

A systematic literature review and report on the efficacy of intravenous immunoglobulin therapy and its risks

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1 Introduction

In the treatment of haematological, immunological, neurological and other disorders, intravenous immunoglobulin (IVIG) is used for a growing range of indications. The treatment is costly and the supply limited; thus, there is a need for clear evidence of whether or not IVIG is effective for specific conditions.

The National Blood Authority (NBA) has contracted Biotext to undertake a systematic literature review of the efficacy and risks of IVIG. A comprehensive cost-effectiveness analysis is also being undertaken. The results of these studies will inform the development of evidence-based clinical practice guidelines for the use of IVIG in Australia.

This report describes the results of Biotext's systematic literature review to evaluate and summarise evidence for the therapeutic efficacy of IVIG and its risks.

This report is structured as follows:

- Section 2: Background — explaining what IVIG is and the type of clinical condition for which it is used.
- Section 3: Literature review — outline of the strategy used to search the literature, the problems encountered and the approach used to extract useful information from the articles retrieved.
- Section 4: Summary of results — tables listing each of the clinical conditions investigated, by category of evidence available (including separate tables showing the same information, split by type of condition — haematological, immunological, neurological or miscellaneous).
This section includes analysis of the information retrieved concerning the risks associated with IVIG. The information is taken from the papers retrieved for specific conditions, and from a separate search of the literature focused on safety of IVIG.
- Section 5: Conclusion.
- Appendix 1: Diseases and outcomes — list of conditions supplied by NBA.
- Appendix 2: Summary data on conditions and papers — 1–2 page summaries for each condition, accompanied by 1–2 page summaries of the relevant papers for each condition.
- Appendix 3: Summary data on safety of IVIG.
- Appendix 4: Excluded references.

2 Background

Immunoglobulins were first used therapeutically in the 1950s, for the treatment of primary immunodeficiency disorders. Immunoglobulin replacement therapy soon became standard for the management of these disorders.¹ However, immunoglobulin G (IgG) aggregates present in these early preparations limited their use; only intramuscular or subcutaneous administration was possible, injection pain restricted dosage size and frequency, and muscle protease degraded the administered immunoglobulin, reducing the amount of circulating protein and delaying the onset of action.¹

In the late 1970s, highly purified monomeric suspensions of IgG for intravenous use (intravenous immunoglobulin, IVIG) became available, which allowed the delivery of larger doses than was possible with intramuscular administration.¹ This development was accompanied by clinical studies demonstrating the efficacy of immunoglobulin treatment in a number of autoimmune and inflammatory conditions.^{1,2}

2.1 Uses of IVIG

IVIG is used clinically to provide antibodies for patients with primary immunodeficiency disorders³ (the most common variants of which are X-linked agammaglobulinaemia, common variable immunodeficiency and selective IgA deficiency)⁴ and secondary immunodeficiencies, where it is used to reduce recurrent infections in conditions such as chronic lymphatic leukaemia, multiple myeloma, and congenital acquired immune deficiency syndrome.¹⁻⁵

IVIG is also used to modulate the immune system; for example, in patients with autoimmune diseases such as idiopathic thrombocytopenic purpura, allogeneic bone marrow transplantation; Kawasaki disease and Guillain-Barré syndrome.¹⁻³

There is some suggestion in the literature that IVIG may be beneficial in other conditions,^{1,2} particularly those in which alternative treatment modalities do not exist or are problematic, as with plasma exchange and long-term use of corticosteroids.

2.2 Mechanism of action

The efficacy of IVIG as replacement IgG therapy in primary and secondary immunodeficiency syndromes probably relates to the provision of a broad spectrum of antibodies against endemic pathogens. IVIG's mechanisms of action in various autoimmune and inflammatory diseases are not fully understood, although evidence suggests that modulation of the immune system is involved.

Proposed mechanisms of action for IVIG in such conditions include^{1,9-11}

- autoantibody neutralisation
- down regulation of autoantibody synthesis
- inhibition of complement-mediated tissue damage
- blockade of Fc receptors on phagocytic cells

- inhibition of complement activation
- down regulation of T or B cell function
- anti-cytokine effects
- neutralisation and enhanced clearance of endogenous pathogenic auto-antibodies
- neutralisation of bacterial toxins and super antigens

Synergy between these mechanisms may be required for a clinical effect; in reality, multiple overlapping mechanisms appear to be involved.⁶

2.3 Adverse reactions^{1,3,9,10}

The reported frequency of adverse reactions ranges from 1 to 15 per cent, but is usually less than 5 per cent. Most adverse reactions are mild, immediate generalised reactions manifesting as:

- pyrogenic reactions (marked by high temperature and systemic symptoms)
- minor systemic reactions (headache, myalgia, fever, chills, light-headedness, nausea and/or vomiting)
- vasomotor or cardiovascular manifestations (changes in blood pressure and tachycardia, possibly associated with shortness of breath and chest tightness).

These generalised reactions are usually self-limiting, and are often alleviated by reducing the rate or volume of infusion, or by premedication with an analgesic or antihistamine. Less frequently, delayed generalised reactions can arise a few days after infusion.

Headache is the most common immediate adverse reaction with IVIG. Migraines may be triggered in susceptible patients and, infrequently, aseptic meningitis syndrome has been reported, presenting as severe headache with fever, photophobia, nausea and vomiting occurring several hours to 2 days after IVIG treatment. This resolves without sequelae within several days of IVIG treatment discontinuation.

Other adverse reactions reported include thrombophlebitis (associated with prolonged administration), positive direct antiglobin tests and red cell haemolysis and neutropenia. Acute renal dysfunction and acute renal failure have been reported rarely, and hypersensitivity reactions very rarely.

2.4 Viral safety^{1,3,10,11}

As with all human plasma products, IVIG preparations may contain infectious agents such as viruses that may be transmitted to the recipient. Measures undertaken to minimise this risk include ensuring plasma quality by screening and excluding high-risk donors, testing blood samples for viral markers, and including virus inactivation and removal procedures during IVIG manufacture.¹ The cold-ethanol fractionation process used for the production of IVIG is extremely 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 can also be used. The viral inactivation method used for the production of IVIG in Australia is a double 14-day incubation at pH 4.25 and 27°C. The capacity of the manufacturing process to inactivate

or remove viruses is assessed by validation studies, which provide assurance of an acceptable level of safety.

The implementation of these procedures provides a high level of confidence that Australian-manufactured IVIG will not transmit blood borne viruses; however, the risk of transmission of an infectious agent cannot be completely eliminated.

2.5 References

1. Australian Health Ministers' Advisory Council. Review of the use and supply of intravenous immunoglobulins in Australia. A report by the Blood and Blood Products Committee, June 2000.
2. Farrugia A, Poulis P. Intravenous immunoglobulin: regulatory perspectives on use and supply. *Transfusion Medicine* 2001; 11: 63–74.
3. Intragam® P Australian Approved Product Information.
4. European Agency for Evaluation of Medicinal products. Committee for Proprietary Medicinal Products: Note for guidance on the clinical investigation of human normal immunoglobulin for intravenous administration (IVIg) CPMP/BPWG/388/95 rev.1.
5. NHS Northern and Yorkshire Regional Drug and Therapeutics Centre. Intravenous immunoglobulin therapy (IVIG) — a guide for purchasers and prescribers. February 1997.
6. Ibanez C, Montoro-Ronsano JB. Intravenous immunoglobulin preparations and autoimmune disorders: mechanisms of action. *Curr Pharm Biotechnol* 2003; 4: 239–7.
7. Dalakas MC. Mechanism of action of intravenous immunoglobulin and therapeutic considerations in the treatment of autoimmune neurologic diseases. *Neurology* 1998; 51 (Suppl 5): S2–8.
8. Association Of British Neurologists. Guidelines for the use of intravenous immunoglobulin in neurological diseases, March 2002.
9. Intravenous immunoglobulin: Prevention and treatment of disease. NIH consensus statement online 1990 May 21–23; 8: 1–23.
10. Duhem C, Dicato MA, Ries F. Side-effects of intravenous immune globulins. *Exp Immunol* 1994; 97 (suppl 1): 79–83.
11. Kiss J E. Taking the next step in blood transfusion safety: viral inactivation of plasma and plasma products. *Transfusion Medicine Update*, July 1994. <http://www.itxm.org/Archive/tmu7-94.htm>, downloaded 26 July 2004.

3 Literature review

The aim of this project was to undertake a systematic literature review 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, including dose regimens
- include studies comparing IVIG with other treatments, including immunoglobulin administered by other routes, when such other treatments have been specifically studied in comparison with IVIG.

To achieve these aims for a range of IVIG uses, NBA supplied a matrix of specified conditions and circumstances for which IVIG has been used, and designated clinical and laboratory markers of process and/or outcome (see Appendix 1).

3.1 Clinical questions

For each condition or circumstance for IVIG use and clinical or laboratory marker, the literature search aimed to identify relevant papers to answer the following clinical question:

In a patient with the condition itemised in Column A in each sheet, does IVIG improve the clinical or laboratory markers listed, compared to no IVIG or a standard treatment?

What specific adverse effects are associated with IVIG treatment in these patients?

3.2 Search strategy

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 (ie from reference lists of key articles)
- contacting key researchers.

Electronic databases and other sources were searched for papers published from 1982–2004.

3.2.1 Electronic databases

The following databases were searched:

- Medline and EMBASE (via ScienceDirect)
- Cinahl
- BioMEDCentral
- Cochrane Library.

3.2.2 Search terms

General search (intravenous immunoglobulins)

The following search terms were used to locate references to intravenous immunoglobulins:

- text words
 - “intravenous immunoglobulin*”
 - IVIG
 - relevant product names
- MESH terms — “Immunoglobulins, Intravenous”

This search retrieved approximately 5000 papers.

Focused search (clinical studies)

To focus on clinical trials, the following search terms were used:

controlled clinical trial.mp.
exp Random Allocation/
exp Double-Blind Method/
exp Single-Blind Method/
exp Clinical Trials/
clinical trial.ti,ab.
randomised controlled trial.ti,ab.
exp Placebos/
placebo\$.ti,ab.
exp Research Design/
comparative study.mp.
exp evaluation studies/
followup studies.mp.
prospective studies.mp.

This narrowed the search to approximately 1250 references.

3.2.3 Additional references

References from the Australian Health Ministers' Advisory Council (AHMAC) *Review of the Use and Supply of Intravenous Immunoglobulins in Australia* and reference lists from recent trials were also checked to identify further papers. In some cases, individual researchers were contacted.

3.2.4 Article retrieval

Articles were initially retrieved and sorted using Procite software (AMPL Software Pty Ltd) and indexed using ISYS (Odyssey Developments Pty Ltd). This allowed all relevant material to be stored electronically and retrieved using text words.

3.2.5 Specific diseases

Using the database of articles from the initial search, each condition or circumstance for use of IVIG was searched for by MeSH heading and by text words for any synonyms. The spreadsheet supplied by NBA was amended to include clinical outcomes and markers for each condition. The outcomes and markers were refined as the search progressed (eg "improvements in lymphocyte counts" was refined to "improvements in CD4+ cells").

3.2.6 Inclusion criteria

Inclusion criteria for each indication were based on the clinical question for that indication (see above).

All systematic reviews, meta-analyses and randomised trials were included. Observational studies, including case studies, were included for indications where RCT evidence was not available, as follows:

- For indications where a Cochrane systematic review was available, this study was included, together with any RCTs published since the review or any RCTs identified as high-quality studies by the Cochrane review but not included in the review due to lack of relevance to the question being answered by the review.
- For indications where at least one well-designed, suitably powered RCT was identified, case study evidence was excluded.
- For indications where there were no well-designed, suitably powered RCTs available, case study evidence was included.

NOTE: Where the database indicates that there are no studies, this means that no RCTs, other experimental studies or observational studies (including case studies) were found.

Using the above inclusion criteria, approximately 280 papers were included in the review.

3.3 Data extraction

We tabulated the data from of the included studies using an Excel spreadsheet. Details recorded included:

- study type and level of evidence
- number of patients
- methods (including clinical and laboratory markers of outcome)
- quality interpretation of the strengths and limitations of the studies (quality of evidence)
- results (including all-cause mortality and duration of remission, taking into account statistical precision and size of effect)
- adverse events.

These fields were based on the CONSORT checklist¹ and the NHMRC dimensions of evidence, as outlined in the publication *How to Use the Evidence: Assessment and Application of Scientific Evidence*.²

Data was initially retrieved from abstracts only, because many of the studies included very few subjects and did not show any significant effect. Within the time frame of this study, it was neither possible nor worthwhile to obtain and extract all the full papers.

Full papers were obtained where there was a significant effect, the study quality and size was sufficient to warrant further detailed analysis of the data, or there were serious adverse effects. Additional data from the full papers was extracted into the database.

The master database was used to create a 1–2 page report for each included study (see Appendix 2).

3.4 Compilation of data

Information from the database was extracted into a summary table sorted by condition. However, not all the studies entered into the master database were extracted to the summary database, for a number of reasons. For example, for some conditions, there was one (or more) high-quality study (such as Cochrane review), and a decision was made to base the final conclusions on such studies, and not include additional small, low-quality RCTs or observational studies.

In the summary database, the data for each condition was assessed and an overall conclusion added (see Appendix 2). The strength of the evidence was classified according to the categories shown in Table 3.1.

Table 3.1 Categories assigned to level of evidence

Category	Studies	Evidence
I	High-quality RCTs	Clear evidence of benefit
IIa	Some RCTs and/or case studies	Possible benefit — research needed
IIb	Some RCTs and/or case studies	Appears to be no significant effect — more research needed
IIc	High-quality RCTs with conflicting results	Conflicting results
III	High-quality RCTs	Clear evidence of no effect
IVa	Small case studies only	Insufficient data
IVb	No studies	—

Information on adverse events was added from both the included and excluded studies from the master database.

3.5 Safety

In extracting data, we recorded any adverse events noted in abstracts or full papers. In addition, we identified papers that reviewed aspects of the safety of IVIG, analysed the information and added it to the database in a separate category of ‘safety’. Summary sheets of these entries are included at Appendix 3.

[Note: Full papers of each of these papers have been obtained, but there has not been time to analyse them in more detail]

3.6 References

1. Moher D, Schulz KF, Altman DG (2001). The CONSORT statement: Revised recommendations for improving the quality of reports of parallel-group randomised trials. *Ann Intern Med.* 134:657–662.
2. NHMRC (2000). *How to Use the Evidence: Assessment and Application of Scientific Evidence.*

4 Summary of results

This section contains tables listing each of the clinical conditions investigated, organised by category of evidence available (see Section 4.1). In Section 4.2, the same data are presented in separate tables, organised by type of condition (ie haematological, immunological, neurological or miscellaneous), and again arranged according to category of evidence available.

Further information on each of the conditions for which studies were found is presented in Appendix 2, which contains a summary sheet for each of these conditions, listing the following information:

- relevant references
- types of study (eg randomised controlled trial (RCT), case series, cohort, etc)
- total sample size
- overall quality of the studies
- a summary of the results
- any adverse events noted
- a conclusion
- category of evidence.

Appendix 2 also contains an additional 1–2 page summary for each of the relevant references, detailing the information extracted from the abstract or the full paper.

Section 4.3 discusses the results from the review of the risks associated with IVIG, based on information from the papers retrieved for specific conditions, and from a separate search of the literature focused on safety of IVIG. The 1-2 page summary sheets for the references specific to safety of IVIG are contained in Appendix 3.

4.1 Clinical conditions by category

Evidence category: I (High-quality RCTs, clear evidence of benefit)

Category	Condition type	Condition
I	Haematological	Immune thrombocytopenia, Idiopathic thrombocytopenic purpura
I	Neurological	Chronic inflammatory demyelinating polyneuropathy
I	Vasculitis/inflammatory	Kawasaki's disease

Evidence category: IIa (Some RCTs and/or case studies, possible benefit — research needed)

Category	Condition type	Condition
IIa	Haematological	Acute leukemia in childhood
IIa	Haematological	Autoantibodies to Factor VIII or Acquired von Willebrand disease
IIa	Haematological	Chronic lymphocytic leukaemia with hypogammaglobulinaemia or persistent serum total IgG deficiency and documented recurrent infections
IIa	Haematological	HIV-associated thrombocytopenia
IIa	Haematological	Multiple myeloma
IIa	Haematological	Neonatal ABO isoimmunisation
IIa	Haematological	Rhesus D haemolytic disease
IIa	HIV/AIDS	HIV/AIDS: Paediatric
IIa	Immunological	Transplantations: kidney - infection (eg BK virus)
IIa	Immunological	Transplantations: kidney - rejection
IIa	Miscellaneous	Burns
IIa	Miscellaneous	Cardiac surgery with bypass-prophylaxis
IIa	Miscellaneous	Congestive cardiac failure
IIa	Miscellaneous	Grave's ophthalmopathy
IIa	Miscellaneous	Other conditions (not listed elsewhere): obsessive compulsive/tic disorders
IIa	Miscellaneous	Trauma
IIa	Neurological	Encephalomyelitis and sensory neuropathy associated with anti- HU antibodies
IIa	Neurological	Epilepsy
IIa	Neurological	Epilepsy: childhood epilepsy resistant
IIa	Neurological	Epilepsy: Landau-Kleffner syndrome
IIa	Neurological	Epilepsy: Lennox - Gastaut syndrome
IIa	Neurological	Guillain Barre syndrome
IIa	Neurological	Multifocal motor neuropathy with persistent conduction block
IIa	Neurological	Muscle diseases: dermatomyositis
IIa	Neurological	Muscle diseases: inclusion body myositis
IIa	Neurological	Muscle diseases: polymyositis
IIa	Neurological	Neuromuscular disorders: Lambert Eaton Syndrome
IIa	Neurological	Neuromuscular disorders: stiff man syndrome
IIa	Neurological	Other disorders: motor neuron disease
IIa	Neurological	Polyneuropathy of critical illness
IIa	Primary immunodeficiencies	B-cell tumours

Category	Condition type	Condition
Ila	Primary immunodeficiencies	Common variable immunodeficiency
Ila	Primary immunodeficiencies	Lymphocytic leukaemia with hypogammaglobulinaemia
Ila	Primary immunodeficiencies	Nephrotic syndrome
Ila	Primary immunodeficiencies	Primary hypogammaglobulinaemia
Ila	Skin diseases	Autoimmune blistering diseases: cicatricial pemphigoid
Ila	Skin diseases	Autoimmune blistering diseases: pemphigoid - oral
Ila	Skin diseases	Autoimmune blistering diseases: pemphigus vulgaris and foliaceus
Ila	Vasculitis/inflammatory	ANCA-positive vasculitis (including Wegener's)
Ila	Vasculitis/inflammatory	Rheumatoid arthritis: juvenile
Ila	Vasculitis/inflammatory	Sepsis: adult sepsis
Ila	Vasculitis/inflammatory	Sepsis: paediatric sepsis
Ila	Vasculitis/inflammatory	Systemic lupus erythematosus (SLE)

Evidence category: IIb
(Some RCTs and/or case studies, appears to be no significant effect — research needed)

Category	Condition type	Condition
IIb	HIV/AIDS	HIV/AIDS: Adult
IIb	Miscellaneous	Acute rheumatic fever
IIb	Miscellaneous	Idiopathic dilated cardiomyopathy
IIb	Miscellaneous	Paediatric head injury
IIb	Neurological	IgM paraproteinaemic neuropathy
IIb	Skin diseases	Autoimmune blistering diseases: atopic dermatitis
IIb	Skin diseases	Toxic epidermal necrolysis

Evidence category: IIc
(High-quality RCTs with conflicting results, conflicting results)

Category	Condition type	Condition
IIc	Haematological	Bone marrow transplantation: allogeneic and autologous
IIc	Miscellaneous	Asthma
IIc	Miscellaneous	Other conditions (not listed elsewhere): IVF failure
IIc	Neurological	Multiple sclerosis: progressive/relapsing or remitting
IIc	Neurological	Myalgic encephalomyelitis
IIc	Neurological	Neuromuscular disorders: myasthenia gravis
IIc	Skin diseases	Stevens Johnson syndrome
IIc	Vasculitis/inflammatory	Rheumatoid arthritis: adult

Evidence category: III
(Clear evidence of no effect)

Category	Condition type	Condition
III	Miscellaneous	Recurrent fetal loss with or without antiphospholipid syndrome
III	Vasculitis/inflammatory	Sepsis: neonatal sepsis: prevention/treatment

**Evidence category: IVa
(Small case studies only, insufficient data)**

Category	Condition type	Condition
IVa	Skin diseases	Autoimmune blistering diseases: epidermolysis bullosa acquisita

**Evidence category: IVb
(No studies)**

Category	Condition type	Condition
IVb	Haematological	Alloimmune thrombocytopenia antenatal
IVb	Haematological	Amegakaryocytic thrombocytopenia
IVb	Haematological	Aplastic anaemia/pancytopenia
IVb	Haematological	Autoimmune haemolytic anaemia (Evan's syndrome)
IVb	Haematological	Autoimmune neutropenia
IVb	Haematological	Autoimmune neutropenia in infancy
IVb	Haematological	Diamond-Blackfan syndrome
IVb	Haematological	Haemolytic transfusion reaction
IVb	Haematological	Haemolytic uraemic syndrome
IVb	Haematological	Post-transfusion purpura
IVb	Haematological	Pure white cell aplasia
IVb	Haematological	Red cell aplasia
IVb	Haematological	Sickle cell anaemia
IVb	Haematological	Virus associated haemophagic syndrome
IVb	Immunological	Transplantations: Heart/Lung/Pancreas
IVb	Miscellaneous	Autism - young adults
IVb	Miscellaneous	Non-obstetric antiphospholipid syndrome
IVb	Neurological	Autoimmune diabetic neuropathy
IVb	Neurological	Other disorders: adrenoleukodystrophy
IVb	Neurological	Other disorders: amyotrophic lateral sclerosis
IVb	Neurological	Other disorders: opsoclonus myoclonus
IVb	Neurological	Other disorders: para neoplastic cerebellar degeneration with NO antibodies
IVb	Primary immunodeficiencies	Paraneoplastic cerebellar degeneration with NO antibodies
IVb	Skin diseases	Autoimmune blistering diseases: linear IgA disease
IVb	Vasculitis/inflammatory	Churg-Strauss vasculitis
IVb	Vasculitis/inflammatory	Henoch-Schonlein pupura
IVb	Vasculitis/inflammatory	Inflammatory bowel disease: Crohn's disease
IVb	Vasculitis/inflammatory	Inflammatory bowel disease: ulcerative colitis

Conditions not reported against but related to other conditions

The conditions listed in the table below were given in the database provided by the NBA (see Appendix 1). They were not specifically reported against in the literature review. However, they are related to other conditions that were reported against (shown in column 3 of the table).

Condition type	Condition	Related conditions reported against
Haematological	Other chronic lymphoproliferative disease with persistent serum total IgG deficiency and documented recurrent infections	See: <ul style="list-style-type: none"> Chronic lymphocytic leukaemia with hypogammaglobulinaemia or persistent serum total IgG deficiency and documented recurrent infections Lymphocytic leukaemia with hypogammaglobulinaemia
Haematological	Septic thrombocytopenia	See: <ul style="list-style-type: none"> Sepsis: adult, paediatric, neonatal Immune thrombocytopenia Idiopathic thrombocytopenic purpura
Immunological	Transplantations: liver	See: <ul style="list-style-type: none"> Transplantations: kidney - infection (eg BK virus)
Immunological	Untransplantability due to anti-HLA antibodies	See: <ul style="list-style-type: none"> Transplantations: kidney - infection (eg BK virus)
Neurological	Acute idiopathic dysautonomia	See: <ul style="list-style-type: none"> Guillain Barre syndrome
Neurological	Epilepsy: mixed seizures of early onset associated with IgG	See: <ul style="list-style-type: none"> Other epilepsy categories
Neurological	Epilepsy: Rasmussen syndrome	See: <ul style="list-style-type: none"> Other epilepsy categories
Neurological	Epilepsy: subclass deficiency	See: <ul style="list-style-type: none"> Other epilepsy categories
Neurological	Muscle diseases: polymyositis and systemic connective tissue disease	See: <ul style="list-style-type: none"> Muscle diseases: polymyositis
Primary immunodeficiencies	Combined immune deficiency including specific syndromes (eg. Wiskott-Aldrich syndrome)	See: <ul style="list-style-type: none"> Common variable immunodeficiency Primary hypogammaglobulinaemia
Primary immunodeficiencies	Hyperimmunoglobulin M Syndrome (Type 1-4) immune deficiency with normal or elevated IgM	See: <ul style="list-style-type: none"> Common variable immunodeficiency Primary hypogammaglobulinaemia
Primary immunodeficiencies	IgG subclass deficiencies including isolated IgG2 deficiency and isolated IgG3 deficiency	See: <ul style="list-style-type: none"> Common variable immunodeficiency Primary hypogammaglobulinaemia
Primary immunodeficiencies	Other primary (inherited) immunodeficiency diseases with defective B cell function	See: <ul style="list-style-type: none"> Common variable immunodeficiency Primary hypogammaglobulinaemia
Primary immunodeficiencies	Severe combined immunodeficiency	See: <ul style="list-style-type: none"> Common variable immunodeficiency Primary hypogammaglobulinaemia
Primary immunodeficiencies	Specific antibody deficiency (with deficiency of IgG subclasses and/or IgA)	See: <ul style="list-style-type: none"> Common variable immunodeficiency Primary hypogammaglobulinaemia
Primary immunodeficiencies	Specific antibody deficiency (with normal IgG subclasses and IgA)	See: <ul style="list-style-type: none"> Common variable immunodeficiency Primary hypogammaglobulinaemia

Condition type	Condition	Related conditions reported against
Primary immunodeficiencies	Transient hypogammaglobulinemia of infancy	<ul style="list-style-type: none"> Primary hypogammaglobulinaemia
Primary immunodeficiencies	X-linked hypogammaglobulinaemia	<ul style="list-style-type: none"> Primary hypogammaglobulinaemia
Skin diseases	Autoimmune blistering diseases: bullous pemphigoid	<ul style="list-style-type: none"> Autoimmune blistering diseases: cicatricial pemphigoid, pemphigoid – oral, pemphigus vulgaris and foliaceus
Skin diseases	Autoimmune blistering diseases: pemphigoid gestationes	<ul style="list-style-type: none"> Autoimmune blistering diseases: cicatricial pemphigoid, pemphigoid – oral, pemphigus vulgaris and foliaceus
Vasculitis/inflammatory	Sepsis: preterm sepsis: prevention/treatment	<ul style="list-style-type: none"> Sepsis: neonatal, paediatric
Vasculitis/inflammatory	Systemic necrotizing vasculitis	<ul style="list-style-type: none"> Systemic lupus erythematosus (SLE)

4.2 Clinical conditions by category and by condition type

4.2.1 Haematological

Category	Condition — haematological
I	Immune thrombocytopenia, Idiopathic thrombocytopenic purpura
IIa	Acute leukaemia in childhood
IIa	Autoantibodies to Factor VIII or Acquired von Willebrand disease
IIa	Chronic lymphocytic leukaemia with hypogammaglobulinaemia or persistent serum total IgG deficiency and documented recurrent infections
IIa	HIV-associated thrombocytopenia
IIa	Multiple myeloma
IIa	Neonatal ABO isoimmunisation
IIa	Rhesus D haemolytic disease
IIc	Bone marrow transplantation: allogeneic and autologous
IVb	Alloimmune thrombocytopenia antenatal
IVb	Amegakaryocytic thrombocytopenia
IVb	Aplastic anaemia/pancytopenia
IVb	Autoimmune haemolytic anaemia (Evan's syndrome)
IVb	Autoimmune neutropenia
IVb	Autoimmune neutropenia in infancy
IVb	Diamond-Blackfan syndrome
IVb	Haemolytic transfusion reaction
IVb	Haemolytic uraemic syndrome
IVb	Post-transfusion purpura
IVb	Pure white cell aplasia
IVb	Red cell aplasia
IVb	Sickle cell anaemia
IVb	Virus associated haemophagic syndrome

Category	Condition — haematological
–	Other chronic lymphoproliferative disease with persistent serum total IgG deficiency and documented recurrent infections See: <ul style="list-style-type: none"> • Chronic lymphocytic leukaemia with hypogammaglobulinaemia or persistent serum total IgG deficiency and documented recurrent infections • Lymphocytic leukaemia with hypogammaglobulinaemia
–	Septic thrombocytopenia See: <ul style="list-style-type: none"> • Sepsis: adult, paediatric, neonatal • Immune thrombocytopenia • Idiopathic thrombocytopenic purpura

4.4.2 HIV/AIDS

Category	Condition — HIV/AIDS
Ila	HIV/AIDS: Paediatric
IIb	HIV/AIDS: Adult

4.4.3 Immunological

Category	Condition — immunological
Ila	Transplantations: kidney - infection (eg BK virus)
Ila	Transplantations: kidney - rejection
IVb	Transplantations: Heart/Lung/Pancreas
–	Transplantations: liver See: <ul style="list-style-type: none"> • Transplantations: kidney - infection (eg BK virus)
–	Untransplantability due to anti-HLA antibodies See: Transplantations: kidney - infection (eg BK virus)

4.4.4 Miscellaneous

Category	Condition — miscellaneous
Ila	Burns
Ila	Cardiac surgery with bypass-prophylaxis
Ila	Congestive cardiac failure
Ila	Grave's ophthalmopathy
Ila	Other conditions (not listed elsewhere): obsessive compulsive/tic disorders
Ila	Trauma
IIb	Acute rheumatic fever
IIb	Idiopathic dilated cardiomyopathy
IIb	Paediatric head injury
IIc	Asthma
IIc	Other conditions (not listed elsewhere): IVF failure
III	Recurrent fetal loss with or without antiphospholipid syndrome
IVb	Autism - young adults
IVb	Non-obstetric antiphospholipid syndrome

4.4.5 Neurological

Category	Condition — neurological
I	Chronic inflammatory demyelinating polyneuropathy
IIa	Encephalomyelitis and sensory neuropathy associated with anti- HU antibodies
IIa	Epilepsy
IIa	Epilepsy: childhood epilepsy resistant
IIa	Epilepsy: Landau-Kleffner syndrome
IIa	Epilepsy: Lennox - Gastaut syndrome
IIa	Guillain Barre syndrome
IIa	Multifocal motor neuropathy with persistent conduction block
IIa	Muscle diseases: dermatomyositis
IIa	Muscle diseases: inclusion body myositis
IIa	Muscle diseases: polymyositis
IIa	Neuromuscular disorders: Lambert Eaton Syndrome
IIa	Neuromuscular disorders: stiff man syndrome
IIa	Other disorders: motor neuron disease
IIa	Polyneuropathy of critical illness
IIb	IgM paraproteinaemic neuropathy
IIc	Multiple sclerosis: progressive/relapsing or remitting
IIc	Myalgic encephalomyelitis
IIc	Neuromuscular disorders: myasthenia gravis
IVb	Autoimmune diabetic neuropathy
IVb	Epilepsy: mixed seizures of early onset associated with IgG
IVb	Other disorders: adrenoleukodystrophy
IVb	Other disorders: amyotrophic lateral sclerosis
IVb	Other disorders: opsoclonus myoclonus
IVb	Other disorders: paraneoplastic cerebellar degeneration with N0 antibodies
-	Acute idiopathic dysautonomia See: <ul style="list-style-type: none"> Guillain-Barre syndrome
-	Muscle diseases: polymyositis and systemic connective tissue disease See: <ul style="list-style-type: none"> Muscle diseases: polymyositis
-	Epilepsy: mixed seizures of early onset associated with IgG See: <ul style="list-style-type: none"> Other epilepsy categories
-	Epilepsy: Rasmussen syndrome See: <ul style="list-style-type: none"> Other epilepsy categories
-	Epilepsy: subclass deficiency See: <ul style="list-style-type: none"> Other epilepsy categories

4.4.6 Primary immunodeficiencies

Category	Condition
Ila	B-cell tumours
Ila	Common variable immunodeficiency
Ila	Lymphocytic leukaemia with hypogammaglobulinaemia
Ila	Nephrotic syndrome
Ila	Primary hypogammaglobulinaemia
IVb	Paraneoplastic cerebellar degeneration with NO antibodies
–	Combined immune deficiency including specific syndromes (eg. Wiskott-Aldrich syndrome) See: <ul style="list-style-type: none"> • Common variable immunodeficiency • Primary hypogammaglobulinaemia
–	Hyperimmunoglobulin M Syndrome (Type 1-4) immune deficiency with normal or elevated IgM See: <ul style="list-style-type: none"> • Common variable immunodeficiency • Primary hypogammaglobulinaemia
–	IgG subclass deficiencies including isolated IgG2 deficiency and isolated IgG3 deficiency See: <ul style="list-style-type: none"> • Common variable immunodeficiency • Primary hypogammaglobulinaemia
–	Other primary (inherited) immunodeficiency diseases with defective B cell function See: <ul style="list-style-type: none"> • Common variable immunodeficiency • Primary hypogammaglobulinaemia
–	Severe combined immunodeficiency See: <ul style="list-style-type: none"> • Common variable immunodeficiency • Primary hypogammaglobulinaemia
–	Specific antibody deficiency (with deficiency of IgG subclasses and/or IgA) See: <ul style="list-style-type: none"> • Common variable immunodeficiency • Primary hypogammaglobulinaemia
–	Specific antibody deficiency (with normal IgG subclasses and IgA) See: <ul style="list-style-type: none"> • Common variable immunodeficiency • Primary hypogammaglobulinaemia
–	Transient hypogammaglobulinemia of infancy See: <ul style="list-style-type: none"> • Primary hypogammaglobulinaemia
–	X-linked hypogammaglobulinaemia See: <ul style="list-style-type: none"> • Primary hypogammaglobulinaemia

4.4.7 Skin diseases

Category	Condition — skin diseases
IIa	Autoimmune blistering diseases: cicatricial pemphigoid
IIa	Autoimmune blistering diseases: pemphigoid - oral
IIa	Autoimmune blistering diseases: pemphigus vulgaris and foliaceus
IIb	Autoimmune blistering diseases: atopic dermatitis
IIb	Toxic epidermal necrolysis
IIc	Stevens Johnson syndrome
IVa	Autoimmune blistering diseases: epidermolysis bullosa acquisita
IVb	Autoimmune blistering diseases: linear IgA disease
–	Autoimmune blistering diseases: bullous pemphigoid See: <ul style="list-style-type: none"> Autoimmune blistering diseases: cicatricial pemphigoid, pemphigoid – oral, pemphigus vulgaris and foliaceus
–	Autoimmune blistering diseases: pemphigoid gestationes See: <ul style="list-style-type: none"> Autoimmune blistering diseases: cicatricial pemphigoid, pemphigoid – oral, pemphigus vulgaris and foliaceus

4.4.8 Vasculitis/inflammatory

Category	Condition — vasculitis/inflammatory
I	Kawasaki's disease
IIa	ANCA-positive vasculitis (including Wegener's)
IIa	Rheumatoid arthritis: juvenile
IIa	Sepsis: adult sepsis
IIa	Sepsis: paediatric sepsis
IIa	Systemic lupus erythematosus (SLE)
IIc	Rheumatoid arthritis: adult
III	Sepsis: neonatal sepsis: prevention/treatment
IVb	Churg-Strauss vasculitis
IVb	Henoch-Schonlein purpura
IVb	Inflammatory bowel disease: Crohn's disease
IVb	Inflammatory bowel disease: ulcerative colitis
–	Sepsis: preterm sepsis: prevention/treatment See: <ul style="list-style-type: none"> Sepsis: neonatal, paediatric
–	Systemic necrotizing vasculitis See: <ul style="list-style-type: none"> Systemic lupus erythematosus (SLE)

4.3 Safety of IVIG

The table below summarises the types of adverse events found in this review (in about 100 papers or abstracts that mentioned adverse events). There was a wide variation in the incidence and severity of the adverse events reported. For example, the incidence of mild adverse events ranged from less than 1% to 42.7%.

Type of adverse event	Number of papers reporting event	Incidence (where given)	Reference number
No adverse effects			
No adverse events observed or none reported	43		
Comparison with other treatments			
IVIG similar to alternative treatment	3		10, 152, 158
Fewer adverse effects for intravenous than for intramuscular immunoglobulin	1		11
Fewer adverse effects for IVIG than for corticosteroids or plasma exchange	3		51, 68, 54
General or specific adverse events			
General adverse events (mild)	8 ⁹	<1– 42.7% (Average 13%)	18, 54, 88, 89, 95, 103, 165, 175, 193
Aseptic meningitis	4 ²	4%, 7.5%, 11%	69, 131
Anaphylactoid reaction	1	4%	131
Back pain	1		95
Benign venulitis	1		47
Chest pain, pleurisy, transfusion-related acute lung injury	1		?
Death due to cardiac complications (unrelated to IVIG)	1		23
Erythroderma	1		183
Fatigue	3		179, 216, 242
Fever or chills	12		40, 49, 76, 95, 132, 146, 174, 190, 192, 216, 252, 278
Headache – mild or self-limiting (or type not specified)	20	45%	49, 69, 75, 76, 82, 132, 146, 165, 174, 179, 190, 192, 199, 216, 234, 236, 237, 242, 243, 278
Headache – severe (requiring treatment or hospitalisation)	3		69, 76, 252
Hepatitis C	3		21, 234, 237
Higher cumulative incidence of relapse of malignancy	1	31%	100
Hypertension (transient)	1		174
Increased TNF alpha production	1		26
Infusion reaction (not specified)	1	7%	96
Nausea or vomiting	5		76, 192, 205, 234, 278

Type of adverse event	Number of papers reporting event	Incidence (where given)	Reference number
Photophobia	1		252
Polyarthralgia	1		40
Renal impairment, possibly irreversible	1	6.7%	24
Severe or fatal venoocclusive disease	2		97, 138
Shortness of breath or watery eyes and flushing	3		40
Skin rash or eczema	13		15, 36, 40, 165, 174, 179, 202, 204, 216, 219, 234, 236, 237
Stroke, myocardial infarction, congestive heart failure	1		246

A review of seven studies of safety of IVIG (see Appendix 3) suggested that certain subpopulations are at higher risk of adverse events. For example, aseptic meningitis appears to be more common among people with a history of migraine. Also, patients with any renal disease are at higher risk of renal impairment from IVIG. This adverse effect can be mitigated by checking renal function before and after administration of IVIG, and measuring serum creatinine 4-5 days after starting high-dose IVIG therapy.

The issues of transmission of viral or other infections (eg CJD) by IVIG were not considered specifically in this review. However, one trial reported a patient becoming infected with hepatitis C during IVIG treatment, while another trial was terminated due to concerns about possible hepatitis C contamination, although no infection with hepatitis C was found.

5 Conclusion

This study shows that, in spite of the widespread use of IVIG, there are few conditions for which there is clear evidence of the efficacy of this agent. There are also few conditions in which there is clear evidence of lack of efficacy of IVIG.

Conditions for which there is clear evidence of benefit are:

- Immune thrombocytopenia, idiopathic thrombocytopenic purpura
- Chronic inflammatory demyelinating polyneuropathy
- Kawasaki's disease.

Conditions for which there is clear evidence of no significant effect are:

- Recurrent fetal loss with or without antiphospholipid syndrome
- Sepsis: neonatal sepsis: prevention/treatment.

Most of the conditions covered by this review fell into the category of 'more research needed', with more data being required to confirm possible benefit or lack of significant effect, or to resolve conflicting evidence.

The relative rarity of some of some disorders for which IVIG is used means that well-designed randomised control trials, with sufficient numbers to be statistically significant, are difficult to achieve. For such conditions, cross-over trials (in which the patient acts as their own control) provide a useful alternative to simple randomised trials.

In some conditions, there appear to be subgroups of patients for whom IVIG may be beneficial. For example

- in epilepsy, there appears to be some benefit of IVIG in patients with partial seizures.
- IVIG may reduce infections in a subgroup of HIV-infected children, although there was no significant effect on overall survival rate
- in poly-juvenile rheumatoid arthritis (poly-JRA), IVIG may be more effective in those with JRA for less than 5 years

There are important safety issues associated with the use of IVIG. Many papers and abstracts did not comment on adverse effects but, in those that did (~100/280 papers), a wide variety of effects were reported, ranging from mild to severe, and with an incidence ranging from <1% to as much as 50%). Transmission of bloodborne diseases is an important issue that is outside the scope of this review. Although preparation of IVIG is designed to minimise the potential for transmission of human viruses, transmission of other types of disease (eg CJD) remains a possibility.

Appendix 1 — Diseases and outcomes¹

The following table was supplied by the National Blood Authority

MISCELLANEOUS DISORDERS

Condition	Clinical Marker		
Autism-young adults			
Grave's ophthalmopathy			
Trauma			
Burns			
Paediatric head injury			
Non-obstetric antiphospholipid syndrome	Thrombosis-event rate,	Anticoagulant sparing	
Recurrent fetal loss with or without antiphospholipid syndrome	Live births	Live births at term	
Cardiac surgery with bypass-prophylaxis	Survival at one year	Length of admission	Episodes of sepsis
Congestive cardiac failure	Disease free survival	Left ventricular function	
Idiopathic dilated cardiomyopathy	Disease free survival	Left ventricular function	
Acute rheumatic fever	Disease free survival	Left ventricular function	
Asthma	Number of admissions	Length of admission	
Other Conditions (not listed elsewhere)			

HAEMATOLOGICAL DISORDERS

Condition	Clinical Marker
Bone marrow transplantation: allogeneic and autologous	reduction in complications such as GVHD (Graft versus Host Disease)
Immune thrombocytopenia, Idiopathic thrombocytopenic purpura	bleeding/haemorrhage

¹ As supplied by National Blood Authority

HIV-associated thrombocytopenia	bleeding/haemorrhage
Autoimmune haemolytic anaemia (Evan's syndrome)	anaemia
Autoimmune neutropenia	infections
Autoimmune neutropenia in infancy	infections
Post-transfusion purpura	bleeding/haemorrhage
Alloimmune thrombocytopenia antenatal	bleeding/haemorrhage
Septic thrombocytopenia	bleeding/haemorrhage
Rhesus D haemolytic disease	need for transfusion
Neonatal ABO isoimmunisation	need for transfusion
Red Cell aplasia	need for transfusion
Pure white cell aplasia	infections
Amegakaryocytic Thrombocytopenia	bleeding/haemorrhage
Aplastic anaemia/pancytopenia	
Diamond-Blackfan syndrome	need for transfusion
Virus associated haemophagic syndrome	
Chronic lymphocytic leukaemia with hypogammaglobulinaemia or persistent serum total IgG deficiency and documented recurrent infections	Reduction in serious relevant infections
Other chronic lymphoproliferative disease with persistent serum total IgG deficiency and documented recurrent infections	Reduction in serious relevant infections
Multiple myeloma	Reduction in serious relevant infections
Autoantibodies to Factor VIII or Acquired von Willebrand disease	Refractory to other therapy
Haemolytic uraemic syndrome	
Sickle cell anaemia	
Acute leukemia in childhood	
Haemolytic transfusion reaction	

HIV/AIDS; SKIN DISEASES;
VASCULITIS/INFLAMMATORY

Condition			
HIV/AIDS			
<i>Paediatric</i>	Reduction in frequency of presumed bacterial sino-pulmonary infections	Prevention (or halt in progress) of bronchiectasis	Acquired Immunodeficiency Syndrome: HIV; Infecton
<i>Adult</i>			
VASCULITIS/INFLAMMATORY			
Kawasaki's disease	Time to resolution of fever	All-cause mortality	Mucocutaneous Lymph Node Syndrome
Systemic necrotizing vasculitis	Disease activity scores	Length of remission	Vasculitis
ANCA-positive vasculitis (including Wegener's)	Disease activity scores	Length of remission	Wegener's Granulomatosis; Antibodies, Antineutrophil Cytoplasmic
Henoch-Schonlein pupura	Disease activity scores	Length of remission	Purpura, Schonlein-Henoch
Churg-Strauss vasculitis	Disease activity scores	Length of remission	Chur-Strauss Syndrome
Systemic lupus erythematosus (SLE)	Disease activity scores	Length of remission	Lupus Erythematosus, Systemic

Rheumatoid arthritis:			
<i>Juvenile</i>	Disease activity scores	Length of remission	Arthritis, Juvenile Rheumatoid
<i>Adult</i>	Disease activity scores (eg Ritchie index)	Length of remission	Arthritis, Rheumatoid
Inflammatory bowel disease:			
<i>Crohn's disease</i>	Disease activity scores	Length of remission	Crohn's Disease
<i>Ulcerative colitis</i>	Disease activity scores	Length of remission	Colitis, Ulcerative
Sepsis:			Sepsis
Preterm sepsis: prevention/treatment	All-cause mortality	Sepsis-related mortality	Sepsis
Neonatal sepsis: prevention/treatment	Survival; All-cause mortality	Bacteraemia rates; Sepsis-related mortality	Sepsis
<i>Adult sepsis</i>	All-cause mortality	Sepsis-related mortality	Sepsis
SKIN DISEASES			
Autoimmune blistering diseases			Autoimmune Diseases

<i>Pemphigus vulgaris and foliaceus</i>	Disease activity scores	Length of remission	Pemphigus
<i>Bullous pemphigoid</i>	Disease activity scores	Length of remission	Pemphigoid, Bullous
<i>Cicatricial pemphigoid</i>	Disease activity scores	Length of remission	Skin disease, vesiculobullous
<i>Pemphigoid gestationes</i>	Disease activity scores	Immunosuppression sparing (eg reduced prednisone dosage)	Skin disease, vesiculobullous
<i>Pemphigoid - oral</i>	Disease activity scores	Length of remission	Pemphigoid, Benign Mucous Membrane; Pemphigoid
<i>Atopic dermatitis</i>	Disease activity scores	Length of remission	Dermatitis, Atopic
<i>Epidermolysis bullosa acquisita</i>	Disease activity scores	Length of remission	Epidermolysis Bullosa Acquisita

<i>Linear IgA disease</i>	Disease activity scores	Length of remission	Skin disease, vesiculobullous
Toxic epidermal necrolysis	Disease activity scores	All-cause mortality	Epidermal Necrolysis Toxic
Stevens Johnson syndrome	Disease activity scores	All-cause mortality	Stevens-Johnson Syndrome

OTHER IMMUNOLOGICAL DISORDERS

Condition	Clinical Marker			
Transplantations				
<i>Kidney - rejection</i>	reversal of rejection			reduction in plasma creatinine
<i>Kidney - infection eg BK virus</i>	reversal of infection	improvement in renal function		reduction in plasma creatinine
<i>Liver</i>				
<i>Heart/Lung/Pancreas</i>				
Untransplantability due to anti-HLA antibodies	Offers of a cadaveric or living donor transplant			reduction in plasma renin activity (PRA)

NEUROLOGICAL

Condition	Clinical Marker			
Guillain Barre syndrome	Time to walk unaided	Time in intensive care	Overall disability sum score (ODSS) or MRC sum score	Nerve Conduction Studies
Chronic inflammatory demyelinating polyneuropathy	Disability score at 6 & 12 weeks			Nerve Conduction Studies
Multifocal motor neuropathy with persistent conduction block	Disability score at 12 weeks			Nerve Conduction Studies; particularly conduction block
IgM paraproteinaemic neuropathy	Neurologic disability score			Nerve Conduction Studies
Autoimmune diabetic neuropathy	Neurologic disability score	Pain relief		Nerve Conduction Studies
Acute idiopathic dysautonomia	Neurologic disability score	Postural hypotension		Nerve Conduction Studies
Polyneuropathy of critical illness	Neurologic disability score			Nerve Conduction Studies
Encephalomyelitis & sensory neuropathy associated with anti HU antibodies	Neurologic disability score			Nerve Conduction Studies
Muscle Diseases:				
Polymyositis	Neurologic disability score	MRC score in involved muscle group		CPK level
Dermatomyositis	Neurologic disability score	MRC score in involved muscle group		CPK level
Polymyositis & systemic connective tissue disease	Neurologic disability score	MRC score in involved muscle group		CPK level

Inclusion body myositis	Neurologic disability score; <i>Disease free survival</i>	MRC score in involved muscle group; <i>Disease activity scores</i>	<i>Serum CK Level</i>	CPK level; <i>Disability indices</i>
Neuromuscular disorders:				
Myasthenia gravis	Neurologic disability score	MRC Score in involved muscle groups	Reduced need for steroid, immunosuppression & Mestinon	EMG - repetitive stimulation
Lambert Eaton Syndrome	Neurologic disability score	MRC Score in involved muscle groups	Reduced need for steroid, immunosuppression & Mestinon	EMG - repetitive stimulation
Stiff man syndrome	Neurologic disability score			Reduction in anti GAD antibodies
Epilepsy:				
Childhood epilepsy resistant	Reduction in seizure frequency			Improvement in EEG
Rasmussen syndrome	Reduction in seizure frequency			Improvement in EEG
Lennox - Gastard syndrome	Reduction in seizure frequency			Improvement in EEG
Mixed seizures of early onset associated with IgG	Reduction in seizure frequency associated with IgG			Improvement in EEG
Subclass deficiency	Reduction in seizure frequency			Improvement in EEG
Other disorders:				
Opsiclonus myoclonus	Improvement in clinical condition as shown by reduction of opsiclonus and myoclonus			Nil

Paraneoplastic cerebellar degeneration with NO antibodies	Stabilisation or improvement in clinical condition - neurologic disability score			Reduction in Y0 antibodies
Amyotrophic lateral sclerosis	Neurologic disability score			
Motor neuron disease	Neurologic disability score			
Adrenoleukodystrophy	Neurologic disability score			MRI scan
Multiple Sclerosis:				
Relapsing & Remitting	Reduction in relapse rate	Extended disability score (EDSS)		MRI improvement
Progressive	Extended disability score (EDSS)			MRI improvement

PRIMARY IMMUNODEFICIENCIES

Condition	Clinical Marker			
X-linked hypogammaglobulinaemia				
Common variable immunodeficiency	Reduction in infections eg sino-pulmonary	Prevention or stabilisation of bronchiectasis	Reduction in frequency of microbiological confirmed bacterial infections	Improvement in sinus Xrays or CT scans
IgG subclass deficiencies including isolated IgG2 deficiency and isolated IgG3 deficiency	Reduction in infections eg sino-pulmonary	Prevention or stabilisation of bronchiectasis		
Specific antibody deficiency (with normal IgG subclasses and IgA)				

Specific antibody deficiency (with deficiency of IgG subclasses and/or IgA)					
Hyperimmunoglobulin M Syndrome (Type 1-4) Immune Deficiency with normal or elevated IgM					
Combined immune deficiency including specific syndromes eg. Wiskott-Aldrich syndrome					
Severe combined immunodeficiency					
Other Primary (inherited) immunodeficiency diseases with defective B cell function					
Transient hypogammaglobulinemia of infancy					

Appendix 2 — Summary data on conditions and papers

This appendix presents the summary data on each of the conditions and the relevant references for each condition. It includes a 1–2 page summary for each condition, accompanied by a 1–2 page summary of each of the relevant papers for each condition.

The data for this appendix are contained in the attached electronic file (Appendix 2 - summary data on conditions and papers (8Sep04).snp). To read this file, download the snapshot viewer program from <http://www.abxair.com/software/downloads.htm>

The data are also presented in hardcopy, with the conditions listed as shown in the index below. Tables 2.1–2.8 show the condition, category and page number in the attached electronic and hardcopy file. Table 2.9 shows papers for which the full reference is available.

Appendix 2.1 Haematological

Condition	Category	Page no.
Acute leukemia in childhood	Ila	1
Alloimmune thrombocytopenia antenatal	IVb	5
Amegakaryocytic thrombocytopenia	IVb	6
Aplastic anaemia/pancytopenia	IVb	7
Autoantibodies to Factor VIII or Acquired von Willebrand disease	Ila	8
Autoimmune haemolytic anaemia (Evan's syndrome)	IVb	11
Autoimmune neutropenia	IVb	12
Autoimmune neutropenia in infancy	IVb	13
Bone marrow transplantation: allogeneic and autologous	IIc	14
Chronic lymphocytic leukaemia with hypogammaglobulinaemia or persistent serum total IgG deficiency and documented recurrent infections	Ila	28
Diamond-Blackfan syndrome	IVb	37
Haemolytic transfusion reaction	IVb	38
Haemolytic uraemic syndrome	IVb	39
HIV-associated thrombocytopenia	Ila	40
Immune thrombocytopenia, Idiopathic thrombocytopenic purpura	I	42
Multiple myeloma	Ila	49
Neonatal ABO isoimmunisation	Ila	53
Other chronic lymphoproliferative disease with persistent serum total IgG deficiency and documented recurrent infections	IVb	55
Post-transfusion purpura	IVb	56
Pure white cell aplasia	IVb	57
Red cell aplasia	IVb	58
Rhesus D haemolytic disease	Ila	59
Septic thrombocytopenia	IVb	61
Sickle cell anaemia	IVb	62
Virus associated haemophagic syndrome	IVb	63

Appendix 2.2 HIV/AIDS

Condition	Category	Page no
HIV/AIDS: Adult	IIb	64
HIV/AIDS: Paediatric	IIa	71

Appendix 2.3 Immunological

Condition	Category	Page no
Transplantations: Heart/Lung/Pancreas	IVb	82
Transplantations: kidney - infection (eg BK virus)	IIa	83
Transplantations: kidney - rejection	IIa	86
Transplantations: liver	IVb	88
Untransplantability due to anti-HLA antibodies	IVb	89

Appendix 2.4 Miscellaneous

Condition	Category	Page no
Acute rheumatic fever	IIb	90
Asthma	IIc	92
Autism - young adults	IVb	96
Burns	IIa	97
Cardiac surgery with bypass-prophylaxis	IIa	99
Congestive cardiac failure	IIa	102
Grave's ophthalmopathy	IIa	105
Idiopathic dilated cardiomyopathy	IIb	109
Non-obstetric antiphospholipid syndrome	IVb	111
Other conditions (not listed elsewhere): IVF failure	IIc	112
Other conditions (not listed elsewhere): obsessive compulsive/tic disorders	IIa	115
Paediatric head injury	IIb	118
Recurrent fetal loss with or without antiphospholipid syndrome	III	120
Trauma	IIa	125

Appendix 2.5 Neurological

Condition	Category	Page no
Acute idiopathic dysautonomia	IVb	130
Autoimmune diabetic neuropathy	IVb	131
Chronic inflammatory demyelinating polyneuropathy	I	132
Encephalomyelitis and sensory neuropathy associated with anti- HU antibody	IIa	134
Epilepsy	IIa	136
Epilepsy: childhood epilepsy resistant	IIa	138
Epilepsy: Landau-Kleffner syndrome	IIa	140
Epilepsy: Lennox - Gastaut syndrome	IIa	142
Epilepsy: mixed seizures of early onset associated with IgG	IVb	146
Epilepsy: Rasmussen syndrome	IVb	147
Epilepsy: subclass deficiency	IVb	148
Guillain Barre syndrome	IIa	149
IgM paraproteinaemic neuropathy	IIb	151
Multifocal motor neuropathy with persistent conduction block	IIa	155
Multiple sclerosis: progressive/relapsing or remitting	IIc	162

Condition	Category	Page no
Muscle diseases: dermatomyositis	Ila	172
Muscle diseases: inclusion body myositis	Ila	174
Muscle diseases: polymyositis	Ila	178
Muscle diseases: polymyositis and systemic connective tissue disease	IVb	180
Myalgic encephalomyelitis	Ilc	181
Neuromuscular disorders: Lambert Eaton Syndrome	Ila	184
Neuromuscular disorders: myasthenia gravis	Ilc	188
Neuromuscular disorders: stiff man syndrome	Ila	190
Other disorders: adrenoleukodystrophy	IVb	192
Other disorders: amyotrophic lateral sclerosis	IVb	193
Other disorders: motor neuron disease	Ila	194
Other disorders: opsiclonus myoclonus	IVb	198
Other disorders: paraneoplastic cerebellar degeneration with NO antibodies	IVb	199
Polyneuropathy of critical illness	Ila	200

Appendix 2.6 Primary immunodeficiencies

Condition	Category	Page no
B-cell tumours	Ila	202
Combined immune deficiency including specific syndromes (eg. Wiskott-Aldrich syndrome)	IVb	204
Common variable immunodeficiency	Ila	205
Hyperimmunoglobulin M Syndrome (Type 1-4) immune deficiency with normal or elevated IgM	IVb	209
IgG subclass deficiencies including isolated IgG2 deficiency and isolated IgG3 deficiency	IVb	210
Lymphocytic leukaemia with hypogammaglobulinaemia	Ila	211
Nephrotic syndrome	Ila	216
Other primary (inherited) immunodeficiency diseases with defective B cell function	IVb	218
Paraneoplastic cerebellar degeneration with NO antibodies	IVb	219
Primary hypogammaglobulinaemia	Ila	220
Severe combined immunodeficiency	IVb	223
Specific antibody deficiency (with deficiency of IgG subclasses and/or IgA)	IVb	224
Specific antibody deficiency (with normal IgG subclasses and IgA)	IVb	225
Transient hypogammaglobulinemia of infancy	IVb	228
X-linked hypogammaglobulinaemia	IVb	229

Appendix 2.7 Skin diseases

Condition	Category	
Autoimmune blistering diseases: atopic dermatitis	IIb	230
Autoimmune blistering diseases: bullous pemphigoid	IVb	232
Autoimmune blistering diseases: cicatricial pemphigoid	IIa	233
Autoimmune blistering diseases: epidermolysis bullosa acquisita	IVa	235
Autoimmune blistering diseases: linear IgA disease	IVb	236
Autoimmune blistering diseases: pemphigoid - oral	IIa	237
Autoimmune blistering diseases: pemphigoid gestationes	IVb	239
Autoimmune blistering diseases: pemphigus vulgaris and foliaceus	IIa	240
Stevens Johnson syndrome	IIc	242
Toxic epidermal necrolysis	IIb	246

Appendix 2.8 Vasculitis/inflammatory

Condition	Category	Page no
ANCA-positive vasculitis (including Wegener's)	IIa	248
Churg-Strauss vasculitis	IVb	251
Henoch-Schonlein pupura	IVb	252
Inflammatory bowel disease: Crohn's disease	IVb	253
Inflammatory bowel disease: ulcerative colitis	IVb	254
Kawasaki's disease	I	255
Rheumatoid arthritis: adult	IIc	257
Rheumatoid arthritis: juvenile	IIa	263
Sepsis: adult sepsis	IIa	266
Sepsis: neonatal sepsis: prevention/treatment	III	275
Sepsis: paediatric sepsis	IIa	278
Sepsis: preterm sepsis: prevention/treatment	IVb	281
Systemic lupus erythematosus (SLE)	IIa	282
Systemic necrotizing vasculitis	IVb	284

Appendix 2.9 References for which full paper is available

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Appendix 3 — Data on safety

This appendix presents the summary data on references relevant to the safety of IVIG.

The data for this appendix is contained in the attached file:

- Appendix 3 - summary data on IVIG safety (8Sep04).snp.

To read this file, download the snapshot viewer program from

<http://www.abxair.com/software/downloads.htm>

Appendix 4 — Excluded references

This appendix lists the references excluded from the review for one of the following reasons:

- content of paper not relevant (eg intramuscular or intra-articular rather than intravenous immunoglobulin)
- paper describes methodology, not outcomes
- results are presented in such a way that it is not possible to determine which results refer to IVIG and which refer to other treatments
- paper superseded by other papers (eg case studies superseded by RCTs).

The data for this appendix is contained in the attached file:

- Appendix 4 - excluded references (8Sep04).snp.

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