Australian Health Ministers' Conference

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

Revisions have been made, see www.nba.gov.au

December 2007

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Disclaimer: Important information about this document

This document is not a substitute for medical advice obtained from an attending clinician in relation to a particular patient's condition. The relevance and appropriateness of the information and recommendations in this document depend, amongst other things, on a correct diagnosis being made, the severity of the relevant condition being properly ascertained, and other relevant circumstances of the particular patient.

This document is designed to provide information to assist clinical decision making. The information and recommendations represent informed opinion based, where possible, upon systematic review of the evidence which was finalised by mid 2006. In the absence of published evidence, recommendations are based on clinical advice provided to the parties involved in developing this document (i.e. the Jurisdictional Blood Committee IVIg Working Party and its clinical advisers and consultants, the Jurisdictional Blood Committee, and the Commonwealth of Australia) up to June 2007.

This document deals only with the use of intravenous immunoglobulin and does not include any advice on other forms of treatment relevant to the conditions described.

Each of the parties involved in developing this document and each of their relevant employees 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 Australian Health Ministers' Conference.

The Jurisdictional Blood Committee would like to acknowledge and thank those who contributed to the compilation of this document, including Dr Chris Brook, the Chair of the IVIg Working Party; members of the IVIg Working Party, Ms Joan Bedford, Dr Jill Carstairs and Dr Bernie Towler; the Director of the Sydney Health Projects Group, University of Sydney, Professor Michael Frommer; staff of the Sydney Health Projects Group; and staff of the National Blood Authority. Additional input was provided by Mr Ashley Eccles, Senior Program Adviser, Blood and Pharmaceutical Programs, Victorian Department of Human Services.

Principal clinical advisers to the IVIg Working Party were Associate Professor John Gibson, Associate Professor Andrew Kornberg and Dr Sean Riminton. The Australian Red Cross Blood Service Transfusion Medicine Team contributed substantially to this review. Many other clinical experts gave generously of their time and expertise and are listed in Appendix F. All contributions are gratefully acknowledged.

It is intended that this document will be updated periodically.

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

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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 appropriate. IVIg is a precious biological product. Its use should be consistent with the evidence-base and for the treatment of patients who are likely to benefit from IVIg therapy and for whom there are no alternative safe and effective treatments.

Immunoglobulin was first used therapeutically in the 1950s for the treatment of primary immunodeficiency disorders. Due to the presence of immunoglobulin aggregates, early preparations could only be given intramuscularly or by subcutaneous infusion and this limited the size of the dose. In the late 1970s, highly purified monomeric suspensions of immunoglobulin became available that could be tolerated intravenously at larger doses. The use of intravenous preparations rapidly subsumed the use of intramuscular preparations as replacement therapy for primary and secondary immunodeficiencies.

Intravenous immunoglobulin therapy has since proven to be of great benefit in appropriately selected patients and clinical settings. IVIg is presently registered in Australia for the treatment of primary humoral immunodeficiencies, chronic lymphocytic leukemia, immunodeficiency syndrome in children, multiple myeloma, allogeneic bone marrow transplantation, Guillain-Barré syndrome, Kawasaki disease and immune thrombocytopenic purpura. In addition, IVIg is used to treat a growing number of unregistered diseases where immunomodulation or immunoglobulin replacement therapy is of benefit. Some applications have a strong foundation in the medical literature. Others have a less conclusive basis in evidence but are supported by clinical consensus.

The growth in demand for IVIg has prompted action by Australian governments to ensure it is reserved for use in those with the greatest need. 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.

The *Criteria for the Clinical Use of Intravenous Immunoglobulin in Australia* 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).

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 institutions. 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 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 for use.

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 in Australia. 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 will 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 because there is insufficient evidence or clinical support.

It is anticipated that IVIg use and effectiveness data will confirm the distribution of conditions within these chapters, and facilitate refinement in future revisions.

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 the development of a system to collect data that will provide information about the effectiveness of IVIg therapy. This information will be assessed by experts and used to inform future reviews of this document.

It is proposed that these criteria will be reviewed three yearly, with the review process commencing two years after the release of each new version, allowing twelve months for consultation and drafting.

This document was prepared with the assistance of the following health professionals:

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The **Australian Red Cross Blood Service Transfusion Medicine Team** contributed substantially to this review. Many other clinical experts gave generously of their time and expertise and are listed in Appendix F. 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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Chapter 5 – Conditions for which IVIg has an established therapeutic role

Chapter 6 – Conditions for which IVIg has an emerging therapeutic role

Chapter 7 – Conditions for which IVIg use is in exceptional circumstances only

Chapter 8 – Conditions for which IVIg use is not indicated

Executive summary

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

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 indications and limiting IVIg supply to patients with the specified indications;
- increasing the manufacture of IVIg in Australia; and
- importing IVIg from overseas.

In the ten years to 2006, the average annual growth in IVIg use in Australia was 14.8%. In 2006–07, use will increase by approximately 11% on the previous year. In 2005, Australia was the fourth highest *per capita* user of IVIg in the world, and in 2006–07 the National Blood Authority will spend, on behalf of Australian governments, in excess of $100 million (or 18% of the total blood and plasma products budget) on IVIg products. The continual double-digit 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 available for those with the greatest clinical need.

The *Criteria for the Clinical Use of Intravenous Immunoglobulin in Australia* describes current arrangements for the supply of IVIg and the recommended indications for its use. It has been developed to assist clinicians and transfusion medicine professionals identify the conditions and circumstances for which the use of IVIg is appropriate.

Production and safety

In recent years, the production of locally made IVIg has fallen short of national consumption and overseas-sourced products have been used to supplement the Australian made product. No blood or plasma products, whether locally manufactured or imported from overseas, can be used in Australia unless they have been assessed and approved by the Therapeutic Goods Administration (TGA). The TGA regulates the safety, quality and efficacy of IVIg products.

Four overseas manufactured IVIg products have been approved and registered for use in Australia. Two of these (Sandoglobulin® and Octagam®) are presently used to supplement supplies of the domestic product (Intragam®P).

Rationale for developing criteria for intravenous immunoglobulin use

Prior to the adoption of these clinical criteria, the management and use of IVIg in Australia were 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 indications for IVIg therapy undergo regular review to ensure that the therapeutic use of IVIg is kept current. These criteria have been developed in response to that recommendation.

In Australia, 'guidelines', such as those endorsed by the National Health and Medical Research Council usually refer to the *management of conditions* (e.g. guidelines for the management of early breast cancer) rather than to the use of specific therapeutic products such as IVIg. The word 'guidelines' connotes the provision of guidance or advice to the management of a condition. The term 'criteria for use' connotes a more directive framework for decisions about the use of a particular treatment. The latter term has been selected to describe the circumstances, based on evidence and clinical experience, under which the clinical use of IVIg is considered appropriate in Australia.

Conditions considered for IVIg therapy

During the development of this document, the effectiveness of IVIg therapy was assessed in light of the available evidence for 94 conditions and/or groups of conditions. Two systematic reviews of the literature covering the period from 1982 to 2005 formed the basis of the assessments and where no studies were found, or the evidence presented was weak or inconclusive, the opinions of clinical experts were sought.

Early versions of the document were circulated broadly to professional colleges, societies and other organisations, as well as to governments, patient groups and individual specialist clinicians with an interest or expertise in the use or management of IVIg, inviting comment. Version 1.3 was also considered at a clinician workshop held in Sydney in November 2006. Written submissions and the outcomes of the clinician workshop were considered by a Jurisdictional Blood Committee IVIg Working Party and a panel of clinical experts prior to the finalisation of this document.

The *Criteria for the Clinical Use of Intravenous Immunoglobulin in Australia* identifies:

- twelve conditions for which IVIg use in Australia 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-one conditions for which IVIg use 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-line therapy when standard therapies have

proven ineffective, have 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-five 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 the majority of 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 exhausted or are contraindicated. For some conditions the priority of the use of IVIg has been reduced in favour of alternative therapies and is now considered exceptional practice (for example, the treatment of acute leukaemia in children and HIV in children); and
- thirty-six conditions for which IVIg therapy is not indicated. IVIg therapy for these conditions is not supported 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 pro-forma is provided detailing the diagnostic parameters and describing the criteria that should be fulfilled if IVIg is to be used. The 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 national implementation of these clinical criteria is expected to facilitate the 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 alternative safe and effective treatments.

1

Introduction

1. Introduction

Intravenous immunoglobulin (IVIg) is a fractionated blood product made from pooled human plasma. It was introduced in the late 1970s and rapidly subsumed the use of intramuscular preparations as replacement therapy in primary and secondary immunodeficiencies.

Intravenous immunoglobulin is increasingly important in replacement therapy and as an immunomodulatory agent in autoimmune disease and transplantation. It is the market driver for the plasma industry in the developed world with an increasing number of clinical indications where some evidence exists for its utility. The continued growth in the number of indications for IVIg has resulted in a significant amount of 'off label' use and double-digit annual increases in the volume consumed.

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, State and Territory governments signed the Agreement in 2003 and, in so doing, agreed to implement a co-ordinated national approach to policy setting, governance and management of the Australian blood sector, including administrative and financial arrangements.

1 National Blood Authority. National Blood Agreement between the Commonwealth of Australia and the States and Territories. Canberra: Commonwealth of Australia; 2003 [cited 7 Dec 2007]. Available from: http://www.nba.gov.au/about_nba/nba_agreement.htm

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
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 indications identified in Chapters 5, 6 and 7 of this document 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, which are considered non-indications for IVIg therapy at this time.

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 pages 26–27).

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

AHMC and AHMAC

The Australian Health Ministers' Conference (AHMC) is the ultimate decision-maker responsible for the oversight and management of the Australian blood sector. The Conference'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).

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 uses.

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.

Plasma for fractionation and fractionated plasma products have been regulated by the TGA since 1991.

Australian Red Cross Blood Service

The Australian Red Cross Blood Service (ARCBS) is responsible for the collection, processing and distribution of blood and blood components sourced from Australian voluntary donors. All plasma collected by the ARCBS for the manufacture of IVIg is presently sent to CSL Limited Bioplasma Division for fractionation. The ARCBS Transfusion Medicine Team provides a consultancy service and issues IVIg based on clinical need.

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 indications should be categorised according to the quality of the available evidence and whether or not it showed that IVIg was beneficial.

b) Increasing the manufacture of IVIg in Australia

Australia has a long-standing commitment to a policy of promoting 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*

2 Blood and Blood Products Committee. 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). Canberra: Blood and Blood Products Committee; June 2000.

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

Domestically produced IVIg is made exclusively by the CSL Limited Bioplasma Division and CSL's Australian product is called Intragam®P. It is manufactured from voluntarily donated plasma collected around Australia by the Australian Red Cross Blood Service (ARCBS). The collection of plasma and the manufacture of Intragam®P have increased in response to increasing demand for plasma products (see Figures 2 and 3).

c) Importing IVIg from overseas suppliers

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

Intravenous Immunoglobulin Standing Offer

The Intravenous Immunoglobulin Standing Offer is an arrangement for the contingent supply of overseas IVIg. Under this arrangement, overseas IVIg is used to supplement the domestic IVIg supply in the event domestic production does not meet demand.

Presently the National Blood Authority has Standing Offer arrangements with two suppliers: CSL Limited for the supply of Sandoglobulin® and Octapharma Australia Proprietary Limited for the supply of Octagam®. The IVIg Standing Offer may be extended to other suppliers as

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: http://www.nba.gov.au/PDF/report.pdf

4 Flood P, Wills P, Lawler P, et al. Review of Australia's Plasma Fractionation Arrangements. Canberra: Commonwealth of Australia; 2006 [cited 7 Dec 2007]. Available from: http://www.health.gov.au/internet/wcms/publishing.nsf/Content/plasma-fractionation-review-overview.htm

their products become registered for use in Australia.

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.

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. In order to optimise shelf life and continuity of patient care there may be occasions when imported IVIg is issued when there are still reserves of domestically produced product.

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 National Blood Authority website at www.nba.gov.au.

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Production of immunoglobulin

2. Production of immunoglobulin

Pooled human plasma is the starting point for the manufacture of IVIg.

Plasma is obtained either by fractionation 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 relatively expensive when compared to whole blood collection and is more time consuming for the donor. It does, however, enable larger quantities of plasma to be collected more frequently from each donor.

In 2004–05, around 14% of plasma and platelet collections in Australia were by apheresis. While plasmapheresis enables larger quantities of plasma to be collected more frequently from each donor, higher yields of some antibodies are observed in plasma recovered from whole blood donations. In this context, a mix of both plasmapheresis-derived plasma (sourced plasma) and plasma recovered from whole blood donations (recovered plasma) is desirable.

Plasma is collected in Australia by the Australian Red Cross Blood Service (ARCBS) on behalf of all Australian Governments. The ARCBS retains the cellular components and a small amount of the plasma for distribution to hospitals and clinics. The bulk of the plasma is frozen and shipped to CSL Limited for separation into individual plasma products. Plasma fractionation is performed by CSL Limited under a contract with the National Blood Authority.

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, today remains the most commonly used method 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. Such chromatographic processes are routinely used throughout the biotechnology industry and enable high levels of purification to be obtained in a consistent manner. The CSL Limited 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 last twenty 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.

The products of major therapeutic value derived from the fractionation of plasma are albumin, immunoglobulins, Factor VIII and Factor IX.

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 supplied and manufactured in Australia. The TGA does not consider issues relating to the cost of products.

A sponsor company that wishes to market an intravenous 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 (1) the chemistry, the standards of manufacture and quality control of the product (CM&QC data)[5]; (2) any preclinical *in vitro* tests and animal studies conducted on the product[6]; and (3) clinical data derived from studies

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.

conducted in humans[7].

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 Agency for the Evaluation of Medicinal Products (EMEA).

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. TGA staff with the relevant expertise and in some cases external experts undertake this work. On completion of the evaluations the application is considered by the Australian Drug Evaluation Committee (ADEC), an independent advisory committee composed mainly of practising specialist clinicians drawn from outside the TGA. The chemistry, manufacturing and quality control data are also considered by the Pharmaceutical Subcommittee of ADEC, which is also comprised of independent experts drawn from outside the TGA. The ADEC provides the TGA with expert advice on any issues that have arisen during the evaluation process and recommends to the TGA whether the product should be included in the register.

Once an IVIg product is registered, the sponsor company is free to commence marketing in Australia. The product's registration imposes certain restrictions and conditions on supply. For example, each IVIg

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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.

product is approved for certain indications and dosage regimens based on the clinical data provided to the TGA for the product. 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 ('blue card') 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 approval. Use of a product for an unapproved indication is commonly referred to as 'off-label use'. Although off-label use is legal, 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 and 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, however, decreased considerably over the past twenty years.

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, with each step capable of reducing lipid enveloped viruses by the order of four log or more.

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. While prions cannot be inactivated by processes used to inactivate viruses, they can be removed through the fractionation processes, 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

There are five intravenous immunoglobulin products currently registered on the Australian Register of Therapeutic Goods and available for use in Australia.

While all products are assessed by the Therapeutic Goods Administration 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 manufacturer. Manufacturers' contact details are available via their web sites. Web addresses and a summary of the available products and their registered uses are available in Appendix E.

3

IV immunoglobulin supply and demand

3. Intravenous immunoglobulin supply and demand

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

International

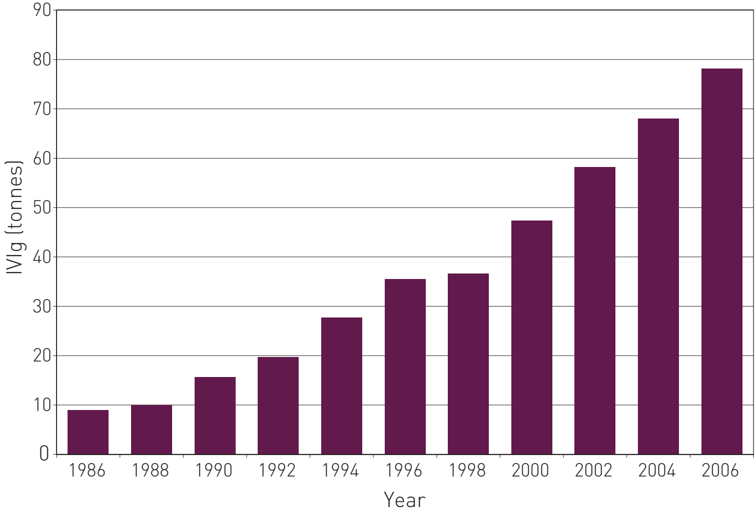
In the late 1990s, rapid growth in the number of indications for IVIg use, particularly in the US, and the temporary closure of a number of US production sites due to regulatory non-compliance contributed to worldwide shortages of IVIg. The imbalance between supply and demand led to dramatic increases in the price, making it attractive for European manufacturers to enter the US market.

The crisis in supply of IVIg was gradually resolved when US FDA and Surgeon General recommendations restricted 'off-label' use and the manufacturing plants closed by the FDA met regulatory requirements and began releasing product. In addition, new players entered the market, including CSL Limited through its ZLB Behring facility in Bern. The result of these activities was that the price of IVIg in the US declined significantly in the early 2000s.

An oversupply of plasma and IVIg in 2002–03 caused many manufacturers to reduce their manufacturing capacity and close commercial plasma collection centres. Supply became tight again in late 2005. In response to increasing prices, manufacturers are now increasing plasma collections and manufacturing output.

Despite fluctuations in demand, the overall worldwide supply of IVIg has increased steadily (Figure 1).

Figure 1: Worldwide supply of intravenous immunoglobulin

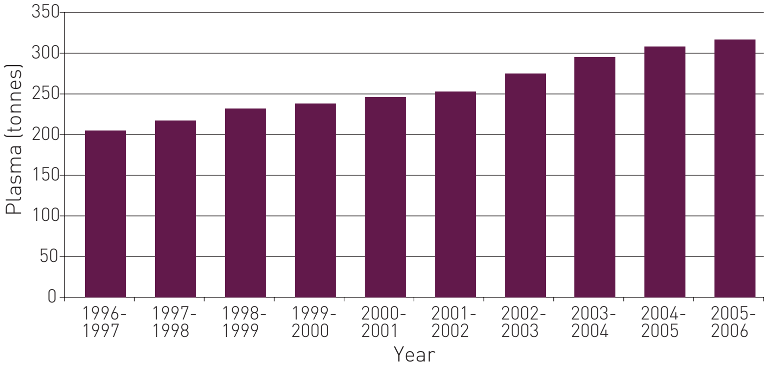


Source: P Robert, International Plasma Protein Congress, Prague, March 2006

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 (ARCBS) collects plasma from Australian voluntary donors on behalf of all Australian Governments. The total amount of plasma collected by the ARCBS over the period from 1994–95 to 2005–06 and sent to CSL Limited for fractionation is shown in Figure 2. CSL Limited is the exclusive manufacturer of IVIg in Australia. All locally produced IVIg is utilised within Australia and supply shortages have been reported from time to time.

Figure 2: Plasma sent to CSL Limited for fractionation



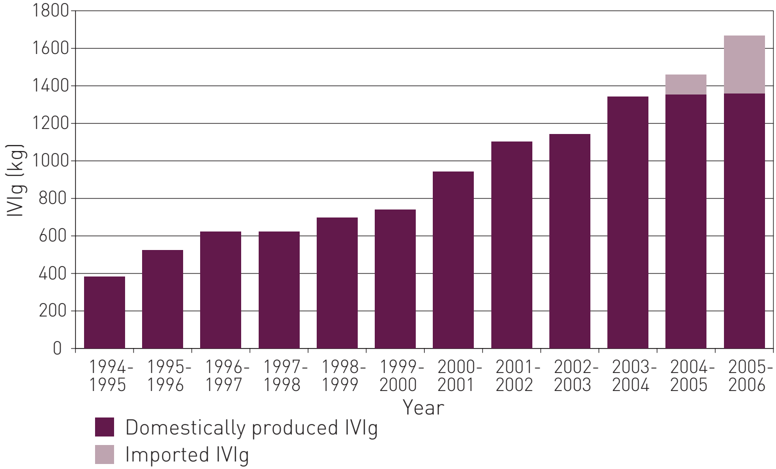
Source: National Blood Authority data on file

The quantity of immunoglobulin that can be isolated from a litre of plasma depends upon the amount in the plasma and the yield of the process used to extract it. Prior to 1999, CSL Limited produced a 6% liquid IVIg called Intragam®. This product was manufactured using a Cohn based process. In 1999–2000, CSL introduced a new chromatographically purified 6% IVIg preparation, called Intragam®P. This product not only had improved specifications over Intragam® but also delivered a higher yield of product from each litre of plasma processed. This increase in product yield is reflected in the increase in the quantity of IVIg issued from 1999–2000 onwards, as shown in Figure 3.

The shortages of IVIg that occurred in the late 1990s catalysed a review of the use of IVIg in Australia by the then Blood and Blood Products Committee of the Australian Health Minister's 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 negotiated a standing offer for imported IVIg in 2004. 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.

Figure 3: IVIg 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 2005–06 was $565.4 million. Approximately $103 million of this was spent on IVIg ($81 million for domestically produced product and $22 million for imported product). These are the product costs only and do not include costs associated with the collection of plasma for fractionation.

World trends

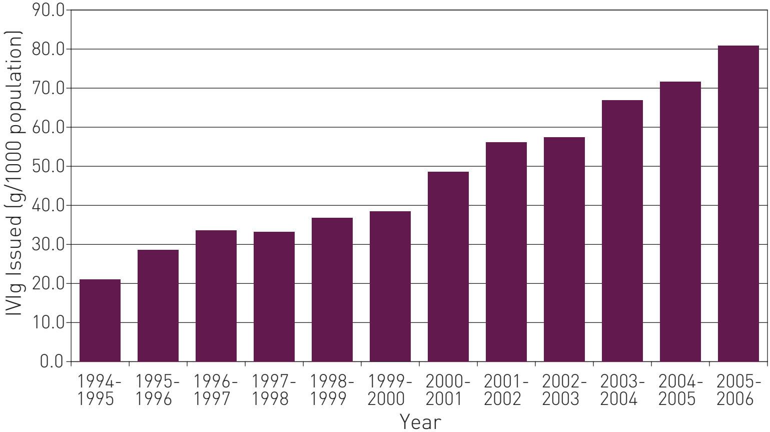
Factors that affect the quantities of plasma products required and produced vary with time but include changes in clinical indications and demographics, the introduction of alternative therapeutics, changes in actual and perceived risks of blood products and modifications to manufacturing processes.

The growth of IVIg use in North America (Canada and the USA) between 1992 and 2005 has averaged 11% per annum. In 2005, more than 34,000 kg of IVIg was issued. This represents 103g/1,000 head of population, making North America the largest user of IVIg in the world. By comparison, IVIg use in Europe is around 25g/1,000 head of population. The growth rate for IVIg usage in Europe since 1992 has been similar to that of North America, at around 12%.

Australian consumption of IVIg lies between that of North America and Europe with a rate of about 72g of IVIg issued/1,000 head of population in 2004–05. The average annual growth rate for the total mass of IVIg issued in Australia over the last decade is 14.8%.

The amount of IVIg issued/1000 head of population has seen a corresponding rise.

Figure 4: Australian IVIg issued in g/1000 head of population



Source: National Blood Authority data on file

Table 1 presents the usage rates of IVIg in g/1000 head of population for a number of countries.

Table 1: International usage rates for IVIg in 2005

Country/Province	Usage (g/1000 population)
USA	105
Canada	92
Sweden	81
Australia	72
Austria	67
Belgium	67
France	47
New Zealand	46
Italy	40

Country/Province	Usage (g/1000 population)
UK	39
Germany	38
Netherlands	35
Japan	28
China	3

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.

4

The clinical criteria

4. The clinical criteria

In Australia, 'guidelines' such as those endorsed by the National Health and Medical Research Council usually refer to the *management of conditions* (e.g. guidelines for the management of early breast cancer) rather than the use of *specific therapeutic products*. The word 'guidelines' connotes the provision of guidance or advice on the management of a condition. This report identifies 'clinical criteria for use', connoting a more directive framework for decisions on the use of a therapeutic product.

The 'clinical criteria' for IVIg use have been developed by a Jurisdictional Blood Committee IVIg Working Party. In accordance with the Working Party's terms of reference (Appendix B), 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.

The purpose of the criteria is to provide a basis for decision making on the appropriate use of IVIg in the treatment of patients with particular manifestations of disease.

Development

Consultation about the development of criteria for IVIg use began in May 2004. In response to concerns that the AHMAC 2000 guidelines were in need of review, the National Blood Authority convened 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 multi-factorial 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.

A systematic literature review of the efficacy of IVIg therapy and its risks was commissioned. This was completed in September 2004.

In April 2005, the Jurisdictional Blood Committee 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 Working Party.

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 and commissioned the development of an 'exposure draft' of national criteria. Detailed discussion of the methods used to develop the exposure draft is provided in Appendix F.

The exposure draft was reviewed by sub-groups of clinical experts in the disciplines of neurology, haematology and immunology before being circulated to the clinical community for comment. The input of the jurisdictional IVIg user groups, professional colleges and specialists in the fields of transplant and transfusion medicine, dermatology, rheumatology, respiratory medicine, obstetrics and intensive care medicine was actively sought.

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.

A second draft of the document was circulated for comment in March 2007. Submissions from this round were considered by the 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.

Systematic reviews

Systematic literature reviews of the efficacy and risks of treatment with IVIg were undertaken in 2004 and 2005. 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 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 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 2.

Table 2: Level of evidence categories

Category	Studies	Evidence
1	High-quality 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	—

Condition pro-forma

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

i) *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;

ii) *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;

iii) *exclusion criteria* – these define the circumstances in which IVIg should not be used in patients who have the specified indication; and

iv) *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.

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.

Replacement and immunomodulation therapy

Most conditions recommended 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.

Immunoglobulin replacement therapy can be administered via the subcutaneous route with the availability of a suitable product. At the time of writing, a new Australian preparation of immunoglobulin for subcutaneous use is in clinical trial. Subcutaneous immunoglobulin is presently not suited to most immunomodulatory indications although it may become adaptable to the maintenance phase of some indications in the future.

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 preventions of infection). This is for three reasons: (i) the human immune system is characterised by the redundancy of host defence mechanisms; (ii) laboratory tests are imperfect in their prediction of immune function; and (iii) 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.

Maintenance

Governments recognise the need for the conditions identified for IVIg therapy and the clinical criteria for IVIg use to be regularly reviewed to take account of the evolving processes of disease diagnosis, treatment and outcome evaluation. It is proposed that these criteria will be reviewed three yearly, with the process commencing two years after the release of each new version, allowing twelve months for the process of consultation and drafting.

In concert with the development of these criteria, the National Blood Authority has been charged by the Jurisdictional Blood Committee with the responsibility of developing plans for their implementation. These plans include the development of a system to collect data that will provide information about the effectiveness of IVIg therapy. This information will be assessed by experts and used to inform future reviews of this document.

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 IVIg use is well established in Australia. There is reasonable quality evidence 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 regimes 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 3: Conditions for which IVIg has an established therapeutic role as immunoglobulin replacement therapy

Condition	Evidence level	Page
Acquired hypogammaglobulinaemia secondary to haematological malignancies (CLL, MM, NHL & other relevant malignancies & post HSCT)	2a	60
Primary immunodeficiency diseases with antibody deficiency	2a	65

Table 4: Conditions for which IVIg has an established therapeutic role as immunomodulation therapy

Condition	Evidence level	Page
Chronic inflammatory demyelinating polyneuropathy	1	68
Guillain-Barré syndrome	1	72
ITP in adults (includes thrombocytopenia arising as a result of HIV infection)	2a	76
Inflammatory myopathies (PM, DM & IBM)	2a	82
Kawasaki disease	1	87
Lambert-Eaton myasthenic syndrome	2a	91
Multifocal motor neuropathy	1	95
Myasthenia gravis	1	100
Neonatal haemochromatosis	2a	104
Stiff person syndrome	2a	107

Medical condition	Acquired hypogammaglobulinaemia secondary to haematological malignancies (CLL, MM, NHL & other relevant malignancies & post HSCT)
Indication	• 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 WHO 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 3 weeks for 1 year. Serious bacterial infections showed a trend to be associated with an IgG level <6.4g/L. Three RCTs and 1 crossover trial of low–moderate quality reported a reduction in infection rates in CLL patients with hypogammaglobulinaemia after 3–4 weekly administration of IVIg for 1 year.

Medical condition	Acquired hypogammaglobulinaemia secondary to haematological malignancies (CLL, MM, NHL & other relevant malignancies & post HSCT)
Justification for evidence category (continued)	One placebo-controlled RCT of monthly IVIg given to 82 multiple myeloma 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.
Qualifying criteria for IVIg therapy	Diagnosis of NHL, CLL, MM or other relevant B-cell tumour with: 1. Recurrent or severe bacterial infection(s) and evidence of hypogammaglobulinaemia (excluding paraprotein); OR 2. Hypogammaglobulinaemia with IgG <4g/L (excluding paraprotein) with a lack of functional IgG response to vaccine challenge. **Note**: For data tracking purposes, the type of malignancy being treated should be recorded with each request for IVIg.
Review criteria for assessing effectiveness of IVIg use	• Six-month review assessing evidence of clinical benefit. • Depending on the clinical circumstance, cessation of IVIg should be considered after 12 months of therapy with repeat clinical and/or immunological evaluation prior to re-commencement of therapy.

Medical condition	Acquired hypogammaglobulinaemia secondary to haematological malignancies (CLL, MM, NHL & other relevant malignancies & post HSCT)
Data items to be collected for monitoring effectiveness of IVIg use	**Note**: The system for collecting outcomes data is presently under development. Reportable data for monitoring the effectiveness of IVIg therapy will be detailed in the next edition.
Dose	Maintenance dose: 0.4g/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 0.4g/kg in the first month of therapy is permitted if the serum IgG level is <4g/L. **Subcutaneous administration** of immunoglobulin can be considered as an alterative to IVIg. A suggested dose is 0.1g/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.**

Bibliography

Biotext. A systematic literature review and report on the efficacy of intravenous immunoglobulin therapy and its risks. Appendix 2 – Summary data on conditions and papers. [online]. Commissioned by the National Blood Authority on behalf of all Australian Governments; 2004 [cited 7 Dec 2007]. Available from: http://www.nba.gov.au/pubs.htm

Cordonnier C, Chevret S, Legrand, M, et al. Should immunoglobulin therapy be used in allogeneic stem cell transplantation? A randomised, double-blind dose effect, placebo-controlled, multicentre trial. Ann Int Med 2003;139:8–18.

Chapel H, Dicato M, Gamm H, et al. Immunoglobulin replacement in patients with chronic lymphocytic leukaemia: a comparison of two dose regimes. Br J Haem 1994;88:209–12.

Chapel HM, Lee M, Hargreaves R, et al. Randomised trial of intravenous immunoglobulin as prophylaxis against infection in plateau-phase multiple myeloma. The UK Group for Immunoglobulin Replacement Therapy in Multiple Myeloma. Lancet 1994;343(8905):1059–63.

Cooperative Group for the Study of Immunoglobulin in Chronic Lymphocytic Leukaemia. Intravenous immunoglobulin for the prevention of infection in chronic lymphocytic leukaemia. A randomised, controlled clinical trial. NEJM 1988;319:902–7.

Couderc B, Dujols JP, Mokhtari F, et al. The management of adult aggressive non-Hodgkin's lymphomas. Crit Rev Oncol Hematol 2000;35(1):33–48.

Molica S, Musto P, Chiurazzi F, et al. Prophylaxis against infections with low dose intravenous immunoglobulins in chronic lymphocytic leukaemia. Results of a crossover study. Haematologica 1996;81:121–6.

Orange JS, Hossny EM, Weiler CR, et al. 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. J Allergy Clin Immunol 2006;117(4):S525–53.

Sklenar I, Schiffman G, Jonsson V, et al. Effect of various doses of intravenous polyclonal IgG on in vivo levels of 12 pneumococcal antibodies in patients with chronic lymphocytic leukaemia and multiple myeloma. Oncology 1993;50(6):466–77.

Thomson D. Lymphatic malignancies – Non-Hodgkin's lymphoma. Hospital Pharmacist 2005;12:353–8.

Winston DJ, Antin JH, Wolff SN, et al. A multicentre randomised double-blind comparison of different doses of intravenous immunoglobulin for prevention of graft-versus-host disease and infection after allogeneic bone marrow transplantation. Bone Marrow Transplant 2001;28:187–96.

Weeks JC, Tierney MR, Weinstein MC. Cost effectiveness of prophylactic intravenous immune globulin in chronic lymphocytic leukaemia. N Engl J Med 1991;325:61–6.

Medical condition	**Primary immunodeficiency diseases with antibody deficiency** This excludes: 1. specific antibody deficiency (see page 118); 2. IgG subclass deficiency (refer to Specific antibody deficiency, page 118).
Indication for IVIg use	Management of infection related to antibody deficiency.
Level of evidence	Evidence of probable benefit (Category 2a).
Description and diagnostic criteria	Primary immunodeficiency diseases (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 (SCID), transient hypogammaglobulinaemia of infancy, Wiskott Aldrich syndrome and X-linked agammaglobulinaemia (XLA). 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 do 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 review (2004) 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 with antibody deficiency
Exclusion criteria for IVIg therapy	The following conditions should not be approved under this indication: 1. Miscellaneous hypogammaglobulinaemia (see Secondary hypogammaglobulinaemia, page 115); 2. Specific antibody deficiency (see page 118); 3. IgG subclass deficiency (refer to Specific antibody deficiency, page 118).
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. • Renal function.
Data to be collected for monitoring effectiveness of IVIg use	**Note**: The system for collecting outcomes data is presently under development. Reportable data for monitoring the effectiveness of IVIg therapy will be detailed in the next edition.
Dose	**Maintenance dose**: 0.4g/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 0.4g/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 [illegible] 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. **Subcutaneous administration** of immunoglobulins (SCIG) is a suitable alternative to IVIg in this disease. **Refer to the current product information sheet for further information.**

SEE REVISIONS

Bibliography

Biotext. A systematic literature review and report on the efficacy of intravenous immunoglobulin therapy and its risks. Appendix 2–Summary data on conditions and papers. [online]. Commissioned by the National Blood Authority on behalf of all Australian Governments; 2004 [cited 7 Dec 2007]:218. Available from: http://www.nba.gov.au/pubs.htm

Bonilla FA, Bernstein L, Khan DA, et al. Practice parameter for the diagnosis and management of primary immunodeficiency. Ann Allergy Asthma Immunol 2005;94(5 Suppl 1):S1–63.

Cooper MD, Schroeder Jr HW. Primary immune deficiency diseases. In: Kasper DL, Braunwald E, Fauci AS, et al (ed). Harrison's Textbook of Medicine. 16th ed. New York: McGraw-Hill; 2005. p. 1939–47.

Orange JS, Hossny EM, Weiler CR, et al. 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. J Allergy Clin Immunol 2006;117(4):S525–53.

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	Chronic inflammatory demyelinating polyneuropathy (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	One Cochrane review of six RCTs with a total sample size of 170. The quality of the studies was low-moderate and found IVIg improved disability in the short-term and had comparable results to treatment with plasma exchange or prednisolone (Biotext, 2004). One low quality RCT with a total sample size of 20 demonstrated more patients responding to immunoadsorption than IVIg, though the baseline disease duration was higher in the IVIg group. Differences were not significant (SHPG, 2005).

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.
Review criteria for assessing the effectiveness of IVIg use	IVIg should be used for 3–6 months (3–6 courses) before determining whether the patient has responded. Most individuals will respond within 3 months unless there is significant axonal degeneration whereby a 6-month course will be necessary. If there is no benefit after 3–6 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. **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 (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)
Data items to be collected for monitoring effectiveness of IVIg use	**Note**: The system for collecting outcomes data is presently under development. Reportable data for monitoring the effectiveness of IVIg therapy will be detailed in the next edition.
Dose	**Induction**: 2g/kg in 2 to 5 divided doses. **Maintenance**: 0.4–1g/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.**

Bibliography

Asia-Pacific IVIg Advisory Board. Bringing consensus to the use of IVIg in neurology. Expert consensus statements on the use of IVIg in neurology. 1st ed. Asia-Pacific IVIg Advisory Board Inc; Nov 2004. p. 21–29.

Biotext. A systematic literature review and report on the efficacy of intravenous immunoglobulin therapy and its risks. Appendix 2 – Summary data on conditions and papers. [online]. Commissioned by the National Blood Authority on behalf of all Australian Governments; 2004 [cited 7 Dec 2007]:132–3. Available from: http://www.nba.gov.au/pubs.htm

Frommer M, Madronio C. The use of intravenous immunoglobulin in Australia. A report for the National Blood Authority, Part B, 2006. Sydney Health Projects Group, University of Sydney, 2006, p. 29–31.

Hughes RAC, Bouche P, Cornblath DR, et al. European Federation of Neurological Societies/Peripheral Nerve Society guideline on management of chronic inflammatory demyelinating polyradiculoneuropathy: report of a joint task force of the European Federation of Neurological Societies and the Peripheral Nerve Society. Eur J Neurol 2006;326–32.

van Schaik IN, Winer JB, de Haan R, et al. Intravenous immunoglobulin for chronic inflammatory demyelinating polyradiculoneuropathy (Cochrane Review). In: The Cochrane Library, Issue 2, 2002. Chichester, UK. John Wiley & Sons, Ltd.

Zinman L, Sutton HD, Ng E, et al. A pilot study to compare the use of the Excorim staphylococcal protein immunoadsorption system and IV IG in chronic inflammatory demyelinating polyneuropathy. Transfus Apher Sci 2005; 33(3): 317–24.

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 2 weeks, although arbitrary definition accepts a limit of 4 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).

Medical condition	Guillain–Barré Syndrome (GBS)
Description and diagnostic criteria (continued)	**Investigations** There is no biological marker for GBS. It is diagnosed by clinical recognition of rapidly evolving paralysis with areflexia. Investigations include: • CSF protein elevation, although the level may be normal in the first 2 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 to hasten 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) where 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 4 weeks than the placebo group (Frommer & Madronio, 2005).
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 4 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
Data items to be collected for monitoring effectiveness of IVIg use	**Note**: The system for collecting outcomes data is presently under development. Reportable data for monitoring the effectiveness of IVIg therapy will be detailed in the next edition.
Dose	2g/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.**

Bibliography

Association of British Neurologists. Guidelines for the use of intravenous immunoglobulin in neurological diseases [online]. London: The Association; 2005 [cited 7 Dec 2007]. Available from: http://www.theabn.org/documents/IVIg-Guidelines-2005.pdf

Biotext. A systematic literature review and report on the efficacy of intravenous immunoglobulin therapy and its risks. Appendix 2 – Summary data on conditions and papers. [online]. Commissioned by the National Blood Authority on behalf of all Australian Governments; 2004 [cited 7 Dec 2007]:149–150. Available from: http://www.nba.gov.au/pubs.htm

Frommer M, Madronio C. The use of intravenous immunoglobulin in Australia. A report for the National Blood Authority, Part B: systematic literature review, 2006. Sydney Health Projects Group, University of Sydney, 2006, p. 32–4.

Hughes RAC, Raphaël J-C, Swan AV, et al. Intravenous immunoglobulin for Guillain Barré Syndrome (Cochrane Review). In: The Cochrane Library, Issue 1, 2006. Chichester, UK. John Wiley & Sons, Ltd.

Korinthenberg R, Schessl J, Kirschner J, et al. Intravenously administered immunoglobulin in the treatment of childhood Guillain-Barré syndrome: a randomized trial. Paediatrics 2005;116(1):8–14.

Kornberg AJ, for the Asia-Pacific IVIg Advisory Board. Bringing consensus to the use of IVIg in neurology. Expert consensus statements on the use of IVIg in neurology. 1st ed. Asia-Pacific IVIg Advisory Board, Melbourne, 2004, p14–20.

Medical condition	Idiopathic (autoimmune) thrombocytopenic purpura (ITP) – adult
Indications for IVIg use	1. **Refractory ITP**: Patients with severe thrombocytopenia (platelets <30x10^9/L) who have not responded to corticosteroid therapy. 2. **ITP with 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. Severe ITP (platelets <30x10^9/L) where corticosteroids and immunosuppression are contraindicated. c. Chronic refractory ITP. 5. **HIV – associated ITP**: Patients with severe ITP associated with HIV infection.
Level of evidence	Evidence of probable benefit (Category 2a).
Description and diagnostic criteria	Idiopathic (autoimmune) thrombocytopenic purpura 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.

Medical condition	Idiopathic (autoimmune) thrombocytopenic purpura (ITP) – adult
Description and diagnostic criteria (continued)	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 3 randomised studies, have demonstrated equivalent efficacy of IVIg in comparison to prednisone 1mg/kg/day and high dose dexamethasone regimen. Overall, the studies find a dose response with more rapid increment in platelet counts at scheduling ≥0.8g/kg on day1 compared with 0.4g/kg/day for 3 days. 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 review, 2004).

Medical condition	Idiopathic (autoimmune) thrombocytopenic purpura (ITP) – adult
Qualifying criteria for IVIg therapy	1. **Refractory ITP**: a. Patients qualify for initial IVIg therapy when conventional doses of corticosteroids have failed. The objective of therapy is to induce a prompt increase in the platelet count (›$30x10^9$/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 immunosuppressive agent and dapsone 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 six 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. 2. **ITP with life-threatening haemorrhage**: IVIg therapy may be given when conventional doses of corticosteroids have failed. The objective of therapy is to induce a prompt increase in the platelet count (›$30x10^9$/L) while other therapies are introduced.

Medical condition	Idiopathic (autoimmune) thrombocytopenic purpura (ITP) – adult
Qualifying criteria for IVIg therapy (continued)	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 (50–100x10^9/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. 5. **HIV associated ITP**: a. Failure of antiretroviral therapy with platelet count <30x10^9/L; OR b. Life-threatening haemorrhage secondary to thrombocytopenia.

Medical condition	Idiopathic (autoimmune) thrombocytopenic purpura (ITP) – adult
Review criteria for assessing the effectiveness of IVIg use	• In chronic refractory ITP, 6-month review assessing evidence of clinical benefit. • Resolution of bleeding. • Increment in platelet count.
Data items to be collected for monitoring effectiveness of IVIg use	**Note**: The system for collecting outcomes data is presently under development. Reportable data for monitoring the effectiveness of IVIg therapy will be detailed in the next edition.
Dose	**Initial therapy**: 1–2g/kg as a single or divided dose. **Ongoing therapy**: When indicated, 1–2g/kg in single or divided dose at 4 to 6 weekly intervals titrated to symptoms and platelet count. **Dosing above 1g/kg per day is contraindicated for some IVIg products. Refer to the current product information sheet for further information.**

Bibliography

Bierling P, Godeau B. Intravenous immunoglobulin for autoimmune thrombocytopenic purpura. Hum Immunol 2005;66(4):387–94.

Biotext. A systematic literature review and report on the efficacy of intravenous immunoglobulin therapy and its risks. Appendix 2 – Summary data on conditions and papers. [online]. Commissioned by the National Blood Authority on behalf of all Australian Governments; 2004 [cited 7 Dec 2007]:42–48. Available from:http://www.nba.gov.au/pubs.htm

British Society for Haematology General Haematology Task Force. Guidelines for the investigation and management of idiopathic thrombocytopenic purpura in adults, children and in pregnancy. Br J Haematol 2003;120(4):574–96.

Frommer M, Madronio C. The use of intravenous immunoglobulin in Australia. A report for the National Blood Authority, Part B: systematic literature review, 2006. Sydney Health Projects Group, University of Sydney, 2006, p. 13–4.

George JN, Woolf SH, Raskob GE, et al. Idiopathic thrombocytopenic purpura: a practice guideline developed by explicit methods for The American Society of Haematology. Blood 1996;88(1):3–40.

Godeau B, Lesage S, Divine M, et al. Treatment of adult chronic autoimmune thrombocytopenic purpura with repeated high-dose intravenous immunoglobulin. Blood 1993;82(5):1415–21.

Godeau B, Caulier MT, Decuypere L, et al. Intravenous immunoglobulin for adults with autoimmune thrombocytopenic purpura: results of a randomised trial comparing 0.5 and 1g/kg b.w. Br J Haematol 1999;107(4):716–9.

Godeau B, Chevret S, Varet B, et al. Intravenous immunoglobulin or high-dose methylprednisolone, with or without oral prednisone, for adults with untreated severe autoimmune thrombocytopenic purpura: a randomised, multicentre trial. Lancet 2002;359(9300): 23–9.

Jacobs P, Wood L, Novitzky N. Intravenous gammaglobulin has no advantages over oral corticosteroids as primary therapy for adults with immune thrombocytopenia: a prospective randomised clinical trial. Am J Med 1994;97(1):55–9

Kurlander RJ, Rosse WF. Efficacy of a 2-day schedule for administering intravenous immunoglobulin in treating adults with ITP. Blood 1986;68:112A.

Perrella O. Idiopathic thrombocytopenic purpura in HIV infection: therapeutic possibilities of intravenous immunoglobulins. J Chemother 1990;2(6):390–3.

Unsal C, Gurkan E, Guvenc B, et al. Anti-D and intravenous immunoglobulin treatments in chronic idiopathic thrombocytopenic purpura. Turkish Journal of Haematology 2004;21(1): 27–32.

Zell SC, Peterson K. Long-Term Remission of HIV-Associated Thrombocytopenia Parallels Ongoing Suppression of Viral Replication. West J Med. 1997;167(6): 433–435.

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 – dermatomyositis (DM), polymyositis (PM), and inclusion body myositis (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. 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).

Medical condition	Inflammatory myopathies: polymyositis (PM), dermatomyositis (DM) and inclusion body myositis (IBM)
Justification for evidence category (continued)	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 four 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 (Lynette Kiers). 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). Weak evidence suggests that it may benefit patients with dysphagia associated with IBM (Asia–Pacific IVIg Advisory Board).
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 nutrition; OR 3. Patients with rapidly progressive IBM.

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Medical condition	Inflammatory myopathies: polymyositis (PM), dermatomyositis (DM) and inclusion body myositis (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 3–6 months (3–6 courses) before determining whether the patient has responded. If there is no benefit after 3–6 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 (ADLs) 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.
Data items to be collected for monitoring effectiveness of IVIg use	**Note**: The system for collecting outcomes data is presently under development. Reportable data for monitoring the effectiveness of IVIg therapy will be detailed in the next edition.

Medical condition	Inflammatory myopathies: polymyositis (PM), dermatomyositis (DM) and inclusion body myositis (IBM)
Dose	**Induction**: 2g/kg in 2 to 5 divided doses. **Maintenance**: 0.4–1g/kg 4–6 weekly. Aim for the **minimum dose** to maintain optimal functional status. **Dosing above 1g/kg per day is contraindicated for some IVIg products. Refer to the current product information sheet for further information.**

Bibliography

Association of British Neurologists. Guidelines for the use of intravenous immunoglobulin in neurological diseases [online]. London: The Association; 2005 [cited 7 Dec 2007]. Available from: http://www.theabn.org/documents/IVIg-Guidelines-2005.pdf

Cherin P, Pelletier S, Teixeira A, et al. Results and long-term follow up of intravenous immunoglobulin infusions in chronic, refractory polymyositis: an open study with thirty-five adult patients. Arthritis Rheum 2002;46(2):467–74.

Choy EHS, Hoogendijk JE, Lecky B, et al. Immunosuppressant and immunomodulatory treatment for dermatomyositis and polymyositis (Cochrane Review). In: The Cochrane Library, Issue 3, 2005. Chichester, UK. John Wiley & Sons, Ltd.

Dalakas MC, Illa I, Dambrosia JM, et al. A controlled trial of high-dose intravenous immune globulin infusions as treatment for dermatomyositis. N Engl J Med 1993;329(27):1993–2000.

Dalakas MC, Koffman B, Fujii M, et al. A controlled study of intravenous immunoglobulin combined with prednisone in the treatment of IBM. Neurology 2001;56(3):323–7.

Dalakas MC, Sonies B, Dambrosia J, et al. Treatment of inclusion body myositis with IVIg: a double-blind, placebo-controlled study. Neurology 1997;48(3):712–6.

Dalakas MC. The use of intravenous immunoglobulin in the treatment of autoimmune neuromuscular diseases: evidence-based indications and safety profile. Pharmacol Ther 2004;102(3):177–93

Dalakas MC. Polymyositis, dermatomyositis, and inclusion body myositis. In: Kasper DL, Braunwald E, Fauci AS, et al (ed). Harrison's Textbook of Medicine. 16th ed. New York: McGraw-Hill; 2005. p2540–2545.

Kornberg AJ, for the Asia-Pacific IVIg Advisory Board. Bringing consensus to the use of IVIg in neurology. Expert consensus statements on the use of IVIg in neurology. 1st ed. Asia-Pacific IVIg Advisory Board, Melbourne, 2004.

Walter MC, Lochmuller H, Toepfer M, et al. High-dose immunoglobulin therapy in sporadic inclusion body myositis: a double-blind, placebo-controlled study. J Neurol 2000;247(1):22–8.

Wiles CM, Brown P, Chapel H, et al. Intravenous immunoglobulin in neurological disease: a specialist review. J Neurol Neurosurg Psychiatry. 2002;72(4):440–8

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; • polymorphous rash; • cervical lymphadenopathy.

Medical condition	Kawasaki disease (mucocutaneous lymph node syndrome)
Description and diagnostic criteria (continued)	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 10–20% of cases, particularly in younger infants, present with fever and less 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 after 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 2g/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 review, 2004).
Qualifying criteria for IVIg therapy	Clinical diagnosis of Kawasaki disease by a paediatrician or immunologist.
Data items to be collected for monitoring effectiveness of IVIg use	**Note**: The system for collecting outcomes data is presently under development. Reportable data for monitoring the effectiveness of IVIg therapy will be detailed in the next edition.

Medical condition	Kawasaki disease (mucocutaneous lymph node syndrome)
Dose	2g/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 2g/kg in a single dose may be given when there is ongoing inflammation. **Dosing above 1g/kg per day is contraindicated for some IVIg products. Refer to the current product information sheet for further information.**

Bibliography

Biotext. A systematic literature review and report on the efficacy of intravenous immunoglobulin therapy and its risks. Appendix 2 – Summary data on conditions and papers. [online]. Commissioned by the National Blood Authority on behalf of all Australian Governments; 2004 [cited 7 Dec 2007]:255–6. Available from:http://www.nba.gov.au/pubs.htm

Burns JC, Glode MP. Kawasaki syndrome. Lancet 2004;364(9433):533–44.

De Zorzi A, Colan SD, Gauvreau K, et al. Coronary artery dimensions may be misclassified as normal in Kawasaki disease. J Pediatr 1998;133(2):254–8.

Durongpisitkul K, Soongswang J, Laohaprasitiporn D, et al. Immunoglobulin failure and retreatment in Kawasaki disease. Paediatr Cardiol 2003;24(2):145–8.

Feigin RD, Cecchin F, Wissman SD. Kawasaki Disease. In: McMillan JA. (ed). Oski's Paediatrics: Principles and Practice. 4th ed. Philadelphia: Lippincott Williams & Wilkins; 2006. p.1015–20.

Newburger JW, Takahashi M, Gerber MA, et al. Diagnosis, treatment, and long-term management of Kawasaki disease: a statement for health professionals from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on

ESTABLISHED THERAPEUTIC ROLE 5

Cardiovascular Disease in the Young, American Heart Association. Paediatrics 2004;114(6):1708–33.

Oates-Whitehead RM, Baumer JH, Haines L, et al. Intravenous Immunoglobulin for the Treatment of Kawasaki Disease in Children (Cochrane Review). In: The Cochrane Library, Issue 4, 2003. Chichester, UK. John Wiley & Sons, Ltd.

Rosenfeld EA, Shulman ST, Corydon KE, et al. Comparative safety and efficacy of two immune globulin products in Kawasaki disease. J Paediatr 1995;126(6):1000–3.

Stiehm ER. Lessons from Kawasaki disease: all brands of IVIg are not equal. J Paediatr 2006;148:6–8.

Tsai MH, Huang YC, Yen MH, et al. Clinical responses of patients with Kawasaki disease to different brands of intravenous immunoglobulin. J Paediatr 2006;148(1):38–43.

Wang CL, Wu YT, Liu CA, et al. Kawasaki disease: infection, immunity and genetics. Paediatr Infect Dis J 2005;24(11):998–1004.

Medical condition	Lambert-Eaton myasthenic syndrome (LEMS)
Indication for IVIg use	Short-term therapy for severely affected non-paraneoplastic LEMS patients.
Level of evidence	Evidence of probable benefit (Category 2a).
Description and diagnostic criteria	Lambert-Eaton myasthenic syndrome (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). One submission to the NBA 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	Mandatory assessment by a neurologist; AND Severely affected non-paraneoplastic 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 3–6 months (3–6 courses) before determining whether the patient has responded. If there is no benefit after 3–6 courses, IVIg therapy should be abandoned. **Review** Regular review by neurologist is required: frequency as determined by clinical status of patient. Initial review 3 to 6 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 (ADLs) 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.
Data items to be collected for monitoring effectiveness of IVIg use	**Note**: The system for collecting outcomes data is presently under development. Reportable data for monitoring the effectiveness of IVIg therapy will be detailed in the next edition.

Medical condition	Lambert-Eaton myasthenic syndrome (LEMS)
Dose	**Induction**: 2g/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.**

Bibliography

Association of British Neurologists. Guidelines for the use of intravenous immunoglobulin in neurological diseases [online]. London: The Association; 2005 [cited 7 Dec 2007]. Available from: http://www.theabn.org/documents/IVIg-Guidelines-2005.pdf

Bain PG, Motomura M, Newsom-Davis J, et al. Effects of intravenous immunoglobulin on muscle weakness and calcium-channel autoantibodies in the Lambert-Eaton myasthenic syndrome. Neurology 1996;47(3):678–83.

Biotext. A systematic literature review and report on the efficacy of intravenous immunoglobulin therapy and its risks. Appendix 2 – Summary data on conditions and papers. [Online]. Commissioned by the National Blood Authority on behalf of all Australian Governments; 2004 [cited 7 Dec 2007]:184–7. Available from:http://www.nba.gov.au/pubs.htm

Dalakas MC. The use of intravenous immunoglobulin in the treatment of autoimmune neuromuscular diseases: evidence-based indications and safety profile. Pharmacol Ther 2004;102(3):177–93.

Kornberg AJ, for the Asia-Pacific IVIg Advisory Board. Bringing consensus to the use of IVIg in neurology. Expert consensus statements on the use of IVIg in neurology. 1st ed. Asia-Pacific IVIg Advisory Board, Melbourne, 2004.

Maddison P, Newsom-Davis J. Treatment for Lambert-Eaton myasthenic syndrome (Cochrane Review). In: The Cochrane Library, Issue 2, 2005. Chichester, UK. John Wiley & Sons, Ltd.

Motomura M, Bain PG, et al. Effects of intravenous immunoglobulin treatment on anti-calcium channel antibody titres in the Lambert-Eaton myasthenic syndrome. J Neurol 1995;242:S44.

Skeie GO, Apostolski S, Evoli A, et al. Guidelines for the treatment of autoimmune neuromuscular transmission disorders. Eur J Neurol 2006;13(7):691–9.

Medical condition	Multifocal motor neuropathy (MMN) with persistent conduction block
Indication for IVIg use	First-line therapy for MMN with persistent conduction block.
Level of evidence	Clear evidence of benefit (Category 1).
Description and diagnostic criteria	Multifocal motor neuropathy (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	Six low-quality case studies or crossover RCT with a total sample size of 68 patients. A possible benefit of IVIg treatment in these patients was observed, though five studies were not controlled (Biotext, 2004). One high-quality systematic review (Cochrane) 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 (SHPG, 2005).

Medical condition	Multifocal motor neuropathy (MMN) with persistent conduction block
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 CIDP. IVIg therapy is usually long term, but the minimum effective dose for each patient should be sought. The South Australian IVIg User Group asserts that there is no proven alternative to IVIg. 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 VIg therapy	Patients who have a multifocal motor neuropathy with persistent conduction block as diagnosed by a neurologist.
Exclusion criteria for IVIg therapy	Presence of upper motor neuron signs.
Review criteria for assessing the effectiveness of IVIg use	IVIg should be used for 3–6 months (3–6 courses) before determining whether the patient has responded. Most individuals will respond within 3 months unless there is significant axonal degeneration whereby a 6-month course will be necessary. If there is no benefit after 3–6 courses, IVIg therapy should be abandoned.

Medical condition	Multifocal motor neuropathy (MMN) with persistent conduction block
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 (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.
Data items to be collected for monitoring effectiveness of IVIg use	**Note**: The system for collecting outcomes data is presently under development. Reportable data for monitoring the effectiveness of IVIg therapy will be detailed in the next edition.

Medical condition	Multifocal motor neuropathy (MMN) with persistent conduction block
Dose	**Induction**: 2g/kg in 2 to 5 divided doses. **Maintenance**: 0.4–2g/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. **Dosing above 1g/kg per day is contraindicated for some IVIg products. Refer to the current product information sheet for further information.**

Bibliography

Association of British Neurologists. Guidelines for the use of intravenous immunoglobulin in neurological diseases [online]. London: The Association; 2005 [cited 7 Dec 2007]. Available from: http://www.theabn.org/documents/IVIg-Guidelines-2005.pdf

European Federation of Neurological Societies; Peripheral Nerve Society, van Schaik IN, Bouche P, et al. European Federation of Neurological Societies/Peripheral Nerve Society guideline on management of multifocal motor neuropathy. Eur J Neurol 2006;13:802–8.

Federico P, Zochodne DW, Hahn AF, et al. Multifocal motor neuropathy improved by IVIg: randomized, double-blind, placebo-controlled study. [comment]. Neurology 2000;55(9):1256–62.

Frommer M, Madronio C. The use of intravenous immunoglobulin in Australia. A report for the National Blood Authority, Part B: systematic literature review, 2006. Sydney Health Projects Group, University of Sydney, 2006, p. 35–7.

Kornberg AJ, for the Asia-Pacific IVIg Advisory Board. Bringing consensus to the use of IVIg in neurology. Expert consensus statements on the use of IVIg in neurology. 1st ed. Asia-Pacific IVIg Advisory Board, Melbourne, 2004, p30–34.

Van den Berg-Vos RM, Franssen H, Wokke JH, et al. Multifocal motor neuropathy: long-term clinical and electrophysiological assessment of intravenous immunoglobulin maintenance treatment. Brain 2002;125(Pt 8):1875–86.

van Schaik IN, van den Berg LH, de Haan R, et al. Intravenous immunoglobulin for multifocal motor neuropathy (Cochrane Review). In: The Cochrane Library, Issue 2, 2005. Chichester, UK. John Wiley & Sons, Ltd.

Medical condition	Myasthenia Gravis (MG)
Indication for IVIg use	1. As an alternative treatment to plasma exchange in acute exacerbation (myasthenic crisis) or prior to 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	Myasthenia gravis (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 2–3Hz, 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 4 RCTs (total 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 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 prior to 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 3–6 months (3–6 courses) before determining whether the patient has responded. If there is no benefit after 3–6 courses, IVIg therapy should be abandoned. **Review** Regular review by neurologist is required: frequency as determined by clinical status of patient. Initial review 3 to 6 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 5 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)
Data items to be collected for monitoring effectiveness of IVIg use	**Note**: The system for collecting outcomes data is presently under development. Reportable data for monitoring the effectiveness of IVIg therapy will be detailed in the next edition.
Dose	**Maintenance**: 0.4–1g/kg 4–6 weekly. **Prior to surgery or during myasthenic crisis**: 1–2g/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.**

Bibliography

Biotext. A systematic literature review and report on the efficacy of intravenous immunoglobulin therapy and its risks. Appendix 2 – Summary data on conditions and papers. [online]. Commissioned by the National Blood Authority on behalf of all Australian Governments; 2004 [cited 7 Dec 2007]:188–9. Available from:http://www.nba.gov.au/pubs.htm

Darabi K, Abdel-Wahab O, Dzik WH. Current usage of intravenous immunoglobulin and the rationale behind it: the Massachusetts General Hospital data and review of the literature. Transfusion 2006;46(5):741–753.

Gajdos P, Chevret S, Toyka K. Intravenous Immunoglobulin for Myasthenia Gravis (Cochrane Review). In: The Cochrane Library, Issue 2, 2003. Chichester, UK. John Wiley & Sons, Ltd.

Kornberg AJ, for the Asia-Pacific IVIg Advisory Board. Bringing consensus to the use of IVIg in neurology. Expert consensus statements on the use of IVIg in neurology. 1st ed. Asia-Pacific IVIg Advisory Board, Melbourne, 2004.

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 review, 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 α-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)
Data items to be collected for monitoring effectiveness of IVIg use	**Note**: The system for collecting outcomes data is presently under development. Reportable data for monitoring the effectiveness of IVIg therapy will be detailed in the next edition.
Dose	1g/kg body weight weekly from the 18th week until the end of gestation. **Refer to the current product information sheet for further information.**

Bibliography

Flynn DM, Mohan N, McKiernan P, et al. Progress in treatment and outcome for children with neonatal haemochromatosis. Arch Dis Child Foetal Neonatal Ed 2003;88(2):F124–7.

Knisely AS, Mieli-Vergani G, Whitington PF. Neonatal haemochromatosis. Gastroenterol Clin North Am 2003;32(3):877–89,vi–vii.

Rodriguez F, Kallas M, Nash R, et al. Neonatal haemochromatosis – medical treatment vs. transplantation: the King's experience. Liver Transpl 2005;11(11):1417–24.

Schneider BL. Neonatal liver failure. Curr Opin Paediatr 1996;8:495–501.

Whittington PF, Hibbard, JU. High-dose immunoglobulin during pregnancy for recurrent neonatal haemochromatosis. Lancet 2004;364:1690–8.

Whittington PF, Kelly S, Ekong UD. Neonatal haemochromatosis: foetal liver disease leading to liver failure in the foetus and newborn. Paediatric Transplantation 2005;9:640–5.

Medical condition	Stiff person syndrome (Moersch-Woltman 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, EMG recordings from stiff muscles that may show continuous discharges of motor unit, and CSF 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.
Justification for evidence category (continued)	According to expert consensus, considering the disabling progressive course of stiff person syndrome, IVIg should be offered as the first line treatment. Though periodic infusions would be required in the majority, further studies are needed to determine optimal dosage and duration (Asia–Pacific Advisory Board).

Medical condition	Stiff person syndrome (Moersch-Woltman 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 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 scores of ADLs • other specialised scoring systems such as Distribution-of-stiffness index and Heightened sensitivity scale.
Data items to be collected for monitoring effectiveness of IVIg use	**Note**: The system for collecting outcomes data is presently under development. Reportable data for monitoring the effectiveness of IVIg therapy will be detailed in the next edition.
Dose	**Induction**: 2g/kg in 2 to 5 divided doses. **Maintenance**: 1–2g/kg 4–6 weekly. Aim for **minimum dose** to maintain optimal functional status. **Dosing above 1g/kg per day is contraindicated for some IVIg products. Refer to the current product information sheet for further information.**

Bibliography

Biotext. A systematic literature review and report on the efficacy of intravenous immunoglobulin therapy and its risks. Appendix 2 – Summary data on conditions and papers. [online]. Commissioned by the National Blood Authority on behalf of all Australian Governments; 2004 [cited 7 Dec 2007]:190–1. Available from:http://www.nba.gov.au/pubs.htm

Dalakas MC. The role of IVIg in the treatment of patients with stiff person syndrome and other neurological diseases associated with anti-GAD antibodies. J Neurol. 2005; 252 Suppl 1:119–25.

Dalakas MC, Fujii M, Li M, et al. High-dose intravenous immune globulin for stiff-person syndrome. [see comment]. N Engl J Med 2001;345(26):1870–6.

Kornberg AJ, for the Asia-Pacific IVIg Advisory Board. Bringing consensus to the use of IVIg in neurology. Expert consensus statements on the use of IVIg in neurology. 1st ed. Asia-Pacific IVIg Advisory Board, Melbourne, 2004, p. 70–72.

Rowland LP, Layzer RB. Stiff man syndrome (Moersch-Woltman Syndrome). In: Merritt's Neurology. 11th ed. Rowland LP (ed). Philadelphia: Lippincott Williams & Wilkins; 2005. p.927.

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 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 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 good evidence exists for the effectiveness of IVIg in antibody-mediated rejection, evidence for its use in cellular rejection is still emerging.

For these conditions, the collection of effectiveness/ outcomes data is of particular importance to inform future revisions of this document.

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 regimes 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 5: Conditions for which IVIg has an emerging therapeutic role as immunoglobulin replacement therapy

Condition	Evidence level	Page
Secondary hypogammaglobulinaemia (including iatrogenic immunodeficiency)	4b	115
Specific antibody deficiency	4a	118

Table 6: Conditions for which IVIg has an emerging therapeutic role as immunomodulation therapy

Condition	Evidence level	Page
Acute disseminated encephalomyelitis	2a	121
ANCA-positive systemic necrotising vasculitis	2a	125
Autoimmune haemolytic anaemia	4a	128
Bullous pemphigoid	4a	131
Cicatricial pemphigoid	2a	134
Evans syndrome (includes autoimmune haemolytic anaemia with immune thrombocytopenia)	4a	138
Foeto-maternal/neonatal alloimmune thrombocytopenia (FMAIT/NAIT)	4a	141
Haemophagocytic syndrome	4a	145
High-risk allogeneic haemopoietic stem cell transplantation (mismatched family or unrelated donor)	2c	148
ITP in children	1	152
IgM paraproteinaemic neuropathy	2c	156
Kidney transplantation	1	160
Multiple sclerosis	2a	166
Opsoclonus myoclonus ataxia	4a	172
Pemphigus foliaceus	4a	175
Pemphigus vulgaris	2a	177
Post-transfusion purpura	4a	180
Toxic epidermal necrolysis/Steven Johnson syndrome (TEN/SJS)	4a	182
Toxic shock syndrome	4a	185

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, including haemopoietic stem cell transplantation. **Note**: The following secondary causes of hypogammaglobulinaemia are considered elsewhere: 1. Acquired hypogammaglobulinaemia secondary to haematological malignancies (see page 60); 2. Paediatric HIV infection (see page 195); 3. Solid organ transplantation (see pages 160 and 207).
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 equivalent 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 HSCT) with all of 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 (see page 60); 2. Paediatric HIV infection (see page 195); 3. Transplantation related immunomodulation (HSCT and solid organ transplantation) (see pages 148, 160 and 207).
Review criteria for assessing the effectiveness of IVIg use	IVIg therapy for a maximum of **one** year with repeat immunological evaluation required prior to recommencement of IVIg.

SEE REVISIONS

Medical condition	Secondary hypogammaglobulinaemia (including iatrogenic immunodeficiency)
Data items to be collected for monitoring effectiveness of IVIg use	**Note**: The system for collecting outcomes data is presently under development. Reportable data for monitoring the effectiveness of IVIg therapy will be detailed in the next edition.
Dose	**Maintenance dose**: 0.4g/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 0.4g/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 9g/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. **Subcutaneous administration** of immunoglobulins (SCIG) is a suitable alternative to IVIg in this disease. **Dosing above 1g/kg per day is contraindicated for some IVIg products. Refer to the current product information sheet for further information.**

Bibliography

Orange JS, Hossny EM, Weiler CR, et al. Use of intravenous immunoglobulin in human disease: A review of primary evidence by members of the Primary Immunodeficiency Committee of the American Academy of Allergy, Asthma and Immunology. J Allergy Clin Immunol 2006;117(4): S525–53.

Medical condition	Specific antibody deficiency
Indication for IVIg use	Prevention of infections in individuals with frequent infections who have demonstrated failure to mount protective antibody responses on 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 use of IVIg replacement for functional antibody deficiency has been considered in two international consensus statements (Orange *et al*. J Allergy Clin Immunol, 2006; 117:S525–53, Bonilla *et al*, Ann Allergy Asthma Immunol, 2005; 94:S1–63). The terms specific or selective antibody deficiency are synonymous with functional antibody deficiency although tend to be 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' (Orange *et al*. J Allergy Clin Immunol, 2006;117:S525–53).

Medical condition	Specific antibody deficiency
Description and diagnostic criteria (continued)	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. Many patients with previously diagnosed IgG subclass deficiency and recurrent infection on IVIg may have functional antibody deficits. Enumeration of peripheral blood CD27+IgM memory B-cells may prove to have value in the assessment of host defence to encapsulated bacteria.
Qualifying criteria for IVIg therapy	1. Approval by a clinical immunologist; AND 2. Frequent bacterial infections despite continuous oral antibiotic therapy for three months; 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 functional antibody deficiency. 2. Low total IgG. This should be considered under primary or secondary immunodeficiency.
Review criteria for assessing the effectiveness of IVIg use	• IVIg therapy for a maximum of **one** year with repeat immunological evaluation required prior to recommencement of IVIg. Consideration should be given to an immunoglobulin washout period of 4 to 6 months prior to repeat immunological evaluation. • Patients previously receiving IVIg therapy for IgG subclass deficiencies should be reviewed under these criteria if they are no longer experiencing serious infections. • IgG trough levels are of no value in this setting.

SEE REVISIONS

Medical condition	Specific antibody deficiency
Data items to be collected for monitoring effectiveness of IVIg use	**Note**: The system for collecting outcomes data is presently under development. Reportable data for monitoring the effectiveness of IVIg therapy will be detailed in the next edition.
Dose	**Maintenance dose**: 0.4g/kg every four 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.**

Bibliography

Bheng YK, Decker PA, O'Byrne MM, et al. Clinical and laboratory characteristics of 75 patients with specific polysaccharide antibody deficiency syndrome. Ann Allergy Asthma Immunol 2006;97(3):306–11.

Bonilla FA, Bernstein L, Khan DA, et al. Practice parameter for the diagnosis and management of primary immunodeficiency. Ann Allergy Asthma Immunol 2005;94(5 Suppl 1):S1–63.

Orange JS, Hossny EM, Weiler CR, et al. Use of intravenous immunoglobulin in human disease: A review of primary evidence by members of the Primary Immunodeficiency Committee of the American Academy of Allergy, Asthma and Immunology. J Allergy Clin Immunol 2006;117(4): S525–53.

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	Acute disseminated encephalomyelitis (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 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 6 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, 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)
Data items to be collected for monitoring effectiveness of IVIg use	**Note**: The system for collecting outcomes data is presently under development. Reportable data for monitoring the effectiveness of IVIg therapy will be detailed in the next edition.
Dose	**Induction**: 2g/kg in 2 to 5 divided doses. **Maintenance dose**: For recurrent or multiphasic ADEM only: 0.4–2g/kg 4–6 weekly. Aim for **minimum dose** to maintain optimal functional status and prevent relapses. In recurrent or multiphasic ADEM, assessment by a neurologist is **mandatory**. **Dosing above 1g/kg per day is contraindicated for some IVIg products. Refer to the current product information sheet for further information.**

Bibliography

Andersen JB, Rasmussen LH, Herning M, et al. Dramatic improvement of severe acute disseminated encephalomyelitis after treatment with intravenous immunoglobulin in a three-year-old boy. Dev Med Child Neurol 2001;43(2):136–8.

Feasby T, Banwell B, Benstead T, et al. Guidelines on the use of intravenous immune globulin for neurologic conditions. Transfus Med Rev 2007;2(2 Suppl 1):S57–107.

Finsterer J, Grass R, Stollberger C, et al. Immunoglobulins in acute, parainfectious, disseminated encephalomyelitis. Clin Neuropharmacol 1998;21:258–61.

Hahn JS, Siegler DJ, Enzmann D. Intravenous gammaglobulin therapy in recurrent acute disseminated encephalomyelitis. Neurology 1996;46(4):1173–4.

Kleiman M, Brunquell P. Acute disseminated encephalomyelitis: response to intravenous immunoglobulin? J Child Neurol 1995;10(6):481–3.

Marchioni E, Marinou-Aktipi K, Uggetti C, et al. Effectiveness of intravenous immunoglobulin treatment in adult patients with steroid-resistant monophasic or recurrent acute disseminated encephalomyelitis. J Neurol 2002;249(1):100–4.

Mariotti P, Batocchi AP, Colosimo C, et al. Multiphasic demyelinating disease involving central and peripheral nervous system in a child. Neurology 2003;60(2):348–9.

Nishikawa M, Ichiyama T, Hayashi T, et al. Intravenous immunoglobulin therapy in acute disseminated encephalomyelitis. Paediatr Neurol 1999;21(2):583–586.

Pittock SJ, Keir G, Alexander M, et al. Rapid clinical and CSF response to intravenous gamma globulin in acute disseminated encephalomyelitis. Eur J Neurol 2001;8(6):725.

Pradhan S, Gupta RP, Shashank S, et al. Intravenous immunoglobulin therapy in acute disseminated encephalomyelitis. J Neurol Sci 1999;165(1):56–61.

Revel-Vilk S, Hurvitz H, Klar A, et al. Recurrent acute disseminated encephalomyelitis associated with acute cytomegalovirus and Epstein-Barr virus infection. J Child Neurol 2000;15(6):421–4.

Sahlas DJ, Miller SP, Guerin M, et al. Treatment of acute disseminated encephalomyelitis with intravenous immunoglobulin. Neurology 2000;54(6):1370–2.

Medical condition	ANCA (PR3 or 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	Anti-neutrophil cytoplasmic antibody (ANCA) associated systemic necrotising vasculitides are life-threatening immune-mediated inflammatory diseases comprising one of four clinical syndromes: 1. Wegener's granulomatosis 2. Microscopic polyangiitis 3. Churg-Strauss Syndrome 4. ANCA (PR3 or MPO)-positive idiopathic rapidly progressive glomerulonephritis. In these cases the ANCA specificity is directed against the neutrophil cytoplasmic antigens proteinase 3 (PR3) and myeloperoxidase (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.
Justification for evidence category	One RT 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 review concluded that there is possible benefit in the treatment of AASV with IVIg if disease activity persists after standard therapy (Biotext review, 2004).

EMERGING THERAPEUTIC ROLE

6

Medical condition	ANCA (PR3 or MPO)-positive systemic necrotising vasculitis
Qualifying criteria for IVIg therapy	MPO or PR3 ANCA positive systemic necrotising vasculitis with both of the following: 1. Current (or within the previous 6 months) standard cytotoxic immunosuppressive ANCA-vasculitis regimens; AND 2. Persistent 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 (BVAS) of more than 50% after 3 months. • Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) concentration. • ANCA titre.
Data items to be collected for monitoring effectiveness	**Note**: The system for collecting outcomes data is presently under development. Reportable data for monitoring the effectiveness of IVIg therapy will be detailed in the next edition.
Dose	2g/kg in single or divided doses. **Dosing above 1g/kg per day is contraindicated for some IVIg products. Refer to the current product information sheet for further information.**

Bibliography

Biotext. A systematic literature review and report on the efficacy of intravenous immunoglobulin therapy and its risks. Appendix 2 – Summary data on conditions and papers. [online]. Commissioned by the National Blood Authority on behalf of all Australian Governments; 2004 [cited 7 Dec 2007]:248-250. Available from: http://www.nba.gov.au/pubs.htm

Foster R, Rosenthal E, Marques S, et al. Primary systemic vasculitis: treatment of difficult cases. Lupus 2006;15(3):143-7.

Jayne DR, Chapel H, Adu D et al. Intravenous immunoglobulin for ANCA-associated systemic vasculitis with persistent disease activity. QJM 2000; 93(7):433-9.

Jayne DR, Davies MJ, Fox CJ, et al. Treatment of systemic vasculitis with pooled intravenous immunoglobulin. Lancet 1991;337(8750):1137-9.

Jayne DR, Rasmussen N. Treatment of antineutrophil cytoplasm autoantibody-associated systemic vasculitis: initiatives of the European Community Systemic Vasculitis Clinical Trials Study Group. Mayo Clin Proc 1997;72(8):737–747.

Jennette JC, Falk RJ, Andrassy K, et al. Nomenclature of systemic vasculitides: proposal of an international consensus conference. Arthritis Rheum 2004;37(2):187-92 (Chapel Hill Consensus criteria).

Orange JS, Hossny EM, Weiler CR, et al. Use of intravenous immunoglobulin in human disease: A review of primary evidence by members of the Primary Immunodeficiency Committee of the American Academy of Allergy, Asthma and Immunology. J Allergy Clin Immunol 2006;117(4): S525-53.

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	Autoimmune haemolytic anaemia (AIHA) is a rare but serious autoimmune disease in which an individual's antibodies recognise antigens on their own red blood cells (RBCs). It 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 LDH 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 recommended 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 <60g/L, except patients with co-morbidities) refractory to conventional therapy with corticosteroids; OR 2. As a temporising measure prior to 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)
Data items to be collected for monitoring effectiveness of IVIg use	**Note**: The system for collecting outcomes data is presently under development. Reportable data for monitoring the effectiveness of IVIg therapy will be detailed in the next edition.
Dose	Up to 2g/kg as a single or divided dose. **Dosing above 1g/kg per day is contraindicated for some IVIg products. Refer to the current product information sheet for further information.**

Bibliography

Besa EC. Rapid transient reversal of anaemia and long-term effects of maintenance intravenous immunoglobulin for autoimmune haemolytic anaemia in patients with lymphoproliferative disorders. Am J Med 1988;84(4):691-8.

Flores G, Cunningham-Rundles C, Newland AC, et al. Efficacy of intravenous immunoglobulin in the treatment of autoimmune haemolytic anaemia: results in 73 patients. Am J Hematol 1993;44(4):237-42

Majer RV, Hyde RD. High-dose intravenous immunoglobulin in the treatment of autoimmune haemolytic anaemia. Clin Lab Haematol 1988;10(4):391-5.

Sherer Y, Levy Y, Fabbrizzi F, et al. Treatment of hematologic disorders other than immune thrombocytopenic purpura with intravenous immunoglobulin (IVIg) – report of seven cases and review of the literature. Eur J Intern Med 2000;11:85-8.

Medical condition	Bullous pemphigoid (BP)
Indication for IVIg use	Bullous pemphigoid 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 6 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 (ACD) 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 identifies a small study (17 cases) where patients who were on IVIg therapy for at least 3 months benefited from the therapy. The same article mentions 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 6 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.
Data items to be collected for monitoring effectiveness of IVIg use	**Note**: The system for collecting outcomes data is presently under development. Reportable data for monitoring the effectiveness of IVIg therapy will be detailed in the next edition.
Dose	Efficacy demonstrated with doses of at least 2g/kg per monthly treatment cycle. Dosing above 1g/kg per day is contraindicated for some IVIg products. Refer to the product information. **Dosing above 1g/kg per day is contraindicated for some IVIg products. Refer to the current product information sheet for further information.**

Bibliography

Ahmed AR, Dahl MV, for the Consensus Development Group. Consensus statement on the use of intravenous immunoglobulin therapy in the treatment of autoimmune mucocutaneous blistering diseases. Arch Dermatol 2003;139:1051–9.

Orange JS, Hossny EM, Weiler CR, et al. Use of intravenous immunoglobulin in human disease: A review of primary evidence by members of the Primary Immunodeficiency Committee of the American Academy of Allergy, Asthma and Immunology. J Allergy Clin Immunol 2006;117(4): S525–53.

Medical condition	Cicatricial pemphigoid (CP) or mucous membrane pemphigoid (MMP)
Indication for IVIg use	Cicatricial pemphigoid resistant to glucocorticoid and immunosuppressive therapy.
Level of evidence	Evidence of probable benefit (Category 2a).
Description and diagnostic criteria	Cicatricial pemphigoid (CP) or mucous membrane pemphigoid (MMP) is a rare, acquired sub-epithelial 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 1–5 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 (SHPG 2005). 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.
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.

Medical condition	Cicatricial pemphigoid (CP) or mucous membrane pemphigoid (MMP)
Review criteria for assessing the effectiveness of IVIg use	• Response demonstrated at review at 6 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.
Data items to be collected for monitoring effectiveness of IVIg use	**Note**: The system for collecting outcomes data is presently under development. Reportable data for monitoring the effectiveness of IVIg therapy will be detailed in the next edition.
Dose	Efficacy demonstrated with doses of at least 2g/kg per monthly treatment cycle. **Dosing above 1g/kg per day is contraindicated for some IVIg products. Refer to the current product information sheet for further information.**

Bibliography

Ahmed AR, Dahl MV, for the Consensus Development Group. Consensus statement on the use of intravenous immunoglobulin therapy in the treatment of autoimmune mucocutaneous blistering diseases. Arch Dermatol 2003;139:1051–9.

Daoud YJ, Amin KG. Comparison of cost of immune globulin intravenous therapy to conventional immunosuppressive therapy in treating patients with autoimmune mucocutaneous blistering diseases. Int Immunopharmacol 2006;6(4):600–6.

Letko E, Miserocchi E, Daoud YJ, et al. A nonrandomized comparison of the clinical outcome of ocular involvement in patients with mucous membrane (cicatricial) pemphigoid between conventional immunosuppressive and intravenous immunoglobulin therapies. Clin Immunol 2004;111(3):303–10.

Orange JS, Hossny EM, Weiler CR, et al. Use of intravenous immunoglobulin in human disease: A review of primary evidence by members of the Primary Immunodeficiency Committee of the American Academy of Allergy, Asthma and Immunology. J Allergy Clin Immunol 2006;117(4): S525–53.

Medical condition	Evans syndrome – autoimmune haemolytic anaemia 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 autoimmune haemolytic anaemia (AIHA) and immune thrombocytopenia (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 provides 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 3 weeks. 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 2g/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 with immune thrombocytopenia
Qualifying criteria for IVIg therapy	Evans syndrome: 1. Refractory to conventional therapy with corticosteroids; OR 2. Where corticosteroids are contraindicated; OR 3. As a temporising measure prior to 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.
Data items to be collected for monitoring effectiveness of IVIg use	**Note**: The system for collecting outcomes data is presently under development. Reportable data for monitoring the effectiveness of IVIg therapy will be detailed in the next edition.
Dose	Up to 2g/kg in divided dose. **Dosing above 1g/kg per day is contraindicated for some IVIg products. Refer to the current product information sheet for further information.**

Bibliography

Darabi K, Abdel-Wahab O, Dzik WH. Current usage of intravenous immunoglobulin and the rationale behind it: the Massachusetts General Hospital data and review of the literature. Transfusion 2006;46(5):741–53.

Mathew P, Chen G, Wang W. Evans syndrome: results of a national survey. J Pediatr Hematol Oncol 1997;19(5):433–7.

Norton A, Roberts I. Management of Evans syndrome. Br J Haematol 2006;132(2):125–37.

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 develops because of maternal sensitisation to foetal platelets that possess a paternally inherited antigen. In Caucasians, the antigen is 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 Australian Red Cross 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	There is evidence that IVIg modulates the course of this condition. See the randomised trials of Bussel and Berkowitz, numerous case series, and the review by Spencer and Burrows. A 2004 Cochrane review reported on 1 RCT comparing IVIg plus dexamethasone with IVIg alone. It was methodologically sound but had inadequate sample size to detect differences among comparison groups.
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).

Medical condition	Foeto-maternal/neonatal alloimmune thrombocytopenia (FMAIT/NAIT): • antenatal • neonatal
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.
Data items to be collected for monitoring effectiveness of IVIg use	**Note**: The system for collecting outcomes data is presently under development. Reportable data for monitoring the effectiveness of IVIg therapy will be detailed in the next edition.
Dose	**Maternal dose**: 1g/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**: 1g/kg. Occasionally more than one dose is required if thrombocytopenia persists. **Refer to the current product information sheet for further information.**

Bibliography

Berkowitz RL, Kolb EA, McFarland JG, et al. Parallel randomized trials of risk-based therapy for fetal alloimmune thrombocytopenia. Obstet Gynecol 2006;107(1):91–6.

Bussel JB, Berkowitz RL, Lynch L, et al. Antenatal management of alloimmune thrombocytopenia with intravenous immunoglobulin: a randomised trial of the addition of low dose steroid to intravenous gamma globulin. Am J Obstet Gynecol 1996;174(5):1414–23.

Kiefel V, Bassler D, Kroll H, et al. Antigen-positive platelet transfusion in neonatal alloimmune thrombocytopenia. Blood 2006;107(9):3761–3.

Rayment R, Brunskill SJ, Stanworth S, et al. Antenatal interventions for fetomaternal alloimmune thrombocytopenia (Cochrane Review). In: The Cochrane Library, Issue 1, 2005. Chichester, UK. John Wiley & Sons, Ltd.

Spencer JA, Burrows RF. Feto-maternal alloimmune thrombocytopenia: a literature review and statistical analysis. Aust N Z J Obstet Gynaecol 2001;41(1):45–55

Yinon Y, Spira M, Solomon O, et al. Antenatal noninvasive treatment of patients at risk for alloimmune thrombocytopenia without a history of intracranial hemorrhage. Am J Obstet Gynecol 2006;195(4):1153–7.

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 but many, mostly small, case series showing 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
Data to be collected for monitoring effectiveness of IVIg use	**Note**: The system for collecting outcomes data is presently under development. Reportable data for monitoring the effectiveness of IVIg therapy will be detailed in the next edition.
Dose	2g/kg is the most widely published dose. Emmenegger *et al* reported that better outcomes were associated with early administration of IVIg in their small series (10 patients). **Dosing above 1g/kg per day is contraindicated for some IVIg products. Refer to the current product information sheet for further information.**

Bibliography

Arlet JB, Le TH, Marinho A, et al. Reactive haemophagocytic syndrome in adult onset Still's disease: report of six patients and review of the literature. Ann Rheum Dis 2006 ;65(12):1596-601. Epub 2006 Mar 15.

Asci G, Toz H, Ozkahya M, et al. High-dose immunoglobulin therapy in renal transplant recipients with hemophagocytic histiocytic syndrome. J Nephrol 2006;19(3):322–6.

Chen RL, Lin KH, Lin DT, et al. Immunomodulation treatment for childhood virus-associated haemophagocytic lymphohistiocytosis. Br J Haematol 1995;89(2):282–90

Emmenegger U, Frey U, Reimers A, et al. Hyperferritinemia as indicator for intravenous immunoglobulin treatment in reactive macrophage activation syndromes. Am J Haematol 2001;68(1):4–10.

Fisman D. Hemophagocytic Syndromes and Infection. Emerg Inf Dis [online]. 2000 [cited 7 Dec 2007]. Available from: http://www.cdc.gov/ncidod/eid/vol6no6/fisman.htm

Freeman B, Rathore MH, Salman E, et al. Intravenously administered immune globulin for the treatment of infection-associated hemophagocytic syndrome. J Pediatr 1993;123(3):479–81.

Ostronoff M, Ostronoff F, Coutinho M, et al. Haemophagocytic syndrome after autologous peripheral blood stem cell transplantation for multiple myeloma; successful treatment with high-dose intravenous immunoglobulin. Bone Marrow Transplant 2006;37(8):797–8.

Medical condition	Haemopoietic stem cell transplantation (HSCT)
Indication for IVIg use	Prevention of graft-versus-host disease in high-risk allogeneic haemopoietic stem cell transplantation (mismatched family or unrelated donor).
Level of evidence	Conflicting evidence of benefit (Category 2c).
Description and diagnostic criteria	HSCT involves eliminating an individual's haemopoietic and immune system by chemotherapy and/or radiotherapy and replacing it with stem cells. The transplanted stem cells may be from another individual (allogeneic) or they may have been previously harvested from the patient (autologous). HSCT encompasses bone marrow transplantation (where stem cells are collected from the bone marrow) or peripheral blood stem cell transplantation (where stem cells are collected from peripheral blood). Human leukocyte antigen (HLA) compatibility between donor and recipient is an essential prerequisite to allogeneic transplants. Apart from graft failure, a complication of allogeneic transplants is graft-versus-host disease (GvHD). The incidence of GvHD varies among clinical units. Several factors influence its occurrence, including: the degree of major histocompatability complex mismatch; age; and sex-matched donors and recipients versus sex-mismatched donors and recipients.

Medical condition	Haemopoietic stem cell transplantation (HSCT)
Description and diagnostic criteria (continued)	Acute GvHD is a primary or contributory cause of death in 15–40% of patients who develop GvHD. The risk of death is directly related to severity. Chronic GvHD occurs in 15–50% of patients who survive 3 months after transplantation. Chronic GvHD most commonly occurs as a transition from acute GvHD, but it can occur *de novo* in 20–30% of patients. Bronchiolitis obliterans contributes to mortality; sepsis remains the most common cause in patients who die with chronic GvHD.
Justification for evidence category	High quality RCTs involving 1830 patients yielded the following results: (1) reduction in hepatic toxicity; (2) reduction in incidence and severity of acute GvHD, but no significant effect on survival rate; (3) higher dose of IVIg found to be associated with less GvHD; (4) IVIg made no significant difference in transplant-related mortality or disease-free survival; (5) no significant difference in effect between 3 doses of IVIg; (6) no significant difference between 2 doses of IVIg; (7) no significant difference in infection rates. In summary, results were conflicting – some showed benefit from higher-dose IVIg, others showed no dose relationship, while others showed no significant difference from placebo (Biotext review, 2004).
Qualifying criteria for IVIg therapy	High-risk allogeneic transplants from unrelated donors, mismatched family donors or multiple cord blood donations.
Exclusion criteria for IVIg therapy	1. Autologous transplants (except where the patient has established humoral deficiency). 2. Uncomplicated matched sibling transplantation.

Medical condition	Haemopoietic stem cell transplantation (HSCT)
Review criteria for assessing the effectiveness of IVIg use	• Review no later than 3 months post transplant. • Occurrence of GvHD. • Grade and severity of GvHD.
Data items to be collected for monitoring effectiveness of IVIg use	**Note**: The system for collecting outcomes data is presently under development. Reportable data for monitoring the effectiveness of IVIg therapy will be detailed in the next edition.
Dose	0.4 g/kg weekly, starting one day before transplantation and continuing to day 100 post-transplant. **Refer to the current product information sheet for further information.**

Bibliography

Biotext. A systematic literature review and report on the efficacy of intravenous immunoglobulin therapy and its risks. Appendix 2 – Summary data on conditions and papers. [online]. Commissioned by the National Blood Authority on behalf of all Australian Governments; 2004 [cited 7 Dec 2007]. Available from: http://www.nba.gov.au/pubs.htm

Cordonnier C, Chevret S, Legrand M et al. Should immunoglobulin therapy be used in allogeneic stem cell transplantation? A randomised, double-blind dose effect, placebo-controlled, multicentre trial. Ann Int Med 2003;139(1):8–18.

Orange JS, Hossny EM, Weiler CR, et al. Use of intravenous immunoglobulin in human disease: A review of primary evidence by members of the Primary Immunodeficiency Committee of the American Academy of Allergy, Asthma and Immunology. J Allergy Clin Immunol 2006;117(4): S525–53.

Winston DJ, Antin JH, Wolff SN, et al. A multicenter, randomized, double-blind comparison of different doses of intravenous immunoglobulin for prevention of graft-versus-host disease and infection after allogeneic bone marrow transplantation. Bone Marrow Transplant 2001;28(2):187–96.

Medical condition	Idiopathic (autoimmune) thrombocytopenic purpura (ITP) – in children 15 years and younger
Indication for IVIg use	ITP with platelet count <30×10^9/L with significant bleeding.
Level of evidence	Clear evidence of benefit (Category 1).
Description and diagnostic criteria	Idiopathic (autoimmune) thrombocytopenic purpura is a reduction in platelet count (thrombocytopenia) resulting from shortened platelet survival due to anti-platelet antibodies. When counts are very low (<30×10^9/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.

Medical condition	Idiopathic (autoimmune) thrombocytopenic purpura (ITP) – in children 15 years and younger
Justification for evidence category	Category 1 classification in 2004 Biotext review was based on four low–moderate quality RCTs. The 2005 review identified a good quality systematic review/meta-analysis of RCTs to support the category 1 classification.
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 <30×10^9/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 (<30×10^9/L) with moderate to severe bleeding symptoms where other therapeutic options have failed or are contraindicated; OR 3. In responsive patients given prior to surgery to elevate the platelet count to haemostatically safe levels.
Exclusion criteria for IVIg therapy	1. Platelet count >30×10^9/L. 2. Absence of significant bleeding.

EMERGING THERAPEUTIC ROLE

6

Medical condition	Idiopathic (autoimmune) thrombocytopenic purpura (ITP) – in children 15 years and younger
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.
Data items to be collected for monitoring effectiveness of IVIg use	**Note**: The system for collecting outcomes data is presently under development. Reportable data for monitoring the effectiveness of IVIg therapy will be detailed in the next edition.
Dose	**Acute ITP:** **Life threatening bleeding**: up to 2g/kg total dose, generally given as 2 doses of 1g/kg. **Other indications**: 0.5g/kg given as a single dose, repeated at 24–48 hr if the response is inadequate. 5–10% of cases may require a higher total dose of 2g/kg. Duration of response to initial dose is typically 2–4 weeks. A repeat dose may be considered if recurrent symptomatic thrombocytopenia occurs. **Chronic ITP:** **Life threatening bleeding**: Up to 2g/kg total dose, generally given as 2 doses of 1g/kg. **Other indications**: 0.5 to 1g/kg at intervals generally ›3 weekly. **Dosing above 1g/kg per day is contraindicated for some IVIg products. Refer to the current product information sheet for further information.**

Bibliography

Beck CE, Nathan PC, Parkin PC, et al. Corticosteroids versus intravenous immune globulin for the treatment of acute immune thrombocytopenic purpura in children: a systematic review and meta-analysis of randomized controlled trials. J Pediatr. 2005;147(4):521–7.

Bierling P, Godeau B. Intravenous immunoglobulin for autoimmune thrombocytopenic purpura. Hum Immunol 2005;66(4):387-94.

Biotext. A systematic literature review and report on the efficacy of intravenous immunoglobulin therapy and its risks. Appendix 2 – Summary data on conditions and papers. [online]. Commissioned by the National Blood Authority on behalf of all Australian Governments; 2004 [cited 7 Dec 2007]. Available from: http://www.nba.gov.au/pubs.htm

British Society for Haematology General Haematology Task Force. Guidelines for the investigation and management of idiopathic thrombocytopenic purpura in adults, children and in pregnancy. Br J Haematol 2003;120(4):574–96.

Frommer M, Madronio C. The use of intravenous immunoglobulin in Australia. A report for the National Blood Authority, Part B: systematic literature review, 2006. Sydney Health Projects Group, University of Sydney, 2006, p. 11–12.

George JN, Woolf SH, Raskob GE, et al. Idiopathic thrombocytopenic purpura: a practice guideline developed by explicit methods for The American Society of Haematology. Blood 1996;88(1):3–40.

Warrier I, Bussel JB, Valdez L, et al. Safety and efficacy of low dose intravenous immune globulin treatment for infants and children with immune thrombocytopenic purpura. J Pediatr Hematol Oncol 1997;19(3):197–201.

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 IgMκ 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 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 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). In 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 (SHPG, 2005).
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 3–6 months (3–6 courses) before determining whether the patient has responded. If there is no benefit after 3–6 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 (ADLs) or quantitative muscle scores or 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.
Data items to be collected for monitoring effectiveness of IVIg use	**Note**: The system for collecting outcomes data is presently under development. Reportable data for monitoring the effectiveness of IVIg therapy will be detailed in the next edition.
Dose	**Induction**: 2g/kg in 2–5 divided doses. **Maintenance**: 0.4–1g/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.**

Bibliography

Biotext. A systematic literature review and report on the efficacy of intravenous immunoglobulin therapy and its risks. Appendix 2 – Summary data on conditions and papers. [online]. Commissioned by the National Blood Authority on behalf of all Australian Governments; 2004 [cited 7 Dec 2007]:151–154. Available from: http://www.nba.gov.au/pubs.htm

Comi G, Roveri L, Swan A, et al. A randomised controlled trial of intravenous immunoglobulin in IgM paraprotein associated demyelinating neuropathy. J Neurol 2002;249(10):1370–7.

Dalakas MC, Quarles RH, Farrer RG, et al. A controlled study of intravenous immunoglobulin in demyelinating neuropathy with IgM gammopathy. Ann Neurol 1996;40(5):792–5.

Frommer M, Madronio C. The use of intravenous immunoglobulin in Australia. A report for the National Blood Authority, Part B: systematic literature review, 2006. Sydney Health Projects Group, University of Sydney, 2006, p. 40–1.

European Federation of Neurological Societies; Peripheral Nerve Society, Hadden RD, Nobile-Orazio E, et al. European Federation of Neurological Societies/Peripheral Nerve Society guideline on management of paraproteinaemic demyelinating neuropathies: report of a joint task force of the European Federation of Neurological Societies and the Peripheral Nerve Society. Eur J Neurol. 2006;13(8):809–18.

Lunn, MPT, Nobile-Orazio E. Immunotherapy for IgM anti-Myelin-Associated Glycoprotein paraprotein-associated peripheral neuropathies (Cochrane Review). In: The Cochrane Library, Issue 2, 2006. Chichester, UK. John Wiley & Sons, Ltd.

Mariette X, Chastang C, Clavelou P, et al. A randomised clinical trial comparing interferon-alpha and intravenous immunoglobulin in polyneuropathy associated with monoclonal IgM. The IgM-associated Polyneuropathy Study Group. J Neurol Neurosurg Psychiatry 1997;63(1):28–34.

Medical condition	Kidney transplantation
Indication for IVIg use	**Pre-transplantation**: Patients in whom an antibody or antibodies prevent transplantation (donor specific anti-HLA antibody/ies or anti-blood group antibody). **Post-transplantation**: a. To treat steroid-resistant acute rejection which may be cellular or antibody mediated. b. 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 between 15 and 30% of renal transplants and is responsive to steroids in over 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 to 10% of renal transplants that have been performed with a compatible cross match. Prior to the use of IVIg and plasma exchange, AbMR failed to respond adequately to therapy in the majority of cases. Additionally, complications from therapy were severe and sometimes fatal. AbMR responds to IVIg with or without plasma exchange in over 85% of patients.
Justification for evidence category	A randomised, double blind, placebo-controlled clinical trial involved adult patients with end stage renal disease (ESRD) who were highly sensitised to HLA antigens. They were followed for two years after transplant. The authors concluded that IVIg is better than placebo in reducing anti-HLA antibody levels in highly sensitised patients with ESRD and that transplant rates are improved with IVIg therapy (NIH IG02 Trial J Am Soc Nephrol 15:3256–62, 2004; SHPG review, 2005). Multiple case series in the literature indicating efficacy in (acute) antibody mediated rejection, and recommended by a consensus conference (Takemoto *et al* 2004). Jordan *et al* combined data from 7 renal transplant recipients and 3 heart transplant recipients with steroid-resistant combined antibody-mediated and cellular rejection. All patients in this series were successfully treated with high-dose IVIg (Jordan *et al*, Transplantation 1998; 66:800–5).

Medical condition	Kidney transplantation
Justification for evidence category (continued)	A small randomised clinical trial 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*, Biotext review, 2004).
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.

Medical condition	Kidney transplantation
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.
Data items to be collected for monitoring effectiveness of IVIg use	**Note**: The system for collecting outcomes data is presently under development. Reportable data for monitoring the effectiveness of IVIg therapy will be detailed in the next edition.
Dose	**IVIg with plasma exchange**: 0.1 to 0.5g/kg post exchange. **IVIg alone**: 2g/kg to a maximum of 140g as a single dose or 2 to 3.5 g/kg in divided dose. When IVIg is used alone, further doses may be warranted 2 to 4 weeks after initial therapy depending on clinical response and/or biopsy findings. **Dosing above 1g/kg per day is contraindicated for some IVIg products. Refer to the current product information sheet for further information.**

Bibliography

Ahsan N, Shah KV. Polyomaviruses: an overview. Graft 2002;5:S9–S18

Biotext. A systematic literature review and report on the efficacy of intravenous immunoglobulin therapy and its risks. Appendix 2 – Summary data on conditions and papers. [online]. Commissioned by the National Blood Authority on behalf of all Australian Governments; 2004 [cited 7 Dec 2007]:86–7. Available from: http://www.nba.gov.au/pubs.htm

Casadei DH, del C Rial M, Opelz G, et al. A randomised and prospective study comparing treatment with high-dose intravenous immunoglobulin with monoclonal antibodies for rescue of kidney grafts with steroid-resistant rejection. Transplantation 2001;71(1):53-8

Conti DJ, Freed BM, Gruber SA, et al. Prophylaxis of primary cytomegalovirus disease in renal transplant recipients. A trial of gancyclovir vs. immunoglobulin. Arch Surg 1994;129(4):443–7.

Frommer M, Madronio C. The use of intravenous immunoglobulin in Australia. A report for the National Blood Authority, Part B: systematic literature review, 2006. Sydney Health Projects Group, University of Sydney, 2006, p. 18–20.

Jordan SC, Vo A, Bunnapradist S, et al. Intravenous immune globulin treatment inhibits cross match positivity and allows for successful transplantation of incompatible organs in living-donor and cadaver recipients. Transplantation 2003;76(4):631–6.

Jordan SC, Tyan D, Stablein D, et al. Evaluation of Intravenous Immunoglobulin as an Agent to Lower Allosensitisation and Improve Transplantation in Highly Sensitized Adult Patients with End-Stage Renal Disease: Report of the NIH IG02 Trial J Am Soc Nephrol 2004;15(12):3256–62.

Jordan SC, Vo AA, Tyan D, et al. Current approaches to treatment of antibody-mediated rejection. Pediatr Transplant 2005;9(3):408–15.

Lian M, Chan W, Slavin M, et al. Miliary tuberculosis in a Caucasian male transplant recipient and the role of intravenous immunoglobulin as an immunosuppressive sparing agent. Nephrology (Carlton) 2006;11(2):156–8.

Luke PP, Scantlebury VP, Jordan ML, et al. Reversal of steroid- and anti-lymphocyte antibody-resistant rejection using intravenous immunoglobulin (IVIg) in renal transplant recipients. Transplantation 2001;72(3):419–22.

Moger V, Ravishankar M, Sakhuja V, et al. Intravenous immunoglobulin: a safe option for treatment of steroid-resistant rejection in the presence of infection. Transplantation 2004;77(9):1455–6.

Orange JS, Hossny EM, Weiler CR, et al. Use of intravenous immunoglobulin in human disease: A review of primary evidence by members of the Primary Immunodeficiency Committee of the American Academy of Allergy, Asthma and Immunology. J Allergy Clin Immunol 2006;117(4): S525–53.

Peraldi MN, Akposso K, Haymann JP et al. Long-term benefit of intravenous immunoglobulins in cadaveric kidney retransplantation. Transplantation 1996; 62(11):1670–3.

Puliyanda D, Radha RK, Amet N, et al. IVIg contains antibodies reactive with polyoma BK virus and may represent a therapeutic option for BK nephropathy. Am J Transplant 2003;3(Suppl 4):393.

Sonnenday CJ, Warren DS, Cooper MC, et al. Plasmapheresis, CMV hyperimmune globulin, and anti-CD20 allow ABO-incompatible renal transplantation without splenectomy. Am J Transplant 2004;4:1315–22.

Takemoto SK, Zeevi A, Feng S, et al. National conference to assess antibody-mediated rejection in solid organ transplantation. Am J Transplant 2004;4(7):1033–41

Tydén G, Kumlien G, Genberg H, et al. ABO incompatible kidney transplantations without splenectomy, using antigen-specific immunoadsorption and rituximab. Am J transplant 2005;5(1):145–8.

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

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 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 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 SHPG update included eight high-quality RCTs and one medium quality double-blinded controlled trial with a total of 708 patients. These studies suggest 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 2 years appeared to reduce annual exacerbation rates in patients with RRMS and SPMS, but its effect on long-term disability is unclear.

Medical condition	Multiple sclerosis (MS)
Qualifying criteria for IVIg therapy	Clinically definite RRMS as defined by McDonald 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 (EDSS)
	  • MS Functional Scores
	  • Other functional measures.

Medical condition	Multiple sclerosis (MS)
Data items to be collected for monitoring effectiveness of IVIg use	**Note**: The system for collecting outcomes data is presently under development. Reportable data for monitoring the effectiveness of IVIg therapy will be detailed in the next edition.
Dose	**Induction**: 1–2g/kg in 2 to 5 divided doses. **Maintenance dose for indications 1 and 2 above**: 0.4–1g/kg 4 to 6 weekly. Aim for **minimum dose** to maintain optimal functional status. **Refer to the current product information sheet for further information.**

Bibliography

Achiron A, Kishner I, Sarova-Pinhas I, et al. Intravenous immunoglobulin treatment following the first demyelinating event suggestive of multiple sclerosis: a randomized, double-blind, placebo-controlled trial. Arch Neurol 2004;61(10):1515–20.

Association of British Neurologists. Guidelines for the use of intravenous immunoglobulin in neurological diseases [online]. London: The Association; 2005 [cited 7 Dec 2007]. Available from: http://www.theabn.org/documents/IVIg-Guidelines-2005.pdf

Barak Y, Gabbay U, Gilad R, et al. Neuropsychiatric assessment as a secondary outcome measure in a multiple sclerosis intravenous immunoglobulin trial. Int J Psychiatr Clin Practice 1999;3(1):31–4.

Deisenhammer F, Fazekas F, Strasser-Fuchs S, et al. Intravenous immunoglobulins in multiple sclerosis: Results of the Austrian Immunoglobulin in Multiple Sclerosis (AIMS) trial. Infusionstherapie und Transfusionsmedizin 1999;26:42–7.

Fazekas F, Sorensen PS, Filippi M, et al. MRI results from the European Study on Intravenous Immunoglobulin in Secondary Progressive Multiple Sclerosis (ESIMS). Mult Scler 2005;11(4):433–40.

Filippi M, Rocca MA, Pagani E, et al. European study on intravenous immunoglobulin in multiple sclerosis: results of magnetization transfer magnetic resonance imaging analysis. Arch Neurol 2004;61(9):1409-12.

Goodin, DS, Frohman EM, Garmany GP, et al. Disease modifying therapies in multiple sclerosis: Subcommittee of the American Academy of Neurology and the MS Council for Clinical Practice Guidelines. Neurology 2002;58:169–78

Gray OM, McDonnell GV, Forbes RB. Intravenous Immunoglobulins for Multiple Sclerosis (Cochrane Review). In: The Cochrane Library, Issue 2, 2004. Chichester, UK. John Wiley & Sons, Ltd.

Lewanska M, Siger-Zajdel M, Selmaj K. No difference in efficacy of two different doses of intravenous immunoglobulins in MS: clinical and MRI assessment. Eur J Neurol 2002;9(6):565–72.

McDonald WI, Compston A, Edan G, et al. Recommended diagnostic criteria for multiple sclerosis: guidelines from the International Panel on the diagnosis of multiple sclerosis. Ann Neurol 2001;50(1):121–7.

Noseworthy JH, O'Brien PC, Weinshenker BG, et al. IV immunoglobulin does not reverse established weakness in MS. Neurology 2000;55(8):1135–43.

Orange JS, Hossny EM, Weiler CR, et al. Use of intravenous immunoglobulin in human disease: A review of primary evidence by members of the Primary Immunodeficiency Committee of the American Academy of Allergy, Asthma and Immunology. J Allergy Clin Immunol 2006;117(4): S525–53.

Oztekin N, Oztekin MF. Intravenous immunoglobulin treatment in relapsing-remitting multiple sclerosis: a double blind cross over study. Mult Scler 1998;4:391.

Roed HG, Langkilde A, Sellebjerg F, et al. A double-blind randomised trial of IV immunoglobulin treatment in acute optic neuritis. Neurology 2005;64:804–10.

Sacher RA, and the IVIg Advisory Panel. Intravenous immunoglobulin consensus statement. J Allergy Clin Immunol 2001;108(4):S139–46.

Soelberg-Sorebsen P, Wanscher B, Schreiber K, et al. Effect of intravenous immunoglobulin on gadolinium enhancing lesions on MRI in multiple sclerosis (MS): final results of a double-blind cross-over trial. Mult Scler 1997;3 Suppl:268.

Soelberg Sorensen P, Haas J, Sellebjerg F, et al. IV immunoglobulins as add-on treatment to methylprednisolone for acute relapses in MS. Neurology 2004;63(11):2008–33.

Sorensen PS, Fazekas F, Lee M. Intravenous immunoglobulin G for the treatment of relapsing-remitting multiple sclerosis: a meta-analysis. Eur J Neurol 2002;9(6):557–63.

Stangel M, Boegner F, Klatt CH, et al. Placebo controlled pilot trial to study the remyelinating potential of intravenous immunoglobulins in multiple sclerosis. J Neurol Neurosurg Psychiatry 2000;68(1):89–92.

Strasser-Fuchs S, Fazekas F, Deisenhammer F, et al. The Austrian Immunoglobulin in MS (AIMS) study: final analysis. Mult Scler 2000;6 Suppl 2:S9–13.

Visser, LH, Beekman R, Tijssen CC, et al. A randomized, double-blind, placebo-controlled pilot study of i.v. immune globulins in combination with IV methylprednisolone in the treatment of relapses in patients with MS. Mult Scler 2004;10(1):89–91.

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	An expert 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 ACTH 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.
Data items to be collected for monitoring effectiveness of IVIg use	**Note**: The system for collecting outcomes data is presently under development. Reportable data for monitoring the effectiveness of IVIg therapy will be detailed in the next edition.
Dose	**Induction**: 1–2g/kg in 2 to 5 divided doses. **Maintenance**: 0.4–1g/kg 4 to 6 weekly. Aim for **minimum dose** to maintain optimal functional status. **Refer to the current product information sheet for further information.**

Bibliography

Glatz K, Meinck HM, Wildemann B. Para-infectious opsoclonus-myoclonus syndrome: high dose intravenous immunoglobulins are effective. J Neurol Neurosurg Psychiatry 2003;74(2):279–80.

Kornberg AJ, for the Asia-Pacific IVIg Advisory Board. Bringing consensus to the use of IVIg in neurology. Expert consensus statements on the use of IVIg in neurology. 1st ed. Asia-Pacific IVIg Advisory Board, Melbourne, 2004, p80–82.

National Institute of Neurological Disorders. NINDS Opsoclonus Myoclonus Information Page. [online] Last updated January 2006 [cited 7 Dec 2007]. Available from: http://www.ninds.nih.gov/disorders/opsoclonus_myoclonus/opsoclonus_myoclonus.htm

Medical condition	Pemphigus foliaceus (PF)
Indication for IVIg use	Pemphigus foliaceus 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 (sub corneal) layers of the epidermis. The lesions are generally well demarcated and do not coalesce to form large eroded areas (as seen in PV). 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.

Medical condition	Pemphigus foliaceus (PF)
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 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 6 months. Improvement to be demonstrated for continuation of supply. • Clinical progression: Treatment is stopped when patients are clinically free of disease and have a negative finding on direct immunofluorescence. • Autoantibody titres reflect the response to systemic therapy.
Data items to be collected for monitoring effectiveness of IVIg use	**Note**: The system for collecting outcomes data is presently under development. Reportable data for monitoring the effectiveness of IVIg therapy will be detailed in the next edition.
Dose	Efficacy demonstrated with doses of at least 2g/kg per monthly treatment cycle. **Dosing above 1g/kg per day is contraindicated for some IVIg products. Refer to the current product information sheet for further information.**

Bibliography

Sami N, Bhol KC, Razzaque A. Influence of IVIg therapy on autoantibody titres to desmoglein 1 in patients with pemphigus foliaceus. Clin Immunol 2002;105(2):192–8.

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 5 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, 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 modality 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 6 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.
Data items to be collected for monitoring effectiveness of IVIg use	**Note**: The system for collecting outcomes data is presently under development. Reportable data for monitoring the effectiveness of IVIg therapy will be detailed in the next edition.

Medical condition	Pemphigus vulgaris (PV)
Dose	Efficacy demonstrated with doses of at least 2g/kg per monthly treatment cycle. Dosing above 1g/kg per day is contraindicated for some IVIg products. Refer to the product information. **Dosing above 1g/kg per day is contraindicated for some IVIg products. Refer to the current product information sheet for further information.**

Bibliography

Biotext. A systematic literature review and report on the efficacy of intravenous immunoglobulin therapy and its risks. Appendix 2 – Summary data on conditions and papers. [online]. Commissioned by the National Blood Authority on behalf of all Australian Governments; 2004 [cited 7 Dec 2007]:240–1. Available from:http://www.nba.gov.au/pubs.htm

Bystryn JC, Jiao D, Natow S. Treatment of pemphigus with intravenous immunoglobulin. J Am Acad Dermatol 2002;47(3):358–63.

Sami N, Oureshi A, Ruocco E, et al. Corticosteroid-sparing effect of intravenous immunoglobulin therapy in patients with pemphigus vulgaris. Arch Dermatol 2002;138:1158–62

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 ARCBS for more information.
Justification for evidence category	The paper by Mueller-Eckhardt and Kiefel 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 52–180g. 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.
Data items to be collected for monitoring effectiveness of IVIg use	**Note**: The system for collecting outcomes data is presently under development. Reportable data for monitoring the effectiveness of IVIg therapy will be detailed in the next edition.
Dose	1g/kg as a total dose, repeated if necessary. **Refer to the current product information sheet for further information.**

Bibliography

Gonzalez CE, Pengetze YM. Post-transfusion purpura. Curr Haematol Rep 2005;4(2):154–9.

Mueller-Eckhardt C, Kiefel V. High-dose IgG for post-transfusion purpura - revisited. Blut 1988;57(4):163–7

Medical condition	Toxic epidermal necrolysis (TEN, Lyell's 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	Toxic epidermal necrolysis (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. 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	One small cohort study (20 patients) without a control group found that there appeared to be no significant effect and that death rate seems to be higher than previously reported (Biotext review, 2004). One small randomised study (4 patients) with a control group of 2 (supportive care only) 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 (SHPG, 2005).

Medical condition	Toxic epidermal necrolysis (TEN, Lyell's syndrome) Stevens Johnson syndrome (SJS)
Qualifying criteria for IVIg therapy	TEN or SJS/TEN overlap with ALL of 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. • ADRAC should be notified of the inciting medication.
Exclusion criteria for IVIg therapy	SJS alone
Data items to be collected for monitoring effectiveness of IVIg use	**Note**: The system for collecting outcomes data is presently under development. Reportable data for monitoring the effectiveness of IVIg therapy will be detailed in the next edition.
Dose	2g/kg, preferably as a single dose, or divided over 3 consecutive days. **Dosing above 1g/kg per day is contraindicated for some IVIg products. Refer to the current product information sheet for further information.**

Bibliography

Bachot N, Revuz J, Roujeau JC. Intravenous immunoglobulin treatment for Stevens-Johnson syndrome and toxic epidermal necrolysis: a prospective non-comparative study showing no benefit on mortality or progression. [comment]. Arch Dermatol 2003; 139(1):85–6.

Biotext. A systematic literature review and report on the efficacy of intravenous immunoglobulin therapy and its risks. Appendix 2 – Summary data on conditions and papers. [online]. Commissioned by the National Blood Authority on behalf of all Australian Governments; 2004 [cited 7 Dec 2007]:242–7. Available from:http://www.nba.gov.au/pubs.htm

Campione E, Marulli GC, Carrozzo AM, et al. High-dose intravenous immunoglobulin for severe drug reactions: efficacy in toxic epidermal necrolysis. Acta Derm Venereol 2003;83(6):430–2.

Frommer M, Madronio C. The use of intravenous immunoglobulin in Australia. A report for the National Blood Authority, Part B: systematic literature review, 2006. Sydney Health Projects Group, University of Sydney, 2006, p. 55–6.

Paquet P, Jacob E, Damas P, et al. Analytical quantification of the inflammatory cell infiltrate and CD95R expression during treatment of drug-induced toxic epidermal necrolysis. Arch Dermatol Res 2005;297(6):266–73.

Prins C, Vittorio C, Padilla RS, et al. Effect of high-dose intravenous immunoglobulin therapy in Stevens-Johnson syndrome: a retrospective, multicentre study. Dermatology 2003; 207(1):96–9.

Trent J, Halem M, French LE, et al. Toxic epidermal necrolysis and intravenous immunoglobulin: a review. Semin Cutan Med Surg 2006;25(2):91–93.

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 (*Strep. pyogenes*) isolated from: (IA) a normally sterile site (e.g. blood, CSF, 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 $\leq 100 \times 10^9$/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)
Description and diagnostic criteria (continued)	**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 1–2 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 $\leq 100 \times 10^9$/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)
Description and diagnostic criteria (continued)	**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 a randomised controlled trial, which was terminated prematurely (Darenberg *et al*, 2003) suggest that IVIg improves outcomes. **Staphylococcal TSS**: *In vitro* and animal studies suggest 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.
Data items to be collected for monitoring effectiveness of IVIg use	**Note**: The system for collecting outcomes data is presently under development. Reportable data for monitoring the effectiveness of IVIg therapy will be detailed in the next edition.

Medical condition	Toxic shock syndrome (TSS)
Dose	2g/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. 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 1g/kg per day is contraindicated for some IVIg products. Refer to the current product information sheet for further information.**

Bibliography

Darenberg J, Ihendyane N, Sjoelin J, et al. Intravenous immunoglobulin G therapy for streptococcal toxic shock syndrome: a European randomised double-blind placebo-controlled trial. Clin Infect Dis 2003;37:333–40.

Darenberg J, Söderquist B, Normark BH, et al. Differences in potency of intravenous polyspecific immunoglobulin G against streptococcal and staphylococcal superantigens; implications for therapy of toxic shock syndrome. Clin Infect Dis 2004;38:836–42.

Kaul R, McGeer A, Norrby-Teglund A, et al. Intravenous immunoglobulin therapy for streptococcal toxic shock syndrome – a comparative observational study. Clin Infect Dis 1999;28:800–7.

Norrby-Teglund A, Muller MP, McGeer A, et al. Successful management of severe group A streptococcal soft tissue infections using an aggressive medical regimen including intravenous polyspecific immunoglobulin together with a conservative surgical approach. Scand J Infect Dis 2005;37(3):166–72.

Schlievert PM. Use of intravenous immunoglobulin in the treatment of staphylococcal and streptococcal toxic shock syndromes and related illnesses. J Allergy Clin Immunol 2001;108(4 Suppl):S107–10

Schrage B, Duan G, Yang LP, et al. Different preparations of intravenous immunoglobulin vary in their efficacy to neutralise streptococcal superantigens: implications for treatment of streptococcal toxic shock syndrome. Clin Infect Dis 2006;43(6):743–6.

Stevens DL. Rationale for the use of intravenous gamma globulin in the treatment of streptococcal toxic shock syndrome. Clin Infect Dis 1998;26(3):639–41

Working Group on Severe Streptococcal Infections: Defining the Group A Streptococcal toxic shock syndrome: rationale and consensus definition. J Am Med Assoc 1993;269:390–401.

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 attract IVIg use, either because there are safe and effective alternative therapies, or because the evidence of benefit does not justify use in the majority of 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 (for example, the treatment of acute leukemia in children and HIV in children).

Requests for IVIg should only occur:

i. when the situation is urgent or life threatening; or
ii. 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 (e.g. there is demonstrable improvement). The collection of effectiveness data for these conditions will be of particular importance to inform future revisions of this document.

Table 7: 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 current product information for further information**	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 current product information for further information** **Reference**: Orange JS, Hossny EM, Weiler CR, et al. 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. J Allergy Clin Immunol 2006;117(4):S525–53.	2a
Sepsis in neonates A meta-analysis of trials found a 6-fold decrease in mortality when IVIg was added to conventional therapies in the treatment of neonatal sepsis. This benefit was far greater than that derived from the prophylactic use of IVIg in preventing neonatal sepsis. **Refer to current product information for further information** **Reference**: Orange JS, Hossny EM, Weiler CR, et al. 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. J Allergy Clin Immunol 2006;117(4):S525–53.	2a

Table 8: Conditions for which IVIg is used as 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 current product information for further information** **References**: Buyon JP, Kim MY, Copel JA, et al.Anti-Ro/SSA antibodies and congenital heart block: necessary but not sufficient. Arthritis Rheum 2001; 44(8):1723-7. Kaaja R, Julkunen H. Prevention of recurrence of congenital heart block with intravenous immunoglobulin and corticosteroid therapy: comment on the editorial by Buyon et al. Arthritis Rheum. 2003 48(1):280-1. Tran HB, Cavill D, Buyon JP, et al. Intravenous immunoglobulin and placental transport of anti-Ro/La antibodies: comment on the letter by Kaaja and Julkunen. Arthritis Rheum 2004;50(1):337-8. Villain E, Coastedoat-Chalumeau N, Marijon E, et al. Presentation and prognosis of complete atrioventricular block in childhood, according to maternal antibody status. J Am Coll Cardiol. 2006; 48(8):1682-7. Wong JP, Kwek KY, Tan JY, et al. Fetal congenital complete heart block: prophylaxis with intravenous gammaglobulin and treatment with dexamethasone. Aust N Z J Obstet Gynaecol 2001;41(3):339-41.	4a
Autoimmune diabetic neuropathy A RCT of IVIg vs. corticosteroids vs. placebo is understood to be in progress but results are not yet available. However, use of steroids in this patient group can be very difficult. IVIg may be indicated in specific circumstances when steroids are not tolerated or not effective in managing the neuropathy. **Refer to current product information for further information**	4a

Condition	Level of evidence
Autoimmune neutropenia 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 current product information for further information** **Reference**: Anderson D, Ali K, Blanchette V, et al. Guidelines on the use of intravenous immune globulin for hematologic conditions. Transfus Med Rev 2007;21(2 Suppl 1):S9–56.	4a
Autoimmune uveitis 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 1.5g/kg/month for 3 months, with further maintenance dependent upon evidence of significant improvement in visual acuity and ocular inflammation. **Dosing above 1g/kg per day is contraindicated for some IVIg products. Refer to the current product information for further information.**	4a

Condition	Level of evidence
References: Orange JS, Hossny EM, Weiler CR, et al. 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. J Allergy Clin Immunol 2006;117(4):S525–53. Rosenbaum JT, George RK, Gordon C. The treatment of refractory uveitis with intravenous immunoglobulin. Am J Ophthalmol 1999;127(5):545–9. Lim LL, Suhler EB, Smith JR. Biologic therapies for inflammatory eye disease. Clin Exp Ophthalmology, 2006;34:365–374.	
Catastrophic antiphospholipid syndrome IVIg is appropriate therapy for the well-defined situation of catastrophic antiphospholipid syndrome. It is not indicated for the treatment of antiphospholipid syndrome in most other cases. **Refer to current product information for further information** **References**: Cervera R, Asherson RA, Font J. Catastrophic antiphospholipid syndrome. Rheum Dis Clin North Am 2006;32(3):575–90. Erkan D. Therapeutic and prognostic considerations in catastrophic antiphospholipid syndrome. Autoimmun Rev 2006 Dec;6(2):98–103.	4a

Condition	Level of evidence
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 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 Malmö protocol for immune tolerance induction. 2. Autoimmune acquired von Willebrand syndrome (AVWS) – correction of FVIII and von Willebrand factor (VWF) levels for the management of bleeding and prior to 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 0.4g/kg for 5 days or 1g/kg for 2 days. Continued therapy 1g/kg once every 3 to 4 weeks.	2a

Condition	Level of evidence
3. Acquired haemophilia A for: a. support of correction of FVIII level for the management of bleeding and prior to invasive procedures in individuals in whom steroid or immunosuppressive therapy is contraindicated or has failed to eradicate the inhibitor (2g/kg over 2 to 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 prior to invasive procedures in cases where other therapeutic approaches have failed or are contraindicated (2g/kg over 2 to 5 days). **Dosing above 1g/kg per day is contraindicated for some IVIg products. Refer to the current product information for further information.** **Reference**: Hay CR, Brown S, Collins PW, et al. The diagnosis and management of factor VIII and IX inhibitors: a guideline from the United Kingdom Haemophilia Centre Doctors Organisation. Br J Haematol 2006;133(6):591–605	

Condition	Level of evidence
Devic disease (neuromyelitis optica) 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 has shown variable benefit in this otherwise devastating disorder. **Refer to current product information for further information** **References**: Lennon VA, Wingerchuk DM, Kryzer TJ, et al. A serum autoantibody marker of neuromyelitis optica: distinction from multiple sclerosis. Lancet 2004;364(9451):2106–12. Lucchinetti CF, Mandler RN, McGavern D, et al. A role for humoral mechanisms in the pathogenesis of Devic's neuromyelitis optica. Brain 2002;125:1450–61. Minagar A, Alexander JS, Fowler MR, et al. Devic disease: clinical course, pathophysiology, and management. Pathophysiology 2002;9(1):33.	4a
Epidermolysis bullosa acquisita IVIg should be considered for severe cases refractory to conventional immunosuppressive therapy. **Refer to current product information for further information**	4a
Epilepsy • Rasmussen syndrome. • Landau-Kleffner syndrome. • Lennox-Gastaut syndrome. IVIg should be considered only in rare childhood cases. **Refer to current product information for further information**	2a

Condition	Level of evidence
Graves ophthalmopathy IVIg may be indicated in select cases. Tagami *et al* 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 current product information for further information** **Reference**: Tagami T, Tanaka K, Sugawa H, et al. High-dose intravenous steroid pulse therapy in thyroid associated ophthalmopathy. Endocr J 1996;43(6):689–99.	2a
Haemolytic disease of the newborn Haemolytic disease of the newborn (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. Kaplan *et al* (1996) identified some factors that may predict response to IVIg. **Refer to current product information for further information** **References**: Gottstein R, Cooke RW. Systematic review of intravenous immunoglobulin in haemolytic disease of the newborn. Arch Dis Child Fetal Neonatal Ed 2003;88(1):F6-10. Kaplan M, Vreman HJ, Hammerman C, et al. Intravenous immune globulin in neonatal ABO isoimmunisation: factors associated with clinical efficacy. Biol Neonate 1996;70:69-72. Miqdad AM, Abdelbasit OB, Shaheed MM, et al. Intravenous immunoglobulin G therapy for significant hyperbilirubinaemia in ABO haemolytic disease of the newborn. J Matern Fetal Neonatal Med 2004;16(3):163-6.	4a

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 current product information for further information** **Reference**: Win N, Madan B, Gale R, et al. Intravenous immunoglobulin given to lymphoma patients with recurrent haemolytic transfusion reactions after transfusion of compatible blood. Hematology 2005;10(5):375-8	4a
Myocarditis in children There is some evidence that IVIg improves cardiac function in children with proven or likely myocarditis. Confirmatory cardiac biopsy or positive viral isolation/PCR at presentation is required. **Refer to current product information for further information** **References**: Drucker NA, Colan SD, Lewis AB, et al. Gamma-globulin treatment of acute myocarditis in the pediatric population. Circulation 1994;89:252-7. Robinson J, Hartling L, Vandermeer B, et al. Intravenous immunoglobulin for presumed viral myocarditis in children and adults (Cochrane Review). In: The Cochrane Library, Issue 1, 2005. Chichester, UK. John Wiley & Sons, Ltd.	4a

Condition	Level of evidence
PANDAS Paediatric autoimmune neuropsychiatric disorder associated with streptococcal infections (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 CNS 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 1-year follow-up. **Refer to current product information for further information** **References**: Singer HS. PANDAS and immunomodulatory therapy. Lancet 1999;354(9185):1137–8 Perlmutter SJ, Leitman SF, Garvey MA, et al. Therapeutic plasma exchange and intravenous immunoglobulin for obsessive-compulsive disorder and tic disorders in childhood. Lancet 1999;354(9185):1153–8.	2a

Condition	Level of evidence
Paraneoplastic neurological syndromes IVIg may be indicated in selected cases where treatment of the underlying disease has not led to an improvement in the neurologic syndrome, where other therapies are contraindicated or have failed, or if the neurologic features warrant urgent intervention. **Refer to current product information for further information** SEE REVISIONS **References**: Darnell RB, Posner JB. Paraneoplastic syndromes involving the nervous system. N Engl J Med 2003;349(16):1543–54 Voltz R. Intravenous immunoglobulin therapy in paraneoplastic neurological syndromes. J Neurol 2006;253(Suppl 5):v33–v38.	4a
Potassium channel antibody-associated encephalopathy Case reports of benefit from various therapies, including IVIg are reviewed by Vincent A et al: Potassium channel antibody-associated encephalopathy: a potentially immunotherapy-responsive form of limbic encephalitis. **Refer to current product information for further information** SEE REVISIONS **References**: Vincent A, Buckley C, Schott JM, et al. Potassium channel antibody-associated encephalopathy: a potentially immunotherapy-responsive form of limbic encephalitis. Brain 2004;127(Pt 3):701–12.	4a

Condition	Level of evidence
Pure red cell aplasia Pure red cell aplasia (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 current product information for further information** **Reference**: Anderson D, Ali K, Blanchette V, et al. Guidelines on the use of intravenous immune globulin for hematologic conditions. Transfus Med Rev 2007;21(2 Suppl 1):S9–56.	4b
Pure white cell aplasia Pure white cell aplasia (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 current product information for further information** **Reference**: Anderson D, Ali K, Blanchette V, et al. Guidelines on the use of intravenous immune globulin for hematologic conditions. Transfus Med Rev 2007;21(2 Suppl 1):S9-56.	4b

Condition	Level of evidence
Scleromyxedema 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 current product information for further information** **References**: Kulczycki A, Nelson M, Eisen A, et al. Scleromyxedema: treatment of cutaneous and systemic manifestations with high-dose intravenous immunoglobulin. Br J Dermatol 2003;149(6):1276-81 Majeski C, Taher M, Grewal P, et al. Combination oral prednisone and intravenous immunoglobulin in the treatment of scleromyxedema. J Cutan Med Surg 2005;9(3):99-104.	4a
Sjogren's syndrome IVIg may be indicated in certain highly selected cases where other treatments have not been effective. **Refer to current product information for further information** **Reference**: Smith A, Jackson M, Wang F, et al. Neutralisation of muscarinic receptor autoantibodies by intravenous immunoglobulin in Sjogren's syndrome. Hum Immunol 2005;66(4):411-6.	4a

Condition	Level of evidence
Solid organ transplantation (other than kidney) IVIg may be indicated in (i) highly sensitised patients awaiting transplantation; (ii) transplant recipients with acute antibody mediated rejection with clinical evidence of graft dysfunction; and (iii) 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, e.g. due to infection such as BK virus. **Refer to current product information for further information** **Reference**: Jordan SC, Vo A, Bunnapradist S, et al. Intravenous immune globulin treatment inhibits cross match positivity and allows for successful transplantation of incompatible organs in living-donor and cadaver recipients. Transplantation 2003;76(4):631–6.	4a
Susac syndrome Susac syndrome is a rare, micro-angiopathic 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: 1–2g/kg/month for one year providing documented clinical improvement. **Dosing above 1g/kg per day is contraindicated for some IVIg products. Refer to the current product information for further information.** Note: Effectiveness of IVIg therapy may be difficult to determine due to the fluctuating course of disease. **References**: Aubart-Cohen F, Klein I, Alexandra J, et al. Long-Term Outcome in Susac Syndrome. Medicine (Baltimore) 2007;86(2):93-102 Fox R, Costello F, Judkins A, et al. Treatment of Susac syndrome with gamma globulin and corticosteroids. J Neurol Sci 2006;251(1-2):17-22.	4a

8

Conditions for which IVIg use is not indicated

8. Conditions for which IVIg use is not indicated

This chapter comprises conditions for which the use of 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.

At the time of writing, clinical trials were proceeding for the use of IVIg in sepsis. The results of these trials may be taken into account in the first review of this document and its recommendations.

Table 9: Conditions for which IVIg use is not indicated

Condition	Level of evidence
Acute optic neuritis IVIg is not recommended in this setting. There is anecdotal evidence for use in Devic's disease but not optic neuritis. **Reference**: HG Roed, A Langkilde, F Sellebjerg, at al. A double-blind randomised trial of intravenous immunoglobulin treatment in acute optic neuritis. Neurol 2005;64:804–10.	2b
Acute rheumatic fever	2b
Adrenoleukodystrophy	4b
Amegakaryocytic thrombocytopenia	4b
Antiphospholipid syndrome (non-obstetric)	4b
Aplastic anaemia/pancytopenia	4b
Asthma	2c
Atopic dermatitis/eczema	2b

Condition	Level of evidence
Autism – young adults	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
Cardiac surgery with bypass – prophylaxis IVIg is not recommended in this setting; preferable alternative treatments available.	2a
Congestive cardiac failure IVIg is not recommended in this setting; preferable alternative treatments 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 nephritis IVIg is not recommended in this setting; preferable alternative treatments available.	2a

Condition	Level of evidence
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
Narcolepsy/cataplexy	4a
Nephrotic syndrome IVIg is not recommended in this setting; preferable alternative treatments available.	2a
Obsessive compulsive disorders IVIg is not recommended in this setting. (See PANDAS)	4a
Paraneoplastic cerebellar degeneration (Yo antibodies)	4b
Polyneuropathy of critical illness	4a
Recurrent foetal loss (with or without antiphospholipid syndrome) **Reference**: Empson M, Lassere M, Craig J, et al. Prevention of recurrent miscarriage for women with antiphospholipid antibody or lupus anticoagulant (Cochrane Review). In: The Cochrane Library, Issue 2, 2005. Chichester, UK. John Wiley & Sons, Ltd.	3
Rheumatoid arthritis IVIg is not recommended in this setting; preferable alternative treatments available.	2c
Sensory neuropathy associated with anti-Hu antibodies	4b

Condition	Level of evidence
Sepsis (other than neonatal – treatment (see page 213)) • **adult** Clinical perspectives vary; while preferable alternative treatments exist for sepsis IVIg is sometimes considered as an adjunct to antibiotics for patients who have septicaemia due to encapsulated bacteria (e.g. Streptococcus pneumoniae) and hypogammaglobulinaemia. To be scrutinised for first revision. • **neonatal – prevention** IVIg not indicated at this time. Despite encouraging trials, there are substantial contradictory data and insufficient overall evidence to support routine administration of IVIg in infants at risk for neonatal infection (Orange *et al.*, 2006). To be scrutinised for first revision. **Reference**: Orange JS, Hossny EM, Weiler CR, et. al. 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. J Allergy Clin Immunol 2006;117(4):S525-53.	2a
• **in nephritic syndrome** IVIg use may be considered under Secondary hypogammaglobulinaemia (including iatrogenic immunodeficiency) in some cases: not for routine use.	
• **paediatric** If IgG levels are low, the use of IVIg should be considered under the PID and Secondary hypogammaglobulinaemia (including iatrogenic immunodeficiency) headings. To be scrutinised for first revision.	
Sickle cell disease	4b
Systemic lupus erythematosus (SLE) IVIg is not recommended in this setting; preferable alternative treatments available.	2a
Ulcerative colitis	4b

Acronyms and abbreviations

AAMR	acute antibody mediated rejection
AASV	ANCA-associated systemic vasculitis
AbMR	antibody mediated rejection
ACD	Australasian College of Dermatologists
AChR	acetylcholine receptor
ACTH	adrenocorticotropic hormone
ADEC	Australian Drug Evaluation Committee
ADL	activities of daily living
ADRAC	Adverse Drug Reactions Advisory Committee
AHCDO	Australian Haemophilia Centre Directors' Organisation
AHMAC	Australian Health Ministers' Advisory Council
AHMC	Australian Health Ministers' Conference
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
ARTG	Australian Register of Therapeutic Goods
ASCIA	Australasian Society of Clinical Immunology and Allergy
AVWS	acquired von Willebrand syndrome
BMT	bone marrow transplant
BP	bullous pemphigoid
BSE	bovine spongiform encephalopathy
BVAS	Birmingham vasculitis activity score
cGMP	code of Good Manufacturing Practice
CHB	congenital heart block

CIDP	chronic inflammatory demyelinating polyneuropathy
CJD	Creutzfeldt Jakob disease
CLL	chronic lymphocytic leukemia
COPD	chronic obstructive pulmonary disease
CP	cicatricial pemphigoid
CRP	C-reactive protein
CSF	cerebrospinal fluid
CSL	CSL Limited
CTEPC	Clinical, Technical & Ethical Principal Committee
CVID	common variable immunodeficiency
DAT	direct anti-globulin test
DM	dermatomyositis
DNA	deoxyribonucleic acid
EDSS	expanded disability status scale
EMEA	European Agency for the Evaluation of Medicinal Products
ESR	erythrocyte sedimentation rate
ESRD	end-stage renal disease
FDA	Food and Drug Administration (US)
FEIBA	Factor Eight Inhibitor Bypassing Activity
FFP	clinical fresh frozen plasma
FIX	factor nine
FMAIT	foeto-maternal alloimmune thrombocytopenia
FVIII	factor eight
g	gram
GBS	Guillain-Barré syndrome
GVHD	graft versus host disease
HAART	highly active anti-retroviral therapy
HBV	hepatitis B virus
HCV	hepatitis C virus

HDN	haemolytic disease of the newborn
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HPA	human platelet antigen
HSANZ	Haematology Society of Australia and New Zealand
HSCT	haemopoietic stem cell transplantation
HTLV	human T-lymphotropic virus
IA	immununoadsorption
IBM	inclusion body myositis
Ig	immunoglobulin(s)
IgG	immunoglobulin G
IMIg	intramuscular immunoglobulin
ITP	immune/idiopathic thrombocytopenia purpura
IV	intravenous
IVF	in-vitro fertilisation
IVIg	intravenous immunoglobulin(s)
JBC	Jurisdictional Blood Committee
JDO	Jurisdictional Direct Order (for imported IVIg)
kg	kilogram
L	litre
LEMS	Lambert-Eaton myasthenic syndrome
LOS	length of stay
MAG	myelin associated glycoprotein
MG	myasthenia gravis
MGUS	monoclonal gammopathy of uncertain significance
MI	myocardial infarction
MM	multiple myeloma
MMN	multi-focal motor neuropathy
MMP	mucous membrane pemphigoid
MRC	Medical Research Council
MRI	magnetic resonance imaging

MS	multiple sclerosis
MPO	myeloperoxidase
n	number
NAIT	neonatal alloimmune thrombocytopenia
NBA	National Blood Authority
NH	neonatal haemochromatosis
NHL	non-Hodgkin's lymphoma
NHMRC	National Health and Medical Research Council
NK	natural killer cell
OMA	opsoclonus myoclonus ataxia
PCR	polymerase chain reaction
PF	pemphigus foliaceus
PM	polymyositis
PID	primary immunodeficiency
PPMS	primary progressive multiple sclerosis
PRA	panel reactive antibodies
PRMS	progressive relapsing multiple sclerosis
PTP	post transfusion purpura
PV	pemphigus vulgaris
®	registered product name
RA	rheumatoid arthritis
RBC	red blood cells
RCPA	Royal College of Pathologists of Australasia
RCT	randomised controlled trial
RhD	Rhesus D
RRMS	relapsing remitting multiple sclerosis
RT	randomised trial
SCID	severe combined immunodeficiency
SCIG	subcutaneous immunoglobulin
SHPG	Sydney Health Projects Group
SJS	Stevens Johnson syndrome

SLE	systemic lupus erythematosus
SPMS	secondary progressive multiple sclerosis
TEN	toxic epidermal necrolysis
TGA	Therapeutic Goods Administration
TSE	transmissible spongiform encephalopathy
TSEAC	Transmissible Spongiform Encephalopathies Advisory Committee
TSS	toxic shock syndrome
vCJD	variant Creutzfeldt Jakob Disease
VWF	von Willebrand factor
WHO	World Health Organisation
WP	working party
XLA	X-linked agammaglobulinaemia

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.
Autologous collection	Blood donation for the donor's own use.
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 certain types of 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	A hereditary or acquired deficiency of clotting factors 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 for an unknown recipient.
Human T-cell lymphotropic virus type 1	A virus associated with adult T-cell leukemia
Hyper immune globulins	Immunoglobulin products prepared from the plasma of donors with high concentrations of specific antibodies.
Immunoglobulins	Proteins that combat infection.
Intramuscular immunoglobulin	An immunoglobulin preparation designed for intramuscular use.
Intravenous immunoglobulin	An immunoglobulin designed for intravenous use.
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 TGA) 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.

General references:

Biotext. A systematic literature review and report on the efficacy of intravenous immunoglobulin therapy and its risks. [online]. Commissioned by the National Blood Authority on behalf of all Australian Governments; 2004 [cited 7 Dec 2007]. Available from: http://www.nba.gov.au/pubs.htm

Blood and Blood Products Committee. 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). Canberra: Blood and Blood Products Committee; June 2000.

Commonwealth of Australia, *National Blood Authority Act 2003*, No 29, 2003. An Act to enhance the management of Australia's bloody supply, and for related purposes. [online]. Canberra: Commonwealth of Australia; 2003 [cited 7 Dec 2007]. Available from: http://www.nba.gov.au/PDF/National%20Blood%20Authority%20Act%202003.pdf

Flood P, Wills P, Lawler P, et al. Review of Australia's Plasma Fractionation Arrangements. [online]. Canberra: Commonwealth of Australia; 2006 [cited 7 Dec 2007]. Available from: http://www.health.gov.au/internet/wcms/publishing.nsf/Content/plasma-fractionation-review-overview.htm

Frommer MS, Madronio C. The use of intravenous immunoglobulin in Australia. A report for the National Blood Authority. Sydney Health Projects Group, University of Sydney; 2006.

National Blood Authority. Intravenous immunoglobulin: development, dissemination and implementation of clinical use guidelines. Discussion paper. Canberra: Commonwealth of Australia; 2005.

National Blood Authority. National Blood Agreement between the Commonwealth of Australia and the States and Territories. [online]. Canberra: Commonwealth of Australia; 2003 [cited 7 Dec 2007]. Available from: http://www.nba.gov.au/about_nba/nba_agreement.htm

National Blood Authority. The supply and use of plasma products in Australia. [online]. Canberra: Commonwealth of Australia; 2006 [cited 7 Dec 2007]. Available from: http://www.nba.gov.au/PDF/supply%20and%20use%20of%20plasma%20products%20publication%20FINAL29%2008%2006.pdf

Orange JS, Hossny EM, Weiler CR, et al. 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. J Allergy Clin Immunol 2006;117(4):S525-53. (Note erratum in: J Allergy Clin Immunol. 2006;117(6):1483 dosage error in text).

BIBLIOGRAPHY

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 Commonwealth 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 funded IVIg for the conditions and uses described in the *Criteria for the Clinical Use of Intravenous Immunoglobulin in Australia* (2007) 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 Agreement is not available for use to treat conditions identified in Chapter 8, which are considered non-indications for IVIg therapy at this time.

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 pages 26–27).

Ongoing review of funded indications

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 the *Criteria for the Clinical Use of Intravenous Immunoglobulin in Australia* (2007), will be regularly reviewed to ensure the qualifying, exclusion, review criteria and indicative dosages for each indication remain, in the light of emerging evidence, appropriate and in keeping with an evidence-based approach.

Appendix B Terms of reference for JBC IVIg Working Party

A. Role

The role of the Working Party is to provide stewardship in the establishment of a framework for the development of national guidelines governing the supply and use of intravenous immunoglobulin (IVIg) in Australia.

B. Specific tasks

- review the report of the AHMAC Blood and Blood Products Committee – *Review of the Use and Supply of Intravenous Immunoglobulins in Australia* (otherwise known as 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.

Appendix C Working party, consultants, clinical advisers and secretariat

Jurisdictional Blood Committee IVIg Working Party

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Executive Director, Rural and Regional Health and Aged Care Services, Victorian Department of Human Services

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Secretariat

Ms Jennifer Roberts	Project Manager
Mr Graham Brown	Project Officer

Appendix D Intravenous immunoglobulin user groups

IVIg user groups have been established in New South Wales, Victoria, Queensland and South Australia. These groups provide advice on their respective States' local distribution and use of IVIg. The organisational relationships of IVIg user groups vary. Some are managed by the respective State ARCBS office, and others are committees of the State health department.

The contact details of the Chair of each user group are shown below.

New South Wales

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Appendix E Currently registered intravenous immunoglobulin products

Table 10 provides a summary of the intravenous immunoglobulin products registered for use in Australia and their registered indications.

Product information is available from the manufacturer's web site.

For Intragam®P, Sandoglobulin® and Sandoglobulin® NF Liquid refer to www.csl.com.au.

For Octagam® refer to www.octapharma.com.

For Gamunex® refer to www.gamunex.com.

Refer to the product information leaflet supplied with each product for information about safety, contraindications, adverse effects and limitations on dosage[8].

8 e.g. Sandoglobulin® NF Liquid has a maximum recommended dose of 1g/kg body weight per day.

Table 10: IVIg products listed on the Australian Register of Therapeutic Goods

	Intragam®P	Sandoglobulin®	Sandoglobulin® NF Liquid	Octagam®	Gamunex®
Sponsor Company	CSL Ltd	CSL Ltd	CSL Ltd	Octapharma	Bayer
Presentation	Solution	Powder	Solution	Solution	Solution
Concentration	6%	3 or 6%	12%	5%	10%
Vial sizes (g)	0.6 (10 mL) 3 (50 mL) 12 (200 mL) 30 (500 mL)	1 3 6 12	6 (50 mL) 12 (100 mL)	1 (20 mL) 2.5 (50 mL) 5 (100 mL) 10 (200 mL)	1 (10 mL) 2.5 (250 mL) 5 (50 mL) 10 (100 mL) 20 (200 mL)
Stabiliser	maltose	sucrose	proline isoleucine nicotinamide	maltose	glycine
Indications:					
Primary Immunodeficiency	√	√	√	√	√
Myeloma, CLL & secondary hypogammaglobulinaemia	√		√	√	
Congenital AIDS & recurrent infections	√		√	√	
Idiopathic Thrombocytopenic Purpura (ITP)	√	√	√	√	√
Allogeneic Bone Marrow Transplantation	√		√	√	
Kawasaki Disease	√		√	√	
Guillain-Barré Syndrome	√		√	√	

Appendix F Methods and contributors

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.

The clinical criteria, presented as a structured pro-forma for each condition of interest, were developed in consultation with specialist clinicians. The criteria were informed by a previous SHPG report commissioned by the NBA in 2005 and the Biotext review commissioned by the NBA in 2004.

In addition to information about clinical criteria, the pro-formas include a definition of each condition and a brief description of its clinical presentation and the main diagnostic parameters.

The clinical criteria

The clinical criteria given in each pro-forma have been set out to cover four major issues:

i. *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.

ii. *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.

iii. *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.

iv. *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.

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.

Targeted development of pro-formas

The JBC IVIg Working Party determined that, in the first instance, pro-formas should be developed for selected priority conditions only. These included the following:

1. All the conditions that together account for approximately 95% of the total national usage of IVIg by volume (2002–06), plus
2. Conditions assigned a 'Category 1' priority for IVIg therapy by AHMAC in 2000; plus
3. Conditions for which the TGA has registered the use of IVIg; plus

4. Conditions for which the Biotext (2004) and SHPG (2005) systematic reviews found high-level evidence for the use of IVIg; plus
5. Any other conditions recommended by consulting specialist clinicians.

As a result, pro-formas were developed for the following 36 priority conditions:

Priority conditions (in descending order of usage by volume, 2002–06)
1. Chronic inflammatory demyelinating polyneuropathy (CIDP)
2. Chronic lymphocytic leukaemia (CLL) with infections due to hypogammaglobulinaemia
3. Common variable immune deficiency (CVID)
4. Idiopathic thrombocytopenic purpura (ITP) – Adult
5. IgG subclass deficiency (now considered as Specific antibody deficiency)
6. Allogeneic stem cell transplantation – infection and graft-versus-host disease
7. Multifocal motor neuropathy (MMN) with persistent conduction block
8. Guillain-Barré syndrome
9. Myasthenia gravis
10. Multiple myeloma
11. Inflammatory myopathies – polymyositis, dermatomyositis and inclusion body myositis
12. Idiopathic thrombocytopenic purpura (ITP) – paediatric
13. Alloimmune thrombocytopenia – antenatal
14. Primary agammaglobulinaemia

Priority conditions (in descending order of usage by volume, 2002–06)
15. Kawasaki disease
16. Solid organ transplantation (heart/lung/pancreas)
17. Autoimmune haemolytic anaemia and Evans syndrome
18. Bullous pemphigoid/pemphigus
19. Stiff person syndrome

Priority conditions, as identified by AHMAC (2000), unless listed above
20. HIV/AIDS: paediatric
21. Acute leukaemia in childhood
22. Post-transfusion purpura
23. IgM paraproteinaemic neuropathy
24. HIV-associated thrombocytopenia
25. Primary immunodeficiency disease (including Wiskott-Aldrich syndrome)
26. Non-Hodgkin's lymphoma (NHL)
27. Vasculitis syndromes: ANCA (PR3 or MPO)-associated idiopathic, rapidly progressing (crescentic) glomerulonephritis, Churg-Strauss syndrome, microscopic polyangiitis and Wegener's granulomatosis
28. Maturational antibody deficiency of infancy with recurrent bacterial infection
29. Neonatal sepsis (now not recommended for IVIg use)
30. Toxic epidermal necrolysis (TEN) and Stevens Johnson syndrome (SJS)
31. Renal transplantation (rejection)

Priority conditions, as identified by AHMAC (2000), unless listed above
32. Renal transplantation (infection)
33. Multiple sclerosis
34. Lambert Eaton myasthenic syndrome
35. Opsoclonus myoclonus ataxia
36. Cicatricial pemphigoid (severe form of bullous pemphigoid)

This list was further refined following written submissions and a clinician workshop on the initial draft document.

Conditions that had been previously listed for consideration in various reviews, e.g. the Biotext review (2004) 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 percent 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.
- The conditions were not identified as high-priority conditions by AHMAC in its 2000 report.

Development of the clinical criteria

Development of the clinical criteria involved the following steps:

a. Draft pro-formas were written, using information from a variety of sources, as described below.
b. The draft pro-formas were reviewed by individual clinical specialists in immunology, neurology, haematology and dermatology. The drafts were amended in the light of their advice.
c. Additional draft pro-formas were prepared for conditions identified as priorities by the clinical specialists.
d. The pro-formas were reviewed by the IVIg Working Party of the Jurisdictional Blood Committee.
e. The pro-formas were further reviewed by small expert panels in immunology, haematology and neurology, and then further amended in the light of their advice.
f. Drafts of the pro-forma 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. Written submissions and the outcomes of the clinician workshop were then considered by the IVIg Working Party and a panel of clinical experts. The pro-forma were then further refined in light of their comments.

Sources of information other than consultations

The pro-formas 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 2006 SHPG paper and systematic review update; and (iii) initial drafts of the criteria for use document..
- Recently published medical textbooks from which some of the material used in defining and describing each condition was derived.
- The Biotext systematic 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 in 2005. This mainly focused on new literature, particularly RCTs, published during 2004–05.
- Recent (2004–2006) clinical guidelines and consensus statements (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'.

Clinical consultations

The selection of conditions for pro-formas and/or the development of the clinical criteria were undertaken in consultation with, or with advice from, the following health professionals:

- Dr Andrea Bendrups (rheumatology)
- Ms Linley Bielby (ARCBS Transfusion Medicine Team)
- Dr Marija Borosak (ARCBS Transfusion Medicine Team)
- Dr Simon Brown (haematology)
- Dr David Burgner (paediatric infectious diseases)
- Associate Professor Steve Chadban (nephrology)
- Dr Shlomo Cohney (nephrology)
- Dr Matthew Cook (immunology)
- Dr James Daly (haematology)
- Dr Diona Damian (dermatology)
- Dr Peta Dennington (ARCBS Transfusion Medicine Team)
- Associate Professor Jo Douglass (immunology and respiratory medicine)
- Professor Henry Ekert (paediatric haematology)
- Clinical Professor Martyn French (immunology)
- Associate Professor John Gibson (haematology)
- Dr David Gillis (immunology)
- Dr David Gottlieb (haematology)
- Clinical Professor Douglas Joshua (haematology)
- Dr Glen Kennedy (haematology)
- Dr Lynette Kiers (neurology)
- Ms Philippa Kirkpatrick (primary immunodeficiencies)
- Associate Professor Andrew Kornberg (paediatric neurology)

- Associate Professor Robert Lindeman (haematology)
- Dr Richard Loh (paediatric immunology)
- Professor Frank Mastaglia (neurology)
- Associate Professor Pamela McCombe (neurology)
- Professor Peter McDonald (heart transplantation)
- Dr Phillip Mondy (ARCBS Transfusion Medicine Team)
- Dr Joanne Pink (ARCBS Transfusion Medicine Team)
- Professor John Pollard (neurology)
- Dr Sean Riminton (immunology)
- Dr Jake Shortt (ARCBS Transfusion Medicine Team)
- Dr Thomas Solano (intensive care)
- Dr Luke Soo (ARCBS Transfusion Medicine Team)
- Dr Judy Spies (neurology)
- Dr Nicole Staples (ARCBS Transfusion Medicine Team)
- Dr Robert Stirling (immunology and respiratory medicine)
- Professor Jeff Szer (bone marrow transplantation)
- Dr Bronwyn Williams (paediatric haematology)
- Dr Melanie Wong (paediatric immunology)
- Dr Erica Wood (ARCBS Transfusion Medicine Team)
- Associate Professor Graham Young (haematology)
- Associate Professor John Ziegler (paediatric immunology).

Specialist clinicians provided advice on: (i) the draft pro-formas, with particular reference to the clinical criteria; (ii) any recent reviews, guidelines or consensus statements (2004–2006) that could contribute to the refinement of clinical criteria; and (iii) additional conditions for which pro-formas should be prepared.

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. RCT-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.

Appendix G Websites for further information

- ACT Department of Health
  www.health.act.gov.au
- Australian Government Department of Health and Ageing
  www.health.gov.au
- Australian Red Cross Blood Service
  www.transfusion.com.au
- CSL Limited
  www.csl.com.au
- National Blood Authority
  www.nba.gov.au
- Northern Territory Department of Health
  www.nt.gov.au/health
- New South Wales Department of Health
  www.health.nsw.gov.au
- Octapharma Australia Pty Ltd
  www.octapharma.com
- Queensland Department of Health
  www.health.qld.gov.au
- South Australian Department of Health
  www.health.sa.gov.au
- Talecris Biotherapeutics
  www.gamunex.com
- Tasmanian Department of Health and Human Services
  www.dhhs.tas.gov.au
- Therapeutic Goods Administration
  www.tga.gov.au
- Victorian Department of Human Services
  www.dhs.vic.gov.au
- Western Australia Department of Health
  www.health.wa.gov.au

Appendix H Guidelines on IVIg treatment in Australia

Guidelines for the clinical use of IVIg in Australia were first developed in 1992.

1992 Guidelines

In response to demand for IVIg outstripping supply, the Australasian Society of Blood Transfusion (ASBT) convened a consensus symposium in 1992 to discuss the indications for the use of IVIg and to formulate a list of recommendations for its use. Evidence for the efficacy of IVIg for each reported indication was assessed based on the reported study type, the findings and the number of people in each particular study. The outcome of the symposium was a set of consensus guidelines (referred to as the 1992 Guidelines) that grouped indications for the use of IVIg into three categories:

- **Category A**: Diseases and situations where the use of IVIg is indicated;
- **Category B**: Potentially severe diseases or situations where IVIg may have a role; and
- **Category C**: Clinical conditions where the evidence for benefit derived from the use of IVIg was either conflicting or anecdotal such that the use of IVIg in those conditions could not be justified.

In spite of these measures, the demand for IVIg became more pressing.

1996 Guidelines

In 1994–95, an annual $8m plasma funding initiative was launched in order to meet national Factor VIII targets. A spin-off of this initiative was that it enabled more IVIg to be produced since Factor VIII and IVIg are derived from different fractions of the plasma.

A further attempt was made to rationalise the use of IVIg in 1996 when a second ASBT Review was carried out. Revised guidelines were drawn up and indications were classified into four categories:

- **Category A**: Proven benefit
- **Category B**: Probable benefit
- **Category C**: Possible benefit
- **Category D**: Unproven benefit

The 1996 Guidelines were not adopted and allocation of IVIg remained in accordance with the 1992 Guidelines.

2000 AHMAC review

Concerns over the adequate supply of IVIg continued. While evidence for the shortage was largely anecdotal, the Australian Health Ministers' Advisory Council (AHMAC) and their Blood and Blood Products Committee initiated a national review of the use and supply of IVIg in Australia.

The review was carried out by a Working Party whose members represented different States, the Commonwealth, CSL Limited, the Australian Red Cross Blood Service, AHMAC, the NSW Department of Health and the Therapeutic Goods Administration. The Working Party was advised and assisted by a Clinical Reference

Group whose members represented the main clinical areas and specialties in which IVIg is used.

Given the variable extent and quality of evidence for IVIg use, successive reviews and guidelines since 1992 have recommended that indications should be categorised according to the quality of the available evidence and whether or not it showed that IVIg was beneficial.

Because of the short time frame of the AHMAC review, a systematic review of the literature about the use and efficacy of IVIg was not feasible. Instead, the Clinical Reference Group selected from available references those it considered the best working papers for each of the indications. These papers were reviewed. Evidence was graded in accordance with the National Health and Medical Research Council guidelines.

The Clinical Reference Group acknowledged that the review was biased in favour of reported studies and that the extent of the bias could not be ascertained.

As in the past, conditions were categorised. However, a new model for categorising the indications/conditions was adopted. This had three categories:

- **Category 1**: Indications for which there is convincing evidence of benefit.
- **Category 2**: Indications for which there is inconclusive evidence of benefit, because of:
  - conflicting evidence
  - low level evidence
  - little research, possibly because the condition is rare

This Category also allowed for special case considerations.

- **Category 3**: Conditions for which there is convincing evidence that IVIg is ineffective.

More than 77 indications were identified. The Clinical Reference Group determined that the published evidence justified the use of IVIg for a small number of these indications, and that for some of the indications, the use of IVIg was only justified under specified conditions.

Evidence for many of the indications was low grade and took the form of open label studies, case series and case reports. The Clinical Reference Group recognised that it was unlikely that randomised, double blind, placebo controlled trials could or would ever be conducted for some of the conditions because of their rarity. This particularly applied to many of the Category 2 conditions. Since a number of these conditions are rare and serious diseases, the Clinical Reference Group considered that they needed to be considered on a case-by-case basis with respect to the provision of IVIg.

Another recommendation of the review Committee was that the indications identified in the various categories undergo regular review (on an annual basis) by a Clinical Reference Group to ensure that the therapeutic use of IVIg is kept current. This recommendation reaffirmed the need for ongoing assessment of IVIg guidelines identified by the ASBT in its earlier work.

2007 criteria for clinical use

A process to review the AHMAC 2000 guidelines commenced in 2004. Over 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 still exist in the evidence base supporting IVIg use.

Because of the nature of conditions for which IVIg is used it is unlikely that these gaps will be filled in the near future. Great potential exists, however, to reduce the uncertainty about indications and variations in IVIg use by the addition of explicit qualifying criteria.

The potential for mandatory data collection as part of the approval process for IVIg supplied under the National Blood Agreement to advance the understanding of efficacy for each indication is also, yet, unrealised. With the application of these clinical criteria and the development of an 'outcome support system' to capture outcome data, Australia is uniquely placed to develop this strategy.

Appendix I Comparison with AHMAC 2000 classification

Table 11 is an alphabetical listing of all conditions considered for IVIg therapy during the compilation of this document. The table enables a comparison of the AHMAC 2000 classification of conditions with the level of evidence of effectiveness identified in this document.

Table 11: Comparison with AHMAC 2000 classification

Condition	AHMAC 2000	Evidence level	Chapter, page
Acquired hypogammaglobulinaemia secondary to haematological malignancies (CLL, MM, NHL & other relevant malignancies & post HSCT)	1 (except NHL)	2a	5, 60
Acute disseminated encephalomyelitis	2	2a	6, 121
Acute leukaemia in children	1	2a	7, 193
Acute optic neuritis	2	2b	8, 208
Acute rheumatic fever	not listed	2b	8, 208
Adrenoleukodystrophy	2	4b	8, 208
Amegakaryocytic thrombocytopenia	not listed	4b	8, 208
ANCA-positive systemic necrotising vasculitis	2	2a	6, 125
Antiphospholipid syndrome – catastrophic	not listed	4a	7, 196

Condition	AHMAC 2000	Evidence level	Chapter, page
Antiphospholipid syndrome – non-obstetric	not listed	4b	8, 208
Aplastic anaemia/pancytopenia	2	4b	8, 208
Asthma	2	2c	8, 208
Atopic dermatitis/eczema	not listed	2b	8, 208
Autism – young adults	2	4b	8, 209
Autoimmune congenital heart block (neonatal lupus)	not listed	4a	7, 194
Autoimmune diabetic neuropathy	2	4a	7, 194
Autoimmune haemolytic anaemia	2	4a	6, 128
Autoimmune neutropenia	2	4a	7, 195
Autoimmune uveitis	not listed	4a	7, 195
Autologous haemopoietic stem cell transplantation	3	2c	8, 209
Bullous pemphigoid	2	4a	6, 131
Cardiac surgery with bypass – prophylaxis	not listed	2a	8, 209
Chronic inflammatory demyelinating polyneuropathy	1	1	5, 68
Cicatricial pemphigoid	2	2a	6, 134

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Condition	AHMAC 2000	Evidence level	Chapter, page
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	2	2a	7, 197
Congestive cardiac failure	not listed	2a	8, 209
Crohn's disease	2	4b	8, 209
Devic disease (neuromyelitis optica)	not listed	4a	7, 199
Diamond Blackfan syndrome	3	4b	8, 209
Epidermolysis bullosa acquisita	not listed	4a	7, 199
Epilepsy – rare childhood cases	2	2a	7, 199
Evans syndrome (includes autoimmune haemolytic anaemia with immune thrombocytopenia)	2	4a	6, 138
Female infertility	not listed	4a	8, 209
Foeto-maternal /neonatal alloimmune thrombocytopenia (FMAIT/NAIT)	not listed	4a	6, 141
Glomerulonephritis – IgA nephritis	not listed	2b	8, 209
Graves ophthalmopathy	2	2a	7, 200
Guillain-Barré syndrome	1	1	5, 72

Condition	AHMAC 2000	Evidence level	Chapter, page
Haemolytic disease of the newborn	2	4a	7, 200
Haemolytic transfusion reaction	2	4a	7, 201
Haemolytic uraemic syndrome	2	4b	8, 209
Haemophagocytic syndrome	2	4a	6, 145
Henoch-Schonlein purpura	2	4b	8, 209
High-risk allogeneic haemopoietic stem cell transplantation (mismatched family or unrelated donor)	1	2c	6, 148
HIV/AIDS – adult	2	2b	8, 209
HIV/AIDS – children	1	2a	7, 193
Idiopathic dilated cardiomyopathy	not listed	2b	8, 209
IgG subclass deficiency	1	-	See p 118
IgM paraproteinaemic neuropathy	1	2c	6, 156
Inflammatory myopathies (PM, DM & IBM)	1	2a	5, 82
ITP – adults	1	2a	5, 76
ITP – child	1	1	6, 152
Kawasaki disease	1	1	5, 87
Kidney transplantation	2	1	6, 160

Condition	AHMAC 2000	Evidence level	Chapter, page
Lambert-Eaton myasthenic syndrome	1	2a	5, 91
Linear IgA disease	not listed	4b	8, 209
Lupus nephritis	not listed	2a	8, 209
Motor neuron disease/ amyotrophic lateral sclerosis	3	4b	8, 210
Multifocal motor neuropathy	1	1	5, 95
Multiple sclerosis	3	2a	6, 166
Myalgic encephalomyelitis	not listed	2c	8, 210
Myasthenia gravis	1	1	5, 100
Myocarditis in children	not listed	4a	7, 201
Narcolepsy/cataplexy	not listed	4a	8, 210
Neonatal haemochromatosis	not listed	2a	5, 104
Nephrotic syndrome	not listed	2a	8, 210
Non Hodgkin's lymphoma (NHL)	not listed	2a	5, 60
Obsessive compulsive disorders	not listed	4a	8, 210
Opsoclonus myoclonus ataxia	2	4a	6, 172
PANDAS	not listed	2a	7, 202
Paraneoplastic cerebellar degeneration (Yo antibodies)	not listed	4b	8, 210
Paraneoplastic neurological syndromes	not listed	4a	7, 203
Pemphigus foliaceus	2	4a	6, 175

Condition	AHMAC 2000	Evidence level	Chapter, page
Pemphigus vulgaris	2	2a	6, 177
Polyneuropathy of critical illness	3	4a	8, 210
Post-transfusion purpura	1	4a	6, 180
Potassium channel antibody-associated encephalopathy	not listed	4a	7, 203
Primary immunodeficiency diseases with antibody deficiency	1	2a	5, 65
Pure red cell aplasia	2	4b	7, 204
Pure white cell aplasia	3	4b	7, 204
Recurrent foetal loss (with or without antiphospholipid syndrome)	not listed	3	8, 210
Rheumatoid arthritis	2	2c	8, 210
Scleromyxedema	not listed	4a	7, 205
Secondary hypogammaglobulinaemia (including iatrogenic immunodeficiency)	not listed	4b	6, 115
Sensory neuropathy associated with anti-Hu antibodies	2	4b	8, 210
Sepsis (except neonatal sepsis – treatment)	not listed	2a	8, 211
Sepsis (neonatal sepsis – treatment)	not listed	2a	7, 193
Sickle cell disease	2	4b	8, 211

Condition	AHMAC 2000	Evidence level	Chapter, page
Sjogren's syndrome	not listed	4a	7, 205
Solid organ transplantation (other than kidney)	2	4a	7, 206
Specific antibody deficiency	not listed	4a	6, 118
Stiff person syndrome	2	2a	5, 107
Susac syndrome	not listed	4a	7, 206
Systemic lupus erythematosus (SLE)	2	2a	8, 211
Toxic epidermal necrolysis/ Steven Johnson syndrome (TEN/SJS)	not listed	4a	6, 182
Toxic shock syndrome	not listed	4a	6, 185
Ulcerative colitis	2	4b	8, 211