic criteria	LEMS is a disorder of neuromuscular transmission first recognised clinically in association with lung cancer and subsequently in cases in which no neoplasm was detected. Patients with LEMS have a presynaptic neuromuscular junction defect. The clinical picture is characterised by proximal muscle weakness with augmentation of strength after exercise, mild oculomotor signs, depressed deep tendon reflexes and autonomic dysfunction (dry mouth, constipation, erectile failure).
Justification for evidence category	In the Biotext (2004) review, one systematic review (containing one RCT with 9 patients) and one case series of 7 patients with a crossover design were included. IVIg appeared to provide some benefit to patients with LEMS. However, both studies only included a small number of patients. Expert consensus states that IVIg produces temporary improvement in patients with LEMS. It therefore has a role as second line therapy (Asia–Pacific IVIg Advisory Board 2004). One submission to the National Blood Authority reported on a randomised controlled trial that showed significant improvement in strength associated with a decline in the level of pathogenic antibodies (NSW IVIg User Group).

Medical condition	Lambert–Eaton myasthenic syndrome (LEMS)
Qualifying criteria for IVIg therapy	1. Mandatory assessment by a neurologist; AND 2. Severely affected nonparaneoplastic LEMS patients in whom other therapy (e.g. with 3,4-diaminopyridine) has failed.
Review criteria for assessing the effectiveness of IVIg use	IVIg should be used for three to six months (three to six courses) before determining whether the patient has responded. If there is no benefit after three to six courses, IVIg therapy should be abandoned. **Review** Regular review by neurologist is required: frequency as determined by clinical status of patient. Initial review three to six monthly. For stable patients on maintenance treatment review by a neurologist is required at least annually. **Effectiveness** Clinical documentation of effectiveness is necessary for continuation of IVIg therapy. Effectiveness can be demonstrated by objective findings of either: 1. Improvement in functional scores activities of daily living (ADL) or quantitative muscle scores or Medical Research Council (MRC) muscle assessment; OR 2. Stabilisation of disease as defined by stable functional scores (ADLs) or quantitative muscle scores or MRC muscle assessment after previous evidence of deterioration in one of these scores.

Medical condition	Lambert–Eaton myasthenic syndrome (LEMS)
Dose	**Induction:** 2 g/kg in 2 to 5 divided doses. **Maintenance:** 0.4–1 g/kg, 2–6 weekly. Aim for minimum dose to maintain optimal functional status. **Refer to the current product information sheet for further information.** **The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.**

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Medical condition	Multifocal motor neuropathy (MMN)
Indication for IVIg use	First-line therapy for MMN.
Level of evidence	Clear evidence of benefit (Category 1).
Description and diagnostic criteria	MMN is a relatively rare disorder characterised by slowly progressive, asymmetric, predominately distal limb weakness without sensory impairment. Weakness often begins in the arms and the combination of weakness, wasting, cramps and fasciculations may suggest a diagnosis of motor neuron disease. However, clinical examination may demonstrate that the pattern of weakness follows the distribution of individual nerves rather than a spinal segmental pattern. Investigations will typically show conduction block on nerve conduction studies. IgM anti-GM-1 antibodies have been reported in a large number of patients with MMN and provide confirmatory evidence but are not essential for the diagnosis.
Justification for evidence category	The Biotext (2004) review found six low-quality case studies or crossover RCTs with a total sample size of 68 patients. A possible benefit of IVIg treatment in these patients was observed, although five studies were not controlled. The Frommer and Madronio (2006) review found one high-quality systematic review (a Cochrane review) of four crossover RCTs with 34 patients. Evidence for improvement in muscle strength with IVIg and limited evidence of a reduction in disability after IVIg administration.

Medical condition	Multifocal motor neuropathy (MMN)
Justification for evidence category continued	Consensus statements assert that IVIg is the only safe treatment demonstrated to work in patients with MMN. It is recommended in those who have significant disability. Dose and monitoring is similar to chronic inflammatory demyelinating polyneuropathy. IVIg therapy is usually long term, but the minimum effective dose for each patient should be sought. Plasma exchange and steroids appear to cause a worsening in the condition of patients with MMN with conduction block. Regular maintenance doses of IVIg are needed. The National Guideline Clearinghouse recommends the use of IVIg in the treatment of patients with progressive, symptomatic MMN that has been diagnosed using electrophysiology, ruling out other possible conditions that may not respond to IVIg treatment.
Qualifying criteria for IVIg therapy	Patients who have multifocal motor neuropathy, with a typical clinical phenotype, with or without persistent conduction block, as diagnosed by a neurologist.
Exclusion criteria for IVIg therapy	• Presence of upper motor neuron signs. • Significant sensory impairment without an adequate alternative explanation.
Review criteria for assessing the effectiveness of IVIg use	IVIg should be used for three to six months (three to six courses) before determining whether the patient has responded. Most individuals will respond within three months unless there is significant axonal degeneration whereby a six-month course will be necessary. If there is no benefit after three to six courses, IVIg therapy should be abandoned.

Medical condition	Multifocal motor neuropathy (MMN)
Review criteria for assessing the effectiveness of IVIg use continued	**Review** Regular review by neurologist is required: frequency as determined by clinical status of patient. For stable patients on maintenance treatment, review by a neurologist is required at least annually. **Effectiveness** Clinical documentation of effectiveness is necessary for continuation of IVIg therapy. Effectiveness can be demonstrated by objective findings of either: 1. Improvement in functional scores activities of daily living (ADLs) or quantitative muscle scores or Medical Research Council (MRC) muscle assessment or neuropathy score; OR 2. Stabilisation of disease as defined by stable functional scores (ADLs) or quantitative muscle scores or MRC muscle assessment or neuropathy score after previous evidence of deterioration in one of these scores.
Dose	**Induction:** 2 g/kg in 2 to 5 divided doses. **Maintenance:** 0.4–2 g/kg, 2–6 weekly. The amount per dose should be titrated to the individual's response. Aim for the minimum dose to maintain optimal functional status. **Dosing above 1 g/kg per day is contraindicated for some IVIg products.**

Medical condition	Multifocal motor neuropathy (MMN)
Dose continued	**Refer to the current product information sheet for further information.** **The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.**

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Medical condition	Myasthenia gravis (MG)
Indication for IVIg use	1. As an alternative treatment to plasma exchange in acute exacerbation (myasthenic crisis) or before surgery and/or thymectomy. 2. As maintenance therapy for moderate to severe MG when other treatments have been ineffective or caused intolerable side effects.
Level of evidence	Clear evidence of benefit (Category 1).
Description and diagnostic criteria	MG is an autoimmune disease associated with the presence of antibodies to acetylcholine receptors (AChR) or to muscle-specific tyrosine kinase (MuSK) at the neuromuscular junction. Some patients with myasthenia gravis are antibody negative. Clinical features are characterised by fluctuating weakness and fatigability of voluntary muscles, namely levator palpebrae, extraocular, bulbar, limb and respiratory muscles. Patients usually present with unilateral or bilateral drooping of eyelid (ptosis), double vision (diplopia), difficulty in swallowing (dysphagia) and proximal muscle weakness. Weakness of respiratory muscles can result in respiratory failure in severe cases or in acute severe exacerbations (myasthenic crisis). Diagnosis is suspected based on the clinical picture described above, without loss of reflexes or impairment of sensation. Repetitive nerve stimulation typically shows a decreasing response at 2–3 Hz, which repairs after brief exercise (exercise facilitation). Edrophonium can be used for confirmation. Other useful investigations include serum anti-AChR or MuSK antibody titre, or SFEMG (single-fibre electromyography).

Medical condition	Myasthenia gravis (MG)
Justification for evidence category	A Cochrane review of four RCTs (a total of 147 children and adult patients) found benefit but no significant difference between IVIg and plasma exchange, and no significant difference between IVIg and methylprednisolone. One of the four studies found no benefit of IVIg (i.e. no significant difference between IVIg and placebo). The individual trials were of poor design and some had small numbers of participants, so more research is needed (Biotext 2004). Anecdotal evidence of efficacy has come from clinicians. There is insufficient placebo-controlled evidence for IVIg use as a steroid-sparing agent or before thymectomy in stable MG, although multiple case reports suggest benefit in this context. The Asia–Pacific Advisory Group (2004) supports the use of IVIg over a single day for the treatment of myasthenia gravis exacerbations, in myasthenic crisis, or in patients with severe weakness poorly controlled with other agents. It does not support the use of IVIg for maintenance in stable moderate or severe MG unless other therapies have failed and IVIg has shown benefit. Effectiveness of IVIg is equivalent to steroids and plasma exchange but IVIg may be easier to administer than plasma exchange and avoids the side effects of steroids.

Medical condition	Myasthenia gravis (MG)
Qualifying criteria for IVIg therapy	Mandatory diagnosis and assessment by a neurologist; AND 1. As an alternative treatment to plasma exchange in acute exacerbation (myasthenic crisis) or before surgery and/or thymectomy; OR 2. As maintenance therapy for moderate to severe MG when other treatments have been ineffective or caused intolerable side effects.
Review criteria for assessing the effectiveness of IVIg use	IVIg should be used for three to six months (three to six courses) before determining whether the patient has responded. If there is no benefit after three to six courses, IVIg therapy should be abandoned. **Review** Regular review by neurologist is required: frequency as determined by clinical status of patient. Initial review three to six monthly. For stable patients on maintenance treatment, review by a neurologist is required at least annually. **Effectiveness** Clinical documentation of effectiveness is necessary for continuation of IVIg therapy. Effectiveness can be demonstrated by improvement in fatigability and weakness. Various scores can be used, including: • forward arm abduction time (up to a full five minutes); • Quantitative Myasthenia gravis score (Duke); • respiratory function (e.g. forced vital capacity); quantitative dynamometry of proximal limb muscles; • variation of a myasthenic muscular score (MSS).

Medical condition	Myasthenia gravis (MG)
Dose	**Maintenance:** 0.4–1 g/kg, 4–6 weekly. **Induction or before surgery, or during myasthenic crisis:** 1–2 g/kg in 2 to 5 divided doses. Aim for minimum dose to maintain optimal functional status. **Note:** smaller dosage may be of greater efficacy. **Refer to the current product information sheet for further information.** **The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.**

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Medical condition	Neonatal haemochromatosis (NH)
Indication for IVIg use	Pregnant women who have had a previous pregnancy affected by neonatal haemochromatosis.
Level of evidence	Evidence of probable benefit (Category 2a).
Description and diagnostic criteria	NH manifests in the foetus and newborn and is characterised by abnormal accumulation of iron in the liver and extra-hepatic tissues. Affected neonates present with fulminant liver failure, usually in the context of a history of prematurity, intrauterine growth retardation and oligohydramnios. NH differs from most other causes of neonatal liver disease, other than congenital infections, in that the condition begins in utero and fulminant liver disease is manifested in the first few days of life. The aetiology and pathogenesis remains uncertain. The NH phenotype may be the outcome of numerous disease processes. There is also evidence, however, that NH is an alloimmune disorder. First, there is an approximate 80% likelihood of NH once a woman has an affected baby. Second, mothers can have affected babies with different fathers. It has not been described that fathers can have affected half-siblings with different mothers. **Symptoms and signs** Affected neonates present with signs of liver failure, including extreme cholestasis, hypoalbuminaemia, coagulopathy, ascites and hypoglycaemia. Diagnosis of neonatal haemochromatosis is made after other causes of neonatal liver failure have been ruled out.

Medical condition	Neonatal haemochromatosis (NH)
Description and diagnostic criteria continued	In addition to extensive iron deposition (siderosis), liver biopsy would show cirrhosis with diffuse fibrosis, bile duct proliferation, and giant cells. Siderosis is also present in other tissues and viscera (e.g. epithelial tissues and the heart) but not in reticuloendothelial cells. **Occurrence** NH is a rare disease but the rate of recurrence after the index case in a sibship is up to 80%. **Prognosis** About 20% survival with medical treatment.
Justification for evidence category	A trial compared the impact of IVIg on pregnancy outcome of women whose most recent pregnancy had resulted in NH with historical controls (randomly selected previously affected pregnancies). All 15 pregnancies resulted in live births. NH was diagnosed in 11 but responded to medical treatment. By contrast, there were 2 successful outcomes in controls (Biotext 2004).
Qualifying criteria for IVIg therapy	Women who are pregnant or attempting to conceive and their most recent pregnancy ended in delivery of a foetus shown to have had NH.
Review criteria for assessing the effectiveness of IVIg use	• Occurrence of NH, or evidence of liver disease (serum ferritin and a-fetoprotein levels, coagulopathy) in the offspring of women who have previously given birth to an NH-affected neonate. • Requirement for liver transplantation in these neonates. • Survival and development of infants following maternal IVIg therapy during pregnancy.

Medical condition	Neonatal haemochromatosis (NH)
Dose	1 g/kg body weight weekly from the 18th week until the end of gestation. **Refer to the current product information sheet for further information.** **The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.**

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Medical condition	Stiff person syndrome (Moersch–Woltmann syndrome)
Indication for IVIg use	Treatment of significant functional impairment in patients who have a verified diagnosis of stiff person syndrome.
Level of evidence	Evidence of probable benefit (Category 2a).
Description and diagnostic criteria	Patients with stiff person syndrome present with symptoms related to muscular rigidity and superimposed episodic spasms. The rigidity insidiously spreads involving axial muscles, primarily abdominal and thoracolumbar, as well as proximal limb muscles. Typically, co-contraction of truncal agonist and antagonistic muscles leads to a board-like appearance with hyperlordosis. Less frequently, respiratory muscle involvement leads to breathing difficulty and facial muscle involvement to a mask-like face. Investigations that may be useful for diagnosis include auto-antibodies to GAD-65 or GAD-67, electromyography recordings from stiff muscles that may show continuous discharges of motor unit, and cerebrospinal fluid oligoclonal bands.
Justification for evidence category	The Biotext (2004) review included one randomised, double blind, placebo-controlled trial with a crossover design of 16 patients with stiff person syndrome and anti-GAD-65 antibodies. A significant treatment effect with IVIg was seen, resulting in patients' decreased stiffness and heightened sensitivity scores. According to expert consensus, considering the disabling progressive course of stiff person syndrome, IVIg should be offered as the first-line treatment. Although periodic infusions would be required in the majority, further studies are needed to determine optimal dosage and duration (Asia–Pacific Advisory Board 2004).

Medical condition	Stiff person syndrome (Moersch–Woltmann syndrome)
Qualifying criteria for IVIg therapy	Significant functional impairment in patients who have a verified diagnosis of stiff person syndrome made by a neurologist.
Review criteria for assessing the effectiveness of IVIg use.	**Review** Regular review by a neurologist is required; frequency as determined by clinical status of patient. For stable patients on maintenance treatment, review by a neurologist is required at least annually. **Effectiveness** Objective indicators of relief of symptoms of stiffness, including: • improvement or stabilisation of activities of daily living scores; • other specialised scoring systems, such as distribution-of-stiffness index and heightened sensitivity scale.
Dose	**Induction:** 2 g/kg in 2 to 5 divided doses. **Maintenance:** 1–2 g/kg, 4–6 weekly. Aim for the minimum dose to maintain optimal functional status. **Dosing above 1 g/kg per day is contraindicated for some IVIg products.** **Refer to the current product information sheet for further information.** **The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.**

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6

Conditions for which IVIg has an emerging therapeutic role

6. Conditions for which IVIg has an emerging therapeutic role

This chapter comprises conditions for which the therapeutic role of intravenous immunoglobulin (IVIg) is either emerging or uncertain. There is clinical support for IVIg use in selected patients, although the quality of evidence supporting use is variable. For many conditions, IVIg use is considered only as second-line therapy when standard therapies have proven ineffective, have become intolerable, or are contraindicated.

Many of the conditions are rare and as a result the evidence of benefit is often patchy and inconclusive. Others are more prevalent, yet the evidence of benefit is either conflicting or uncertain, requiring more research. For some conditions, the use of IVIg may represent a relatively new direction in their management and evidence of benefit is still emerging.

One exception to this is immune thrombocytopenic purpura (ITP) in children. While the effectiveness of IVIg is not disputed, clinical experts advise that most children with ITP do not require IVIg. Its use in childhood ITP is considered only for the relatively small proportion of children who do not remit spontaneously or respond to standard care.

Another example is kidney transplantation. While evidence from good quality studies exists for the effectiveness of IVIg in antibody-mediated rejection, evidence for its use in cellular rejection is still emerging.

The information provided is not intended to be a definitive reference on any of the conditions, or to be used by clinicians for actual diagnosis or management. Expert clinical opinion about treatment regimens should always be sought. In particular, dose and schedule information is provided as a guide only. The aim in each case is to find the minimal effective dose and optimise the treatment of each individual.

Table 4 Conditions for which IVIg has an emerging therapeutic role as immunoglobulin replacement therapy

Condition	Evidence level	Page
Secondary hypogammaglobulinaemia (including iatrogenic immunodeficiency)	4b	106
Specific antibody deficiency	4a	110

Table 5 Conditions for which IVIg has an emerging therapeutic role as immunomodulation therapy

Condition	Evidence level	Page
Acute disseminated encephalomyelitis	2a	115
ANCA-positive systemic necrotising vasculitis	2a	119
Autoimmune haemolytic anaemia	4a	123
Bullous pemphigoid	4a	126
Cicatricial pemphigoid	2a	129
Evans syndrome - autoimmune haemolytic anaemia with immune thrombocytopenia	4a	133
Foeto-maternal/neonatal alloimmune thrombocytopenia (FMAIT/NAIT)	4a	136
Haemophagocytic syndrome	4a	141
Idiopathic (autoimmune) thrombocytopenia purpura (ITP) in children	1	144
IgM paraproteinaemic neuropathy	2c	148
Kidney transplantation	1	152
Multiple sclerosis	2a	158
Opsoclonus-myoclonus ataxia	4a	164
Pemphigus foliaceus	4a	166
Pemphigus vulgaris	2a	168
Post-transfusion purpura	4a	171
Toxic epidermal necrolysis/Stevens–Johnson syndrome (TEN/SJS)	4a	173
Toxic shock syndrome	4a	177

Medical condition	Secondary hypogammaglobulinaemia (including iatrogenic immunodeficiency)
Indication for IVIg use	Replacement therapy for life-threatening infection due to hypogammaglobulinaemia related to other diseases or medical therapy. **Note:** The following secondary causes of hypogammaglobulinaemia are considered elsewhere: 1. Acquired hypogammaglobulinaemia secondary to haematological malignancies or stem cell transplantation (see page 48) 2. HIV in children (see page 185) 3. Solid organ transplantation (see page 208)
Level of evidence	No included studies (Category 4b).
Description and diagnostic criteria	Recurrent and/or severe bacterial infections may arise from hypogammaglobulinaemia of diverse causes. Hypogammaglobulinaemia may arise from protein losing states, malnutrition and medical immunosuppression. In most cases, successful management of the underlying condition will reverse the immunodeficiency, restoring immunocompetence. In some cases, recurrent or severe infection may arise from secondary immunodeficiency where the underlying cause cannot be reversed, or where there are unwanted effects of removing or reducing immunosuppressive therapy. New immunosuppressive regimens such as monoclonal B-cell depletion with Rituximab or similar agents do not generally induce hypogammaglobulinaemia at standard doses. However, repeated cycles of B-cell depletion in combination with other agents used to treat life-threatening immune-mediated diseases may increase rates of infection related to hypogammaglobulinaemia.

Medical condition	Secondary hypogammaglobulinaemia (including iatrogenic immunodeficiency)
Qualifying criteria for IVIg therapy	Hypogammaglobulinaemia secondary to underlying disease or medical therapy (including haemopoietic stem cell transplantation [HCST]) with all the following: 1. Serum IgG less than the lower limit of the reference range on two separate occasions; AND 2. Underlying cause of hypogammaglobulinaemia cannot be reversed or reversal is contraindicated; AND 3. At least one of the following: a. One invasive or life-threatening bacterial infection (e.g. pneumonia, meningitis, sepsis) in the previous year; or b. Clinically active bronchiectasis confirmed by radiology.
Exclusion criteria for IVIg therapy	Reversible underlying cause of hypogammaglobulinaemia. The following conditions should not be approved under this indication: 1. Acquired hypogammaglobulinaemia secondary to haematological malignancies or stem cell transplantation (see page 48); 2. HIV in children (see page 185); or 3. Transplantation related immunomodulation (solid organ transplantation; see page 208).

Medical condition	Secondary hypogammaglobulinaemia (including iatrogenic immunodeficiency)
Review criteria for assessing the effectiveness of IVIg use	Six-monthly review to assess clinical benefit. Cessation of IVIg should be considered, at least after each 12 months of therapy, extended as required to enable cessation of therapy in September/October, with repeat clinical and/or immunological evaluation before re-commencement of therapy. Written confirmation from the treating physician that: • an annual review has been undertaken; • the patient had demonstrated clinical benefit; • a trial period of cessation of IVIg for the purpose of immunological evaluation is medically contraindicated on safety grounds. In principle, IVIg should be continued or renewed only if there is a demonstrated clinical benefit.
Dose	**Maintenance dose:** 0.4 g/kg every four weeks, modified to achieve IgG trough level of at least the lower limit of the age-specific serum IgG reference range. **Loading dose:** One additional dose of 0.4 g/kg in the first month of therapy is permitted if the serum IgG level is markedly reduced. **Chronic suppurative lung disease:** Dosing to achieve IgG trough level of up to 9 g/L is permitted if chronic suppurative lung disease is not adequately controlled at an IgG trough level at the lower limit of the age-specific serum IgG reference range.

Medical condition	Secondary hypogammaglobulinaemia (including iatrogenic immunodeficiency)
Dose continued	Subcutaneous administration of immunoglobulins is a suitable alternative to IVIg in this disease. **Dosing above 1 g/kg per day is contraindicated for some IVIg products.** **Refer to the current product information sheet for further information.** **The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.**

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Medical condition	Specific antibody deficiency
Indication for IVIg use	Prevention of infections in individuals with frequent infections who have demonstrated failure to mount protective IgG antibody responses to vaccine antigen challenge despite normal total serum IgG levels.
Level of evidence	Small case studies only, insufficient data (Category 4a).
Description and diagnostic criteria	The term 'specific antibody deficiency' describes failure of specific antibody response to an antigen challenge, and is most often used in the more restrictive sense of applying to polysaccharide antibody responses only. Patients who have normal total IgG levels but impaired production of specific antibodies, including those with isolated deficient responses to numerous polysaccharide antigens after vaccination, can present a diagnostic challenge. IgG replacement therapy should be provided when there is well-documented severe polysaccharide non-responsiveness and evidence of recurrent infections with a documented requirement for antibiotic therapy and ongoing recurrent infections despite antibiotic prophylaxis (Orange et al 2006). It is now generally agreed that IgG subclass level estimation in serum is relatively poorly predictive of infectious risk and is of limited value in the definition of those patients most likely to benefit from IVIg therapy. Further research investigating clinical and laboratory features of this disorder is required.

Medical condition	Specific antibody deficiency
Qualifying criteria for IVIg therapy	To access IVIg for a period of 12 months, the following qualifying criteria must be met: 1. A clinical immunologist must be consulted to confirm the diagnosis; AND 2. Frequent bacterial infections despite oral antibiotic therapy consistent with best practice recommendations; AND 3. Documented failure of serum antibody response to unconjugated pneumococcal or protein vaccine challenge.
Exclusion criteria for IVIg therapy	1. Isolated IgG subclass deficiency in the absence of evidence of specific antibody deficiency. 2. Low total IgG. This should be considered under primary or secondary immunodeficiency.
Review criteria for assessing the effectiveness of IVIg use	Natural history of specific antibody deficiency remains poorly defined, although antibody production will improve for many patients over time, particularly children. To be eligible to receive IVIg for a further 12 months, the following is required: Written confirmation from the treating clinical immunologist that: • an annual review has been undertaken; • the patient had demonstrated clinical benefit; • a trial period of cessation of IVIg for the purpose of immunological evaluation is medically contraindicated on safety grounds.

Medical condition	Specific antibody deficiency
Review criteria for assessing the effectiveness of IVIg use continued	Cessation of IVIg should be considered, at least after each 12 months of therapy extended as required to enable cessation of therapy in September/October. This should particularly be considered in patients who do not have suppurative lung disease or bronchiectasis. An immunoglobulin washout period of four to six months is necessary to enable an accurate assessment. Prophylactic antibiotics may be considered to cover the period of IVIg cessation. Patients may qualify for further IVIg therapy: • under other immunodeficiency criteria (e.g. common variable immunodeficiency [CVID]) depending on the results of subsequent immune evaluation; or • rarely under specific antibody deficiency following re-emergence of severe significant infection requiring hospitalisation. In principle, IVIg should only be continued or renewed if there is a demonstrated clinical benefit. Note that re-vaccination with pneumococcal polysaccharide vaccine is not recommended because of safety concerns, and the potential for specific hyporesponsiveness induced by repeated vaccination (O'Brien et al 2007). **IgG subclass deficiency** *1. New patients* IVIg is not funded for new patients diagnosed with IgG subclass deficiency. *2. Patients who were receiving IVIg for IgG subclass deficiency before initial publication of the Criteria (December 2007)*

Medical condition	Specific antibody deficiency
Review criteria for assessing the effectiveness of IVIg use continued	• Without clinically active bronchiectasis or suppurative lung disease: These patients should have ceased IVIg and had their immunological status re-evaluated. Patients with a confirmed IgG deficiency have become eligible under another indication (e.g. primary immunodeficiency with antibody deficiency). Patients without a confirmed IgG deficiency have ceased IVIg therapy. • With clinically active bronchiectasis or suppurative lung disease over the previous 12 months: To be eligible to receive IVIg for a further 12 months, the following is required: 1. Written confirmation from the treating clinical immunologist that : • an annual review has been undertaken; • the patient has demonstrated clinical benefit; and • a trial period of cessation of IVIg for the purpose of immunological evaluation is medically contraindicated on safety grounds. AND 2. Written confirmation by a second physician that cessation of IVIg for the purpose of immunological evaluation is medically contraindicated on safety grounds. Cessation of IVIg should be considered, at least after each 12 months of therapy extended as required to enable cessation of therapy in September/October. **NOTE:** The above criteria for initial and ongoing access to IVIg funded by all governments under the National Blood Arrangements will be reviewed in light of emerging evidence at the next review of *the Criteria*.

Medical condition	Specific antibody deficiency
Dose	**Maintenance dose:** 0.4 g/kg every 4 weeks. **Loading dose:** not approved. Subcutaneous administration of immunoglobulins (SCIg) is a suitable alternative to IVIg in this setting. **Refer to the current product information sheet for further information.** **The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.**

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Medical condition	Acute disseminated encephalomyelitis (ADEM)
Indication for IVIg use	1. ADEM unresponsive to steroid therapy or where steroids are contraindicated (e.g. suspicion of CNS infection). 2. Recurrent or multiphasic ADEM unresponsive to steroid therapy or where steroid therapy has become intolerable or is contraindicated.
Level of evidence	Evidence of probable benefit (Category 2a).
Description and diagnostic criteria	ADEM is a monophasic inflammatory condition of the central nervous system that usually presents in children and young adults. It typically occurs following a viral prodrome with multifocal neurological disturbance and altered conscious state. ADEM usually follows a monophasic course, but patients may experience recurrence of the initial symptom complex (recurrent ADEM) or a second episode of ADEM (multiphasic ADEM). The majority make a full recovery. ADEM is thought to have an autoimmune basis. Pathologic similarities to experimental allergic encephalomyelitis (EAE), an animal model of inflammatory demyelination, support this theory. It is postulated that a common antigen shared by an infectious agent and a myelin epitope results in an autoimmune response. Patients show multiple demyelinating lesions on magnetic resonance imaging (MRI) in the deep and subcortical white matter. The differential diagnosis includes other inflammatory demyelinating disorders, such as multiple sclerosis, optic neuritis and transverse myelitis.

Medical condition	Acute disseminated encephalomyelitis (ADEM)
Description and diagnostic criteria continued	High-dose corticosteroids are first-line treatment of ADEM. IVIg has been used for patients who fail to respond to steroid therapy or in patients where steroids are contraindicated. Most patients with ADEM recover completely over a period of six weeks from onset. There is no biological marker for ADEM. Diagnosis is by clinical recognition of the multifocal neurological disturbance and altered conscious state, with the typical MRI findings of demyelination.
Justification for evidence category	On review of multiple case series of IVIg use for paediatric ADEM found that children with monophasic ADEM completely recovered after administration of IVIg or IVIg plus corticosteroids. In recurrent ADEM, children either completely recovered after IVIg, or showed improvement. Adults with monophasic or recurrent ADEM recovered after treatment with IVIg.
Qualifying criteria for IVIg therapy	1. ADEM unresponsive to steroid therapy or where steroids are contraindicated (e.g. suspicion of CNS infection). **Note:** Assessment by a neurologist is recommended, but not mandatory. OR 2. Recurrent or multiphasic ADEM unresponsive to steroid therapy, or where steroid therapy has become intolerable or is contraindicated, with assessment by a neurologist mandatory.
Review criteria for assessing the effectiveness of IVIg use	Objective evidence of improvement in relapse rate in comparison to pre-treatment levels. Six-monthly review by a neurologist is required for recurrent or multiphasic ADEM.

Medical condition	Acute disseminated encephalomyelitis (ADEM)
Dose	**Induction:** 2 g/kg in 2 to 5 divided doses. **Maintenance dose:** For recurrent or multiphasic ADEM only: 0.4–2 g/kg, 4–6 weekly. Aim for the minimum dose to maintain optimal functional status and prevent relapses. In recurrent or multiphasic ADEM, assessment by a neurologist is **mandatory.** **Dosing above 1 g/kg per day is contraindicated for some IVIg products.** **Refer to the current product information sheet for further information.** **The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.**

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Medical condition	Anti-neutrophil cytoplasmic antibody (ANCA) [Proteinase 3 (PR3) or myeloperoxidase (MPO)]-positive systemic necrotising vasculitis
Indication for IVIg use	Control of vasculitic activity in rare cases of ANCA-positive systemic necrotising vasculitis failing to respond to corticosteroids and cytotoxic immunosuppression.
Level of evidence	Evidence of probable benefit (Category 2a).
Description and diagnostic criteria	ANCA associated systemic necrotising vasculitides are life-threatening immune-mediated inflammatory diseases comprising one of four clinical syndromes: 1. Wegener granulomatosis; 2. microscopic polyangiitis; 3. Churg–Strauss syndrome; and 4. ANCA (PR3 or MPO)-positive idiopathic rapidly progressive glomerulonephritis. In these cases the ANCA specificity is directed against the neutrophil cytoplasmic antigens PR3 and MPO. ANCA that lack MPO or PR3 specificity tend to be non-specific. Biopsy of affected tissue is required to establish the diagnosis. Standard combinations of corticosteroids and cytotoxic immunosuppression are generally effective at controlling disease, but relapses are common. IVIg has a limited role as one of several therapeutic options in relapsing disease.

Medical condition	Anti-neutrophil cytoplasmic antibody (ANCA) [Proteinase 3 (PR3) or myeloperoxidase (MPO)]-positive systemic necrotising vasculitis
Justification for evidence category	The Biotext (2004) review found one randomised trial of 34 patients and one case series of 7 patients with ANCA-associated systemic vasculitis (AASV). Different AASVs were represented in the studies. The Biotext (2004) review concluded that there is possible benefit in the treatment of AASV with IVIg if disease activity persists after standard therapy.
Qualifying criteria for IVIg therapy	MPO or PR3 ANCA-positive systemic necrotising vasculitis with both of the following: 1. Current (or within the previous six months) standard cytotoxic immunosuppressive ANCA-vasculitis regimens; AND 2. Persisent active disease.
Exclusion criteria for IVIg therapy	Initial therapy
Review criteria for assessing the effectiveness of IVIg use	• Six-month review assessing evidence of clinical benefit. • Reduction in the Birmingham vasculitis activity score of more than 50% after three months. • Erythrocyte sedimentation rate and C-reactive protein concentration. • ANCA titre.

Medical condition	Anti-neutrophil cytoplasmic antibody (ANCA) [Proteinase 3 (PR3) or myeloperoxidase (MPO)]-positive systemic necrotising vasculitis
Dose	2 g/kg in single or divided doses. **Dosing above 1 g/kg per day is contraindicated for some IVIg products.** **Refer to the current product information sheet for further information.** **The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.**

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Medical condition	Autoimmune haemolytic anaemia (AIHA)
Indication for IVIg use	To reduce haemolysis in patients not responding to corticosteroid therapy.
Level of evidence	Small case studies only; insufficient data (Category 4a).
Description and diagnostic criteria	AIHA is a rare but serious autoimmune disease in which an individual's antibodies recognise antigens on their own red blood cells. AIHA presents as an acute or chronic anaemia characterised by the occurrence of biochemical parameters of red cell destruction associated with a positive direct antiglobulin test indicating the presence of antibodies and/or complement on the red cell surface. It may be secondary to a number of underlying disorders or drugs. **Investigations** A full blood count will confirm the presence of anaemia. A peripheral blood smear may reveal evidence of spherocytes along with polychromasia due to reticulocytosis. A direct antiglobulin test is usually positive, the serum lactate dehydrogenase is raised, and there is a reduction in serum haptoglobin. **Prognosis** The prognosis of AIHA is good in most cases although severe refractory AIHA can cause cardio-respiratory problems because of severe anaemia, especially in adults. **Standard therapy** Corticosteroid administration is the cornerstone of therapy. For those with relapsing disease, splenectomy and immunosuppression are second line treatments while anti-CD20 antibodies have shown promise in individual cases of refractory disease.

Medical condition	Autoimmune haemolytic anaemia (AIHA)
Justification for evidence category	An analysis of 73 patients with AIHA in 1993 based on three pilot studies and a literature review showed a 40% response to IVIg given together with corticosteroids. A lower initial haemoglobin concentration and hepatomegaly were positive correlates of response. Several small case series have suggested a benefit for IVIg in AIHA associated with lymphoproliferative diseases, especially CLL. On the basis of these findings, IVIg is not supported as standard therapy for AIHA, only in cases refractory to conventional corticosteroid therapy, as a temporising measure before splenectomy or as maintenance therapy where splenectomy or immunosuppression are not appropriate.
Qualifying criteria for IVIg therapy	1. Symptomatic or severe AIHA (Hb ‹60 g/L, except patients with co-morbidities) refractory to conventional therapy with corticosteroids; OR 2. As a temporising measure before splenectomy; OR 3. As initial and maintenance therapy in AIHA in patients unsuitable for splenectomy or immunosuppression.
Exclusion criteria for IVIg therapy	Patients in whom a trial of corticosteroids has not been undertaken.
Review criteria for assessing the effectiveness of IVIg use	• Resolution of haemolytic anaemia (rising haemoglobin concentrations, falling bilirubin and LDH). • Clinical improvement in symptoms and signs.

Medical condition	Autoimmune haemolytic anaemia (AIHA)
Dose	Up to 2 g/kg as a single or divided dose. **Dosing above 1 g/kg per day is contraindicated for some IVIg products.** **Refer to the current product information sheet for further information.** **The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.**

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Medical condition	Bullous pemphigoid (BP)
Indication for IVIg use	BP resistant to topical and systemic glucocorticoids and immunosuppressive therapy.
Level of evidence	Small case studies only; insufficient data (Category 4a).
Description and diagnostic criteria	BP is a rare disease of elderly people characterised by tense blisters and vesicles with a prominent inflammatory component. The cause is unknown. Lesions result from a failure of basal keratinocytes to adhere to the epidermal basement membrane. The course of BP is characterised by exacerbations and remissions. Pruritis is a common feature and an increase in pruritis may herald an exacerbation. In most patients, BP is not a life-threatening disease. The side effects of systemic immunosuppressive therapy need to be managed. In most patients, the disease spontaneously clears within six years and all medication can be stopped. In a small group, the disease recurs after treatment is stopped. Skin infection is the most common complication. A submission by the Australasian College of Dermatologists recommends IVIg use in BP only in severe cases where improvement with conventional therapy is not readily achieved.
Justification for evidence category	The 2003 Harvard consensus statement identified a small study (17 cases) where patients who were on IVIg therapy for at least three months benefited from the therapy. The same article mentioned another small study (15 cases) where patients with BP could not be controlled with high-dose systemic corticosteroids and multiple immunosuppressive agents. IVIg produced prolonged clinical remission sustained after IVIg therapy was discontinued.

Medical condition	Bullous pemphigoid (BP)
Qualifying criteria for IVIg therapy	Moderate to severe disease diagnosed by a dermatologist AND 1. Corticosteroids or immunosuppressive agents are contraindicated; OR 2. Condition is unresponsive to corticosteroids and immunosuppressive agents; OR 3. Presenting with severe side effects of therapy.
Review criteria for assessing the effectiveness of IVIg use	• Response demonstrated at review at six months. Improvement to be demonstrated for continuation of supply. • Reduction in recurrence of disease or relapse. • Ability to reduce dose or discontinue other therapies. • Improved quality of life. • Resolution of blisters and healing of affected skin. • Resolution of pruritis.
Dose	Efficacy demonstrated with doses of at least 2 g/kg per monthly treatment cycle. **Dosing above 1 g/kg per day is contraindicated for some IVIg products.** **Refer to the current product information sheet for further information.** **The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.**

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Medical condition	Cicatricial pemphigoid (CP) or mucous membrane pemphigoid (MMP)
Indication for IVIg use	CP resistant to glucocorticoid and immunosuppressive therapy.
Level of evidence	Evidence of probable benefit (Category 2a).
Description and diagnostic criteria	CP or MMP is a rare, acquired subepithelial blistering disease characterised by erosive lesions of mucous membranes and skin. Serious complications may occur due to erosions and scarring. Hoarseness, pain, tissue loss and even upper airway destruction can occur with nasopharyngeal or laryngeal involvement, and oesophageal and urogenital lesions may lead to stenosis or strictures. CP is usually a chronic, progressive disorder. The aim of long-term treatment is cessation of the self-destructive autoimmune process. Failure to do so results in invariable progression of the disease, culminating in progressive scarring. Permanent remission is usually possible if the disease is diagnosed early and treated sufficiently for one to five years. For the 70% of patients who have eye involvement, the disease progresses to conjunctival scarring and shrinkage, but may take 10–20 years to reach the end stage of bilateral blindness.

Medical condition	Cicatricial pemphigoid (CP) or mucous membrane pemphigoid (MMP)
Justification for evidence category	Prolonged clinical remission and reduction in side effects was demonstrated in one small case series (15 cases) of patients with CP/MMP unresponsive to systemic corticosteroids and immuno-suppressive agents or presenting with multiple side effects of therapy (Biotext 2004). A small non-randomised, non-blinded trial (16 patients) showed significant improvement in the mean time for clinical control, recurrence, disease progression and drug-related side effects among patients receiving IVIg compared to conventional immunosuppressive therapy (Frommer and Madronio 2006). The (2003) consensus statement from the Harvard Medical School Department of Dermatology identified a study of 10 MMP patients who had progressive ocular involvement and did not respond to corticosteroids or immunosuppressants. IVIg administration as monotherapy arrested the progression and vision was maintained after IVIg was discontinued. The authors cited two other studies of oral pemphigoid in 15 and 7 patients respectively who could not be treated with dapsone; IVIg was compared to immunosuppressants. IVIg led to early and long-term remission and no disease progression.

Medical condition	Cicatricial pemphigoid (CP) or mucous membrane pemphigoid (MMP)
Qualifying criteria for IVIg therapy	Moderate to severe disease diagnosed by a dermatologist; AND 1. Corticosteroids or immunosuppressive agents are contraindicated; OR 2. Condition is unresponsive to corticosteroids and immunosuppressive agents; OR 3. Presenting with severe side effects of therapy.
Review criteria for assessing the effectiveness of IVIg use	• Response demonstrated at review at six months. Improvement to be demonstrated for continuation of supply. • Disease recurrence or relapse and duration of clinical remission. • Ability to reduce dose or discontinue other therapies. • Resolution of conjunctival inflammation. • Reduction of drug-related side effects.
Dose	Efficacy demonstrated with doses of at least 2 g/kg per monthly treatment cycle. **Dosing above 1 g/kg per day is contraindicated for some IVIg products.** **Refer to the current product information sheet for further information.** **The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.**

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Medical condition	Evans syndrome — autoimmune haemolytic anaemia (AIHA) with immune thrombocytopenia
Indication for IVIg use	To reduce platelet destruction and improve haemolysis in patients not responding to corticosteroid therapy.
Level of evidence	Small case studies only; insufficient data (Category 4a).
Description and diagnostic criteria	Evans syndrome is a rare but serious autoimmune disease defined by the simultaneous or sequential occurrence of AIHA and immune thrombocytopenia purpura (ITP) without underlying aetiology. As such, it is a diagnosis of exclusion and other disorders, such as collagen vascular diseases, especially systemic lupus erythematosus (SLE) and scleroderma should be ruled out. The 2005 review by Norton and Roberts provided perspective on diagnosis, clinical features and management.
Justification for evidence category	A 2005 review on the management of Evans syndrome, based on Massachusetts Hospital data and a literature review, showed a transient response in all patients unless IVIg was given every three weeks (Norton and Roberts 2006). The review concluded that the data supported a role for IVIg in first-line therapy. It was not clear whether it was important for steroids to be given at the same time, although this is common practice. A total dose of 2 g/kg in divided doses appeared to be sufficient. The review also stated that there might be a role for IVIg in preference to steroids in the acute setting in very young children.

Medical condition	Evans syndrome — autoimmune haemolytic anaemia (AIHA) with immune thrombocytopenia
Qualifying criteria for IVIg therapy	1. Refractory to conventional therapy with corticosteroids; OR 2. Where corticosteroids are contraindicated; OR 3. As a temporising measure before splenectomy.
Exclusion criteria for IVIg therapy	Patients in whom a trial of corticosteroids has not been undertaken (providing corticosteroids are not contra-indicated and can be tolerated at the required doses).
Review criteria for assessing the effectiveness of IVIg use	• Maintenance therapy rarely required. • Resolution of haemolytic anaemia. • Improvement in platelet count. • Clinical improvement in symptoms and signs.
Dose	Up to 2 g/kg in divided dose. **Dosing above 1 g/kg per day is contraindicated for some IVIg products.** **Refer to the current product information sheet for further information.** **The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.**

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Medical condition	Foeto-maternal/neonatal alloimmune thrombocytopenia (FMAIT/NAIT): • antenatal • neonatal
Indication for IVIg use	Prevention or treatment of foetal or neonatal thrombocytopenia or haemorrhage.
Level of evidence	Small case studies only; insufficient data (Category 4a).
Description and diagnostic criteria	FMAIT/NAIT develops because of maternal sensitisation to foetal platelets that possess a paternally inherited antigen. In Caucasians, the antigen is human platelet antigen (HPA) 1a in 80% of cases and HPA-5b in 15%, but other antigens are also implicated. The mother's antibodies cross the placenta and coat the baby's platelets, with accelerated platelet clearance leading to thrombocytopenia. This may result in serious and potentially life-threatening bleeding in the foetus or neonate. Pathogenesis is analogous to that of haemolytic disease of the newborn due to red cell antigen-antibody incompatibility. The aim of management of the thrombocytopenic foetus or neonate is to increase the platelet count. If foetal blood sampling reveals thrombocytopenia, IVIg may be administered weekly to the mother, with or without steroids, until delivery. Recent studies using IVIg weekly from around 20 weeks gestation, without foetal blood sampling, have shown reduced foetal and neonatal morbidity. This approach may be used for current pregnancies where the condition in a previous pregnancy was not associated with a foetal death or severe haemorrhage. Testing on maternal blood for foetal DNA or early genetic testing of the foetus (for platelet genotype) may predict the need to use IVIg.

Medical condition	Foeto-maternal/neonatal alloimmune thrombocytopenia (FMAIT/NAIT): • antenatal • neonatal
Description and diagnostic criteria continued	Management of this condition is a specialised area and may include administration of HPA-compatible intrauterine and/or neonatal platelet transfusions. Further information regarding specialised platelet support is available from the Blood Service. Random (non-HPA-matched) platelets may be of benefit in the neonatal setting when matched platelets are not available (Kiefel 2006).
Justification for evidence category	Evidence from randomised trials (Berkowitz et al 2006, Bussel et al 1996), case series (Kiefel et al 2006, Yinon et al 2006) and a review (Spencer and Burrows 2001) shows that IVIg modulates the course of this condition. A 2004 Cochrane review (Rayment et al 2005) reported on one randomised controlled trial (RCT) comparing IVIg plus dexamethasone with IVIg alone. This RCT was methodologically sound, but too small to detect differences among comparison groups.

Medical condition	Foeto-maternal/neonatal alloimmune thrombocytopenia (FMAIT/NAIT): • antenatal • neonatal
Qualifying criteria for IVIg therapy	Clinical suspicion of FMAIT in antenatal or neonatal setting based on clinical and laboratory features, including: 1. Thrombocytopenia or spontaneous haemorrhage in the foetus; OR 2. Thrombocytopenia with or without haemorrhage in the neonate; OR 3. Unexplained foetal death in a previous pregnancy and the presence of maternal platelet-specific alloantibodies that are known or suspected to cause this condition (most commonly HPA-1a or HPA-5b).
Review criteria for assessing the effectiveness of IVIg use	• Foetal or neonatal morbidity and mortality in the context of maternal alloantibodies. • Occurrence and severity of thrombocytopenia in the neonate. • Maternal HPA-1a antibody level (if assay is available). Note that the strength/titre of maternal antibody level, even if available, is not proven clinically relevant and not able to be compared readily between laboratories at this time.

Medical condition	Foeto-maternal/neonatal alloimmune thrombocytopenia (FMAIT/NAIT): • antenatal • neonatal
Dose	Maternal dose: 1 g/kg weekly throughout pregnancy, with starting time tailored to individual risk profile and history if relevant. Other doses and schedules have been used and some studies have used IVIg in conjunction with steroids. Treatment of the neonate: 1 g/kg. Occasionally more than one dose is required if thrombocytopenia persists. **Refer to the current product information sheet for further information.** **The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.**

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Medical condition	Haemophagocytic syndrome
Indication for IVIg use	Management of severe haemophagocytic syndrome not responding to other treatments.
Description and diagnostic criteria	Haemophagocytic syndrome is characterised by fever, splenomegaly, jaundice, rash and the pathologic finding of haemophagocytosis (phagocytosis by macrophages of erythrocytes, leukocytes, platelets and their precursors) in bone marrow and other tissues with peripheral blood cytopenias. Haemophagocytic syndrome has been associated with a wide range of infectious, autoimmune, malignant and other disorders (modified from Fisman 2000). Mortality is high.
Level of evidence	Small case studies only; insufficient data (Category 4a).
Justification for evidence category	No RCTs have been done, although many, mostly small, case series show evidence of benefit.
Qualifying criteria for IVIg therapy	Bone marrow diagnosis or other biopsy evidence of haemophagocytosis in the characteristic clinical setting. **Note:** Since other therapies (cytotoxic agents) have major potential side effects, optimal therapy is not yet defined.
Review criteria for assessing the effectiveness of IVIg use	Amelioration of cytopenia(s), hepato/splenomegaly and lymphadenopathy if present. Survival or death.

Medical condition	Haemophagocytic syndrome
Dose	2 g/kg is the most widely published dose. Emmenegger et al (2001) reported that better outcomes were associated with early administration of IVIg in their small case series (10 patients). **Dosing above 1 g/kg per day is contraindicated for some IVIg products.** **Refer to the current product information sheet for further information.** **The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.**

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Medical condition	Idiopathic (autoimmune) thrombocytopenic purpura (ITP) — in children 15 years and younger
Indication for IVIg use	ITP with platelet count ‹30x10^9/L with significant bleeding.
Level of evidence	Clear evidence of benefit (Category 1).
Description and diagnostic criteria	ITP is a reduction in platelet count (thrombocytopenia) resulting from shortened platelet survival due to anti-platelet antibodies. When counts are very low (‹30x10^9/L) bleeding into the skin (purpura) and mucous membranes can occur. Bone marrow morphology is normal. In some cases, there is additional impairment of platelet function related to antibody binding to glycoproteins on the platelet surface. ITP is divided into chronic and acute forms. In children, the acute form is the most common. The disease tends to present abruptly with dramatic evidence of bleeding into the skin (petechiae and purpura) and mucous membranes (gum bleeding, nose bleeds, blood blisters). **Occurrence** Girls and boys are affected equally. In 75% of patients, the episode follows vaccination or a viral infection such as varicella or infectious mononucleosis. **Prognosis** At least 80–90% of children will have spontaneous remission of their disease within 6–12 months. In 5–10% of cases, the disease may become chronic (lasting ›6 months). Morbidity and mortality from acute ITP is very low.
Justification for evidence category	Category 1 classification in the Biotext (2004) review was based on four low–moderate quality RCTs. The Frommer and Madronio (2006) review identified a good-quality systematic review/meta-analysis of RCTs to support the Category 1 classification.

Medical condition	Idiopathic (autoimmune) thrombocytopenic purpura (ITP) — in children 15 years and younger
Qualifying criteria for IVIg therapy	**Note:** While the effectiveness of IVIg is not disputed, clinical experts advise that most children with ITP do not require IVIg therapy; indeed, no treatment at all is required for many children. Corticosteroids are the alternative therapy to IVIg. **Acute ITP** 1. Life-threatening bleeding due to thrombocytopenia; OR 2. Thrombocytopenia with platelet count ‹30x10^9/L and moderate to severe mucosal and/or cutaneous bleeding. **Chronic ITP** 1. Life-threatening bleeding due to thrombocytopenia; OR 2. In responsive patients for treatment of thrombocytopenia (‹30x10^9/L) with moderate to severe bleeding symptoms where other therapeutic options have failed or are contraindicated; OR 3. In responsive patients given before surgery to elevate the platelet count to haemostatically safe levels.
Exclusion criteria for IVIg therapy	1. Platelet count ›30x10^9/L. 2. Absence of significant bleeding.
Review criteria for assessing the effectiveness of IVIg use	• Platelet count at 48 hours. • Control or resolution of bleeding. • Duration of effect. • Progression to chronic ITP.

Medical condition	Idiopathic (autoimmune) thrombocytopenic purpura (ITP) — in children 15 years and younger
Dose	**Acute ITP** Life-threatening bleeding: up to 2 g/kg total dose, generally given as 2 doses of 1 g/kg. Other indications: 0.5 g/kg given as a single dose, repeated at 24–48 hours if the response is inadequate. A higher total dose of 2 g/kg may be required in 5–10% of cases. Duration of response to initial dose is typically two to four weeks. A repeat dose may be considered if recurrent symptomatic thrombocytopenia occurs. **Chronic ITP** Life-threatening bleeding: up to 2 g/kg total dose, generally given as 2 doses of 1 g/kg. **Other indications:** 0.5 to 1 g/kg at intervals generally › three weekly. **Dosing above 1 g/kg per day is contraindicated for some IVIg products.** **Refer to the current product information sheet for further information.** **The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.**

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Medical condition	IgM paraproteinaemic neuropathy
Indication for IVIg use	Patients with IgM paraproteinaemic neuropathy with functional impairment in whom other therapies have failed or are contraindicated or undesirable.
Level of evidence	Conflicting evidence of benefit (Category 2c).
Description and diagnostic criteria	IgM paraproteinaemic neuropathy is a slowly progressive, predominantly sensory neuropathy that may eventually produce disabling motor symptoms. The condition is associated with IgM paraprotein, which is a monoclonal antibody to myelin associated glycoprotein (MAG). IgM paraproteinaemic neuropathy is the most common subgroup of the monoclonal gammopathy of undetermined significance (MGUS) group. It is distinguishable from chronic inflammatory demyelinating polyneuropathy (CIDP) by: • the presence of tremor; • a greater severity of sensory loss, with ataxia and relatively mild or no weakness; • damage tends to be permanent and the degree of improvement in IgM paraproteinaemic neuropathy is much smaller than the improvement observed in CIDP patients. Nerve conduction studies usually show uniform symmetrical conduction slowing with prolonged distal latencies and distal attenuation (distal index is prolonged). Test for antibodies to neural antigens (MAG or other neural antigens) may be helpful.

Medical condition	IgM paraproteinaemic neuropathy
Justification for evidence category	The Biotext (2004) review included three low quality studies (one RCT, one case-control and one case-series) with 20 patients. No benefit from treatment with IVIg was demonstrated in the case-control study (Biotext 2004). The Frommer and Madronio (2006) found a Cochrane systematic review of five medium-quality RCTs with 97 patients of any age with a diagnosis of MGUS. There was inadequate evidence of efficacy of IVIg in anti-myelin-associated glycoprotein paraprotein peripheral neuropathies.
Qualifying criteria for IVIg therapy	Diagnosis by a neurologist of IgM paraproteinaemic neuropathy with: 1. Functional impairment of activities of daily living; AND 2. Other therapies have failed or are contraindicated or undesirable.
Review criteria for assessing the effectiveness of IVIg use	IVIg should be used for three to six months (three to six courses) before determining whether the patient has responded. If there is no benefit after three to six courses, IVIg therapy should be abandoned. **Review** Regular review by neurologist is required; frequency as determined by clinical status of patient. For stable patients on maintenance treatment review by a neurologist is required at least annually.

Medical condition	IgM paraproteinaemic neuropathy
Review criteria for assessing the effectiveness of IVIg use continued	**Effectiveness** Clinical documentation of effectiveness is necessary for continuation of IVIg therapy. Effectiveness can be demonstrated by objective findings of either: 1. Improvement in functional scores (activities of daily living — ADLs) or quantitative muscle scores, or Medical Research Council (MRC) muscle assessment or neuropathy score; or 2. Stabilisation of disease as defined by stable functional scores (ADLs) or quantitative muscle scores, or MRC muscle assessment or neuropathy score after previous evidence of deterioration in one of these scores.
Dose	**Induction:** 2 g/kg in 2 to 5 divided doses. **Maintenance:** 0.4–1 g/kg, 2 to 6 weekly. Maintenance treatment only with clear, objective improvement. Aim for minimum dose to maintain optimal functional status. **Refer to the current product information sheet for further information.** **The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.**

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Medical condition	Kidney transplantation
Indication for IVIg use	**Pre-transplantation** Patients in whom an antibody or antibodies prevent transplantation (donor specific anti-human leukocyte antigen (HLA) antibody/ies or anti-blood group antibody). **Post-transplantation** To treat steroid-resistant acute rejection which may be cellular or antibody mediated. For prevention and/or treatment of rejection where other therapies are contraindicated or pose a threat to the graft or patient.
Level of evidence	Clear evidence of benefit (Category 1).
Description and diagnostic criteria	Transplant rejection occurs when a recipient's immune system attacks a transplanted organ or tissue. Despite the use of immunosuppressants, one or more episodes of rejection can occur after transplantation. Both cellular and humoral (antibody-mediated) effector mechanisms can play a role. The presence and pattern of rejection need to be established by biopsy. Laboratory tests to assess the presence and strength of antibodies to the donor antigens can provide additional useful information. Clinical assessment, blood tests, ultrasound and nuclear imaging are used primarily to exclude other causes of organ dysfunction. Acute cellular rejection occurs in 15–30% of renal transplants and is responsive to steroids in more than 90% of cases. When rejection is steroid resistant, IVIg is a safer therapy than anti-T cell antibody therapy with equal efficacy.

Medical condition	Kidney transplantation
Description and diagnostic criteria continued	Antibody mediated rejection (AbMR) occurs in 5–10% of renal transplants that have been performed with a compatible cross match. Before the use of IVIg and plasma exchange, AbMR failed to respond adequately to therapy in most cases. Additionally, complications from therapy were severe and sometimes fatal. AbMR responds to IVIg with or without plasma exchange in more than 85% of patients.
Justification for evidence category	An RCT enrolling adult patients with end stage renal disease (ESRD) who were highly sensitised to HLA antigens found that IVIg was better than placebo in reducing anti-HLA antibody levels in highly sensitised patients with ESRD (followed for two years after transplant), and that transplant rates were improved with IVIg therapy (Jordan et al 2004). Multiple case series have been reported in the literature, indicating efficacy in (acute) antibody mediated rejection, and recommended by a consensus conference (Takemoto et al 2004). Jordan et al (1998) combined data from seven renal transplant recipients and three heart transplant recipients with steroid-resistant combined antibody-mediated and cellular rejection. All patients in this series were successfully treated with high-dose IVIg. A small RCT of transplanted patients with a five-year follow-up period showed that IVIg was as effective as OKT3 monoclonal antibodies in the treatment of steroid resistant rejection (survival rate at two years was 80% in both groups) but IVIg generated fewer side effects (Casadei et al 2001).

Medical condition	Kidney transplantation
Qualifying criteria for IVIg therapy	**Pre-transplantation** Patients in whom an antibody or antibodies prevent transplantation (donor-specific anti-HLA antibody/ies or anti-blood group antibody). **Post-transplantation** 1. Biopsy proven cellular rejection unresponsive to steroids with clinical evidence of graft dysfunction; OR 2. Acute antibody mediated rejection with clinical evidence of graft dysfunction; OR 3. As treatment or prophylaxis for rejection where conventional immunosuppressive therapy is contraindicated, for example: • in a patient with life-threatening infection in whom conventional immunosuppression will place the patient at even greater risk; • when the transplant is at risk (e.g. due to BK virus infection).
Review criteria for assessing the effectiveness of IVIg use	• Allograft organ function tests. • Biopsy response. • Laboratory monitoring of anti-HLA antibody and/or anti-blood group antibody responses. • Duration of graft and patient survival. • Reversal of clinical graft dysfunction.

Medical condition	Kidney transplantation
Dose	**IVIg with plasma exchange:** 0.1 to 0.5 g/kg post exchange. **IVIg alone:** 2 g/kg to a maximum of 140 g as a single dose, or 2 to 3.5 g/kg in a divided dose. When IVIg is used alone, further doses may be warranted two to four weeks after initial therapy depending on clinical response and/or biopsy findings. **Dosing above 1 g/kg per day is contraindicated for some IVIg products.** **Refer to the current product information sheet for further information.** **The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.**

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UK National Kidney Federation 2002, 'Transplant'. Available from: www.kidney.org.uk/Medical-Info/transplant.html#rej [cited 7 Dec 2007]

Medical condition	Multiple sclerosis (MS)
Indication for IVIg use	Short-term therapy in patients with clinically definite relapsing remitting MS in the following circumstances: 1. Pregnancy and the immediate post-partum period when other immunomodulation is contraindicated; 2. Young patients with severe relapsing remitting disease in whom other therapies have failed; 3. Severe relapse with no response to high-dose methylprednisolone.
Level of evidence	Evidence of probable benefit (Category 2a).
Description and diagnostic criteria	MS is a chronic disorder of the central nervous system (CNS) characterised by a triad of inflammation, demyelination and gliosis. Lesions of MS, known as plaques, are typically disseminated in time and location throughout the brain and spinal cord. Four clinical types of MS have been described: relapsing/remitting MS (RRMS), primary progressive MS (PPMS), secondary progressive MS (SPMS), and progressive/relapsing MS (PRMS). Diagnosis requires two or more episodes of symptoms and two or more signs that reflect pathology in anatomically non-contiguous white matter tracts of the CNS. Symptoms must last ›24 hours and occur as separate episodes at least one month apart. At least one of the two signs must be present on neurological examination, while the other may be detected by paraclinical tests such as intrathecal IgG (oligoclonal bands and visual evoked potentials).

Medical condition	Multiple sclerosis (MS)
Justification for evidence category	The Biotext (2004) literature review included one systematic review, six RCTs, three case-control studies and one case-series with a total sample size of 849. The quality of the included studies varied widely. The systematic review found some benefit. No benefit was found in two of the RCTs (IVIg did not appear to reverse established muscle weakness), and significant benefit was reported in two RCTs. The other two RCTs were identified by Biotext from the Cochrane register of trials, but no further information about the studies was obtained. The review by Frommer and Madronio (2006) included eight high-quality RCTs and one medium-quality double-blinded controlled trial with a total of 708 patients. These studies suggested that the occurrence of relapse may be reduced by IVIg at three years, but conclusive evidence in relation to the use of IVIg in reducing relapse rates and severity of relapse in established disease could not be demonstrated. IVIg treatment for the first year from onset of the first neurological event significantly lowered the incidence of second attacks and reduced disease activity as measured by MRI. IVIg administered in monthly pulses for up to two years appeared to reduce annual exacerbation rates in patients with RRMS and SPMS, but its effect on long-term disability was unclear.

Medical condition	Multiple sclerosis (MS)
Qualifying criteria for IVIg therapy	Clinically definite RRMS as defined by McDonald et al (2001) criteria and confirmed by a neurologist with one of the following indications: 1. Pregnancy and immediate post partum period when other immunomodulation is contraindicated; OR 2. Young patients with severe relapsing remitting disease in whom other therapies have failed; OR 3. Severe relapse with no response to high-dose methylprednisolone. Application for IVIg use for these indications will be considered on a case-by-case basis and may be reviewed by an expert neurologist in MS in each state **Note:** There are numerous immunomodulatory therapies available for multiple sclerosis. IVIg is not available for routine ongoing treatment for patients with MS.
Exclusion criteria for IVIg therapy	1. Primary progressive MS. 2. Progressive phase of MS without relapses.
Review criteria for assessing the effectiveness of IVIg use	• Six-monthly review by a neurologist is required. • Objective evidence of improvement in relapse rate in comparison to pre-treatment levels. • Other measures that may be useful include: - expanded disability status scale; - MS functional scores; - other functional measures.

Medical condition	Multiple sclerosis (MS)
Dose	**Induction:** 1–2 g/kg in 2 to 5 divided doses. **Maintenance dose for indications 1 and 2 above:** 0.4–1 g/kg, 4 to 6 weekly. Aim for minimum dose to maintain optimal functional status. **Refer to the current product information sheet for further information.** **The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.**

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Medical condition	Opsoclonus-myoclonus ataxia (OMA)
Indication for IVIg use	Long-term maintenance therapy of OMA in association with other tumour therapies.
Description and diagnostic criteria	OMA is an immune-mediated monophasic or multiphasic disorder consisting of opsoclonus (conjugate chaotic eye movements), cerebellar ataxia, and arrhythmic myoclonus affecting the trunk, the head and the extremities. OMA may be either paraneoplastic or idiopathic, presumably para-infectious (e.g. post-viral). In children, OMA complicates about 2–3% of neuroblastomas. In adults, it may occur in association with several cancers, most commonly small-cell lung cancer and breast cancer.
Level of evidence	Small case studies only; insufficient data (Category 4a).
Justification for evidence category	The Asia–Pacific IVIg Advisory Board (2004) consensus statement summarises several case reports suggesting that IVIg is useful in idiopathic OMA and childhood paraneoplastic OMA associated with neuroblastoma.
Qualifying criteria for IVIg therapy	Diagnosis of OMA by a neurologist: 1. In children; OR 2. As second-line treatment following the use of adrenocorticotrophic hormone or corticosteroids. **Note:** Given the rarity of OMA and its devastating effects, IVIg should be used where it is considered appropriate by a neurologist.
Exclusion criteria for IVIg therapy	Adult paraneoplastic OMA.

Medical condition	Opsoclonus-myoclonus ataxia (OMA)
Review criteria for assessing the effectiveness of IVIg use	**Review** Regular review by neurologist is required; frequency as determined by clinical status of patient. For stable patients on maintenance treatment, review by a neurologist is required at least annually. **Effectiveness** Objective indicators of relief of symptoms of OMA and improvement or stabilisation of scores of ADLs.
Dose	**Induction:** 1–2 g/kg in 2 to 5 divided doses. **Maintenance:** 0.4–1 g/kg, 4 to 6 weekly. Aim for the minimum dose to maintain optimal functional status. **Refer to the current product information sheet for further information.** **The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.**

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Medical condition	Pemphigus foliaceus (PF)
Indication for IVIg use	PF resistant to corticosteroids and immunosuppressive therapy or when these agents are contra-indicated.
Level of evidence	Small case studies only; insufficient data (Category 4a).
Description and diagnostic criteria	PF is a rare autoimmune blistering skin disease characterised by loss of cohesion of cells (acantholysis) in the superficial (subcorneal) layers of the epidermis. The lesions are generally well demarcated and do not coalesce to form large eroded areas (as seen in pemphigus vulgaris). It is mediated by an autoantibody that targets desmoglein 1, a cell-to-cell protein molecule that binds the desmosomes of neighbouring keratinocytes in the epidermis. The disease has a long-term course with patients maintaining satisfactory health. Spontaneous remissions occasionally occur.
Justification for evidence category	Habif (2004) concluded that IVIg was effective as monotherapy for PF and particularly useful in patients who experienced life-threatening complications from immunosuppression. Sami et al (2002) observed that autoantibody titres to desmoglein 1 in a series of 15 PF patients declined persistently following IVIg therapy.
Qualifying criteria for IVIg therapy	Severe widespread PF, defined as disease involving 30% or more of body surface area, diagnosed by a dermatologist; AND 1. Corticosteroids or immunosuppressive agents are contraindicated; OR

Medical condition	Pemphigus foliaceus (PF)
Qualifying criteria for IVIg therapy continued	2. Condition is unresponsive to corticosteroids and immunosuppressive agents; OR 3. Presenting with severe side effects of therapy.
Review criteria for assessing the effectiveness of IVIg use	• Response demonstrated at review at six months. Improvement to be demonstrated for continuation of supply. • Clinical progression: Treatment is stopped when patients are clinically free from disease and have a negative finding on direct immunofluorescence. • Autoantibody titres reflect the response to systemic therapy.
Dose	Efficacy demonstrated with doses of at least 2 g/kg per monthly treatment cycle. **Dosing above 1 g/kg per day is contraindicated for some IVIg products.** **Refer to the current product information sheet for further information.** **The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.**

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Medical condition	Pemphigus vulgaris (PV)
Indication for IVIg use	Moderate to severe PV as an adjuvant to prolonged corticosteroid treatment.
Level of evidence	Evidence of probable benefit (Category 2a).
Description and diagnostic criteria	PV is a rare but potentially fatal condition accounting for approximately 70% of pemphigus cases. While the cause is unknown, an immuno-genetic predisposition is well established. PV may also be drug-induced. Drugs reported to be most significantly associated with PV include penicillamine, captopril and other thiol-containing compounds. Rifampicin and emotional stress have recently been reported as triggers for PV. The oral cavity is almost always affected and erosions can be scattered and extensive, with subsequent dysphagia. Blistering and erosions secondary to the rupture of blisters may be painful and limit the patient's daily activities. Pemphigus may occur in patients with other autoimmune diseases, particularly myasthenia gravis and thymoma. **Prognosis** The severity and natural history of PV are variable. Before the advent of steroids, most patients with PV died. Treatment with systemic steroids has reduced the mortality rate to 5–15%. Most deaths occur during the first few years of disease and if the patient survives five years, the prognosis is good. Early disease is easier to control than widespread disease and mortality may be higher if therapy is delayed. Morbidity and mortality are related to the extent of disease, the maximum dose of corticosteroid required to induce remission, and the presence of other diseases.

Medical condition	Pemphigus vulgaris (PV)
Justification for evidence category	In a retrospective cohort study, 15 corticosteroid-dependent patients with moderate to severe PV were treated with IVIg and followed over a mean period of 6.2 years. All 15 patients had a satisfactory clinical response to IVIg therapy. IVIg had a demonstrable corticosteroid-sparing effect and was considered a safe and effective alternative treatment in patients who were dependent on systemic corticosteroids or who developed significant adverse effects as a result of their use (Biotext 2004).
Qualifying criteria for IVIg therapy	Moderate to severe disease diagnosed by a dermatologist; AND 1. Corticosteroids or immunosuppressive agents are contraindicated; OR 2. Condition is unresponsive to corticosteroids and immunosuppressive agents; OR 3. Presenting with severe side effects of therapy.
Review criteria for assessing the effectiveness of IVIg use	• Response demonstrated at review at six months. Improvement to be demonstrated for continuation of supply. • Titres of serum antibodies against keratinocytes. • Whether systemic corticosteroids can be gradually discontinued. • Total dose and duration of corticosteroid therapy, and number of relapses before and after the initiation of IVIg therapy.

Medical condition	Pemphigus vulgaris (PV)
Dose	Efficacy demonstrated with doses of at least 2 g/kg per monthly treatment cycle. **Dosing above 1 g/kg per day is contraindicated for some IVIg products.** **Refer to the current product information sheet for further information.** **The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.**

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Medical condition	Post-transfusion purpura (PTP)
Indication for IVIg use	Treatment of profound thrombocytopenia associated with bleeding.
Level of evidence	Small case studies only; insufficient data (Category 4a).
Description and diagnostic criteria	PTP is caused by antibodies to platelet-specific antigens, usually anti-HPA1a. PTP may result in profound thrombocytopenia with associated life-threatening bleeding. While the platelet count typically recovers spontaneously, this can take several weeks or more. Specialised investigations (antibody screening, patient/donor genotyping) and antigen-matched platelet and/or red cell transfusion support may be required — contact the Blood Service for more information.
Justification for evidence category	Mueller-Eckhardt and Kiefel (1988) evaluated the effect of high-dose IgG (HDIgG) in 11 PTP cases investigated in one institution and summarised clinical data on 8 additional reported cases. Of 17 cases, 16 had good or excellent response to HDIgG, attaining normal platelet counts within a few days; only one failure was observed. Five patients relapsed, but attained complete remission after a second course (dose) of IgG. Total IgG doses per course were in the range 52–180 g. Five different IgG preparations were used and seemed similarly effective. No adverse reactions were observed. The authors conclude that HDIgG is the treatment of choice for PTP.

Medical condition	Post-transfusion purpura (PTP)
Qualifying criteria for IVIg therapy	Clinical diagnosis/suspicion of PTP with thrombocytopenia associated with life-threatening bleeding. **Note:** Laboratory confirmation is desirable where possible in the time frame (usually an urgent, life-threatening clinical situation).
Review criteria	• Platelet counts in the days and weeks following IVIg. • Resolution of bleeding.
Dose	1 g/kg as a total dose, repeated if necessary. **Refer to the current product information sheet for further information.** **The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.**

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Medical condition	Toxic epidermal necrolysis (TEN; Lyell syndrome) Stevens–Johnson syndrome (SJS)
Indication for IVIg use	To limit progression of TEN or SJS/TEN when administered in early stages.
Level of evidence	Small case studies only; insufficient data (Category 4a).
Description and diagnostic criteria	TEN is a rare, life-threatening hypersensitivity reaction to certain medications, such as sulphonamides, antibiotics, non-steroidal anti-inflammatory drugs and anti-convulsants. Drug-induced epidermal apoptosis has been proposed as possible pathogenesis. Stevens–Johnson syndrome (SJS) is a less extensive manifestation of the same phenomenon. TEN and SJS are characterised by severe bullous reaction with extensive destruction of the epidermis, and morphologically by ongoing apoptotic keratinocyte cell death that results in the separation of the epidermis from the dermis. The term SJS is now used to describe patients with blistering and skin detachment involving a total body surface area of ‹10%. SJS/TEN describes patients with 10–30% detachment, and TEN describes patients with ›30% skin detachment.
Justification for evidence category	The Biotext (2004) review identified one small cohort study (20 patients) without a control group, which found that there appeared to be no significant effect and that death rate seems to be higher than previously reported.

Medical condition	Toxic epidermal necrolysis (TEN; Lyell syndrome) Stevens–Johnson syndrome (SJS)
Justification for evidence category continued	The Frommer and Madronio (2006) review found one small randomised study (four patients) with a control group of two patients (supportive care only). This study found that there was some improvement in epithelialisation and prominent difference in CD95 receptor between treated patients and controls. However, neither IVIg nor its comparison group could completely stop the TEN process.
Qualifying criteria for IVIg therapy	TEN or SJS/TEN overlap with *all* the following: 1. Diagnosis by a dermatologist; AND 2. Body surface area (erythema and/or erosions) of 10% or more; AND 3. Evidence of rapid evolution. **Notes:** • IVIg should be initiated as early as possible, preferably within 24 hours of diagnosis. • Urgent skin biopsy should be performed for confirmation but should not delay IVIg therapy if indicated. • The Adverse Drug Reactions Advisory Committee should be notified of the inciting medication.
Exclusion criteria for IVIg therapy	SJS alone

Medical condition	Toxic epidermal necrolysis (TEN; Lyell syndrome) Stevens–Johnson syndrome (SJS)
Dose	2 g/kg, preferably as a single dose, or divided over three consecutive days. **Dosing above 1 g/kg per day is contraindicated for some IVIg products.** **Refer to the current product information sheet for further information.** **The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.**

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Medical condition	Toxic shock syndrome (TSS)
Indication for IVIg use	**Streptococcal TSS:** In view of the high mortality risk, IVIg is indicated for early use in both adults and children. **Staphylococcal TSS:** IVIg is indicated where rapid improvement is not obtained with fluid resuscitation and inotropes. In both conditions IVIg is used in addition to surgical intervention, antibiotic therapy and supportive measures.
Level of evidence	Small case studies only; insufficient data (Category 4a).
Description and diagnostic criteria	TSS is a life-threatening illness characterised by hypotension and multi-organ failure. It may be caused by Staphylococcus aureus (rarely isolated) or Streptococcus pyogenes that produce and release superantigenic exotoxins. The exotoxins activate T-cells on a large scale resulting in a massive release of inflammatory cytokines. **Streptococcal TSS** is defined by: I Group A Streptococci *(S. pyogenes)* isolated from: • (IA) a normally sterile site (e.g. blood, cerebrospinal fluid, pleural or peritoneal fluid, tissue biopsy, surgical wound); or • (IB) a non-sterile site (e.g. throat, sputum, vagina, superficial skin lesion). IIA. Hypotension: systolic blood pressure = 90 mmHg in adults or in the 5th percentile for age in children; and

Medical condition	Toxic shock syndrome (TSS)
Description and diagnostic criteria continued	IIB. Two or more of the following: 1. Renal impairment: serum creatinine for adults at least twice the upper limit of normal for age; in patients with existing renal disease, elevation over baseline by a factor of at least 2; 2. Coagulopathy: platelet count of ≤100x10^9/L or disseminated intravascular coagulation, defined by prolonged clotting times, low fibrinogen level, and the presence of fibrin degradation products; 3. Liver involvement: alanine aminotransferase (ALT), aspartate aminotransferase (AST), or total bilirubin level at least twice the upper limit of normal for age; in patients with existing liver disease, elevation over baseline by a factor of 2; 4. Adult respiratory distress syndrome, defined by acute onset of diffuse pulmonary infiltrates and hypoxaemia in the absence of cardiac failure; or evidence of diffuse capillary leak manifested by acute onset or generalised oedema; or pleural or peritoneal effusions with hypoalbuminaemia; 5. Generalised erythematous macular rash that may desquamate; 6. Soft tissue necrosis, including necrotising fasciitis or myositis; or gangrene. A *definite* case is an illness fulfilling criteria IA and II (A and B). A *probable* case is an illness fulfilling criteria IB and II (A and B) where no other aetiology is identified. (Working Group on Severe Streptococcal Infections 1993).

Medical condition	Toxic shock syndrome (TSS)
	Staphylococcal TSS is defined by: 1. Fever: temperature ≥38.9°C; 2. Hypotension: systolic blood pressure ≤90 mmHg in adults or in the 5th percentile for age in children; 3. Diffuse macular rash with subsequent desquamation one to two weeks after onset (including palms and soles); 4. Multisystem involvement (three or more of the following): a. Hepatic: bilirubin or aminotransferase ≥2 times normal; b. Haematologic: platelet count ≤100x10^9/L; c. Renal: blood urea nitrogen or serum creatinine level ≥2 times normal; d. Mucous membranes: vaginal, oropharyngeal or conjunctival hyperaemia; e. Gastrointestinal: vomiting or diarrhoea at onset of illness; f. Muscular: severe myalgia or serum creatine phosphokinase level ≥2 times upper limit; g. Central nervous system: disorientation or alteration in consciousness without focal neurological signs and in the absence of fever or hypotension. A *confirmed* case is a case with all of the manifestations described above. However, in severe cases death may occur before desquamation develops. A *probable* case is an illness with all but any one of the manifestations described above (Wharton et al 1990).

Medical condition	Toxic shock syndrome (TSS)
	Prognosis Streptococcal TSS has a mortality rate of 30–80% in adults and 5–10% in children, with most deaths secondary to shock and respiratory failure. Staphylococcal TSS can also be fatal but mostly has a better prognosis.
Justification for evidence category	**Streptococcal TSS:** A small case series (Norrby-Teglund et al 2005), a cohort study (Kaul et al 1999) and an RCT, which was terminated prematurely (Darenberg et al 2003), suggested that IVIg improves outcomes. **Staphylococcal TSS:** In vitro and animal studies suggested that IVIg is effective in neutralising staphylococcal superantigens. Anecdotal reports refer to the clinical effectiveness of IVIg in staphylococcal TSS.
Qualifying criteria for IVIg therapy	1. Diagnosis of streptococcal or staphylococcal TSS in accordance with criteria listed above, preferably with isolation of organism; AND 2. Failure to achieve rapid improvement with fluid resuscitation, inotropes, surgery, antibiotic therapy and other supportive measures.
Dose	2 g/kg as a single dose. Schrage et al (2006) reported differences between various preparations of IVIg and their ability to neutralise streptococcal superantigens. They commented that 'the variations between IVIg preparations from different manufacturers are most likely caused by the different geographical regions from which the plasma samples were collected and might reflect differences in ... group A streptococcal ... exposure.' The clinical significance of these findings is not yet known.

Medical condition	Toxic shock syndrome (TSS)
Dose continued	Darenberg et al (2004) suggested that higher doses of IVIg might be required for staphylococcal TSS than streptococcal TSS, based on in vitro neutralisation of superantigens. **Dosing above 1 g/kg per day is contraindicated for some IVIg products.** **Refer to the current product information sheet for further information.** **The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.**

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7

Conditions for which IVIg use is in exceptional circumstances only

7. Conditions for which IVIg use is in exceptional circumstances only

This chapter comprises conditions that rarely, if ever, would require intravenous immunoglobulin (IVIg) use, either because there are safe and effective alternative therapies, or because the evidence of benefit does not justify use in most cases. IVIg is considered to have a therapeutic role only in exceptional circumstances, such as in urgent or life-threatening circumstances, or in circumstances in which significant morbidity would be expected and other clinically appropriate standard therapies have been either exhausted or are contraindicated.

There are some conditions listed for which the priority of IVIg use has been reduced in favour of alternative therapies and is now considered exceptional practice (e.g. the treatment of acute leukaemia in children and HIV in children).

Requests for IVIg should only occur:

1. when the situation is urgent or life threatening; or
2. in circumstances in which significant morbidity would be expected and other clinically appropriate standard therapies have been exhausted or are contraindicated.

Patients receiving IVIg for these conditions should be reviewed regularly to ensure the treatment remains appropriate (i.e. there is demonstrable improvement).

Table 6 Conditions for which IVIg is used as immunoglobulin replacement therapy in exceptional circumstances

Condition	Level of evidence
Acute leukaemia in children [Includes acute lymphoblastic or lymphoid leukaemia (ALL) and acute myeloblastic leukaemia (AML)]. IVIg may be considered in cases of ALL or AML with neutropenic sepsis in patients aged ≤15 years in whom conventional antimicrobial therapy has been ineffective and who have life-threatening infection. **Refer to the current product information sheet for further information.** **The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.**	2a
HIV in children The need for IVIg in paediatric HIV has been substantially reduced with the advent of highly active antiretroviral therapy (HAART). A trial of therapy may however be considered in children with significant recurrent bacterial infections despite HAART. **Refer to the current product information sheet for further information.** **The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.**	2a

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Table 7 **Conditions for which IVIg is used in immunomodulation therapy in exceptional circumstances**

Condition	Level of evidence
Autoimmune congenital heart block (neonatal lupus) IVIg therapy may be indicated during pregnancy when there is a history of autoimmune congenital heart block in at least one previous pregnancy and maternal SS-A and/or SS-B antibodies are present. **Refer to the current product information sheet for further information.** **The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.**	4a

References

Buyon, JP, Kim, MY, Copel, JA, et al 2001, 'Anti-Ro/SSA antibodies and congenital heart block: necessary but not sufficient', *Arthritis & Rheumatism,* vol. 44, no. 8, pp. 1723–7.

Kaaja, R & Julkunen, H 2003, 'Prevention of recurrence of congenital heart block with intravenous immunoglobulin and corticosteroid therapy: comment on the editorial by Buyon et al', *Arthritis & Rheumatism,* vol. 48, no. 1, pp. 280–1.

Tran, HB, Cavill, D, Buyon, JP, et al 2004, 'Intravenous immunoglobulin and placental transport of anti-Ro/La antibodies: comment on the letter by Kaaja and Julkunen', *Arthritis & Rheumatism*, vol. 50, no. 1, pp. 337–8.

Villain, E, Coastedoat-Chalumeau, N, Marijon, E, et al 2006, 'Presentation and prognosis of complete atrioventricular block in childhood, according to maternal antibody status', *Journal of the American College of Cardiology*, vol. 48, no. 8, pp. 1682–7.

Wong, JP, Kwek, KY, Tan, JY, et al 2001, 'Fetal congenital complete heart block: prophylaxis with intravenous gammaglobulin and treatment with dexamethasone', *Australia New Zealand Journal of Obstetrics and Gynaecology*, vol. 41, no. 3, pp. 339–41.

Condition	Level of evidence
Autoimmune neutropenia	4a

Autoimmune neutropenia is a rare disorder caused by peripheral destruction of antibody-sensitised neutrophils by cells of the reticuloendothelial system. IVIg may be considered among treatment options in rare circumstances when the standard treatment of G-CSF fails.

Refer to the current product information sheet for further information.

The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.

Reference

Anderson, D, Ali, K, Blanchette, V, et al 2007, 'Guidelines on the use of intravenous immune globulin for hematologic conditions', *Transfusion Medicine Reviews*, vol. 21, no. 2, suppl. 1, pp. S9–56.

Condition	Level of evidence
Autoimmune uveitis	4a
Uveitis refers to inflammation of the uvea of the eye and can be caused by infection, exposure to toxins or autoimmune disorders. Symptoms may include redness of the eye, blurred vision, unusual sensitivity to light, dark floating spots in the vision and eye pain. Ocular inflammation of this kind may threaten sight and be resistant to standard immunosuppression. IVIg therapy may be considered for immune-mediated, sight-threatening uveitis with persistent activity despite both oral corticosteroid and systemic immunosuppressive therapy. Uveitis of non-immune origin is not indicated. Recommended dose is 1.5 g/kg/month for three months, with further maintenance dependent upon evidence of significant improvement in visual acuity and ocular inflammation. Dosing above 1 g/kg per day is contraindicated for some IVIg products. **Refer to the current product information sheet for further information.** **The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.**	

Condition	Level of evidence
Autoimmune uveitis (cont)	4a
References Lim, LL, Suhler, EB & Smith, JR 2006, 'Biologic therapies for inflammatory eye disease', *Clinical and Experimental Ophthalmology*, vol. 34, pp. 365–74. Orange, JS, Hossny, EM, Weiler, CR, et al 2006, 'Use of intravenous immunoglobulin in human disease: a review of evidence by members of the Primary Immunodeficiency Committee of the American Academy of Allergy, Asthma and Immunology', *Journal of Allergy and Clinical Immunology*, vol. 117, no. 4, pp. S525–53. Rosenbaum, JT, George, RK & Gordon, C 1999, 'The treatment of refractory uveitis with intravenous immunoglobulin', *American Journal of Ophthalmology*, vol. 127, no. 5, pp. 545–9.	
Catastrophic antiphospholipid syndrome IVIg may be appropriate therapy for catastrophic antiphospholipid syndrome, a term that describes the accelerated form of antiphospholipid syndrome characterised by widespread small vessel thrombosis leading to multiorgan failure. It is not indicated for the treatment of antiphospholipid syndrome in other cases. Please see *Antiphospholipid syndrome (non-obstetric)* in Chapter 8 (page 214) and *Recurrent foetal loss (with or without antiphospholipid syndrome)* in Chapter 8 (page 216). **Qualifying criteria for IVIg therapy** A patient will qualify for IVIg when *all* the following criteria are met: 1. Evidence of rapidly evolving thrombosis involving two or more organs;	4a

Condition	Level of evidence
Catastrophic antiphospholipid syndrome (cont)	4a

2. Unequivocal laboratory evidence of antiphospholipid antibodies (lupus anticoagulant and/or anticardiolipin antibodies and/or beta 2 glycoprotein I antibodies); and
3. Other causes of thrombotic microangiopathy are considered less likely.

Confirmation by histopathology of thrombotic small vessel occlusion in at least one organ or tissue is desirable but should not delay IVIg therapy if indicated.

A single treatment is usually sufficient, based on a dose of 2 g/kg divided over 2–5 days. The potential pro-thrombotic effect of IVIg should be considered in this indication.

Refer to the current product information sheet for further information.

The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.

References

Asherson, RA, Cervera, R, de Groot, PG, Erkan, D, Boffa, M-C, Piette, J-C, et al 2003, 'Catastrophic antiphospholipid syndrome: international consensus statement on classification criteria and treatment guidelines', *Lupus*, vol. 12, pp. 530–34.

Asherson RA, et al 2002, 'Catastrophic antiphospholipid syndrome: proposed guidelines for diagnosis and treatment', *Journal of Clinical Rheumatology*, vol. 8, no. 3, pp. 157–65.

Cervera, R, Asherson, RA & Font, J 2006, 'Catastrophic antiphospholipid syndrome', *Rheumatic Disease Clinics of North America*, vol. 32, no. 3, pp. 575–90.

Erkan, D 2006, 'Therapeutic and prognostic considerations in catastrophic antiphospholipid syndrome', *Autoimmunity Reviews*, vol. 6, no. 2, pp. 98–103.

Condition	Level of evidence
Coagulation factor inhibitors (alloantibodies and autoantibodies), including acquired haemophilia, acquired von Willebrand syndrome, inhibitors to factor VIII in haemophilia A, and inhibitors to factor IX in haemophilia B Management of these rare and severe bleeding disorders should be undertaken only by or in consultation with haemophilia treatment centres. When indicated, IVIg only forms part of the management of these complex patients, with additional haemostatic support required. IVIg may be considered in the following circumstances: 1. Inhibitors to factor VIII (FVIII) in haemophilia A and inhibitors to factor IX (FIX) in haemophilia B, especially in cases where there has been failure of immune tolerisation and poor response to recombinant factor VIIa or factor eight inhibitor bypassing activity (FEIBA) — only as part of the Bonn–Malmö protocol for immune tolerance induction. 2. Autoimmune acquired von Willebrand syndrome — correction of FVIII and von Willebrand factor levels for the management of bleeding and before invasive procedures, except cases associated with IgM paraprotein where response is unlikely. Use is indicated in failure to respond to chemotherapy/immunosuppressants or where there is insufficient time for chemotherapy/immunosuppressants to be given. Initial therapy either 0.4 g/kg for 5 days or 1 g/kg for 2 days. Continued therapy 1 g/kg once every 3–4 weeks.	2a

Condition	Level of evidence
Coagulation factor inhibitors (alloantibodies and autoantibodies), including acquired haemophilia, acquired von Willebrand syndrome, inhibitors to factor VIII in haemophilia A, and inhibitors to factor IX in haemophilia B (cont)	2a
3. Acquired haemophilia A for: a. Support of correction of FVIII level for the management of bleeding, and before invasive procedures in individuals in whom steroid or immunosuppressive therapy is contraindicated or has failed to eradicate the inhibitor (2 g/kg over 2–5 days); or b. Support of correction of FVIII level following failure of first line therapies (steroids and immunosuppressants) and poor response to recombinant factor VIIa or FEIBA when used as part of the Bonn–Malmö protocol. 4. Other acquired (autoimmune) coagulation inhibitors (e.g. acquired Factor V inhibitors) to correct factor level for the management of bleeding and before invasive procedures in cases where other therapeutic approaches have failed or are contraindicated (2 g/kg over 2 to 5 days). Dosing above 1 g/kg per day is contraindicated for some IVIg products. **Refer to the current product information sheet for further information.** **The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.** **Reference** Hay, CR, Brown, S, Collins, PW, et al 2006, 'The diagnosis and management of factor VIII and IX inhibitors: a guideline from the United Kingdom Haemophilia Centre Doctors Organisation', *British Journal of Haematology*, vol. 133, no. 6, pp. 591–605.	

Condition	Level of evidence
Devic disease (neuromyelitis optica)	4a

Devic disease is an idiopathic inflammatory demyelinating disorder of the central nervous system characterised by recurrent bouts of optic neuritis and myelitis. It is distinct from multiple sclerosis and evidence of B-cell autoimmunity has been found. A circulatory antibody to aquaporin-4 is found in many patients providing further evidence of B-cell autoimmunity in its pathogenesis and suggestive of a role for IVIg therapy. Single case reports of various therapies, including IVIg, have shown variable benefit in this otherwise devastating disorder.

Refer to the current product information sheet for further information.

The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.

References

Lennon, VA, Wingerchuk, DM, Kryzer, TJ, et al 2004, 'A serum autoantibody marker of neuromyelitis optica: distinction from multiple sclerosis', *Lancet*, vol. 364, no. 9451, pp. 2106–12.

Lucchinetti, CF, Mandler, RN, McGavern, D, et al 2002, 'A role for humoral mechanisms in the pathogenesis of Devic's neuromyelitis optica', *Brain*, vol. 125, pp. 1450–61.

Minagar, A, Alexander, JS, Fowler, MR, et al 2002, 'Devic disease: clinical course, pathophysiology, and management', *Pathophysiology*, vol. 9, no. 1, p. 33.

Condition	Level of evidence
Diabetic amyotrophy (diabetic proximal neuropathy or diabetic lumbosacral radiculoplexus neuropathy) IVIg may be considered in exceptional circumstances for intractable pain or progressive muscle weakness in patients in whom steroids are ineffective or cannot be tolerated. This condition is monophasic and usually self-limiting. A single treatment may be sufficient, although monthly infusions for up to six months may be required for recurrent pain. **Refer to the current product information sheet for further information.** **The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.**	4a
Epidermolysis bullosa acquisita IVIg should be considered for severe cases refractory to conventional immunosuppressive therapy. **Refer to the current product information sheet for further information.** **The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.**	4a
Epilepsy • Landau–Kleffner syndrome • Lennox–Gastaut syndrome IVIg should be considered in childhood cases only after failure of all conventional therapies and full assessment by a paediatric neurologist. **Refer to the current product information sheet for further information.** **The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.**	2a

Condition	Level of evidence
Graves ophthalmopathy	2a
IVIg may be indicated in select cases. Tagami et al (1996) have shown that IVIg is effective in this condition. Other studies have shown IVIg to be as effective as corticosteroids with fewer side effects. May be indicated where steroids have failed or are contraindicated.	
Refer to the current product information sheet for further information.	
The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.	
Reference	
Tagami, T, Tanaka, K, Sugawa, H, et al 1996, 'High-dose intravenous steroid pulse therapy in thyroid associated ophthalmopathy', *Endocrinology Journal*, vol. 43, no. 6, pp. 689–99.	

Condition	Level of evidence
Haemolytic disease of the newborn (HDN)	4a

HDN arises from foetomaternal antigen incompatibility and can result in clinically significant foetal/neonatal haemolysis, severe anaemia and hyperbilirubinaemia.

Although prophylaxis programs have reduced the frequency of Rhesus (Rh) D HDN, antibodies to RhD remain the most common cause in Australia. Antibodies to other antigens in the Rh system (e.g. Rhc, E), ABO and other antigens (e.g. K) may also cause disease ranging from mild to life-threatening.

IVIg may be used in selected cases in consultation with experts in foetomaternal medicine and transfusion medicine.

Refer to the current product information sheet for further information.

The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.

References

Gottstein, R & Cooke, RW 2003, 'Systematic review of intravenous immunoglobulin in haemolytic disease of the newborn', *Archives of Disease in Childhood – Fetal Neonatal Edition*, vol. 88, no. 1, pp. F6–10.

Kaplan, M, Vreman, HJ, Hammerman, C, et al 1996, 'Intravenous immune globulin in neonatal ABO isoimmunisation: factors associated with clinical efficacy', *Biology of the Neonate*, vol. 70, pp. 69–72.

Miqdad, AM, Abdelbasit, OB, Shaheed, MM, et al 2004, 'Intravenous immunoglobulin G therapy for significant hyperbilirubinaemia in ABO haemolytic disease of the newborn', *Journal of Maternal-Fetal and Neonatal Medicine*, vol. 16, no. 3, pp. 163–6.

Condition	Level of evidence
Haemolytic transfusion reaction IVIg may be considered in the management or prevention of severe haemolytic transfusion reaction not responding to other interventions (e.g. corticosteroids). **Refer to the current product information sheet for further information.** **The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.** **Reference** Win, N, Madan, B, Gale, R, et al 2005, 'Intravenous immunoglobulin given to lymphoma patients with recurrent haemolytic transfusion reactions after transfusion of compatible blood', *Hematology*, vol. 10, no. 5, pp. 375–8.	4a
Hashimoto encephalopathy (steroid-responsive encephalopathy associated with autoimmune thyroiditis) IVIg is not supported as first-line treatment, because preferable alternative treatments are available. IVIg may be considered in exceptional circumstances where there is progressive neurologic decline despite appropriate steroid therapy. **Refer to the current product information sheet for further information.** **The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.** **Reference** Jacob, S & Rajabally, YA 2005, 'Hashimoto's encephalopathy: steroid resistance and response to intravenous immunoglobulins', *Journal of Neurology, Neurosurgery and Psychiatry*, vol. 76, no. 3, pp. 455–6.	4a

Condition	Level of evidence
Limbic encephalitis — nonparaneoplastic	4a
There appears to be a role for IVIg in nonparaneoplastic limbic encephalitis associated with neuronal antibodies to cell surface antigens. This includes VGKC antibodies, as well as NMDA receptor antibodies and AMPA receptor antibodies. **Refer to the current product information sheet for further information.** **The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.**	
Myocarditis in children	4a
There is some evidence that IVIg improves cardiac function in children with proven or likely viral myocarditis. **Refer to the current product information sheet for further information.** **The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.**	

References

Drucker, NA, Colan, SD, Lewis, AB, et al 1994, 'Gamma-globulin treatment of acute myocarditis in the pediatric population', *Circulation*, vol. 89, pp. 252–7.

Robinson, J, Hartling, L, Vandermeer, B, et al 2005, 'Intravenous immunoglobulin for presumed viral myocarditis in children and adults (Cochrane Review)', in *The Cochrane Library*, Issue 1, John Wiley & Sons, Ltd, Chichester, UK.

Condition	Level of evidence
Paediatric autoimmune neuropsychiatric disorder associated with streptococcal infection (PANDAS)	2a

PANDAS was first described in the early 1990s. PANDAS is characterised by rapid-onset tics associated with obsessive-compulsive disorder (OCD) in the context of recovery from streptococcal infection. Molecular mimicry between streptococcal antigens and the central nervous system is thought to underlie the cause. Symptomatic therapy is used with variable response.

A single randomised placebo-controlled trial using IVIg for PANDAS showed very prolonged and significant improvement in obsessive-compulsive symptoms, anxiety, depression, emotional lability and overall function compared with placebo. Improvements in symptoms were still evident at one-year follow-up.

Refer to the current product information sheet for further information.

The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.

References

Singer, HS 1999, 'PANDAS and immunomodulatory therapy', *Lancet*, vol. 354, no. 9185, pp. 1137–8.

Perlmutter, SJ, Leitman, SF, Garvey, MA, et al 1999, 'Therapeutic plasma exchange and intravenous immunoglobulin for obsessive-compulsive disorder and tic disorders in childhood', *Lancet*, vol. 354, no. 9185, pp. 1153–8.

Condition	Level of evidence
Paraneoplastic neurological syndromes	4a
Paraneoplastic subacute sensory neuropathy	
IVIg may be indicated in select cases, in combination with tumour therapy (tumour resection and/or oncological treatment) where the latter has not led to an improvement in the neurologic syndrome; where other immunomodulatory therapies are contraindicated or have failed; or if the neurologic features warrant urgent intervention.	
Refer to the current product information sheet for further information.	
The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.	
Paraneoplastic cerebellar degeneration	
IVIg may be indicated in select cases, in combination with tumour therapy (tumour resection and/or oncological treatment) where the latter has not led to an improvement in the neurologic syndrome; where other immunomodulatory therapies are contraindicated or have failed; or if the neurologic features warrant urgent intervention.	
Refer to the current product information sheet for further information.	
The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.	

Condition	Level of evidence
Paraneoplastic neurological syndromes (cont)	4a
Limbic encephalitis — paraneoplastic	
IVIg may be indicated in select cases, in combination with tumour therapy (tumour resection and/or oncological treatment) where the latter has not led to an improvement in the neurologic syndrome; where other immunomodulatory therapies are contraindicated or have failed; or if the neurologic features warrant urgent intervention.	
Refer to the current product information sheet for further information.	
The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.	
References	
Bataller, L, Galiano, R, Garcia-Escrig, M, Martinez, B, Sevilla, T, Blasco, R, et al 2010, 'Reversible paraneoplastic limbic encephalitis associated with antibodies to the AMPA receptor', *Neurology*, vol. 74, no. 3, pp. 265–7.	
Henry, C, Husson, H, de Broucker, T 2009, 'Autoimmune limbic encephalitis with anti-NMDA receptor antibodies and ovarian teratoma: a treatable form of paraneoplastic limbic encephalitis' (in French), *Revue neurologique* (Société de neurologie de Paris), vol. 165, no. 1, pp. 70–5.	

Condition	Level of evidence
Potassium channel antibody-associated encephalopathy	4a

Potassium channel antibody-associated neurologic syndromes include limbic encephalitis/subacute amnesic encephalopathy, Morvan syndrome, peripheral nerve hyperexcitability and autonomic ganglionopathy.

Potassium channel antibody-associated encephalopathy is considered to be an autoimmune, nonparaneoplastic, potentially treatable syndrome, but may respond to a variety of immunomodulatory agents, including IVIg.

Refer to the current product information sheet for further information.

The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.

References

Vincent, A, Buckley, C, Schott, JM, et al 2004, 'Potassium channel antibody-associated encephalopathy: a potentially immunotherapy-responsive form of limbic encephalitis', *Brain*, vol. 127, pt 3, pp. 701–12.

Hudson, LA, et al 2008, 'Reduplicative paramnesia in Morvan's syndrome', *Journal of the Neurological Sciences*, vol. 267, no. 1–2, pp. 154–7.

Condition	Level of evidence
Pure red cell aplasia (PRCA)	4b
PRCA is a rare syndrome of severe anaemia, reticulocytopenia and a selective deficiency of erythroid progenitors. IVIg should be considered as first-line therapy for viral PRCA associated with parvovirus B19 in immunocompromised patients. IVIg is a reasonable option for patients with immunological PRCA who have failed other therapies (e.g. prednisone or cyclosporine). **Refer to the current product information sheet for further information.** **The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.** **Reference** Anderson, D, Ali, K, Blanchette, V, et al 2007, 'Guidelines on the use of intravenous immune globulin for hematologic conditions', *Transfusion Medicine Reviews*, vol. 21, no. 2, suppl. 1, pp. S9–56.	

Condition	Level of evidence
Pure white cell aplasia (PWCA)	4b
PWCA is a rare syndrome of severe neutropenia and a selective deficiency of granulocyte progenitors. IVIg is a reasonable option for patients with immunological PWCA who have failed other therapies (e.g. prednisone or cyclosporine). **Refer to the current product information sheet for further information.** **The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.** **Reference** Anderson, D, Ali, K, Blanchette, V, et al 2007, 'Guidelines on the use of intravenous immune globulin for hematologic conditions', *Transfusion Medicine Reviews*, vol. 21, no. 2, suppl. 1, pp. S9–56.	

Condition	Level of evidence
Pyoderma gangrenosum	4a

Use of IVIg is limited to patients with significant pyoderma gangrenosum, diagnosed by a dermatologist, unresponsive to corticosteroids and other immunosuppressive agents.

Induction dose: 2 g/kg divided over 3 days.

Maintenance therapy: 1–2 g/kg divided over 2 days, monthly for 4–6 months.

IVIg should be ceased in patients who fail to respond after three cycles.

Refer to the current product information sheet for further information.

The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.

References

Cummins, DL, Anhalt, GJ, Monahan, T & Meyerle, JH 2007, 'Treatment of pyoderma gangrenosum with intravenous immunoglobulin', *British Journal of Dermatology*, vol. 157, no. 6, pp. 1235–39.

Kreuter, A, Reich-Schupke, S, Stucker, M, Altmeyer, P & Gambichler T 2008, 'Intravenous immunoglobulin for pyoderma gangrenosum', *British Journal of Dermatology*, vol. 158, no. 4, pp. 856–7.

Condition	Level of evidence
Rasmussen syndrome	2a
Rasmussen syndrome is a chronic, progressive, focal encephalitis that is commonly accompanied by focal seizures, hemiparesis and cognitive decline. It is generally considered to be a disease of childhood, with most cases occurring in children younger than 10 years, although adult onset cases do occur. Conventional anticonvulsant therapy is usually ineffective and hemispherectomy may be helpful in the correct setting. Immunomodulatory therapy may be useful and, of the different therapies, IVIg may be most useful. Other therapies to consider include methylprednisolone and rituximab. Ongoing supply of IVIg would be based on evidence of stabilisation of either seizure frequency or cognitive decline. **Refer to the current product information sheet for further information.** **The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.**	

Condition	Level of evidence
Scleromyxedema	4a
IVIg may be indicated in select cases not responding to steroids, or when steroids and other alternative treatments (e.g. thalidomide) are contraindicated. **Refer to the current product information sheet for further information.** **The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.** **References** Kulczycki, A, Nelson, M, Eisen, A, et al 2003, 'Scleromyxedema: treatment of cutaneous and systemic manifestations with high-dose intravenous immunoglobulin', *British Journal of Dermatology*, vol. 149, no. 6, pp. 1276–81. Majeski, C, Taher, M, Grewal, P, et al 2005, 'Combination oral prednisone and intravenous immunoglobulin in the treatment of scleromyxedema', *Journal of Cutaneous Medicine and Surgery*, vol. 9, no. 3, pp. 99–104.	
Sjogren's syndrome	4a
IVIg may be indicated in certain highly selected cases where other treatments have not been effective. **Refer to the current product information sheet for further information.** **The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.** **Reference** Smith, A, Jackson, M, Wang, F, et al 2005, 'Neutralisation of muscarinic receptor autoantibodies by intravenous immunoglobulin in Sjogren's syndrome', *Human Immunology*, vol. 66, no. 4, pp. 411–6.	

Condition	Level of evidence
Solid organ transplantation (other than kidney)	4a

IVIg may be indicated in:

- highly sensitised patients awaiting transplantation;
- transplant recipients with acute antibody-mediated rejection with clinical evidence of graft dysfunction; and
- transplant recipients as treatment or prophylaxis for rejection where conventional immunosuppressive therapy is contraindicated; for example, in a patient with life-threatening infection in whom conventional immunosuppression will place the patient at greater risk, or when the transplant is at risk.

Refer to the current product information sheet for further information.

The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.

Reference

Jordan, SC, Vo, A, Bunnapradist, S, et al 2003, 'Intravenous immune globulin treatment inhibits cross match positivity and allows for successful transplantation of incompatible organs in living-donor and cadaver recipients', *Transplantation*, vol. 76, no. 4, pp. 631–6.

Condition	Level of evidence
Susac syndrome	4a
Susac syndrome is a rare, microangiopathic disorder characterised by encephalopathy, hearing loss and retinal artery branch occlusions. Case reports show benefit of IVIg therapy in combination with corticosteroids, with or without other immunosuppressive agents. **Dose:** 1–2 g/kg/month for one year providing documented clinical improvement. Dosing above 1 g/kg per day is contraindicated for some IVIg products. Note: Effectiveness of IVIg therapy may be difficult to determine due to the fluctuating course of disease. **Refer to the current product information sheet for further information.** **The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.** **References** Aubart-Cohen, F, Klein, I, Alexandra, J, et al 2007, 'Long-term outcome in Susac syndrome', *Medicine* (Baltimore), vol. 86, no. 2, pp. 93–102. Fox, R, Costello, F, Judkins, A, et al 2006, 'Treatment of Susac syndrome with gamma globulin and corticosteroids', *Journal of the Neurological Sciences*, vol. 251, no. 1–2, pp. 17–22.	

Condition	Level of evidence
Systemic capillary leak syndrome (SCLS)	4a
SCLS is an extremely rare condition that is characterised by life-threatening attacks of reversible capillary hyperpermeability accompanied by haemoconcentration and hypoalbuminaemia. A diagnosis by a consultant physician, emergency specialist or intensive care unit specialist is required. Other therapies may be appropriate. Approval will be provided for an initial period of 12 months only. Clinicians requesting ongoing IVIg therapy after the initial 12 month period are required to confirm in writing that the patient experienced a reduced number of severe episodes requiring hospital admission when treated with IVIg. Maximum dose of 1–2 g/kg per month. **Refer to the current product information sheet for further information.** **The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.**	

Condition	Level of evidence
Systemic capillary leak syndrome (SCLS) (cont)	4a

References

Abueguen, P, Chennebault, JM & Pichard, E 2010, 'Immunoglobulins for the treatment of systemic capillary leak syndrome', *Americal Journal of Medicine*, vol. 123, pp. e3–4.

Druey, KM & Greipp, PR 2010, 'Narrative review: the systemic capillary leak syndrome', *Annals of Internal Medcine*, vol. 153, pp. 90–8.

Gousseff, M, Arnaud, L, Lambert, M, et al 2011, 'The systemic capillary leak syndrome: a case series of 28 patients from a European registry', *Annals of Internal Medicine*, vol. 154, pp. 464–71.

Govig, BA & Javaheri, S 2010, 'The systemic capillary leak syndrome (letter)', *Annals of Internal Medicine*, vol. 153, p. 764.

Lambert, M, Launay, D, Hachulla, E, et al 2008, 'High-dose intravenous immunoglobulins dramatically reverse systemic capillary leak syndrome', *Critical Care Medicine*, vol. 36, pp. 2184–7.

Zipponi, M, Eugster, R & Birrenbach, T 2011, 'High-dose intravenous immunoglobulins: A promising therapeutic approach for idiopathic systemic capillary leak syndrome', *BMJ Case Reports*, doi:10.1136/bcr.12.2010.3599.

8

Conditions for which IVIg use is not supported

8. Conditions for which IVIg use is not supported

This chapter comprises conditions for which the use of intravenous immunoglobulin (IVIg) therapy is not supported at this time, because there is evidence of no benefit, insufficient evidence of benefit, or some evidence of benefit but preferred alternative therapies are available.

Table 8 Conditions for which IVIg use is not supported

Condition	Level of evidence
Acute optic neuritis IVIg is not supported in this setting. There is anecdotal evidence for use in Devic disease but not optic neuritis. **Reference** Roed, HG, Langkilde, A, Sellebjerg, F, et al 2005, 'A double-blind randomised trial of intravenous immunoglobulin treatment in acute optic neuritis', *Neurology*, vol. 64, pp. 804–10.	2b
Acute rheumatic fever	2b
Adrenoleukodystrophy	4b
Amegakaryocytic thrombocytopenia	4b
Antiphospholipid syndrome (non-obstetric)	4b
Aplastic anaemia/pancytopenia	4b
Asthma	2c
Atopic dermatitis/eczema — adult	2b
Autism	4b
Autologous haemopoietic stem cell transplantation Use of IVIg in autologous stem cell transplant recipients is not supported unless the patient has established humoral deficiency (see Secondary hypogammaglobulinaemia).	2c

Condition	Level of evidence
Behçet's disease	4b
Cardiac surgery with bypass — prophylaxis IVIg is not supported in this setting; preferable alternative treatments are available.	2a
Congestive cardiac failure IVIg is not supported in this setting; preferable alternative treatments are available.	2a
Crohn's disease	4b
Diamond Blackfan syndrome	4b
Female infertility	4a
Glomerulonephritis — IgA nephritis	2b
Haemolytic uraemic syndrome	4b
Henoch–Schonlein purpura	4b
HIV/AIDS — adult (see Secondary hypogammaglobulinaemia and/or ITP in adults)	2b
Idiopathic dilated cardiomyopathy	2b
Linear IgA disease	4b
Lupus cerebritis IVIg is not supported as preferable alternative treatments are available.	4a
Lupus nephritis IVIg is not supported in this setting; preferable alternative treatments are available.	2a
Motor neuron disease/amyotrophic lateral sclerosis Note: IVIg is sometimes used when the diagnosis of motor neuron disease has not yet been established and an alternative diagnosis of multifocal motor neuropathy has not been ruled out.	4b
Myalgic encephalomyelitis	2c

Condition	Level of evidence
Narcolepsy/cataplexy	4a
Nephrotic syndrome IVIg is not supported in this setting; preferable alternative treatments are available.	2a
Obsessive compulsive disorders IVIg is not supported in this setting (see PANDAS).	4a
Polyneuropathy of critical illness	4a
Recurrent foetal loss (with or without antiphospholipid syndrome) **Reference** Empson, M, Lassere, M, Craig, J, et al 2005, 'Prevention of recurrent miscarriage for women with antiphospholipid antibody or lupus anticoagulant (Cochrane Review)', in *The Cochrane Library*, Issue 2, John Wiley & Sons, Ltd, Chichester, UK.	3
Rheumatoid arthritis IVIg is not supported in this setting; preferable alternative treatments are available.	2c
Sepsis *Adult and paediatric treatment or prevention* If IgG levels are low, the use of IVIg should be considered under PID and/or secondary hypogammaglobulinaemia (including iatrogenic immunodeficiency). *Neonatal prevention* IVIg is not supported. Therapy with intravenous immune globulin had no effect on the outcomes of suspected or proven neonatal sepsis (Brockelhurst et al 2011).	2a

Condition	Level of evidence
Sepsis (cont)	2a
References	
Alejandria Marissa, M, Lansang, M-AD, Dans Leonila, F & Mantaring, III JB 2002, 'Intravenous immunoglobulin for treating sepsis, severe sepsis and septic shock', *Cochrane Database of Systematic Reviews*, vol. 1, doi:10.1002/14651858.CD001090.	
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Sickle cell disease	4b
Systemic lupus erythematosus (SLE)	2a
IVIg is not supported in this setting; preferable alternative treatments are available.	
Ulcerative colitis	4b

Acronyms and abbreviations

AASV	ANCA-associated systemic vasculitis
AbMR	antibody-mediated rejection
AChR	acetylcholine receptor
ADEM	acute disseminated encephalomyelitis
ADL	activities of daily living
AHMC	Australian Health Ministers' Conference
AHMAC	Australian Health Ministers' Advisory Council
AIDS	acquired immunodeficiency syndrome
AIHA	autoimmune haemolytic anaemia
ALL	acute lymphoblastic or lymphoid leukaemia
AML	acute myeloid or myelogenous leukaemia
ANCA	anti-neutrophil cytoplasmic antibody
ARCBS	Australian Red Cross Blood Service (the Blood Service)
ARTG	Australian Register of Therapeutic Goods
BP	bullous pemphigoid
CIDP	chronic inflammatory demyelinating polyneuropathy
CLL	chronic lymphocytic leukemia
CP	cicatricial pemphigoid
3	cerebrospinal fluid
CTEPC	Clinical, Technical & Ethical Principal Committee of AHMAC
CVID	common variable immunodeficiency
DM	dermatomyositis
DNA	deoxyribonucleic acid
ESRD	end-stage renal disease
FEIBA	factor eight inhibitor bypassing agent
FIX	clotting factor nine
FMAIT	foeto-maternal alloimmune thrombocytopenia

FVIII	clotting factor eight
g	gram
GBS	Guillain–Barré syndrome
GMP	good manufacturing practice
HAART	highly active anti-retroviral therapy
HDN	haemolytic disease of the newborn
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HPA	human platelet antigen
HSCT	haemopoietic stem cell transplantation
IBM	inclusion body myositis
Ig	immunoglobulin
IgG	immunoglobulin G
ITP	immune/idiopathic thrombocytopenia purpura
IV	intravenous
IVIg	intravenous immunoglobulin
JBC	Jurisdictional Blood Committee
JDO	Jurisdictional Direct Order (for imported IVIg)
kg	kilogram
L	litre
LEMS	Lambert–Eaton myasthenic syndrome
MAG	myelin-associated glycoprotein
MG	myasthenia gravis
MGUS	monoclonal gammopathy of uncertain significance
MM	multiple myeloma
MMN	multifocal motor neuropathy
MMP	mucous membrane pemphigoid
MPO	myeloperoxidase

MRC	Medical Research Council
MRI	magnetic resonance imaging
MS	multiple sclerosis
n	number
NAIT	neonatal alloimmune thrombocytopenia
NBA	National Blood Authority
NH	neonatal haemochromatosis
NHL	non-Hodgkin lymphoma
NHMRC	National Health and Medical Research Council
NICRWG	National IVIg Criteria Working Group
OMA	opsoclonus myoclonus ataxia
PANDAS	paediatric autoimmune neuropsychiatric disorder associated with streptococcal infections
PF	pemphigus foliaceus
PICO	population, intervention, comparator, outcome
PID	primary immunodeficiency
PM	polymyositis
PPMS	primary progressive multiple sclerosis
PRMS	progressive relapsing multiple sclerosis
PTP	post transfusion purpura
PV	pemphigus vulgaris
RCT	randomised controlled trial
RhD	Rhesus D
RRMS	relapsing remitting multiple sclerosis
SCLS	systemic capillary leak syndrome
SCoH	Standing Council on Health
SJS	Stevens–Johnson syndrome
SLE	systemic lupus erythematosus
SPMS	secondary progressive multiple sclerosis

TEN	toxic epidermal necrolysis
TGA	Therapeutic Goods Administration
the Criteria	*Criteria for the clinical use of intravenous immunoglobulin in Australia*
TSEAC	Transmissible Spongiform Encephalopathies Advisory Committee
TSS	toxic shock syndrome

Glossary of terms

Albumin	The major protein in plasma that is important in maintaining blood volume.
Allogeneic blood	The term allogeneic blood has exactly the same meaning as homologous blood.
Antibody	A protein usually produced by the immune system (an immunoglobulin) and found in the response to the presence of antigens.
Antigen	A substance that causes the formation of an antibody.
Apheresis	A procedure in which blood is temporarily withdrawn, one or more components are selectively removed, and the remainder of the blood is re-infused into the donor.
Blood group	Complex chemical substances found on or in the surface of red cells that distinguish each blood group. The two more important blood group systems in transfusion work are the ABO and Rh systems.
Bovine spongiform encephalopathy	An infection of the nervous system in cows. Also known as 'mad cow' disease.
Code of Good Manufacturing Practice	A set of standards that provide assurance that a manufacturer has a quality system in place that meets the requirements for the product being made.
Creutzfeldt–Jakob disease	A central nervous system disease that causes pre-senile dementia, myoclonus, and distinctive electroencephalographic changes caused by a prion.

Cryoprecipitate	A clotting factor preparation derived from plasma. Its main use is as a source of fibrinogen. It includes factor VIII and is used in the treatment of massive bleeding.
Cytomegalovirus	A common virus that causes an illness similar to glandular fever.
Factor VIII	Clotting factor — absent in haemophilia A.
Factor IX	Clotting factor — absent in haemophilia B (also known as Christmas disease).
Fractionation	The separation of a substance into its basic constituents.
Haemophilia	An hereditary or acquired deficiency of a clotting factor(s) in blood.
Hepatitis B	Viral disease of the liver caused by the hepatitis B virus.
Hepatitis C	Viral disease of the liver caused by the hepatitis C virus.
Homologous blood	Blood donation given for transfusion to an unknown recipient.
Human T-cell lymphotropic virus type 1	A virus associated with adult T-cell leukaemia.
Hyper immune globulins	Immunoglobulin products prepared from the plasma of donors with high concentrations of specific antibodies.
Immunoglobulins	Proteins that combat infection.
Intramuscular immunoglobulin	A normal human immunoglobulin preparation designed for intramuscular administration.
Intravenous immunoglobulin	A normal human immunoglobulin preparation designed for intravenous administration.

Meta-analysis	Statistical methods used to combine the results of different studies.
Nucleic acid amplification testing	Highly sensitive method for detecting and identifying minute amounts of genetic material.
Off-label use	Use of a therapeutic agent to treat conditions for which the relevant regulatory authority (e.g. the Therapeutic Goods Administration) has not registered its use.
Pathogen	Disease-causing agent.
Plasma	Liquid portion of blood that contains proteins.
Plasmapheresis	Automated procedure for removing whole blood from the donor, separating out and retaining the plasma, and returning remaining components to the donor.
Prophylaxis	The prevention of disease; preventive treatment.
Transmissible spongiform encephalopathy	A group of transmissible infections of the nervous system caused by a prion, including CJD.
Variant CJD	A form of Creutzfeldt–Jacob disease thought to be caused by eating beef infected with bovine spongiform encephalopathy (BSE) or mad cow disease.

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Appendixes

Appendix A: Funding policy statement

Policy principles

Under the National Blood Agreement, blood products are provided at no direct cost to patients. The blood sector is funded by the Australian Government (63%) and collectively by the states and territories (37%), with the funding provided by each state and territory based on the quantity of product provided to each particular state and territory.

The National Blood Agreement's primary policy objectives are:

1. to provide an adequate, safe, secure and affordable supply of blood products, blood-related products and blood-related services in Australia; and
2. to promote safe, high-quality management and use of blood products, blood-related products and blood-related services in Australia.

A supporting policy aim is that blood and blood-related products are provided to patients free of charge and based on clinical need and appropriate clinical practice.

Funding for IVIg

Guided by these policy objectives and aims, governments have agreed to provide IVIg under the National Blood Arrangements for the conditions and uses described in the latest edition of the *Criteria for the clinical use of intravenous immunoglobulin in Australia* in Chapters 5, 6 and 7 (conditions for which there is reasonable evidence and/or clinical support for the use of IVIg therapy). IVIg funded under the National Blood Arrangements is not available to treat conditions identified in Chapter 8. For conditions not described in Chapters 5, 6 or 7, Approved Recipients may obtain IVIg via the Jurisdictional Direct Order component of the IVIg Standing Offer arrangements (see page 22).

Ongoing review of funded conditions

Under the National Blood Agreement, governments review expenditure twice a year and health ministers approve revised funding annually. The use of IVIg, as guided by latest edition of the *Criteria for the clinical use of intravenous immunoglobulin in Australia*, will be regularly reviewed to ensure the qualifying, exclusion, review criteria and indicative dosages for each condition remain, in the light of emerging evidence, appropriate and in keeping with an evidence-based approach.

Appendix B: National Stewardship Expectations

AUSTRALIAN HEALTH MINISTERS' CONFERENCE STATEMENT ON NATIONAL STEWARDSHIP EXPECTATIONS FOR THE SUPPLY OF BLOOD AND BLOOD PRODUCTS

The Australian Health Ministers' Conference (AHMC) has determined that a clear statement is needed on governments' stewardship expectations for the providers of blood and blood products within the health sector. Stewardship, in this context, means responsible, sustainable and appropriate use of blood and blood products.

Blood and blood products are provided under the *National Blood Agreement* 2003 to which all Commonwealth, State and Territory Governments are signatories. Achieving a blood supply that can meet the growing needs of an ageing population at an affordable cost requires the commitment from blood donors to be matched by an equal commitment from other parties in the supply chain.

All governments are committed to:

- Providing an adequate, safe, secure and affordable supply of blood products, blood related products and blood related services; and
- Promoting safe, high quality management and use of blood products, blood related products and blood related services in Australia.

A key component of the blood sector and one which plays an invaluable part is that of the health providers of blood and blood products. Hospitals, doctors, laboratories and other health providers serve a vital role in ensuring these key resources reach the patients in need.

In fulfilling this role, Ministers expect that these health providers will contribute to the sustainability of the blood supply by adopting these stewardship measures for their own organisation and requiring their adoption by any other party to whom they supply blood.

Blood Stewardship Principles

Blood should be managed in ways that ensure:

- All blood products are used in a clinically appropriate manner in accord with relevant professional guidelines and standards;
- Informed patient consent procedures are implemented for all patients;
- Processes, programs and facilities are in place to minimise the wastage of blood products;
- Facilities are accredited with the appropriate bodies to meet all quality and safety obligations; and
- Transfusion related adverse event information is collected and managed according to jurisdictional requirements.

National blood product planning, management and governance are supported by:

- Health providers having an ordering and receipt verification process in place which provides adequate financial accountability as required by governments; and
- Inventory data is provided on a regular and timely basis to assist in supply and demand planning, especially in times of national shortages.

Governments and the National Blood Authority will continue to manage the Australian blood supply to meet the needs of the community. Health providers play a vital role in making sure that products are available to meet clinical need, when and where required. The contribution of these health providers to safe and appropriate use, including minimisation of cost and wastage in the supply, is equally important. Ministers look to health providers to increase their efforts in these areas to ensure that Australia has a sustainable and affordable blood supply into the future.

Statement Approved by the Australian Health Ministers' Conference, 12 November 2010.

Appendix C: Development of the *Criteria for the clinical use of IVIg in Australia* (First Edition)

National workshop

A process to review the Australian Health Ministers' Advisory Council (AHMAC) (2000) guidelines commenced in 2004, with the National Blood Authority (NBA) convening a workshop of clinicians and others with an interest in IVIg to gather information about changes in the use of IVIg. The workshop suggested a range of strategies to improve the management of IVIg, including:

- national harmonisation of use and access to IVIg;
- thorough examination of existing data to inform decision making;
- the development of new guidelines with multifactorial criteria for accessing IVIg that provide a more practical decision-making framework;
- a representative committee continually reviewing the guidelines;
- the development of an interactive, web-based decision-making approval system for the issue of IVIg and data collection on treatment outcomes;
- audits of the supply of IVIg to encourage accountability; and
- active participation in clinical trials that improve the evidence base.

Systematic reviews

Systematic literature reviews of the efficacy and risks of treatment with IVIg were undertaken in 2004 and 2006 by Biotext Pty Ltd and the Sydney Health Projects Group (SHPG) (Frommer and Madronio 2006). The aims of the reviews were to:

- identify and critically appraise the scientific literature regarding the efficacy and risks of treatment with IVIg;
- analyse scientific publications, including existing guidelines, which identify the key issues in IVIg therapy; and
- include studies comparing IVIg with other treatments, including immunoglobulin administered by other routes, when such other treatments have been studied in comparison with IVIg.

A variety of approaches were used to identify relevant papers, including:

- searching electronic databases of published literature;
- searching the Internet generally for policy documents, government reports and other unpublished or non-mainstream published reports and information;
- cascade searching (e.g. from reference lists of key articles); and
- contacting key researchers.

Electronic databases and other sources were searched for papers published from 1982 to 2005. Information from these papers was extracted into a summary table sorted by condition. Each condition was then assessed and an overall conclusion added. The strength of the evidence was classified according to the categories shown in Table 1.

More than 90 conditions were assessed for IVIg therapy. Despite the proliferation of research and possible indications for IVIg use, the evidence base for IVIg remains patchy and in some cases conflicted. Major gaps exist in the evidence base supporting IVIg use.

In addition, Australian Healthcare Associates reported *the Review of the cost effectiveness of intravenous immunoglobulin in Australia: cost effectiveness analyses of selected clinical uses of intravenous immunoglobulin* in November 2004.

This review analysed the cost effectiveness of IVIg in the following 10 selected conditions: chronic inflammatory demyelinating polyneuropathy (CIDP), idiopathic thrombocytopenic purpura (ITP), Kawasaki disease, polymyositis/dermatomyositis, allogeneic bone marrow/stem cell transplantation (ABM/BMT), IgG subclass deficiency, lymphoproliferative disorders, multifocal motor neuropathy (MMN), toxic epidermal necrolysis/Stevens–Johnson syndrome and ANCA-positive necrotising vasculitis. These conditions accounted for 58% of IVIg use in 2003–04.

Jurisdictional Blood Committee IVIg Working Party

In April 2005, the JBC established the IVIg Working Party to oversee the development of new guidelines based on the findings of the literature review and outcomes of the 2004 workshop. Clinical specialists from the disciplines of neurology, haematology, and immunology were engaged to provide expert advice to the IVIg Working Party.

The IVIg Working Party was to establish a framework for the development of national guidelines governing the supply and use of IVIg in Australia.

Terms of reference

Specifically, the IVIg Working Party was to:

- review the report of the AHMAC Blood and Blood Products Committee — *Review of the use and supply of intravenous immunoglobulins in Australia* (the AHMAC 2000 IVIg guidelines) with respect to its current and future applicability;

- gather quality contemporary information and data from a wide variety of sources, including specialist groups, government agencies, individuals and other stakeholders with an interest in IVIg (including overseas sources);
- invite comment from specialist groups and colleges with particular reference to product use within their profession and taking into account the findings of the following reports
  - the 2004 and 2005 literature reviews on IVIg;
  - the 2004 cost-effectiveness analysis into selected clinical uses of IVIg in Australia;
  - the report on the IVIg workshop of 26 May 2004;
- draw on national activity (especially via jurisdictional IVIg user groups, the Australian Red Cross Blood Service and the National Blood Authority) to identify emerging needs and trends in the use of IVIg in Australia;
- establish a process to coordinate and analyse input from stakeholder groups;
- conduct one or more consensus forums or conferences of interested groups and individuals to assist in the development of a national consensus;
- develop guidelines based on the best available evidence taking into account consensus use;
- develop a communications plan that facilitates widespread dissemination and uptake of the guidelines; and
- establish a review mechanism that ensures maintenance of their currency.

Membership

Dr Chris Brook (Chair) — Executive Director, Rural and Regional Health and Aged Care Services, Victorian Department of Human Services

Ms Joan Bedford — Senior Portfolio Officer, Health Department of Western Australia

Dr Jill Carstairs — Senior Analyst, Clinical Policy, New South Wales Department of Health

Dr Bernie Towler — Senior Medical Adviser, Acute Care Division, Australian Government Department of Health and Ageing

Clinical advisers

Associate Professor John Gibson — Institute of Haematology, Royal Prince Alfred Hospital, Camperdown, New South Wales

Associate Professor Andrew Kornberg — Department of Neurology, Royal Children's Hospital, Parkville, Victoria

Dr Sean Riminton — Department of Immunology and Allergy, Concord Hospital, Concord, New South Wales

Secretariat support

Ms Jennifer Roberts	Project Manager
Mr Graham Brown	Project Officer

Development and consultation

Discussion paper

In August 2005, a discussion paper about the development of the new guidelines was circulated for comment. Submissions from the clinical community were subsequently synthesised into a report that proposed options for the development of criteria for use. The IVIg Working Party accepted the recommendations of the report.

Targeted development of proformas

The JBC IVIg Working Party determined that proformas should be developed for selected priority conditions only. These included the following:

- All the conditions that together account for approximately 95% of the total national usage of IVIg by volume (2002–06); plus
- Conditions assigned a 'Category 1' priority for IVIg therapy by AHMAC in 2000; plus
- Conditions for which the TGA has registered the use of IVIg; plus
- Conditions for which the Biotext (2004) and Frommer and Madronio (2006) systematic reviews found high-level evidence for the use of IVIg; plus
- Any other conditions recommended by consulting specialist clinicians.

As a result, proformas were developed for 36 priority conditions.

Conditions that had been previously listed for consideration in various reviews, such as the Biotext (2004) review, were not examined in detail for one or more of the following reasons:

- individually, they accounted for a very small proportion of the national usage of IVIg (of the order of 0.1% or less);
- research evidence was available to show that IVIg was ineffective for these conditions, or had an adverse effect;
- no research evidence was available to show whether IVIg was effective for these conditions and clinical specialists recommended against the use of IVIg in their management; and
- the conditions were not identified as high-priority conditions by AHMAC in its 2000 report.

Development of the clinical criteria and exposure draft

The development of clinical criteria for the proforma involved the following steps:

1. Draft proformas were written, using information from a variety of sources.
2. The draft proformas were reviewed by individual clinical specialists in immunology, neurology, haematology and dermatology. The drafts were amended in the light of their advice.
3. Additional draft proformas were prepared for conditions identified as priorities by the clinical specialists.
4. The proformas were reviewed by the IVIg Working Party.
5. The proformas were further reviewed by small expert panels in immunology, haematology, and neurology, and then further amended in the light of their advice.
6. Drafts of the proformas were circulated broadly to professional colleges, societies and other organisations, governments, patient groups and individual specialist clinicians with an interest or expertise in the use or management of IVIg inviting comment. Drafts were also considered at a clinician workshop held in Sydney in November 2006.

The clinical criteria

The clinical criteria given in each proforma were set out to cover four major issues:

1. Indication for IVIg use — this specifies the purpose for which IVIg treatment would be considered once the condition has been confirmed using the proposed diagnostic parameters. The indication generally refers to the prevention or management of a particular manifestation of disease.
2. Qualifying criteria — these are the criteria that should be fulfilled if IVIg is to be used. The qualifying criteria generally refer to matters such as patient selection, particular disease

characteristics, disease severity, and any requirement for other treatments to have been demonstrably unsuccessful before IVIg is considered. The qualifying criteria are additional to diagnostic criteria.

3. Exclusion criteria — these define the circumstances in which IVIg should not be used in patients who have the specified indication and fulfil the qualifying condition.
4. Review criteria — these are the major clinical factors that should be taken into account when reviewing the progress of a patient who is receiving IVIg. They comprise parameters that indicate the patient's response to IVIg, and may be used to decide whether to cease or continue IVIg use, or to alter the dose or frequency of administration.

In addition to information about clinical criteria, the proformas include a definition of each condition and a brief description of its clinical presentation and the main diagnostic parameters. The clinical criteria are to be used in addition to: a) the diagnostic criteria that may indicate consideration of a patient for the use of IVIg therapy; and b) the category of available evidence on the effectiveness of IVIg therapy for a diagnosed condition.

Clinical workshop

A workshop of clinicians with an interest in IVIg was held in November 2006. Workshop participants agreed that the document ought to recommend IVIg use only in those conditions where:

- a genuine health benefit can be shown to be derived from the use of IVIg; and
- this benefit is supported by evidence

The workshop also identified the need for the system of approval of IVIg usage under the National Blood Agreement to have flexibility and discretion to deal with unusual requests to use IVIg in justifiable circumstances. It was argued that a

system that could allow limited one-off approvals for IVIg would strengthen the overall supply and approval mechanism and obviate the need for every rare condition to be covered in the document in detail.

Sources of information and assessment

The clinical criteria for IVIg use were developed by a JBC IVIg Working Party. In accordance with the Working Party's terms of reference, information and data from a wide variety of sources, including systematic reviews of the literature, specialist groups, government agencies and individuals with an interest in IVIg, were considered.

Evidence of benefit categories

The Biotext and SHPG reviews were used to identify the category of evidence on the effectiveness of IVIg therapy for each condition, as derived from the clinical research examined in these documents. Advice from specialists on conditions not reviewed by Biotext or the SHPG was also taken into consideration.

Overall, the systematic reviews demonstrated that, while a large body of evidence about IVIg exists, the quality of research is limited. Given the rarity of many of the conditions and their severity, high-level analytical (i.e. randomised controlled trial-based) evidence is often not available.

Weighing up and integrating information

A high level of concordance was apparent among the various sources of information, including clinicians' recommendations.

Where discrepancies emerged among the various sources of information about the clinical criteria, the final determination was made by clinicians.

Sources of information other than consultations

The proformas were drafted with reference to the following sources of information:

- Written submissions to the NBA from stakeholders. Stakeholders were invited to provide submissions on (i) a 2005 paper on the [then] current status of IVIg use, prepared by the NBA, (ii) the SHPG review (Frommer and Madronio 2006) and systematic review update; and (iii) initial drafts of the criteria for use document.
- Recently published medical textbooks, from which some of the material was used in defining and describing each condition was derived.
- The Biotext (2004) review of the literature on the efficacy of IVIg therapy, covering the period up to 2004.
- The update of the Biotext review conducted by SHPG (Frommer and Madronio 2006). This mainly focused on new literature, particularly randomised controlled trials, published during 2004–05.
- Clinical guidelines and consensus statements from 2004-06 (used to identify additional clinical qualifying, exclusion and review criteria that are currently recommended for use in Australia or overseas). The relevant clinical guidelines and consensus statements were primarily identified by means of: (i) advice from specialist clinicians, based on their knowledge and professional networks; and (ii) searches conducted using Google and MEDLINE. Search terms comprised 'intravenous immunoglobulins' and 'guideline(s)' or 'consensus' or 'review'.

Contributors

Consultants — Sydney Health Projects Group

The Sydney Health Projects Group (SHPG) was commissioned in July 2006 by the National Blood Authority (NBA) to develop clinical criteria for the use of IVIg in Australia.

Clinical consultations

The selection of conditions for proformas and/or the development of the clinical criteria were undertaken in consultation with, or with advice from, 42 clinicians.

Specialist clinicians provided advice on: (i) the draft proformas, with particular reference to the clinical criteria; (ii) any recent reviews, guidelines or consensus statements (2004–06) that could contribute to the refinement of clinical criteria; and (iii) additional conditions for which proformas should be prepared.

Finalisation and approval

Written submissions and the outcomes of the clinician workshop were then considered by the IVIg Working Party and a panel of clinical experts. The proforma were then further refined in light of their comments.

A second draft of the document was circulated for comment in March 2007. Submissions from this round were considered by the IVIg Working Party and a committee of clinical experts and further amendments made in light of those considerations.

The amended document was presented to the Jurisdictional Blood Committee in May 2007 and finalised in June 2007. This led to the first edition of *the Criteria* being approved by Health Ministers in December 2007 and coming into effect from 3 March 2008.

Appendix D: 2010–11 Criteria Review

National IVIg Criteria Review Working Group

A National IVIg Criteria Review Working Group (NICRWG) was established to oversee the 2010–11 Criteria Review process. The NICRWG comprised representatives from both clinical and government sectors and individual experts who were engaged in the initial review.

Terms of reference

The NICRWG was responsible for:

- calling for submissions from governments, and members of the clinical community — individuals or groups, including clinical colleges and societies;
- assessing submissions and determining whether a systematic review was required to address the submission;
- determining and agreeing on *the Criteria* wording in response to submissions that did not require systematic review;
- facilitating and supporting the procurement process to engage a systematic reviewer;
- conducting a consensus process for recommendations that had lower than level IV evidence to facilitate agreement on the recommended wording for the revised *Criteria*;
- ensuring appropriate clinical and public consultation processes were conducted;
- producing an exposure draft of the revised *Criteria*;
- conducting a cost analysis of the proposed changes to *the Criteria*; and
- providing the Jurisdictional Blood Committee (JBC) with recommendations for consideration, on the basis of the systematic review, clinical consultation and cost analysis.

NICRWG representative members were also responsible for seeking and consolidating input from represented organisations as appropriate throughout the systematic review and drafting process.

Membership

- JBC Representatives (Ms Joan Bedford and Ms Carolyn Duck)
- National Blood Authority (NBA) Representative (Principal Medical Officer — Dr Chris Hogan)
- Department of Health and Ageing (DoHA) Clinical Representative (Professor Henry Ekert)
- Australasian Society of Clinical Immunology and Allergy Representative (Dr Jane Peake)
- Australian Red Cross Blood Service (Blood Service) Representative (Dr Marija Borosak)
- Australian and New Zealand Association of Neurologists (Associate Professor Lyn Kiers)
- Haematology Society of Australia and New Zealand Representative (Dr Philip Crispin)

Chair

JBC appointed Ms Joan Bedford as the chair of the NICRWG for the duration of the review.

Individual experts

The clinicians who chaired the discipline specific subgroups during the development of the first edition of *the Criteria* were invited to participate as individual experts on the NICRWG. These experts were:

- Associate Professor Andrew Kornberg — neurology
- Associate Professor John Gibson — haematology
- Associate Professor Sean Riminton — clinical immunology

Secretariat support

- Ms Jennifer Roberts — Project Director
- Ms Julie Bland — Project Manager (to August 2011)
- Ms Sandra Russell — Project Manager (from August 2011)
- Ms Donna Cassoni — Project Officer

Additional expert advice

The following colleges and societies provided additional expert advice;

- Australasian College of Dermatologists
- Australian & New Zealand Intensive Care Society
- Bone Marrow Transplant Society of Australia and New Zealand
- National Asthma Council Australia
- Perinatal Society of Australia and New Zealand
- Thoracic Society of Australia and New Zealand

Many other clinical experts gave generously of their time and expertise. All contributions are gratefully acknowledged.

Formal submission process

In preparation for the 2010–11 Criteria Review, clinical stakeholders were advised about the 2010–11 Criteria Review in mid-2009 in order to gauge interest from the clinical community, and gain insight into the type of, and number of formal submissions that the NBA expected to receive.

Individuals, organisations and representative bodies who had indicated they would make a submission and those who had sought clarification were notified directly of the formal submission process. Members of IVIg user groups and clinicians ordering IVIg were informed of the submission process and timetable.

Formal submissions from the clinical community were accepted from December 2009 to February 2010 for:

- removal of an existing condition;
- a change to the documented content of an existing condition; and
- a new condition.

As part of the formal submission process, the clinical community was asked to provide supporting documentation, including:

- journal articles;
- case reports (published or unpublished);
- support from relevant clinical society/college; and
- other relevant information.

Review of submissions

All formal submissions were provided to the NICRWG for consideration and to determine what approach would be used to assess each submission. Based on the information provided with the formal submissions and expert opinion, the NICRWG decided the process of consideration for each submission:

- a systematic review;
- a consensus process without systematic review, due to limited availability of published evidence;
- minor wording adjustments followed by a consensus process; or
- no action.

Systematic review

The NBA engaged Biotext Pty Ltd to conduct a systematic review of the literature on IVIg for a number of specific conditions identified by the formal submission process and subsequent NICRWG discussions.

The literature review focused on four areas:

- pyoderma gangrenosum;
- diabetic amyotrophy;
- autoimmune encephalopathies and neuropathies (a total of 10 indications); and
- sepsis (a total of nine indications).

The reviews followed the methods described in the National Health and Medical Research Council (NHMRC) handbook, *How to review the evidence: systematic review and assessment of the scientific literature* (NHMRC 2000)[11] and the *Evidence-based practice workbook* published by BMJ Books (Glasziou et al 2007)[12]. Reviews were restricted to studies published since 2004 (the date of the last major systematic literature review conducted on the indications for IVIg use), and aimed to:

- identify and critically appraise the scientific literature regarding the efficacy and risks of IVIg therapy;
- analyse scientific publications (including existing guidelines) that identify the key therapeutic issues in IVIg therapy; and
- include studies comparing IVIg with other treatments, including immunoglobulin administered by other routes, when such other treatments have been studied in comparison with intravenous administration.

11 National Health and Medical Research Council, 2000, *Handbook: how to review the evidence: systematic review and assessment of the scientific literature*, NHMRC, Canberra.

12 Glasziou P, Mar CD, Salisbury J 2007, *Evidence-based practice workbook: bridging the gap between health care*, 2nd ed, Wiley-Blackwell, Massachusetts.

Biotext Pty Ltd worked closely with the NICRWG to develop review questions based on the 'PICO' method (population/problem, indication, comparator, and outcome) for each condition included in the review.

An evidence statement was developed for each clinical question using the NHMRC Evidence Statement Form as described in *Additional levels of evidence and grades for recommendations for guideline developers* (NHMRC 2008).[13]

For each systematic review undertaken, an evidence report was prepared. The evidence reports included specific details of the review methods and search terms used for that particular condition.

As this was a partial review of *the Criteria*, and to ensure consistency in any revised edition, each evidence report includes an assessment of the alignment of the literature against the categories previously used in *the Criteria,* outlined in Table 1. As many of the systematically reviewed conditions are rare and there is limited published clinical evidence, this approach also assisted the consensus process.

Development of revised wording

For each condition, the NICRWG agreed required amendments or a new indication being considered for inclusion, draft wording or amendments to existing wording were prepared, by either:

- NICRWG clinical experts;
- a NICRWG member representing an appropriate college or society; or
- a clinical expert from a relevant college or society not represented on the NICRWG.

13 http://www.nhmrc.gov.au/_files_nhmrc/file/guidelines/levels_grades05.pdf

Consensus process

For many rare and complex conditions, there is insufficient high-quality data in the clinical literature to produce evidence-based recommendations. Therefore, there is a role for expert opinion and consensus in the development of materials to guide clinical use.

For the 2010–11 Criteria Review, the consensus process consisted of informal and formal consensus processes. Where consensus could not be reached, no amendments to the previously published content were made.

Informal consensus process

Where necessary, advice on proposed wording was sought from a relevant college or society. Proposed wording, along with any other advice received from relevant colleges and societies was considered by the NICRWG. This usually occurred during meetings of the NICRWG or via electronic correspondence.

Consensus was reached when all members either strongly agreed or agreed to the proposed new wording or amendments. For some amendments, this was an iterative process, but where consensus was not reached, the formal consensus process was implemented.

Formal consensus process

The formal consensus process allowed participants to discuss the issue of concerns face to face. The structured process facilitated contributions from all members, recognised relevant expertise, and limited the capacity of any one member to dominate. The formal consensus process was based on an agreed set of guiding principles and values.

The consensus process was facilitated by the Chair of the NICRWG and consisted of:

- *A pre-meeting process* — where members had access to all materials relating to the proposed change, including advice from experts outside the NICRWG and evidence reports.

- *A consensus meeting* — where each item requiring consensus followed an agreed process:
  - overview of the recommendation
  - open discussion — where members could clarify the recommendation and then each member had the opportunity to highlight or state any concerns they had with the proposed recommendation
  - a summary of concerns — where all concerns were summarised and an opportunity was provided for the concern to be resolved through modification to the recommendation or proposed wording
- *Finalisation* — if all concerns have been resolved the Chair called for consensus. However, if concerns had been discussed but remained unresolved and consensus was not reached, consideration was given to the formal consensus guiding principles and values, before another call for consensus was made. If consensus could not be reached this second time, the recommendation was not accepted and no amendments were proposed.

Public consultation

Various stakeholders were consulted to help inform the discussions and decisions of the NICRWG. In particular, advice was obtained from a range of colleges and societies to inform the decisions around changes and proposed wording amendments.

Once agreement on the proposed amendments was reached, an exposure draft outlining these changes was developed. Public consultation, seeking feedback on the proposed amendments to *the Criteria*, was undertaken for an eight-week period from 25 June to 19 August 2011.

Stakeholders were advised of the public consultation process through:

- a national newspaper advertisement;
- a direct email to specific colleges and societies;
- a direct email to stakeholders who registered their interest in participating via the NBA's website;
- a direct email to stakeholders involved in the clarification processes; and
- materials on the NBA's website

Comments on the proposed amendments to *the Criteria* contained in the 31 submissions provided during the public consultation process were considered by the NICRWG.

The consensus processes outlined above were used to develop additional amendments or to confirm the drafted entry. A number of additional changes were agreed primarily to clarify and improve consistency in understanding of the entry.

Finalisation and approval

The NICWRG completed their terms of reference in October 2011 by providing JBC with recommendations for consideration, on the basis of the systematic review, clinical consultation and cost analysis. The finalised Criteria document was endorsed by the Jurisdictional Blood Committee in December 2012. This led to the second edition of *the Criteria* being approved by Health Ministers.

Appendix E: Alphabetical index of conditions

Condition	Evidence level	Chapter, page
Acquired coagulation factor inhibitors (alloantibodies and autoantibodies), including acquired haemophilia, acquired von Willebrand syndrome, inhibitors to FVIII in haemophilia A, and inhibitors to FIX in haemophilia B (see coagulation factor inhibitors)		
Acquired hypogammaglobulinaemia secondary to haematological malignancies (chronic lymphocytic leukaemia, multiple myeloma, non-Hodgkin lymphoma, and other relevant malignancies and post-haemopoietic stem cell transplantation)	2a	5, 48
Acute autonomic neuropathy (see Guillain–Barré syndrome)		
Acute disseminated encephalomyelitis	2a	6, 115
Acute inflammatory demyelinating polyneuropathy (see Guillain–Barré syndrome)		
Acute leukaemia in children	2a	7, 185
Acute motor axonal neuropathy (see Guillain–Barré syndrome)		
Acute motor sensory axonal neuropathy (see Guillain–Barré syndrome)		
Acute optic neuritis	2b	8, 214
Acute rheumatic fever	2b	8, 214
Adrenoleukodystrophy	4b	8, 214
Amegakaryocytic thrombocytopenia	4b	8, 214

Condition	Evidence level	Chapter, page
Amyotrophic lateral sclerosis (see motor neuron disease)		
ANCA-positive systemic necrotising vasculitis	2a	6, 119
Antiphospholipid syndrome — non-obstetric	4b	8, 214
Aplastic anaemia/pancytopenia	4b	8, 214
Asthma	2c	8, 214
Atopic dermatitis/eczema (adult)	2b	8, 214
Autism	4b	8, 214
Autoimmune congenital heart block (neonatal lupus)	4a	7, 186
Autoimmune haemolytic anaemia	4a	6, 123
Autoimmune haemolytic anaemia with immune thrombocytopenia (see Evans syndrome)		
Autoimmune neutropenia	4a	7, 187
Autoimmune uveitis	4a	7, 188
Autologous haemopoietic stem cell transplantation	2c	8, 214
Behçet's disease	4b	8, 215
Bickerstaff's brainstem encephalitis (see Guillain–Barré syndrome)		
Bullous pemphigoid	4a	6, 126
Capillary leak syndrome (see Systemic capillary leak syndrome)		
Cardiac failure — congestive	2a	8, 215
Cardiac surgery with bypass — prophylaxis	2a	8, 215
Cataplexy (see narcolepsy)		
Catastrophic antiphospholipid syndrome	4a	7, 189
Chronic inflammatory demyelinating polyneuropathy (CIDP)	1	5, 58

Condition	Evidence level	Chapter, page
Cicatricial pemphigoid	2a	6, 129
Coagulation factor inhibitors (alloantibodies and autoantibodies) — including acquired haemophilia, acquired von Willebrand syndrome, inhibitors to FVIII in haemophilia A, and inhibitors to FIX in haemophilia B	2a	7, 191
Common variable immunodeficiency (CVID) (see primary immunodeficiency)		
Congenital heart block (see autoimmune congenital heart block)		
Congestive cardiac failure	2a	8, 215
Crohn's disease	4b	8, 215
Dermatitis/eczema atopic (adult) (see atopic dermatitis/eczema)		
Demyelinating polyneuropathy (see chronic inflammatory)		
Dermatomyositis (see inflammatory myopathies)		
Devic disease (neuromyelitis optica)	4a	7, 193
Diabetic amyotrophy	4a	7, 194
Diabetic lumbosacral radiculoplexus neuropathy (See diabetic amyotrophy)		
Diabetic proximal neuropathy (See diabetic amyotrophy)		
Diamond Blackfan syndrome	4b	8, 215
Eczema, atopic dermatitis (adult) (see atopic dermatitis/eczema)		
Encephalomyelitis - acute disseminated (see acute disseminated)		
Encephalopathy (see Hashimoto)		
Encephalopathy (see limbic - nonparaneoplastic)		

Condition	Evidence level	Chapter, page
Encephalopathy (see limbic - paraneoplastic)		
Encephalopathy (see potassium channel)		
Epidermolysis bullosa acquisita	4a	7, 194
Epilepsy — rare childhood cases	2a	7, 194
Evans syndrome - autoimmune haemolytic anaemia with immune thrombocytopenia	4a	6, 133
Female infertility	4a	8, 215
Foeto-maternal/neonatal alloimmune thrombocytopenia (FMAIT/NAIT)	4a	6, 136
Glomerulonephritis - IgA nephritis	2b	8, 215
Glomerulonephritis (see lupus nephritis)		
Graves ophthalmopathy	2a	7, 195
Guillain–Barré syndrome (GBS)	1	5, 62
Haemolytic anaemia (see autoimmune haemolytic anaemia)		
Haemolytic anaemia — autoimmune with immune thrombocytopenia (see Evans syndrome)		
Haemolytic disease of the newborn	4a	7, 196
Haemolytic transfusion reaction	4a	7, 197
Haemolytic uraemic syndrome	4b	8, 215
Haemophagocytic syndrome	4a	6, 141
Haemopoietic stem cell transplant (see autologous)		
Hashimoto encephalopathy	4a	7, 197
Heart block (see autoimmune congenital)		
Henoch–Schonlein purpura	4b	8, 215
HIV/AIDS — adult	2b	8, 215
HIV/AIDS — children	2a	7, 185

Condition	Evidence level	Chapter, page
Iatrogenic immunodeficiency (see secondary hypogammaglobulinaemia)		
Idiopathic dilated cardiomyopathy	2b	8, 215
Idiopathic thrombocytopenic purpura (ITP) — adults	2a	5, 66
Idiopathic thrombocytopenic purpura (ITP) — child	1	6, 144
IgA nephritis (see glomerulonephritis)		
IgG subclass deficiency (see specific antibody deficiency)		
IgM paraproteinaemic neuropathy	2c	6, 148
Inclusion body myositis (see inflammatory myopathies)		
Inflammatory myopathies (polymyositis, dermatomyositis, inclusion body myositis)	2a	5, 73
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Kawasaki disease	1	5, 79
Kidney transplantation	1	6, 152
Lambert–Eaton myasthenic syndrome	2a	5, 83
Landau–Keffner syndrome (see Epilepsy)		
Lennox–Gastaut syndrome (see Epilepsy)		
Leukaemia in children (see acute leukaemia in children)		
Lewis-Sumner syndrome variant (see Guillain–Barré syndrome)		
Limbic encephalitis, nonparaneoplastic	4a	7, 198

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Lupus cerebritis	4a	8, 215
Lupus nephritis	2a	8, 215
Lyell syndrome (see Toxic epidermal necrolysis)		
Miller Fisher syndrome (see Guillain–Barré syndrome)		
Moersch-Woltman syndrome (see Stiff person syndrome)		
Motor neuron disease/amyotrophic lateral sclerosis	4b	8, 215
Mucocutaneous lymph node syndrome (see Kawasaki Disease)		
Mucous membrane pemphigoid (see cicatricial pemphigoid)		
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Multiple sclerosis	2a	6, 158
Myalgic encephalomyelitis	2c	8, 215
Myasthenia gravis	1	5, 92
Myocarditis in children	4a	7, 198
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Neonatal haemochromatosis	2a	5, 96
Neonatal lupus (see autoimmune congenital heart block)		
Nephrotic syndrome	2a	8, 216
Neuromyelitis optica (see Devic disease)		
Neuropathy (see Chronic inflammatory demyelinating)		

Condition	Evidence level	Chapter, page
Neuropathy (see diabetic amyotrophy)		
Neuropathy (see IgM paraproteinaemic)		
Neuropathy (see multifocal motor)		
Neuropathy (see paraneoplastic subacute sensory)		
Neuropathy (see polyneuropathy of critical illness)		
Neutropenia (see autoimmune neutropenia)		
Obsessive compulsive disorders	4a	8, 216
Opsoclonus-myoclonus ataxia	4a	6, 164
Optic neuritis (see acute optic neuritis)		
Paediatric autoimmune neuropsychiatric disorder associated with streptococcal infections (PANDAS)	2a	7, 199
Pancytopenia (see aplastic anaemia)		
Paraneoplastic cerebellar degeneration	4a	7, 200
Paraneoplastic limbic encephalitis (see limbic encephalitis – paraneoplastic)		
Paraneoplastic neurological syndromes (see paraneoplastic subacute sensory neuropathy, Paraneoplastic cerebellar degeneration, limbic encephalitis paraneoplastic)		
Paraneoplastic subacute sensory neuropathy	4a	7, 200
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Sepsis	2a	8, 216
Sickle cell disease	4b	8, 217
Sjogren's syndrome	4a	7, 207
Solid organ transplantation (other than kidney)	4a	7, 208
Specific antibody deficiency	4a	6, 110
Steroid-responsive encephalopathy associated with autoimmune thyroiditis (see Hashimoto)		
Stevens–Johnson syndrome (see toxic epidermal necrolysis/SJS)		
Stiff person syndrome	2a	5, 99
Susac syndrome	4a	7, 209
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Condition	Evidence level	Chapter, page
Systemic necrotising vasculitis (see ANCA-positive systemic necrotising vasculitis)		
Thrombocytopenia (see amegakaryocytic)		
Thrombocytopenia (see Evans syndrome)		
Thrombocytopenia (see idiopathic thrombocytopenia purpura)		
Thrombocytopenia (see neonatal alloimmune thrombocytopenia)		
Thrombocytopenia (see post-transfusion purpura)		
Transient hypogammaglobulinaemia of infancy (see primary immunodeficiency disease)		
Toxic epidermal necrolysis/Stevens–Johnson syndrome (TEN/SJS)	4a	6, 173
Toxic shock syndrome	4a	6, 177
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