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

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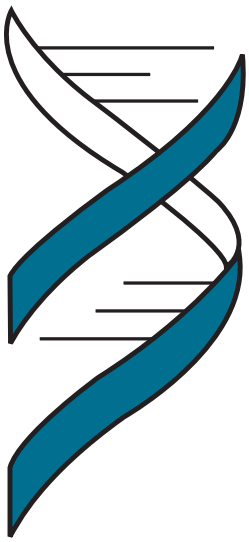

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1 Introduction

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 disorders[3] (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 checklist[1] 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 sydnrome
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
IIa	Primary immunodeficiencies	Common variable immunodeficiency
IIa	Primary immunodeficiencies	Lymphocytic leukaemia with hypogammaglobulinaemia
IIa	Primary immunodeficiencies	Nephrotic syndrome
IIa	Primary immunodeficiencies	Primary hypogammaglobulinaemia
IIa	Skin diseases	Autoimmune blistering diseases: cicatricial pemphigoid
IIa	Skin diseases	Autoimmune blistering diseases: pemphigoid - oral
IIa	Skin diseases	Autoimmune blistering diseases: pemphigus vulgaris and foliaceus
IIa	Vasculitis/inflammatory	ANCA-positive vasculitis (including Wegener's)
IIa	Vasculitis/inflammatory	Rheumatoid arthritis: juvenile
IIa	Vasculitis/inflammatory	Sepsis: adult sepsis
IIa	Vasculitis/inflammatory	Sepsis: paediatric sepsis
IIa	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 N0 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	Inflamatory bowel disease: Crohn's disease
IVb	Vasculitis/inflammatory	Inflamatory 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: • Chronic lymphocytic leukaemia with hypogammaglobulinaemia or persistent serum total IgG deficiency and documented recurrent infections • Lymphocytic leukaemia with hypogammaglobulinaemia
Haematological	Septic thrombocytopenia	See: • Sepsis: adult, paediatric, neonatal • Immune thrombocytopenia • Idiopathic thrombocytopenic purpura
Immunological	Transplantations: liver	See: • Transplantations: kidney - infection (eg BK virus)
Immunological	Untransplantability due to anti-HLA antibodies	See: • Transplantations: kidney - infection (eg BK virus)
Neurological	Acute idiopathic dysautonomia	See: • Guillain Barre syndrome
Neurological	Epilepsy: mixed seizures of early onset associated with IgG	See: • Other epilepsy categories
Neurological	Epilepsy: Rasmussen syndrome	See: • Other epilepsy categories
Neurological	Epilepsy: subclass deficiency	See: • Other epilepsy categories
Neurological	Muscle diseases: polymyositis and systemic connective tissue disease	See: • Muscle diseases: polymyositis
Primary immunodeficiencies	Combined immune deficiency including specific syndromes (eg. Wiskott-Aldrich syndrome)	See: • Common variable immunodeficiency • Primary hypogammaglobulinaemia
Primary immunodeficiencies	Hyperimmunoglobulin M Syndrome (Type 1-4) immune deficiency with normal or elevated IgM	See: • Common variable immunodeficiency • Primary hypogammaglobulinaemia
Primary immunodeficiencies	IgG subclass deficiencies including isolated IgG2 deficiency and isolated IgG3 deficiency	See: • Common variable immunodeficiency • Primary hypogammaglobulinaemia
Primary immunodeficiencies	Other primary (inherited) immunodeficiency diseases with defective B cell function	See: • Common variable immunodeficiency • Primary hypogammaglobulinaemia
Primary immunodeficiencies	Severe combined immunodeficiency	See: • Common variable immunodeficiency • Primary hypogammaglobulinaemia
Primary immunodeficiencies	Specific antibody deficiency (with deficiency of IgG subclasses and/or IgA)	See: • Common variable immunodeficiency • Primary hypogammaglobulinaemia
Primary immunodeficiencies	Specific antibody deficiency (with normal IgG subclasses and IgA)	See: • Common variable immunodeficiency • Primary hypogammaglobulinaemia

Condition type	Condition	Related conditions reported against
Primary immunodeficiencies	Transient hypogammaglobulinemia of infancy	• Primary hypogammaglobulinaemia
Primary immunodeficiencies	X-linked hypogammaglobulinaemia	• Primary hypogammaglobulinaemia
Skin diseases	Autoimmune blistering diseases: bullous pemphigoid	• Autoimmune blistering diseases: cicatricial pemphigoid, pemphigoid – oral, pemphigus vulgaris and foliaceus
Skin diseases	Autoimmune blistering diseases: pemphigoid gestationes	• Autoimmune blistering diseases: cicatricial pemphigoid, pemphigoid – oral, pemphigus vulgaris and foliaceus
Vasculitis/inflammatory	Sepsis: preterm sepsis: prevention/treatment	• Sepsis: neonatal, paediatric
Vasculitis/inflammatory	Systemic necrotizing vasculitis	• 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: • Chronic lymphocytic leukaemia with hypogammaglobulinaemia or persistent serum total IgG deficiency and documented recurrent infections • Lymphocytic leukaemia with hypogammaglobulinaemia
–	Septic thrombocytopenia See: • Sepsis: adult, paediatric, neonatal • Immune thrombocytopenia • Idiopathic thrombocytopenic purpura

4.4.2 HIV/AIDS

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

4.4.3 Immunological

Category	Condition — immunological
IIa	Transplantations: kidney - infection (eg BK virus)
IIa	Transplantations: kidney - rejection
IVb	Transplantations: Heart/Lung/Pancreas
–	Transplantations: liver See: • 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
IIa	Burns
IIa	Cardiac surgery with bypass-prophylaxis
IIa	Congestive cardiac failure
IIa	Grave's ophthalmopathy
IIa	Other conditions (not listed elsewhere): obsessive compulsive/tic disorders
IIa	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 antibodie
IIa	Epilepsy
IIa	Epilepsy: childhood epilepsy resistant
IIa	Epilepsy: Landau-Kleffner syndrome
IIa	Epilepsy: Lennox - Gastaut sydnrome
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: opsiclonus myoclonus
IVb	Other disorders: paraneoplastic cerebellar degeneration with N0 antibodies
–	Acute idiopathic dysautonomia See: • Guillain-Barre syndrome
–	Muscle diseases: polymyositis and systemic connective tissue disease See: • Muscle diseases: polymyositis
–	Epilepsy: mixed seizures of early onset associated with IgG See: • Other epilepsy categories
–	Epilepsy: Rasmussen syndrome See: • Other epilepsy categories
–	Epilepsy: subclass deficiency See: • Other epilepsy categories

4.4.6 Primary immunodeficiencies

Category	Condition
IIa	B-cell tumours
IIa	Common variable immunodeficiency
IIa	Lymphocytic leukaemia with hypogammaglobulinaemia
IIa	Nephrotic syndrome
IIa	Primary hypogammaglobulinaemia
IVb	Paraneoplastic cerebellar degeneration with NO antibodies
–	Combined immune deficiency including specific syndromes (eg. Wiskott-Aldrich syndrome) See: • Common variable immunodeficiency • Primary hypogammaglobulinaemia
–	Hyperimmunoglobulin M Syndrome (Type 1-4) immune deficiency with normal or elevated IgM See: • Common variable immunodeficiency • Primary hypogammaglobulinaemia
–	IgG subclass deficiencies including isolated IgG2 deficiency and isolated IgG3 deficiency See: • Common variable immunodeficiency • Primary hypogammaglobulinaemia
–	Other primary (inherited) immunodeficiency diseases with defective B cell function See: • Common variable immunodeficiency • Primary hypogammaglobulinaemia
–	Severe combined immunodeficiency See: • Common variable immunodeficiency • Primary hypogammaglobulinaemia
–	Specific antibody deficiency (with deficiency of IgG subclasses and/or IgA) See: • Common variable immunodeficiency • Primary hypogammaglobulinaemia
–	Specific antibody deficiency (with normal IgG subclasses and IgA) See: • Common variable immunodeficiency • Primary hypogammaglobulinaemia
–	Transient hypogammaglobulinemia of infancy See: • Primary hypogammaglobulinaemia
–	X-linked hypogammaglobulinaemia See: • 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: • Autoimmune blistering diseases: cicatricial pemphigoid, pemphigoid – oral, pemphigus vulgaris and foliaceus
–	Autoimmune blistering diseases: pemphigoid gestationes See: • 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 pupura
IVb	Inflamatory bowel disease: Crohn's disease
IVb	Inflamatory bowel disease: ulcerative colitis
–	Sepsis: preterm sepsis: prevention/treatment See: • Sepsis: neonatal, paediatric
–	Systemic necrotizing vasculitis See: • 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, tranfusion-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 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 outcomes[1]

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	
Idipathic 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			
Paediatric	Reduction in frequency of presumed bacterial sino-pulmonary infections	Prevention (or halt in progress) of bronchiectasis	Acquired Immunodeficiency Syndrome: HIV; Infecton
Adult			
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:			
Juvenile	Disease activity scores	Length of remission	Arthritis, Juvenile Rheumatoid
Adult	Disease activity scores (eg Ritchie index)	Length of remission	Arthritis, Rheumatoid
Inflamatory bowel disease:			
Crohn's disease	Disease activity scores	Length of remission	Crohn's Disease
Ulcerative colitis	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
Adult sepsis	All-cause mortality	Sepsis-related mortality	Sepsis
SKIN DISEASES			
Autoimmune blistering diseases			Autoimmune Diseases

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

Linear IgA disease	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				
Kidney - rejection	reversal of rejection			reduction in plasma creatinine
Kidney - infection eg BK virus	reversal of infection	improvement in renal function		reduction in plasma creatinine
Liver				
Heart/Lung/Pancreas				
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; *Disease free survival*	MRC score in involved muscle group; *Disease activity scores*	*Serum CK Level*	CPK level; *Disability indices*
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 disablity 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 sydnrome	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 N0 antibodies	Stabilisation or improvement in clinical condition - neurologic disability score			Reduction in Y0 antibodies
Amyotrophic lateral sclerosis	Neurologic disabilty score			
Motor neuron disease	Neurologic disablity score			
Adrenoleukodystrophy	Neurologic disablity 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	IIa	1
Alloimmune thrombocytopenia antenatal	IVb	5
Amegakaryocytic thrombocytopenia	IVb	6
Aplastic anaemia/pancytopenia	IVb	7
Autoantibodies to Factor VIII or Acquired von Willebrand disease	IIa	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	IIa	28
Diamond-Blackfan syndrome	IVb	37
Haemolytic transfusion reaction	IVb	38
Haemolytic uraemic syndrome	IVb	39
HIV-associated thrombocytopenia	IIa	40
Immune thrombocytopenia, Idiopathic thrombocytopenic purpura	I	42
Multiple myeloma	IIa	49
Neonatal ABO isoimmunisation	IIa	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	IIa	59
Septic thrombocytopenia	IVb	61
Sickle cell anaemia	IVb	62
Virus associated haemophagic syndrome	IVb	63

Appendix 2.2 HIV/AIDS

Appendix 2.3 Immunological

Appendix 2.4 Miscellaneous

Appendix 2.5 Neurological

Condition	Category	Page no
Muscle diseases: dermatomyositis	IIa	172
Muscle diseases: inclusion body myositis	IIa	174
Muscle diseases: polymyositis	IIa	178
Muscle diseases: polymyositis and systemic connective tissue disease	IVb	180
Myalgic encephalomyelitis	IIc	181
Neuromuscular disorders: Lambert Eaton Syndrome	IIa	184
Neuromuscular disorders: myasthenia gravis	IIc	188
Neuromuscular disorders: stiff man syndrome	IIa	190
Other disorders: adrenoleukodystrophy	IVb	192
Other disorders: amyotrophic lateral sclerosis	IVb	193
Other disorders: motor neuron disease	IIa	194
Other disorders: opsiclonus myoclonus	IVb	198
Other disorders: paraneoplastic cerebellar degeneration with N0 antibodies	IVb	199
Polyneuropathy of critical illness	IIa	200

Appendix 2.6 Primary immunodeficiencies

Condition	Category	Page no
B-cell tumours	IIa	202
Combined immune deficiency including specific syndromes (eg. Wiskott-Aldrich syndrome)	IVb	204
Common variable immunodeficiency	IIa	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	IIa	211
Nephrotic syndrome	IIa	216
Other primary (inherited) immunodeficiency diseases with defective B cell function	IVb	218
Paraneoplastic cerebellar degeneration with NO antibodies	IVb	219
Primary hypogammaglobulinaemia	IIa	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
Inflamatory bowel disease: Crohn's disease	IVb	253
Inflamatory 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

Reference	Ref no
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Kress HG, Scheidewig C, Schmidt H, Silber R. Reduced incidence of postoperative infection after intravenous administration of an immunoglobulin A- and immunoglobulin M-enriched preparation in anergic patients undergoing cardiac surgery.[see comment]. Crit Care Med 1999; 27(7):1281-7.	23
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Wiles CM, Brown P, Chapel H, Guerrini R, Hughes RA, Martin TD, McCrone P, Newsom-Davis J, Palace J, Rees JH, Rose MR, Scolding N, Webster AD. Intravenous immunoglobulin in neurological disease: a specialist review. J Neurol Neurosurg Psychiatry. 2002 Apr;72(4):440-8.	268
Dalakas MC, Koffman B, Fujii M, Spector S, Sivakumar K, Cupler E. A controlled study of intravenous immunoglobulin combined with prednisone in the treatment of IBM. Neurology. 2001 Feb 13;56(3):323-7.	273
Walter MC, Lochmuller H, Toepfer M, Schlotter B, Reilich P, Schroder M, Muller-Felber W, Pongratz D. High-dose immunoglobulin therapy in sporadic inclusion body myositis: a double-blind, placebo-controlled study. J Neurol. 2000 Jan;247(1):22-8.	274
Dalakas MC, Sonies B, Dambrosia J, Sekul E, Cupler E, Sivakumar K. Treatment of inclusion-body myositis with IVIg: a double-blind, placebo-controlled study. Neurology. 1997 Mar;48(3):712-6.	275
Blanchette VS, Luke B, Andrew M, Sommerville-Nielsen S, Barnard D, de Veber B, Gent M. A prospective, randomized trial of high-dose intravenous immune globulin G therapy, oral prednisone therapy, and no therapy in childhood acute immune thrombocytopenic purpura. J Pediatr. 1993 Dec;123(6):989-95.	277
Blanchette V, Imbach P, Andrew M, Adams M, McMillan J, Wang E, Milner R, Ali K, Barnard D, Bernstein M, et al. Randomised trial of intravenous immunoglobulin G, intravenous anti-D, and oral prednisone in childhood acute immune thrombocytopenic purpura. Lancet. 1994 Sep 10;344(8924):703-7.	278

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.

To read this file, download the snapshot viewer program from http://www.abxair.com/software/downloads.htm

Appendix 2 — Summary data on conditions and papers

Haematological

Condition summary	Acute leukemia in childhood
Reference list:	137 Sumer T, Abumelha A, al-Mulhim I, al-Fadil M. Treatment of fever and neutropenia with antibiotics versus antibiotics plus intravenous gammaglobulin in childhood leukemia. Eur J Pediatr 1989; 148(5):401-2. 279 Gebauer E, Tomic J, Stevanovic S. Intravenous immunoglobulin in the treatment of infections in children with acute leukemias Med Pregl. 1994 Jan-Feb;47(1-2):52-5. 280 Gimesi A, Eibl M, Koos R, Somlo P, Magyarossy E, Kardos G, Fazekas E, Schmidt M, Borsi J, Schuler D. Immunoglobulin prophylaxis during intensive treatment of acute lymphoblastic leukemia in children. Acta Paediatr Hung. 1992;32(2):115-25.
Types of study:	Three RCTs.
Total sample size:	141
Quality:	Low
Result:	Significantly less febrile episodes, less febrile days.
Adverse events:	None reported.
Conclusion:	Possible benefit, based on 3 small RCTs (only 1 in English).
Category:	IIa

Condition studies: Acute leukemia in childhood

137 Sumer T, Abumelha A, al-Mulhim I, al-Fadil M. Treatment of fever and neutropenia with antibiotics versus antibiotics plus intravenous gammaglobulin in childhood leukemia. Eur J Pediatr 1989; 148(5):401-2.

Study design: RCT **Length of follow-up:**

Sample size: 33 children **Population:**

Intervention: IVIG, cefataxim and amikacin.

Comparison / control: Same antibiotics, no IVIG.

Outcome(s) measured: Duration of fever, neutropenia, hospitalisation and interruption of chemotherapy.

Quality assessment (internal validity)

Placebo: No

Follow-up:

Results

Intervention groups: Duration of fever shorter, other outcomes not significantly different. **Control / comparison group(s):**

P-value:

Adverse events:

Conclusions / Comments: Some benefit (in reducing duration of fever).

Condition studies: Acute leukemia in childhood

279

Gebauer E, Tomic J, Stevanovic S. Intravenous immunoglobulin in the treatment of infections in children with acute leukemias Med Pregl. 1994 Jan-Feb;47(1-2):52-5.

Study design: RCT

Length of follow-up:

Sample size: Sample of 48 children.

Population:

Intervention: IVIG (100mg.kg), with antibiotics.

Comparison / control:

Outcome(s) measured:

Quality assessment (internal validity)

Placebo:

Follow-up:

Results

Intervention groups: Less febrile episodes ($p < 0.01$); less febrile days ($p < 0.05$).

Control / comparison group(s):

P-value:

Adverse events:

Conclusions / Comments: Possible benefit.

Condition studies: Acute leukemia in childhood

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Gimesi A, Eibl M, Koos R, Somlo P, Magyarossy E, Kardos G, Fazekas E, Schmidt M, Borsi J, Schuler D. Immunoglobulin prophylaxis during intensive treatment of acute lymphoblastic leukemia in children. Acta Paediatr Hung. 1992;32(2):115-25.

Study design: RCT **Length of follow-up:**

Sample size: 60 children **Population:**

Intervention: IVIG (100mg/kg/week) for 3 months, 2 x 200mg/kg/month during 4, 5 and 6 months.

Comparison / control:

Outcome(s) measured: Days with fever, number of infections, length and frequency of antibiotic therapy.

Quality assessment (internal validity)

Placebo:

Follow-up:

Results

Intervention groups:

Control / comparison group(s):

P-value:

Adverse events:

Conclusions / Comments: Possible benefit.

Haematological

Condition summary	Alloimmune thrombocytopenia antenatal
Category:	IVb

Haematological

Condition summary	Amegakaryocytic thrombocytopenia
Category:	IVb

Haematological

Condition summary	Aplastic anaemia/pancytopenia
Category:	IVb

Haematological

Condition summary	Autoantibodies to Factor VIII or Acquired von Willebrand disease
Reference list:	99 Federici, A. B.; Stabile, F.; Castaman, G.; Canciani, M. T., and Mannucci, P. M. (Angelo Bianchi Bonomi Hemophilia and Thrombosis Center, IRCCS Maggiore Hospital, University of Milano and Department of Hematology, S. Bortolo Hospital, Vicenza, Italy. Augusto.Federici@unimi.it). Treatment of acquired von Willebrand syndrome in patients with monoclonal gammopathy of uncertain significance: comparison of three different therapeutic approaches. Blood. 1998 Oct 15; 92(8):2707-11. 125 Schwartz, R. S.; Gabriel, D. A.; Aledort, L. M.; Green, D., and Kessler, C. M. (Department of Clinical Research, Miles Inc., Berkeley, CA 94710, USA). A prospective study of treatment of acquired (autoimmune) factor VIII inhibitors with high-dose intravenous gammaglobulin. Blood. 1995 Jul 15; 86(2):797-804.
Types of study:	Two cohort studies.
Total sample size:	29
Quality:	Low
Result:	In one study, IVIg reduced laboratory abnormalities and bleeding during surgery (short and long-term therapy) in IgG-MGUS, but was ineffective in IgM-MGUS. In one study, acquired factor VIII inhibitors were reduced in ~25% of patients and disappeared in 3 patients with low level inhibitors.
Adverse events:	None reported.
Conclusion:	Possible benefit, based on 2 small cohort studies.
Category:	IIa

Condition studies: Autoantibodies to Factor VIII or Acquired von Willebrand disease

99

Federici, A. B.; Stabile, F.; Castaman, G.; Canciani, M. T., and Mannucci, P. M. (Angelo Bianchi Bonomi Hemophilia and Thrombosis Center, IRCCS Maggiore Hospital, University of Milano and Department of Hematology, S. Bortolo Hospital, Vicenza, Italy. Augusto.Federici@unimi.it). Treatment of acquired von Willebrand syndrome in patients with monoclonal gammopathy of uncertain significance: comparison of three different therapeutic approaches. Blood. 1998 Oct 15; 92(8):2707-11.

Study design:	Cohort	**Length of follow-up:**	Patients were followed up 2 days post IVIG intervention. Two patients were followed up 21 days post IVIG intervention
Sample size:	10 total	**Population:**	Patients with monoclonal gammopathy of uncertain significance (MGUS) and acquired von Willebrand syndrome (AvWS) (8 IgG, 2 IgM).

Intervention: Desmopressin, factor VIII concentrate and IVIG (1g/kg/day for 2 days) (and IVIG every 21 days in 2 IgG patients).

Comparison / control: The outcomes of the 3 interventions were compared to each other.

Outcome(s) measured: Improvement in lab abnormalities, bleeding (chronic GI and during surgery).

Quality assessment (internal validity)

Placebo: No

Follow-up: No reference to follow-up is made.

Results

Intervention groups:	In IgG-MGUS, IVIg provided some improvement in laboratory abnormalities and prevention of bleeding during surgery (in short and long-term therapy) but was not effective in IgM-MGUS.	**Control / comparison group(s):**	N/A

P-value: Other

Adverse events: No adverse effects were reported.

Conclusions / Comments: Small cohort of patients, low quality.

Condition studies:	Autoantibodies to Factor VIII or Acquired von Willebrand disease

125	Schwartz, R. S.; Gabriel, D. A.; Aledort, L. M.; Green, D., and Kessler, C. M. (Department of Clinical Research, Miles Inc., Berkeley, CA 94710, USA). A prospective study of treatment of acquired (autoimmune) factor VIII inhibitors with high-dose intravenous gammaglobulin. Blood. 1995 Jul 15; 86(2):797-804.

Study design:	Cohort	**Length of follow-up:**	No specific mention of length of follow up is made however, it is stated that outcomes in certain patients were reached ranging from several weeks to months post intervention
Sample size:	19	**Population:**	Patients with acquired factor VIII inhibitors.

Intervention:	IGIV at either 1000mg/kg for 2 consecutive days or 400mg/kg for 5 consecutive days.
Comparison / control:	Outcomes of the two dose regimes were compared to each other.
Outcome(s) measured:	A reduction in inhibitor titer; response rate.

Quality assessment (internal validity)

Placebo:	No
Follow-up:	Six of the 19 patients were assessed. Of these patients, 6 met the criteria for response. Two of these patients were concurrently being treated with prednisone, therefore reponse rate was calculated from 4 patients.

Results

Intervention groups:	Outcomes are descriptively reported. Reduction of 25% or more was observed in 8/16 assessible patients. The inhibitor disappeared in 3 patients with low level inhibitors.	**Control / comparison group(s):**	N/A
P-value:			

Adverse events:	No adverse effects were reported.
Conclusions / Comments:	This is a comparative study. No mention is made as to how patients were assigned to the interventions that were compared. This study is low quality.

Haematological

Condition summary	Autoimmune haemolytic anaemia (Evan's syndrome)
Category:	IVb

Haematological

Condition summary	Autoimmune neutropenia
Category:	IVb

Haematological

Condition summary	Autoimmune neutropenia in infancy
Category:	IVb

Haematological

Condition summary

Bone marrow transplantation: allogeneic and autologous

Reference list:

86 Abdel-Mageed, A.; Graham-Pole, J.; Del Rosario, M. L. U.; Longmate, J.; Ochoa, S.; Amylon, M.; Elfenbein, G. J.; Janiec, J.; Jansen, J., and Lazarus, H. M. Comparison of two doses of intravenous immunoglobulin after allogeneic bone marrow transplants. Bone Marrow Transplantation. 1999; 23(9):929-932.

97 Cordonnier, C.; Chevret, S.; Legrand, M.; Rafi, H.; Dhedin, N.; Lehmann, B.; Bassompierre, F.; Gluckman, E., and GREFIG Study Group (Assistance Publique-Hopitaux de Paris, Creteil, France. carlcord@club-internet.fr). Should immunoglobulin therapy be used in allogeneic stem-cell transplantation? A randomized, double-blind, dose effect, placebo-controlled, multicenter trial.[see comment]. Annals of Internal Medicine. 2003 Jul 1; 139(1):8-18.

100 Feinstein, L. C.; Seidel, K.; Jocum, J.; Bowden, R. A.; Anasetti, C.; Deeg, H. J.; Flowers, M. E.; Kansu, E.; Martin, P. J.; Nash, R. A.; Storek, J.; Etzioni, R.; Applebaum, F. R.; Hansen, J. A.; Storb, R., and Sullivan, K. M. Reduced dose intravenous immunoglobulin does not decrease transplant-related complications in adults given related donor marrow allografts. Biology of Blood & Marrow Transplantation. 1999; 5(6):369-78.

121 Poynton, C. H.; Jackson, S.; Fegan, C.; Barnes, R. A., and Whittaker, J. A. Use of IgM enriched intravenous immunoglobulin (Pentaglobin) in bone marrow transplantation. Bone Marrow Transplantation. 1992 Jun; 9(6):451-7.

132 Winston, D. J.; Antin, J. H.; Wolff, S. N.; Bierer, B. E.; Small, T.; Miller, K. B.; Linker, C.; Kaizer, H.; Lazarus, H. M.; Petersen, F. B.; Cowan, M. J.; Ho, W. G.; Wingard, J. R.; Schiller, G. J.; Territo, M. C.; Jiao, J.; Petrarca, M. A., and Tonetta, S. A. (Department of Medicine, UCLA Center for the Health Sciences, Los Angeles, CA 90095, USA). 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 Transplantation. 2001 Jul; 28(2):187-96.

133 Winston, D. J.; Ho, W. G.; Bartoni, K., and Champlin, R. E. (Department of Medicine, UCLA Center for the Health Sciences). Intravenous immunoglobulin and CMV-seronegative blood products for prevention of CMV infection and disease in bone marrow transplant recipients. Bone Marrow Transplantation. 1993 Sep; 12(3):283-8.

135 Zikos, P.; Van Lint, M. T.; Lamparelli, T.; Gualandi, F.; Occhini, D.; Mordini, N.; Berisso, G.; Bregante, S., and Bacigalupo, A. (Divisione Ematologia II, Ospedale San Martino, Genoa, Italy). A randomized trial of high dose polyvalent intravenous immunoglobulin (HDIgG) vs. Cytomegalovirus (CMV) hyperimmune IgG in allogeneic hemopoietic stem cell transplants (HSCT). Haematologica. 1998 Feb; 83(2):132-7.

138 Wolff SN, Fay JW, Herzig RH et al. High-dose weekly intravenous immunoglobulin to prevent infections in patients undergoing autologous bone marrow transplantation or severe myelosuppressive therapy. A study of the American Bone Marrow Transplant Group. Ann Intern Med 1993; 118(12):937-42.

Types of study:	8 RCTs
Total sample size:	1830
Quality:	High
Result:	One RCT - reduction in hepatic toxicity; 1 RCT- reduction in incidence and severity of acute GVHD, but no sign effect on survival rate; 1 RCT – higher dose associated with less GVHD; 1 RCT – no significant difference in transplant-related mortality or disease-free survival; 1 RCT – no significant difference between 3 doses of IVIG; 1 RCT – no significant difference between 2 doses of IVIG; 1 RCT – no significant difference in infection rates.
Adverse events:	Higher incidence of severe or fatal hepatic veno-occlusive disease in patients receiving IVIG was reported (in 2 RCTs, dose-related in 1 RCT); cumulative incidence of relapse of malignancy was higher in IVIg recipients than in controls (31 vs. 18%, p = 0.03 (1 RCT)); chills, headaches.
Conclusion:	Conflicting results - large RCTs showing benefit of higher dose, others showing no dose effect, others showing no significant difference from placebo.

Category:	IIc

Condition studies: Bone marrow transplantation: allogeneic and autologous

86	Abdel-Mageed, A.; Graham-Pole, J.; Del Rosario, M. L. U.; Longmate, J.; Ochoa, S.; Amylon, M.; Elfenbein, G. J.; Janiec, J.; Jansen, J., and Lazarus, H. M. Comparison of two doses of intravenous immunoglobulin after allogeneic bone marrow transplants. Bone Marrow Transplantation. 1999; 23(9):929-932.

Study design:	RCT	**Length of follow-up:**	Interventions were given from day -8 to day +111
Sample size:	350	**Population:**	Bone marrow transplant recipients.

Intervention:	IGIV at either 250mg/kg or 500mg/kg.
Comparison / control:	Outcomes of the two dose regimes were compared to each other.
Outcome(s) measured:	Event-free survival, systemic infection and acute graft-versus-host disease.

Quality assessment (internal validity)

Placebo:	No
Follow-up:	Group of 18 patients excluded due to inadequate data or protocol deviation, remaining 322 analysed.

Results

Intervention groups:	Outcomes are descriptively reported. The study reports that the 2 dose cohorts had similar event-free survival and infection frequencies, with the higher dose (500mg/kg) associated with less acute graft-versus-host disease.	**Control / comparison group(s):**	N/A

P-value:	P = 0.03
Adverse events:	No adverse effects were reported.
Conclusions / Comments:	Higher dose associated with less acute graft-versus host disease.

Condition studies:	Bone marrow transplantation: allogeneic and autologous

97	Cordonnier, C.; Chevret, S.; Legrand, M.; Rafi, H.; Dhedin, N.; Lehmann, B.; Bassompierre, F.; Gluckman, E., and GREFIG Study Group (Assistance Publique-Hopitaux de Paris, Creteil, France. carlcord@club-internet.fr). Should immunoglobulin therapy be used in allogeneic stem-cell transplantation? A randomized, double-blind, dose effect, placebo-controlled, multicenter trial.[see comment]. Annals of Internal Medicine. 2003 Jul 1; 139(1):8-18.

Study design:	RCT	**Length of follow-up:**	Interventions were given from day -7 to day 100 post transplanation; outcome measurements were assessed at 6 months and 2 years post transplantation
Sample size:	200 patients	**Population:**	Patients who had allogeneic stem-cell transplantation from HLA-identical sibling donors.
Intervention:	Immunoglobulin at doses of 50mg/kg biody wieght, 250mg/kg or 500 mg/kg.		
Comparison / control:	Placebo.		
Outcome(s) measured:	Cumulative incidence of infection, graft-versus-host disease, veno-occlusive disease, interstitial pneumonia, and transplantation-related mortality.		

Quality assessment (internal validity)

Placebo:	Yes
Follow-up:	Six months after transplantation.

Results

Intervention groups:	92% of patients had one or more infections; no dose-effect relationships were evident; Grade 3 (severe) veno-occlusive disease occurred more frequently as the immunoglobulin dose increased.	**Control / comparison group(s):**	90% of patients had one or more infections.
P-value:	? 0.01		
Adverse events:	Grade 3 (severe) veno-occlusive disease occurred more frequently as the IVIG dose increased.		
Conclusions / Comments:	No significant difference from placebo, no dose-effect relationships evident - use of prophylactic IVIG in allogeneic recipients of stem-cell transplant from HLA-identical sibling donors not recommended.		

Condition studies:	Bone marrow transplantation: allogeneic and autologous

100	Feinstein, L. C.; Seidel, K.; Jocum, J.; Bowden, R. A.; Anasetti, C.; Deeg, H. J.; Flowers, M. E.; Kansu, E.; Martin, P. J.; Nash, R. A.; Storek, J.; Etzioni, R.; Applebaum, F. R.; Hansen, J. A.; Storb, R., and Sullivan, K. M. Reduced dose intravenous immunoglobulin does not decrease transplant-related complications in adults given related donor marrow allografts. Biology of Blood & Marrow Transplantation. 1999; 5(6):369-78.

Study design:	RCT	**Length of follow-up:**	Patients received the intervention from day -6 to day 90 post transplanation
Sample size:	241 patients (121 intervention and 120 control)	**Population:**	Patients greater or equal to 20 years of agewho were given related donar marrow allografts.

Intervention:	IVIG prophylaxis (500 mg/kg/d loading from day -6 to -1 and then 100 mg/kg every 3 days from day 3 to 90).
Comparison / control:	No IVIG
Outcome(s) measured:	GVHD (Graft versus host disease); transplant related mortality; CMV infection; interstitial pneumonia; bacteremia.

Quality assessment (internal validity)

Placebo:	No
Follow-up:	

Results

Intervention groups:	Incidence of acute GVHD did not differ between the two groups however, acute GVHD was less frequent among IVIg recipients achieving maximum serum IgG levels >3000 mg/dL (60 vs. 79%); Neither transplant-related mortality nor disease-free survival was significantly altered by Ig prophylaxis. However, the cumulative incidence of relapse of malignancy was higher in IVIg recipients than in controls (31 vs. 18%); Pretransplant IVIg loading and posttransplant maintenance achieved median serum IgG levels >1350 mg/dL, which were approximately twofold greater than the untreated controls (p<0.01); White blood cell and platelet	**Control / comparison group(s):**	See comparison to intervention group.

	recoveries were similar for the two groups, although control patients required fewer units of platelets per day (2.5 vs. 3.3, p = 0.008); No significant differences in incidence of CMV infection, interstitial pneumonia, or bacteremia were observed.
P-value:	? 0.01
Adverse events:	Cumulative incidence of relapse of malignancy was higher in IVIg recipients than in controls (31 vs. 18%, p = 0.03).
Conclusions / Comments:	Neither transplant-related mortality nor disease-free survival was significantly altered by Ig prophylaxis.

Condition studies:	Bone marrow transplantation: allogeneic and autologous

121	Poynton, C. H.; Jackson, S.; Fegan, C.; Barnes, R. A., and Whittaker, J. A. Use of IgM enriched intravenous immunoglobulin (Pentaglobin) in bone marrow transplantation. Bone Marrow Transplantation. 1992 Jun; 9(6):451-7.

Study design:	RCT	**Length of follow-up:**	100 days post transplant
Sample size:	72	**Population:**	Allogeneic and autologous bone marrow transplant patients, aged over 16 years.

Intervention:	IgM and IgA enriched IVIG (Pentaglobin).
Comparison / control:	Control patients (no treatment).
Outcome(s) measured:	Endotoxin levels; clinical sequelae of infection.

Quality assessment (internal validity)

Placebo:	
Follow-up:	Nine out of 72 withdrawn, 63 analysed.

Results

Intervention groups:	Patients who received Pentaglobin were significantly protected from dying from infection in the first 100 days after the transplant; peak endotoxin levels were significantly reduced; liver enzyme abnormalities correlated significantly with the presence of endotoxaemia greater than 25 pg/ml; up to 70% of pyrexial episodes were associated with endotoxaemia.	**Control / comparison group(s):**	Results were compared to intervention group.

P-value:	P = 0.02 (reduced peak endotoxin levels)
Adverse events:	
Conclusions / Comments:	Pentaglobulin useful in reducing hepatic toxicity.

Condition studies:	Bone marrow transplantation: allogeneic and autologous

132	Winston, D. J.; Antin, J. H.; Wolff, S. N.; Bierer, B. E.; Small, T.; Miller, K. B.; Linker, C.; Kaizer, H.; Lazarus, H. M.; Petersen, F. B.; Cowan, M. J.; Ho, W. G.; Wingard, J. R.; Schiller, G. J.; Territo, M. C.; Jiao, J.; Petrarca, M. A., and Tonetta, S. A. (Department of Medicine, UCLA Center for the Health Sciences, Los Angeles, CA 90095, USA). 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 Transplantation. 2001 Jul; 28(2):187-96.

Study design:	RCT	**Length of follow-up:**	Interventions were given until one year post transplant
Sample size:	618 (206; 208; 204 per intervention)	**Population:**	Patients undergoing allogeneic marrow transplantation.
Intervention:	Doses of 100 mg/kg, 250 mg/kg, or 500 mg/kg of intravenous immunoglobulin (IVIG) (each dose was given weekly for 90 days and monthly for a period of 1 year post transplant).		
Comparison / control:	There was no control, comparisons were made between interventions.		
Outcome(s) measured:	Graft versus host disease (GVHD); infection; pneumonia; replapse of haematological malignancy; survival.		

Quality assessment (internal validity)

Placebo:	No
Follow-up:	Nine out of 627 did not receive treatment, excluded from analysis.

Results

Intervention groups:	Acute GVHD (grades 2-4) occurred in 39% of the patients (80/206) in the 100 mg/kg group, 42% of the patients (88/208) in the 250 mg/kg group, and in 35% of the patients (72/204) in the 500 mg/kg group;a higher dose of intravenous immunoglobulin (500 mg/kg) was associated with less acute GVHD in patients with unrelated marrow donors; the incidences of chronic GVHD, infection and interstitial pneumonia were similar for all three doses; dose of intravenous immunoglobulin also had no effect on the types of infection, relapse of hematological malignancy or survival.	**Control / comparison group(s):**	N/A

P-value:	
Adverse events:	Adverse events were similar for all three doses but more frequent chills and headaches were evident in patients given the 500 mg/kg or 250 mg/kg doses.
Conclusions / Comments:	No significant difference between 3 doses of IVIG tested (trial not designed to test efficacy of IVIG, but results suggest further research needed).

Condition studies:	Bone marrow transplantation: allogeneic and autologous

133

Winston, D. J.; Ho, W. G.; Bartoni, K., and Champlin, R. E. (Department of Medicine, UCLA Center for the Health Sciences). Intravenous immunoglobulin and CMV-seronegative blood products for prevention of CMV infection and disease in bone marrow transplant recipients. Bone Marrow Transplantation. 1993 Sep; 12(3):283-8.

Study design:	RCT	**Length of follow-up:**	Patients were given the IVIG intervention up to day +120
Sample size:	51	**Population:**	Patients were CMV-seronegative allogeneic BMTs with a CMV-seronegative or CMV-seropositive marrow donor.

Intervention:	Patients received either immunoglobulin (IVIG 1.0 g/kg once weekly) plus CMV-seronegative blood products or CMV-seronegative blood products alone.
Comparison / control:	There was no control, comparisons were made between interventions.
Outcome(s) measured:	CMV infection, symptomatic CMV disease, other infections and GVHD after BMT.

Quality assessment (internal validity)

Placebo:	No
Follow-up:	

Results

Intervention groups:	CMV infection occurred in 2/25 patients (7%) receiving IVIG plus CMV-seronegative blood and in 2/23 patients (9%) receiving CMV-seronegative blood alone; There were no cases of CMV-related interstitial pneumonia; Grade > or = II GVHD was less frequent in patients given IVIG 5/25 patients (20%) vs. 11/23 patients (48%); number of bacterial and fungal infections was similar in both groups; Fewer non-CMV viral infections 9/27 patients (33%) vs. 15/24 patients (63%) and fewer deaths associated with infection 1/27 patients (4%) vs. 5/24 patients (21%) occurred in recipients of immunoglobulin; survival nor risk of leukemia	**Control / comparison group(s):**	

	relapse was changed by the immunoglobulin.
P-value:	P = 0.04 for reduction in acute GVHD.
Adverse events:	No adverse effects were reported.
Conclusions / Comments:	Reduction in incidence and severity of acute GVHD, but no improvement in survival rate.

Condition studies:	Bone marrow transplantation: allogeneic and autologous

135	Zikos, P.; Van Lint, M. T.; Lamparelli, T.; Gualandi, F.; Occhini, D.; Mordini, N.; Berisso, G.; Bregante, S., and Bacigalupo, A. (Divisione Ematologia II, Ospedale San Martino, Genoa, Italy). A randomized trial of high dose polyvalent intravenous immunoglobulin (HDIgG) vs. Cytomegalovirus (CMV) hyperimmune IgG in allogeneic hemopoietic stem cell transplants (HSCT). Haematologica. 1998 Feb; 83(2):132-7.

Study design:	RCT	**Length of follow-up:**	Patients were given the intervention at day -7 and followed up to day +100
Sample size:	Sample of 128; 64 in group A (CMV-IgG) and 64 in Group B (HDIgG).	**Population:**	Allogeneic hemopoietic stem cell transplants (HSCT) patients.

Intervention:	Given 400mg/kg/week of intravenous IgG (HDIgG); 100mg/kg/week of hyperimmune CMV IgG (CMV-IgG).
Comparison / control:	There was no control, comparisons were made between interventions.
Outcome(s) measured:	Occurrence of post-transplant CMV antigenemia (CMVAg-emia); severity of acute and chronic graft-versus-host disease (GvHD); infections and transplant related mortality (TRM).

Quality assessment (internal validity)

Placebo:	No
Follow-up:	

Results

Intervention groups:	Actuarial risk at 1 year of CMV antigenemia was lower for CMV-IgG 61% vs. 71% (n=39/64, 45/64); CMVAg-emia occurred at the same interval from HSCT (47 vs. 48 days) with a comparable number of CMVAg positive cells (3 vs. 3); 8 patients died of interstitial pneumonia (IP) (4 in each group), two in group A of CMV-IP; Acute GvHD was scored as O-I, II and III-IV in 39 vs. 35, 23 vs. 22 and 2 vs. 7 patients respectively for the two groups; The actuarial risk of developing acute GvHD grade II-IV was lower for CMV-IgG 39% vs. 45% (n=25/64, 29/64); Chronic GvHD scored as absent in 7 vs. 10 patients, limited in 39 vs. 37 and extensive in 19 vs. 17	**Control / comparison group(s):**	N/A

	patients; Numbered days with intravenous antibiotics, days in hospital, days of fever, number of local and disseminated infections, number of patients with fever of unknown origin were not significantly different; Actuarial 1 year TRM was 18% (n = 11/64) vs 19% (12/64).
P-value:	
Adverse events:	Actuarial 1 year TRM was reported as 18% vs 19% in the two groups.
Conclusions / Comments:	CMV antigenemia comparable in with hyperimmune CMV-IgG and high-dose IVIG; potential immunomodulating effect on acute GvHD and transplant mortality is similar with 100 or 400 mg of IgG/kg.

Condition studies:	Bone marrow transplantation: allogeneic and autologous

138	Wolff SN, Fay JW, Herzig RH et al. High-dose weekly intravenous immunoglobulin to prevent infections in patients undergoing autologous bone marrow transplantation or severe myelosuppressive therapy. A study of the American Bone Marrow Transplant Group. Ann Intern Med 1993; 118(12):937-42.

Study design:	RCT	**Length of follow-up:**	Interventions were given at the initiation of cytotoxic therapy to the resolutin of neutropenia
Sample size:	Sample of 170 patients (82 intervention and 88 control).	**Population:**	Patients undergoing autologous bone marrow transplantation or severe myelosuppressive therapy.
Intervention:	IVIG (500mg/kg)		
Comparison / control:	No treatment.		
Outcome(s) measured:	The development of bloodstream or other clinically proven infection, platelet use, and the development of alloimmunity to platelet transfusion.		

Quality assessment (internal validity)

Placebo:	No
Follow-up:	

Results

Intervention groups:	Clinical infection, bacteremia, and fungemia occurred in 43% (n=35/82), 35% (n=29/82), and 6% (n=5/82) of the IVIG-treated patients; Gram-positive bacteremia and gram-negative bacteremia occurred in 28% (n=23/82) and 11% (n=9/82) of the IVIG group; Death due to infection occurred in 4.9% (n=4/82) of IVIG recipients; Survival to hospital discharge was achieved in 86.6% (n=71/82) of the IVIG group.	**Control / comparison group(s):**	Clinical infection, bacteremia, and fungemia occurred in 44% (n=39/88), 34% (n=30/88), and 9% (n=8/88) of the control patients; Gram-positive bacteremia and gram-negative bacteremia occurred in 23% (n=20/88) and 13% (n=11/88) of the control group; Death due to infection occurred in 2.3% (n=2/88) of controls; Survival to hospital discharge was achieved in 96.6% (n=85/88) of the control group.
P-value:	NS		
Adverse events:	A higher incidence of fatal hepatic veno-occlusive disease in patients receiving IVIG was reported.		

Conclusions / Comments:	IVIG show no significant effect in prevention of infection.

Haematological

Condition summary	Chronic lymphocytic leukaemia with hypogammaglobulinaemia or persistent serum total IgG deficiency and documented recurrent infections

Reference list:

89 Anonymous. Intravenous immunoglobulin for the prevention of infection in chronic lymphocytic leukemia. A randomized, controlled clinical trial. Cooperative Group for the Study of Immunoglobulin in Chronic Lymphocytic Leukemia. N Engl J Med 1988; 319(14):902-7.

90 Boughton, B. J.; Jackson, N.; Lim, S., and Smith, N. (Department of Haematology, Queen Elizabeth Hospital, Edgbaston, Birmingham, UK). Randomized trial of intravenous immunoglobulin prophylaxis for patients with chronic lymphocytic leukaemia and secondary hypogammaglobulinaemia. Clinical & Laboratory Haematology. 1995 Mar; 17(1):75-80.

93 Bunch, C. (Nuffield Department of Clinical Medicine, University of Oxford, UK). Immunoglobulin replacement in chronic lymphocytic leukaemia. [Review] [13 refs]. Nouvelle Revue Francaise d Hematologie. 1988; 30(5-6):419-22.

95 Chapel, H.; Dicato, M.; Gamm, H.; Brennan, V.; Ries, F.; Bunch, C., and Lee, M. (Department of Immunology, John Radcliffe Hospital, Oxford). Immunoglobulin replacement in patients with chronic lymphocytic leukaemia: a comparison of two dose regimes. British Journal of Haematology. 1994 Sep; 88(1):209-12.

102 Gamm, H.; Huber, C.; Chapel, H.; Lee, M.; Ries, F., and Dicato, M. A. (Universitatsklinik Mainz, Abt. Hamatologie, Germany). Intravenous immune globulin in chronic lymphocytic leukaemia. Clinical & Experimental Immunology. 97 Suppl 1:17-20, 1994 Jul.

117 Molica, S.; Musto, P.; Chiurazzi, F.; Specchia, G.; Brugiatelli, M.; Cicoira, L.; Levato, D.; Nobile, F.; Carotenuto, M.; Liso, V., and Rotoli, B. Prophylaxis against infections with low-dose intravenous immunoglobulins (IVIG) in chronic lymphocytic leukemia. Results of a crossover study. Haematologica. 1996 Mar-1996 Apr 30; 81(2):121-6.

123 Schedel, I. Intravenous immunoglobulin replacement in secondary antibody deficiency syndrome. DIAGN-INTENSIVTHER. 1982; 7(10):254-263.

180 Chapel HM, Lee M. Immunoglobulin replacement in patients with chronic lymphocytic leukemia (CLL): kinetics of immunoglobulin metabolism. J Clin Immunol 1992; 12(1):17-20.

Types of study:	Three RCTs, 1 cross-over.
Total sample size:	204
Quality:	Low-Moderate
Result:	Decrease in incidence of bacterial infections (significant in some studies), no significant difference between doses.
Adverse events:	Minor - chills, fever, back pain.
Conclusion:	Some benefit of IVIG in reducing incidence of bacterial infections, based on 4 small studies (3 RCTs); studies comparing IVIG with prophylactic antibiotics would be useful.
Category:	IIa

Condition studies:	Chronic lymphocytic leukaemia with hypogammaglobulinaemia or persistent serum total IgG deficiency and documented recurrent infections

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Anonymous. Intravenous immunoglobulin for the prevention of infection in chronic lymphocytic leukemia. A randomized, controlled clinical trial. Cooperative Group for the Study of Immunoglobulin in Chronic Lymphocytic Leukemia. N Engl J Med 1988; 319(14):902-7.

Study design:	RCT	**Length of follow-up:**	
Sample size:	84	**Population:**	Chronic lymphocytic leukemia with hypogammaglobulinemia and/or history of infection.
Intervention:	IVIG 400 mg/kg every 3 weeks for 1 year.		
Comparison / control:	Placebo every 3 weeks for 1 year.		
Outcome(s) measured:	Number of bacterial infections.		

Quality assessment (internal validity)

Placebo:	Yes
Follow-up:	82/84 completed.

Results

Intervention groups:	Fewer bacterial infections for patients who completed a full year (P=0.001); length to first infection longer (P=0.026); no sign difference in incidence of viral and fungal infections.	**Control / comparison group(s):**	
P-value:	See above.		
Adverse events:	Minor reactions to 23/1235 infusions.		
Conclusions / Comments:	Selected patients with chronic lymphocytic leukemia who are at risk of bacterial infection can be substantially protected from this complication by the regular administration of IIVIG.		

Condition studies:	Chronic lymphocytic leukaemia with hypogammaglobulinaemia or persistent serum total IgG deficiency and documented recurrent infections

90	Boughton, B. J.; Jackson, N.; Lim, S., and Smith, N. (Department of Haematology, Queen Elizabeth Hospital, Edgbaston, Birmingham, UK). Randomized trial of intravenous immunoglobulin prophylaxis for patients with chronic lymphocytic leukaemia and secondary hypogammaglobulinaemia. Clinical & Laboratory Haematology. 1995 Mar; 17(1):75-80.

Study design:	RCT	**Length of follow-up:**	12 months
Sample size:	42	**Population:**	CLL, serum IgG less than 5.5g/l and history of 2 or more recent infections, 40-70 years.
Intervention:	18g IVIG every 3 weeks; switched to 24g IVIG if treatment failed.		
Comparison / control:	0.6g albumin; switched to 18g IVIG if treatment failed.		
Outcome(s) measured:	Number of infections.		

Quality assessment (internal validity)

Placebo:	Yes
Follow-up:	Three patients lost (died from disease progression).

Results

Intervention groups:	Had 122 infections during 12 months, 4 associated with neutropenia. 65% of infections in 10 patients. Decrease in total and serious infections in IVIG group, approximately 50% of treatment failures switched to IVIG (18 to 24 g or placebo to 18g) remained infection free.	**Control / comparison group(s):**	
P-value:			
Adverse events:			
Conclusions / Comments:	Some benefit of IVIG in CLL, particularly in patients with serum IgG levels < 3g/l and recurrent bacterial upper respiratory tract infections.		

Condition studies: Chronic lymphocytic leukaemia with hypogammaglobulinaemia or persistent serum total IgG deficiency and documented recurrent infections

93 Bunch, C. (Nuffield Department of Clinical Medicine, University of Oxford, UK). Immunoglobulin replacement in chronic lymphocytic leukaemia. [Review] [13 refs]. Nouvelle Revue Francaise d Hematologie. 1988; 30(5-6):419-22.

Study design: RCT **Length of follow-up:**

Sample size: 84 **Population:** Chronic lymphocytic leukemia with hypogammaglobulinemia.

Intervention: IVIG 400 mg/kg every 3 weeks for 1 year.

Comparison / control: Saline.

Outcome(s) measured: Number of infections.

Quality assessment (internal validity)

Placebo:

Follow-up:

Results

Intervention groups: Fewer bacterial infections for patients who completed a full year P = 0.001. **Control / comparison group(s):**

P-value: See above.

Adverse events:

Conclusions / Comments: Appears to be same study as reference no 89.

Condition studies:	Chronic lymphocytic leukaemia with hypogammaglobulinaemia or persistent serum total IgG deficiency and documented recurrent infections

95	Chapel, H.; Dicato, M.; Gamm, H.; Brennan, V.; Ries, F.; Bunch, C., and Lee, M. (Department of Immunology, John Radcliffe Hospital, Oxford). Immunoglobulin replacement in patients with chronic lymphocytic leukaemia: a comparison of two dose regimes. British Journal of Haematology. 1994 Sep; 88(1):209-12.

Study design:	RCT	**Length of follow-up:**	1 year
Sample size:	34	**Population:**	Patients with B-cell CLL, IgG below lower limit of normal or recent history of 1 or more serious infections.
Intervention:	500mg/kg every 4 weeks		
Comparison / control:	250mg/kg every 4 weeks		
Outcome(s) measured:	Rates of infection.		

Quality assessment (internal validity)

Placebo:	No
Follow-up:	Nine patients did not complete (3 on high-dose regime).

Results

Intervention groups:	Both dose regimes achieved serial serum IgG levels greater than 6g/l and reduced incidence of serious infection (rates not sign diff between 2 regimes).	**Control / comparison group(s):**	
P-value:			
Adverse events:	Mild adverse reactions in 10/378 infusions - 2 in high-dose regime and 8 in low-dose regime (chills, fever, back pain).		
Conclusions / Comments:	Patients with low-grade B cell malignancies benefit from IVIG therapy at 250mg/kg/month. Studies comparing IVIG with prophylactic antibiotics would be useful.		

Condition studies:	Chronic lymphocytic leukaemia with hypogammaglobulinaemia or persistent serum total IgG deficiency and documented recurrent infections

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Gamm, H.; Huber, C.; Chapel, H.; Lee, M.; Ries, F., and Dicato, M. A. (Universitatsklinik Mainz, Abt. Hamatologie, Germany). Intravenous immune globulin in chronic lymphocytic leukaemia. Clinical & Experimental Immunology. 97 Suppl 1:17-20, 1994 Jul.

Study design: RCT **Length of follow-up:**

Sample size: 36 **Population:**

Intervention: IVIG (500mg/kg every 4 weeks).

Comparison / control: Dose of 250mg/kg every 4 weeks.

Outcome(s) measured:

Quality assessment (internal validity)

Placebo:

Follow-up:

Results

Intervention groups: **Control / comparison group(s):**

P-value:

Adverse events:

Conclusions / Comments: Possible benefit of IVIG as prophylaxis against infection in patients with CLL, effect; no significant difference between 2 doses.

Condition studies:	Chronic lymphocytic leukaemia with hypogammaglobulinaemia or persistent serum total IgG deficiency and documented recurrent infections

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Molica, S.; Musto, P.; Chiurazzi, F.; Specchia, G.; Brugiatelli, M.; Cicoira, L.; Levato, D.; Nobile, F.; Carotenuto, M.; Liso, V., and Rotoli, B. Prophylaxis against infections with low-dose intravenous immunoglobulins (IVIG) in chronic lymphocytic leukemia. Results of a crossover study. Haematologica. 1996 Mar-1996 Apr 30; 81(2):121-6.

Study design:	Crossover	**Length of follow-up:**	
Sample size:	42	**Population:**	Chronic lymphocytic leukemia patients with IgG <600 mg/dL and history of at least 1 episode of severe infection in last 6 months.

Intervention:	IVIG 300mg/kg every 4 weeks for 6 months then switched to no treatment or observation for 6 months (not clear from paper).
Comparison / control:	No treatment, then switched to IVIG; then switched to no therapy.
Outcome(s) measured:	Number of infections.

Quality assessment (internal validity)

Placebo:	No
Follow-up:	Group of 17 completed IVIG therapy and had observation for 12 months; 30 completed for 6 months; 2 patients lost to followup, 13 died.

Results

Intervention groups:	Significantly lower incidence of infectious episodes during IVIG in 30 patients completing 6 months, same for 17 patients completing 12 months.	**Control / comparison group(s):**	

P-value:	P < 0.01 at 6 months; P < 0.02 at 12 months.
Adverse events:	
Conclusions / Comments:	Some benefit from IVIG (lower incidence of infections), but not cost effective.

Condition studies:	Chronic lymphocytic leukaemia with hypogammaglobulinaemia or persistent serum total IgG deficiency and documented recurrent infections

123 Schedel, I. Intravenous immunoglobulin replacement in secondary antibody deficiency syndrome. DIAGN-INTENSIVTHER. 1982; 7(10):254-263.

Study design:	RCT (prospective)	**Length of follow-up:**	
Sample size:	37 in IVIG arm, 33 in control?	**Population:**	Group of 37 patients with secondary antibody deficiency syndrome (38 with multiple myeloma, 14 with Waldenstrom's macroglobulinaemia, 18 with chronic lymphatic leukemia).
Intervention:	IVIG		
Comparison / control:	See paper.		
Outcome(s) measured:	Cough and expectoration in patients with chronic bronchitis.		

Quality assessment (internal validity)

Placebo:	See paper.
Follow-up:	

Results

Intervention groups:	Decrease in cough and expectoration in chronic bronchitis (18/37 in IVIG arm), no sign of infection in asymptomatic patients.	**Control / comparison group(s):**	No decrease in cough and expectoration in chronic bronchitis.
P-value:			
Adverse events:			
Conclusions / Comments:	Too little data.		

Condition studies:	Chronic lymphocytic leukaemia with hypogammaglobulinaemia or persistent serum total IgG deficiency and documented recurrent infections

180	Chapel HM, Lee M. Immunoglobulin replacement in patients with chronic lymphocytic leukemia (CLL): kinetics of immunoglobulin metabolism. J Clin Immunol 1992; 12(1):17-20.

Study design:		**Length of follow-up:**	
Sample size:	15	**Population:**	Patients with low grade B cell tumours.
Intervention:	IVIG 0.4 g/kg 3 weekly infusions for 1 year.		
Comparison / control:			
Outcome(s) measured:	Serum IgG measured at pre, post, day 7, day 21 of treatment.		

Quality assessment (internal validity)

Placebo:

Follow-up:

Results

Intervention groups:	Catabolic rate of IgG is normal in these patients and is not altered by IVIG infusions.	**Control / comparison group(s):**	

P-value:

Adverse events:

Conclusions / Comments:	No efficacy data for IVIG.

Haematological

Condition summary	Diamond-Blackfan syndrome
Category:	IVb

Haematological

Condition summary	Haemolytic transfusion reaction
Category:	IVb

Haematological

Condition summary	Haemolytic uraemic syndrome
Category:	IVb

Haematological

Condition summary	HIV-associated thrombocytopenia
Reference list:	120 Perrella, O. Idiopathic thrombocytopenic purpura in HIV infection: therapeutic possibilities of intravenous immunoglobulins. Journal of Chemotherapy. 1990 Dec; 2(6):390-3.
Types of study:	RCT
Total sample size:	20
Quality:	Low
Result:	Improved restoration and maintenance of platelet count.
Adverse events:	None reported.
Conclusion:	Possible benefit, based on 1 small RCT.
Category:	IIa

Condition studies: HIV-associated thrombocytopenia

120 Perrella, O. Idiopathic thrombocytopenic purpura in HIV infection: therapeutic possibilities of intravenous immunoglobulins. Journal of Chemotherapy. 1990 Dec; 2(6):390-3.

Study design:

Length of follow-up:

Sample size: 10 (in each arm)

Population: HIV positive patients with severe thrombocytopenia.

Intervention: IVIG 1g/kg/day.

Comparison / control:

Outcome(s) measured: Platelet count.

Quality assessment (internal validity)

Placebo:

Follow-up:

Results

Intervention groups:

Control / comparison group(s):

P-value:

Adverse events:

Conclusions / Comments: Possible benefit for the restoration and the maintenance of the platelet count and therefore for the duration of the hemorrhagic disorders, but numbers very small.

Haematological

Condition summary	Immune thrombocytopenia, Idiopathic thrombocytopenic purpura
Reference list:	104 Imbach, P.; Wagner, H. P.; Berchtold, W.; Gaedicke, G.; Hirt, A.; Joller, P.; Mueller-Eckhardt, C.; Muller, B.; Rossi, E., and Barandun, S. Intravenous immunoglobulin versus oral corticosteroids in acute immune thrombocytopenic purpura in childhood. Lancet. 1985 Aug 31; 2(8453):464-8. 131 Warrier, I.; Bussel, J. B.; Valdez, L.; Barbosa, J., and Beardsley, D. S. Safety and efficacy of low-dose intravenous immune globulin (IVIG) treatment for infants and children with immune thrombocytopenic purpura. Journal of Pediatric Hematology/Oncology. 1997; 19(3):197-201. 277 Blanchette VS, Luke B, Andrew M, Sommerville-Nielsen S, Barnard D, de Veber B, Gent M. A prospective, randomized trial of high-dose intravenous immune globulin G therapy, oral prednisone therapy, and no therapy in childhood acute immune thrombocytopenic purpura. J Pediatr. 1993 Dec;123(6):989-95. 278 Blanchette V, Imbach P, Andrew M, Adams M, McMillan J, Wang E, Milner R, Ali K, Barnard D, Bernstein M, et al. Randomised trial of intravenous immunoglobulin G, intravenous anti-D, and oral prednisone in childhood acute immune thrombocytopenic purpura. Lancet. 1994 Sep 10;344(8924):703-7.
Types of study:	Four RCTs.
Total sample size:	331
Quality:	Low-Moderate
Result:	Similar effect to corticosteroids in improvements in platelet numbers.
Adverse events:	Two severe (1 anaphylactoid reaction, 1 aseptic meningitis), mild (fever, nausea, vomiting, headache).
Conclusion:	Benefit (equivalent to prednisolone, more effective in some subgroups), based on 4 RCTs of low-moderate quality.
Category:	I

Condition studies:	Immune thrombocytopenia, Idiopathic thrombocytopenic purpura

104	Imbach, P.; Wagner, H. P.; Berchtold, W.; Gaedicke, G.; Hirt, A.; Joller, P.; Mueller-Eckhardt, C.; Muller, B.; Rossi, E., and Barandun, S. Intravenous immunoglobulin versus oral corticosteroids in acute immune thrombocytopenic purpura in childhood. Lancet. 1985 Aug 31; 2(8453):464-8.

Study design:	RCT	**Length of follow-up:**	
Sample size:	108	**Population:**	Children up to 15 years with acute immune thrombocytopenic purpura.
Intervention:	IVIG (0.4g/kg) on 5 consecutive days (55 IVIG, 53 corticosteroids).		
Comparison / control:	Oral corticosteroids (60mg/m2) for 21 days.		
Outcome(s) measured:	Serum IgG level, platelet associated IgG index.		

Quality assessment (internal validity)

Placebo:	No
Follow-up:	47/55 completed in IVIG group; 47/53 completed in steroid group

Results

Intervention groups:	After 180 days, 20/47 patients on corticosteroids and 15/47 on IVIG had chronic (not acute) ITP. Effects of both treatments were identical in rapid responders (62% patients). IVIG better in patients requiring more than initial treatment.	**Control / comparison group(s):**	
P-value:			
Adverse events:	One death in IVIG group (due to active ITP).		
Conclusions / Comments:	For acute ITP in childhood, IVIG justifiable as first therapy, as subgroup responding poorly to IVIG or corticosteroids responded better if initially given IVIG.		

Condition studies:	Immune thrombocytopenia, Idiopathic thrombocytopenic purpura

131	Warrier, I.; Bussel, J. B.; Valdez, L.; Barbosa, J., and Beardsley, D. S. Safety and efficacy of low-dose intravenous immune globulin (IVIG) treatment for infants and children with immune thrombocytopenic purpura. Journal of Pediatric Hematology/Oncology. 1997; 19(3):197-201.

Study design:	RCT	**Length of follow-up:**	3 months
Sample size:	24	**Population:**	Children (12 years and under) with immune thrombocytopenic purpura.
Intervention:	Low dose IVIG: 250 mg/kd/day, 400 mg/kg/day or 500 mg/kg/day for 2 days.		
Comparison / control:	High dose IVIG: 1 g/kg for 2 days.		
Outcome(s) measured:	Platelet levels, adverse events.		

Quality assessment (internal validity)

Placebo:	No
Follow-up:	23/24 patients completed study.

Results

Intervention groups:	IVIG increased platelets (>30,000/microlitre over baseline) in 16/17 patients in the low dosage group, within 10 days of therapy.	**Control / comparison group(s):**	IVIG increased platelets (>30,000/microlitre over baseline) in 6/6 patients in the low dosage group, within 10 days of therapy.
P-value:			
Adverse events:	Two serious adverse events: 1 anaphylactoid reaction in 400 mg/kg group and 1 aseptic meningitis in 1 g/kg group. Significantly less adverse events in children under 5.		
Conclusions / Comments:	Low-dose IVIG (200, 400 and 500 mg/kg/day) rapidly reversed thrombocytopaenia just as effectively as high dose IVIG (1 g/kg/day).		

Condition studies:	Immune thrombocytopenia, Idiopathic thrombocytopenic purpura

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Blanchette VS, Luke B, Andrew M, Sommerville-Nielsen S, Barnard D, de Veber B, Gent M. A prospective, randomized trial of high-dose intravenous immune globulin G therapy, oral prednisone therapy, and no therapy in childhood acute immune thrombocytopenic purpura. J Pediatr. 1993 Dec;123(6):989-95.

Study design:	RCT	**Length of follow-up:**	4-5 months
Sample size:	53	**Population:**	Children aged 7 months to 14.4 years, with typical acute ITP and platelet counts of < or = 10 10(9)/L.
Intervention:	IVIG (1g/kg 2 consecutive days).		
Comparison / control:	Oral prednisone or no therapy.		
Outcome(s) measured:	Platelet counts.		

Quality assessment (internal validity)

Placebo: No

Follow-up:

Results

Intervention groups:	In both IVIG and prednisone, significantly fewer days with platelet counts < or = 20 x 10(9)/L compared to no therapy (median, 1 and 2 days vs 4 days; corresponding ranges, 1-20 and 1-11 days vs 1-132 days; p < 0.01). Number of days taken to achieve a platelet count of > or = 50 x 10(9)/L significantly faster in IVIG group (median, 2 days; range, 1 to 34 days) than in prednisone group(median, 4 days; range, 2 to 13 days; p < 0.001) or no therapy (median, 16 days; range, 2 to 132 days; p < 0.001).	**Control / comparison group(s):**	

P-value: See above.

Adverse events:

Conclusions / Comments:	Results support the use of IVIG or high doses of prednisone as initial therapy in children with acute immune thrombocytopenic purpura and severe thrombocytopenia (platelet counts < or = 20 x 10(9)/L).

Condition studies:	Immune thrombocytopenia, Idiopathic thrombocytopenic purpura

278 Blanchette V, Imbach P, Andrew M, Adams M, McMillan J, Wang E, Milner R, Ali K, Barnard D, Bernstein M, et al. Randomised trial of intravenous immunoglobulin G, intravenous anti-D, and oral prednisone in childhood acute immune thrombocytopenic purpura. Lancet. 1994 Sep 10;344(8924):703-7.

Study design:	RCT	**Length of follow-up:**	28 days
Sample size:	146	**Population:**	Children with acute ITO and platelet counts equal to or less than 20X109/L, aged 6 months to 18 years.

Intervention: IVIG (1g/kg on 2 consecutive days or 0.8g/kg once).

Comparison / control: IV-anti-D (0.8g/kg) or oral prednisone (4mg/kg).

Outcome(s) measured: Platelet counts.

Quality assessment (internal validity)

Placebo: No

Follow-up:

Results

Intervention groups:	Number of days with platelet counts at 20 x 10(9)/L or lower and the time taken to achieve a platelet count 50 x 10(9)/L or more was significantly faster for both IVIgG groups than for the anti-D group ($p < 0.05$); the difference between prednisone and IVIgG was significant ($p < 0.05$) only for the IVIgG 0.8 g/kg group, and responses to the two IgG groups were similar. Differences reflected in the percentages of children with platelet counts of 20 x 10(9)/L or lower at 72 hours following the start of treatment: 3% (IVIgG 0.8 g/kg x 1), 6% (IVIgG 1 g/kg x 2), 18% (anti-D), and 21% (oral prednisone 4 mg/kg/day).	**Control / comparison group(s):**	

P-value: See above.

Adverse events:	Significantly more fever, nausea, vomiting, headache in IVIG group, fall in haemoglobin greatest in anti-D group, weight gain in prednisone group.
Conclusions / Comments:	Single dose of 0.8 g/kg IVIgG offers the fastest recovery for the least treatment; additional IgG or oral prednisone can be reserved for the one-third of children who continue to have platelet counts of 20 x 10(9)/L or less at 48-72 hours after the start of treatment. IV anti-D cannot be recommended as initial therapy for children with acute ITP and platelet counts of 20 x 10(9)/L or lower.

Haematological

Condition summary	Multiple myeloma
Reference list:	96 Chapel, H. M.; Lee, M.; Hargreaves, R.; Pamphilon, D. H., and Prentice, A. G. (Department of Immunology, John Radcliffe Hospital, Oxford, UK). Randomised trial of intravenous immunoglobulin as prophylaxis against infection in plateau-phase multiple myeloma. The UK Group for Immunoglobulin Replacement Therapy in Multiple Myeloma.[see comment]. Lancet. 1994 Apr 30; 343(8905):1059-63. 103 Gordon, D. S.; Hearn, E. B.; Spira, T. J.; Reimer, C. B.; Phillips, D. J., and Schable, C. Phase I study of intravenous gamma globulin in multiple myeloma. American Journal of Medicine. 1984 Mar 30; 76(3A):111-6. 123 Schedel, I. Intravenous immunoglobulin replacement in secondary antibody deficiency syndrome. DIAGN-INTENSIVTHER. 1982; 7(10):254-263.
Types of study:	Two RCTs.
Total sample size:	152
Quality:	Low
Result:	In 1 RCT, significant reduction in septicaemia or pneumonia, serious infections, recurrent infections; maximum benefit in patients with poor pneumococcal IVIG; in 1 RCT, decrease in cough and expectoration in chronic bronchitis.
Adverse events:	Infusion reactions in 3 patients (2 mild, 1 moderate).
Conclusion:	Possible benefit, based on 2 small RCTs.
Category:	IIa

Condition studies: Multiple myeloma

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Chapel, H. M.; Lee, M.; Hargreaves, R.; Pamphilon, D. H., and Prentice, A. G. (Department of Immunology, John Radcliffe Hospital, Oxford, UK). Randomised trial of intravenous immunoglobulin as prophylaxis against infection in plateau-phase multiple myeloma. The UK Group for Immunoglobulin Replacement Therapy in Multiple Myeloma.[see comment]. Lancet. 1994 Apr 30; 343(8905):1059-63.

Study design: RCT

Length of follow-up:

Sample size: 82

Population: Stable multiple myeloma.

Intervention: IVIG 0.4 g/kg monthly for I year.

Comparison / control: Placebo 0.4% albumin IV for 1 year.

Outcome(s) measured: Number of infections.

Quality assessment (internal validity)

Placebo:

Follow-up: Twelve out of 42 in IVIG group and 10 out of 41 in control group withdrew.

Results

Intervention groups: Ten cases of septicaemia or pneumonia in placebo but none in IVIG (P=0.002). 19 serious infections in IVIG group, 38 in placebo (P=0.019). Fewer recurrent infections in IVIG (P=0.021), maximum benefit of IVIG in patients with poor pneumococcal IVIG.

Control / comparison group(s): See above.

P-value: See above.

Adverse events: Three out of 42 patients withdrew due to infusion reactions (2 mild, 1 moderate).

Conclusions / Comments: IVIG protects against life-threatening infections and significantly reduces risk of recurrent infections. Most benefit in individuals with poor pneumococcal responses.

Condition studies: Multiple myeloma

103 Gordon, D. S.; Hearn, E. B.; Spira, T. J.; Reimer, C. B.; Phillips, D. J., and Schable, C. Phase I study of intravenous gamma globulin in multiple myeloma. American Journal of Medicine. 1984 Mar 30; 76(3A):111-6.

Study design: Case-series **Length of follow-up:**

Sample size: 17 **Population:** Patients with multiple myeloma.

Intervention: IVIG 150 mg/kg to 500 mg/kg during 1 month study.

Comparison / control:

Outcome(s) measured: Clinical toxicity (hepatic and renal), IgG levels, number of infections.

Quality assessment (internal validity)

Placebo:

Follow-up:

Results

Intervention groups: **Control / comparison group(s):**

P-value:

Adverse events: Three transientepisodes of mild toxicity (from 27 infusions).

Conclusions / Comments: Phase I trial, no efficiacy data.

Condition studies:	Multiple myeloma

123	Schedel, I. Intravenous immunoglobulin replacement in secondary antibody deficiency syndrome. DIAGN-INTENSIVTHER. 1982; 7(10):254-263.

Study design:	RCT (prospective)	**Length of follow-up:**	
Sample size:	Sample of 37 in IVIG arm, 33 in control.	**Population:**	Group of 37 patients with secondary antibody deficiency syndrome (38 with multiple myeloma, 14 with Waldenstrom's macroglobulinaemia, 18 with chronic lymphatic leukemia).
Intervention:	IVIG		
Comparison / control:			
Outcome(s) measured:	Cough and expectoration in patients with chronic bronchitis.		

Quality assessment (internal validity)

Placebo:	No
Follow-up:	

Results

Intervention groups:	Decrease in cough and expectoration in chronic bronchitis (18/37 in IVIG arm), no evidence of infection in asymptomatic patients.	**Control / comparison group(s):**	No decrease in cough and expectoration in chronic bronchitis .
P-value:			
Adverse events:			
Conclusions / Comments:	Possible benefit.		

Haematological

Condition summary	Neonatal ABO isoimmunisation
Reference list:	87 Alcock, G. S. and Liley, H. Immunoglobulin infusion for isoimmune haemolytic jaundice in neonates. Alcock GS, Liley H. Immunoglobulin Infusion for Isoimmune Haemolytic Jaundice in Neonates (Cochrane Review). In: The Cochrane Library, Issue 1, 2004. Chichester, UK: John Wiley & Sons, Ltd.
Types of study:	One systemic review.
Total sample size:	Three RCTs (189).
Quality:	Moderate
Result:	IVIG+phototherapy significantly reduced incidence of exchange transfusion (typical RR 0.28, 95% CI 0.17, 0.47; typical RD -0.37, 95% CI -0.49, -0.26; NNT 2.7) and mean number of exchange transfusions per infant (WMD -0.52, 95% CI -0.70, -0.35) compared to phototherapy alone.
Adverse events:	None reported.
Conclusion:	Possible benefit of IVIG, in 3 low quality trials (inadequate randomisation, allocation concealment and blinding).
Category:	IIa

Condition studies:	Neonatal ABO isoimmunisation

87	Alcock, G. S. and Liley, H. Immunoglobulin infusion for isoimmune haemolytic jaundice in neonates. Alcock GS, Liley H. Immunoglobulin Infusion for Isoimmune Haemolytic Jaundice in Neonates (Cochrane Review). In: The Cochrane Library, Issue 1, 2004. Chichester, UK: John Wiley & Sons, Ltd.

Study design:	Three RCTs or quasi RCTs.	**Length of follow-up:**	
Sample size:	189	**Population:**	Neonates with isoimmune haemolytic jaundice.
Intervention:	IVIG: single dose in combination with phototherapy.		
Comparison / control:	Phototherapy alone.		
Outcome(s) measured:	Use of exchange transfusion, simple transfusion, serum bilirubin, duration of phototherapy, length of hospital stay, incidence of sensorineural hearing loss, incidence of kernicterus, incidence of cerebral palsy. Safety: neonatal mortality, adverse reactions.		

Quality assessment (internal validity)

Placebo:

Follow-up:

Results

Intervention groups:	Significantly reduced incidence of exchange transfusion and mean number of exchange transfusions per infant. No difference in other outcomes for phototherapy/IVIG compared to phototherapy alone.	**Control / comparison group(s):**	
P-value:			
Adverse events:	Considered safe.		
Conclusions / Comments:	Level IIa - Studies were of weak design (unclear allocation concealment and blinding of outcome assessment), no placebo in control group. Routine use of IVIG not recommended by reviewers. Future research needed.		

Haematological

Condition summary	Other chronic lymphoproliferative disease with persistent serum total IgG deficiency and documented recurrent infections
Reference list:	
Types of study:	
Total sample size:	
Quality:	
Result:	
Adverse events:	
Conclusion:	
Category:	See: Chronic lymphocytic leukaemia with hypogammaglobulinaemia or persistent serum total IgG deficiency and documented recurrent infections; Lymphocytic leukaemia with hypogammaglobulinaemia

Haematological

Condition summary	Post-transfusion purpura
Category:	IVb

Haematological

Condition summary	Pure white cell aplasia
Category:	IVb

Haematological

Condition summary	Red cell aplasia
Category:	IVb

Haematological

Condition summary	Rhesus D haemolytic disease
Reference list:	98 Dagoglu, T.; Ovali, F.; Samanci, N., and Bengisu, E. High-dose intravenous immunoglobulin therapy for rhesus haemolytic disease. Journal of International Medical Research. 1995 Jul-1995 Aug 31; 23(4):264-71.
Types of study:	One RCT.
Total sample size:	41
Quality:	Low
Result:	Significantly less transfusions needed in IVIG group (average of 0.18/patient), compared to average of 1.05 transfusions/patient in controls.
Adverse events:	None seen.
Conclusion:	Possible benefit, based on 1 small, unblinded RCT.
Category:	IIa

Condition studies:	Rhesus D haemolytic disease

98	Dagoglu, T.; Ovali, F.; Samanci, N., and Bengisu, E. High-dose intravenous immunoglobulin therapy for rhesus haemolytic disease. Journal of International Medical Research. 1995 Jul-1995 Aug 31; 23(4):264-71.

Study design:	RCT	**Length of follow-up:**	4 months
Sample size:	22 in study group, 19 in control	**Population:**	
Intervention:	IVIG at 500mg/kg, usually within 2 h of birth.		
Comparison / control:	Nothing		
Outcome(s) measured:	Reduction in number of exchange transfusions needed.		

Quality assessment (internal validity)

Placebo:	No
Follow-up:	

Results

Intervention groups:	Significantly less transfusions needed in IVIG group (average of 0.18/patient).	**Control / comparison group(s):**	Average of 1.05 transfusions/patient.
P-value:	P < 0.001		
Adverse events:	None seen.		
Conclusions / Comments:	IVIG reduces the need for exchange transfusion.		

Haematological

Condition summary	Septic thrombocytopenia
Reference list:	
Types of study:	
Total sample size:	
Quality:	
Result:	
Adverse events:	
Conclusion:	
Category:	See: Sepsis: adult, paediatric, neonatal; Immune thrombocytopenia; Idiopathic thrombocytopenic purpura

Haematological

Condition summary	Sickle cell anaemia
Category:	IVb

Haematological

Condition summary	Virus associated haemophagic syndrome
Category:	IVb

HIV/AIDS

Condition summary

HIV/AIDS: Adult

Reference list:	92 Brunkhorst, U.; Sturner, M.; Willers, H.; Deicher, H., and Schedel, I. (Medizinische Hochschule, Zentrum Innere Medizin, Hannover, FR Germany). Efficacy of intravenous immunoglobulins in patients with advanced HIV-1 infection. A randomized clinical study. Infection. 1990 Mar-1990 Apr 30; 18(2):86-90. 105 Jablonowski, H.; Sander, O.; Willers, R.; Adams, O.; Bartmann, P., and Wahn, V. (Klinik fur Gastroenterologie, Heinrich-Heine-Universitat Dusseldorf). The use of intravenous immunoglobulins in symptomatic HIV infection. Results of a randomized study. [Review] [23 refs]. Clinical Investigator. 1994 Feb; 72(3):220-4. 110 Krueger, G. R.; Ramon, A.; Degenhardt, S.; Schrappe-Bacher, M.; Rasokat, H.; Koch, B., and Deninger, J. Cellular immunologic parameters in HIV-positive patients with AIDS-related complex and intravenous immunoglobulin therapy. Vox Sanguinis. 1990; 59 Suppl 1:30-7. 124 Schrappe-Bacher, M.; Rasokat, H.; Bauer, P.; Bendick, C.; Bube, F. W.; Degenhardt, S.; Fatkenheuer, G.; Heiniger, H. J.; Heitmann, K.; Imbach, P. and others. High-dose intravenous immunoglobulins in HIV-1-infected adults with AIDS-related complex and Walter-Reed 5. Vox Sanguinis. 1990; 59 Suppl 1:3-14. 130 Wagner, N.; Bialek, R.; Radinger, H.; Brackmann, H. H., and Becker, M. (Department of Paediatrics, University of Bonn, Federal Republic of Germany). Intravenous immunoglobulin in HIV-I infected haemophilic patients. Archives of Disease in Childhood. 1992 Oct; 67(10):1267-71. 134 Wintergerst, U.; Niinivaara-Kreuzer, K.; Notheis, G.; Auberger, K.; Bruckmann, C.; Gandenberger, S., and Belohradsky, B. H. (Universitats-Kinderkliniken, Ludwig-Maximilians-Universitat, Munchen, Germany). High-dose intravenous immunoglobulins in the treatment of adolescent and adult HIV-infected hemophiliacs. Clinical Investigator. 1994 Jan; 72(2):122-6.
Types of study:	Four RCTs, 1 open trial, 1 cohort.
Total sample size:	105 (RCTs); 51 (other)
Quality:	Low
Result:	No significant effect on progression of disease; no significant effect in HIV-infected hemophiliacs; some clinical benefit (fatigue, fevers) in 2 RCTs. No significant prophylactic effect; some improvement in clinical status in advanced HIV; no significant difference in HIV-infected haemophiliacs.
Adverse events:	None reported.
Conclusion:	Appears to be no or minor significant effect, based on 6 small studies (4 RCTs).
Category:	IIb

Condition studies:	HIV/AIDS: Adult

92	Brunkhorst, U.; Sturner, M.; Willers, H.; Deicher, H., and Schedel, I. (Medizinische Hochschule, Zentrum Innere Medizin, Hannover, FR Germany). Efficacy of intravenous immunoglobulins in patients with advanced HIV-1 infection. A randomized clinical study. Infection. 1990 Mar-1990 Apr 30; 18(2):86-90.

Study design:	RCT	**Length of follow-up:**	Average observation period of 13.8 months
Sample size:	Sample of 40 (20 treatment, 20 no treatment).	**Population:**	Adults with symptomatic HIV-1 infection (AIDS related complex [ARC] WR 2B-4B or AIDS WR 5-6).
Intervention:	IVIG 200mg/kg every second week or no such treatment.		
Comparison / control:	No IVIG treatment.		
Outcome(s) measured:	Frequency of opportunistic infections, "B"-symptoms, number of T-helper cells, change of disease stage, delayed cutaneous hypersensitivity, onset and clinical course of Kaposi's sarcoma, neurological manifestations and proportion of patients alive.		

Quality assessment (internal validity)

Placebo:

Follow-up:

Results

Intervention groups:	Decreased mortality in WR 5-6 patients; no significant differences in frequency and microbial spectrum of opportunistic infections, or other parameters.	**Control / comparison group(s):**	
P-value:	$p < 0.004$		
Adverse events:			
Conclusions / Comments:	No significant effect of IVIG in adults with symptomatic HIV-1 infection, small patient numbers and not placebo-controlled.		

Condition studies: HIV/AIDS: Adult

105 Jablonowski, H.; Sander, O.; Willers, R.; Adams, O.; Bartmann, P., and Wahn, V. (Klinik fur Gastroenterologie, Heinrich-Heine-Universitat Dusseldorf). The use of intravenous immunoglobulins in symptomatic HIV infection. Results of a randomized study. [Review] [23 refs]. Clinical Investigator. 1994 Feb; 72(3):220-4.

Study design:	RCT	**Length of follow-up:**	1 year
Sample size:	35 patients	**Population:**	HIV patients with CD4 lymphocyte counts below 300/microliter.

Intervention: In addition to standard HIV treatment (e.g., zidovudine, aerosolized pentamidine), 13 patients were treated with 7.5 g and 11 with 40 g of a 7 S intravenous IgG preparation every 4 weeks over a period of 1 year.

Comparison / control: A control group of 11 patients remained on standard treatment (e.g., zidovudine, aerosolized pentamidine).

Outcome(s) measured: Clinical and laboratory parameters, HIV-specific immunological abnormalities, the course of HIV infection.

Quality assessment (internal validity)

Placebo:

Follow-up:

Results

Intervention groups:	Laboratory data and course of HIV infection (fever, antibiotic treatment, hospitalization, Candida and herpes simplex or cytomegalovirus infection) remained unchanged.	**Control / comparison group(s):**	

P-value:

Adverse events:

Conclusions / Comments: Data do not support use of IVIG treatment in adult symptomatic HIV-infected patients with CD4 counts <300/microliter.

Condition studies:	HIV/AIDS: Adult

110	Krueger, G. R.; Ramon, A.; Degenhardt, S.; Schrappe-Bacher, M.; Rasokat, H.; Koch, B., and Deninger, J. Cellular immunologic parameters in HIV-positive patients with AIDS-related complex and intravenous immunoglobulin therapy. Vox Sanguinis. 1990; 59 Suppl 1:30-7.

Study design:	RCT	**Length of follow-up:**	
Sample size:	Sample of 30 in total.	**Population:**	Group of 30 HIV-1-positive patients with AIDS-related complex or stage Walter-Reed 5 disease.
Intervention:	IVIG (0.4g/kg every other week for 169 days).		
Comparison / control:	Placebo (albumin).		
Outcome(s) measured:	Clinical score, lymphocyte phenotypes, activation markers, immunoglobulins and subclasses, lymphocyte turnover, indicators of acute inflammation.		

Quality assessment (internal validity)

Placebo:	No
Follow-up:	Nine did not complete, 5 in IVIG, 4 in placebo.

Results

Intervention groups:	Improvement in clinical score; no significant changes in lymphocyte phenotypes, activation markers, immunoglobulins and subclasses, lymphocyte turnover or indicators of acute inflammation.	**Control / comparison group(s):**	
P-value:			
Adverse events:			
Conclusions / Comments:	No significant prophylactic effect.		

Condition studies:	HIV/AIDS: Adult

124	Schrappe-Bacher, M.; Rasokat, H.; Bauer, P.; Bendick, C.; Bube, F. W.; Degenhardt, S.; Fatkenheuer, G.; Heiniger, H. J.; Heitmann, K.; Imbach, P. and others. High-dose intravenous immunoglobulins in HIV-1-infected adults with AIDS-related complex and Walter-Reed 5. Vox Sanguinis. 1990; 59 Suppl 1:3-14.

Study design:	RCT	**Length of follow-up:**	26 weeks
Sample size:	15 in each arm (30 total)	**Population:**	Adults;28 males, 2 females; median age 41 (24-64) years with ARC (n = 8), WR5 (n = 12) and both (n = 10).
Intervention:	0.4 g/kg IVIG every other week for 26 weeks.		
Comparison / control:	Placebo (albumin 0.03%) every other week for 26 weeks.		
Outcome(s) measured:	Clinical score consisting of fever, diarrhea, night sweats, fatigue, weight loss, oral candidiasis and mucosal or cutaneous herpes simple.		

Quality assessment (internal validity)

Placebo:	Yes
Follow-up:	

Results

Intervention groups:	After 26 weeks, and at termination of the study after 52 weeks, the clinical score (particularly fatigue and fever) was significantly improved in the treatment group. The T4 cell count and other clinical and immunological parameters remained unaltered.	**Control / comparison group(s):**	
P-value:	? 0.05		
Adverse events:	None reported.		
Conclusions / Comments:	Some improvement in clinical status (fatigue and fever) of patients with advanced HIV-1 infection without obvious correction of underlying impaired cellular immunity.		

Condition studies: HIV/AIDS: Adult

130

Wagner, N.; Bialek, R.; Radinger, H.; Brackmann, H. H., and Becker, M. (Department of Paediatrics, University of Bonn, Federal Republic of Germany). Intravenous immunoglobulin in HIV-I infected haemophilic patients. Archives of Disease in Childhood. 1992 Oct; 67(10):1267-71.

Study design:	Prospective controlled open trial.	**Length of follow-up:**	24 months
Sample size:	18 in each arm (36 total)	**Population:**	Patients (aged 6-19 years) with haemophilia and early stages of HIV infection (without AIDS or AIDS related complex).
Intervention:	0.3 g/kg IVIG at two-week intervals.		
Comparison / control:			
Outcome(s) measured:	Progression of HIV disease assessed by the modified Brodt/Helm classification, number of infectious events and HIV associated thrombocytopenia, and the CD4+ T cell count.		

Quality assessment (internal validity)

Placebo:	Yes
Follow-up:	

Results

Intervention groups:	Seven patients deteriorated according to their staging, with one patient developing AIDS; thrombocytopenia and infectious events, but no severe bacterial infections, occurred in both groups in similar numbers; absolute CD4+ T cell count decreased by a mean value of 284/microliters.	**Control / comparison group(s):**	Five patients deteriorated according to their staging, with one patient developing AIDS; thrombocytopenia and infectious events, but no severe bacterial infections, occurred in both groups in similar numbers; absolute CD4+ T cell count decreased by a mean value of 143/microliters.
P-value:	NS		
Adverse events:	None reported.		
Conclusions / Comments:	IVIG was not effective in the early stages of HIV infection in patients with haemophilia, did not slow the progression of disease and did not prevent the development of an immunodeficiency as assessed by the CD4+ T-cell count.		

Condition studies:	HIV/AIDS: Adult

134	Wintergerst, U.; Niinivaara-Kreuzer, K.; Notheis, G.; Auberger, K.; Bruckmann, C.; Gandenberger, S., and Belohradsky, B. H. (Universitats-Kinderkliniken, Ludwig-Maximilians-Universitat, Munchen, Germany). High-dose intravenous immunoglobulins in the treatment of adolescent and adult HIV-infected hemophiliacs. Clinical Investigator. 1994 Jan; 72(2):122-6.

Study design:	Cohort	**Length of follow-up:**	Average treatment period 32 months
Sample size:	17	**Population:**	HIV-infected hemophiliacs aged 9-30 years.
Intervention:	Monthly intravenous immunoglobulins for an average of 32 months.		
Comparison / control:	nil		
Outcome(s) measured:	Manifestation rate of AIDS and prognostic markers.		

Quality assessment (internal validity)

Placebo:	No
Follow-up:	

Results

Intervention groups:	At the end of the study, 8 years after the HIV infection, three patients (18%) had progressed to AIDS; average decrease in CD4 cells was 81 cells/microliter per year; no patients developed severe bacterial infections during the study period.	**Control / comparison group(s):**	The natural history of HIV infection in hemophiliacs in this age group shows a manifestation rate of AIDS between 11% and 26% 6-8 years after seroconversion and an average yearly decrease in CD4 lymphocytes of 68-110 cells/microliters.
P-value:			
Adverse events:			
Conclusions / Comments:	No difference in the manifestation rate of AIDS or in prognostic markers in this small cohort of HIV-infected hemophiliacs treated for more than 30% of their latency period with IVIG compared to the well-documented natural history of HIV-infected hemophiliacs.		

HIV/AIDS

Condition summary

HIV/AIDS: Paediatric

Reference list:

88 Anonymous. Intravenous immune globulin for the prevention of bacterial infections in children with symptomatic human immunodeficiency virus infection. The National Institute of Child Health and Human Developments Intravenous Immunoglobulin Study Group.[comment]. New England Journal of Medicine. 1991 Jul 11; 325(2):73-80.

106 Jimenez, E.; Carrer, M. T.; Perez Dieppa, I.; Ortiz, L., and Fernandez, M. [Experience with the use of immune intravenous immunoglobulin in symptomatic children with human immunodeficiency virus infection]. [Spanish]. Boletin - Asociacion Medica De Puerto Rico. 1991 Dec; 83(12):538-42.

113 Mofenson, L. M.; Bethel, J.; Moye, J. Jr; Flyer, P., and Nugent, R. (Adolescent and Maternal AIDS Branch, National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD 20892). Effect of intravenous immunoglobulin (IVIG) on CD4+ lymphocyte decline in HIV-infected children in a clinical trial of IVIG infection prophylaxis. The National Institute of Child Health and Human Development Intravenous Immunoglobulin Clinical Trial Study Group. Journal of Acquired Immune Deficiency Syndromes. 1993 Oct; 6(10):1103-13.

114 Mofenson, L. M.; Korelitz, J.; Pelton, S.; Moye, J. Jr; Nugent, R., and Bethel, J. (Pediatric, Adolescent, and Maternal AIDS Branch, National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, Maryland 20892-7510, USA). Sinusitis in children infected with human immunodeficiency virus: clinical characteristics, risk factors, and prophylaxis. National Institute of Child Health and Human Development Intravenous Immunoglobulin Clinical Trial Study Group. Clinical Infectious Diseases. 1995 Nov; 21(5):1175-81.

115 Mofenson, L. M.; Moye, J. J. r.; Bethel, J.; Hirschhorn, R.; Jordan, C., and Nugent, R. Prophylactic intravenous immunoglobulin in HIV-infected children with CD4+ counts of 0.20 x 109/L or more: Effect on viral, opportunistic, and bacterial infections. J AM MED ASSOC. 1992; 268(4):483-488.

116 Mofenson, L. M. and Moye, J. Jr (Pediatric, Adolescent and Maternal AIDS Branch, National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, Maryland 20852). Intravenous immune globulin for the prevention of infections in children with symptomatic human immunodeficiency virus infection. [Review] [52 refs]. Pediatric Research. 1993 Jan; 33(1 Suppl):S80-7; discussion S87-9.

127 Spector, S. A.; Gelber, R. D.; McGrath, N.; Wara, D.; Barzilai, A.; Abrams, E.; Bryson, Y. J.; Dankner, W. M.; Livingston, R. A., and Connor, E. M. (University of California, San Diego, La Jolla 92093-0672). A controlled trial of intravenous immune globulin for the prevention of serious bacterial infections in children receiving zidovudine for advanced human immunodeficiency virus infection. Pediatric AIDS Clinical Trials Group.[see comment]. New England Journal of Medicine. 1994 Nov 3; 331(18):1181-7.

134 Wintergerst, U.; Niinivaara-Kreuzer, K.; Notheis, G.; Auberger, K.; Bruckmann, C.; Gandenberger, S., and Belohradsky, B. H. (Universitats-Kinderkliniken, Ludwig-Maximilians-Universitat, Munchen, Germany). High-dose intravenous immunoglobulins in the treatment of adolescent and adult HIV-infected hemophiliacs. Clinical Investigator. 1994 Jan; 72(2):122-6.

Types of study:	One RCT, 2 uncontrolled.
Total sample size:	A sample of 376 in RCT; 77 in uncontrolled.
Quality:	Low-High
Result:	RCT - reduction in serious bacterial and viral infections (in some children); uncontrolled studies, no significant effect in HIV-infected hemophiliacs or in reducing sinusitis.
Adverse events:	Minor adverse reactions noted for <1% of infusions.
Conclusion:	Some evidence of benefit in reducing infections in subgroup of HIV-infected children, but no significant effect on overall survival rate, based on 1 large RCT.
Category:	IIa

Condition studies:	HIV/AIDS: Paediatric

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Anonymous. Intravenous immune globulin for the prevention of bacterial infections in children with symptomatic human immunodeficiency virus infection. The National Institute of Child Health and Human Developments Intravenous Immunoglobulin Study Group.[comment]. New England Journal of Medicine. 1991 Jul 11; 325(2):73-80.

Study design:	RCT	**Length of follow-up:**	median 17 months
Sample size:	Sample of 372 total.	**Population:**	HIV-infected children (mean age, 40 months) with clinical or immunologic evidence of HIV disease.
Intervention:	IVIG (400 mg per kilogram of body weight) or placebo every 28 days.		
Comparison / control:	Placebo (0.1 percent albumin) every 28 days.		
Outcome(s) measured:	Time free from serious infection; number of serious and minor bacterial infections; number of hospitalizations for acute care; mortality.		

Quality assessment (internal validity)

Placebo:	Yes
Follow-up:	

Results

Intervention groups:	For CD4+ counts ? 0.2 x 10(9)/L (? 200 per cubic millimeter), estimated 24-month infection-free rate 67%; overall reduction in number of serious and minor bacterial infections (RR, 0.68); reduction in number of hospitalizations for acute care (RR 0.65); for group 1 trend toward improved 24-month infection-free survival (31%); for group 2, estimated survival without serious infection was 73 %; no benefits for children with CD4+ counts < 0.2 x 10(9) per liter at entry.	**Control / comparison group(s):**	For CD4+ counts ? 0.2 x 10(9)/L, estimated 24-month infection-free rate 48 %; 25%; 53%.
P-value:			
Adverse events:	Minor adverse reactions noted for <1% of infusions.		

Conclusions / Comments:	In symptomatic HIV-infected children, prophylactic IVIG is safe and significantly increases the time free from serious bacterial infections for those entering treatment with CD4+ lymphocyte counts greater than or equal to 0.2 x 10(9) per liter.

Condition studies:	HIV/AIDS: Paediatric

106	Jimenez, E.; Carrer, M. T.; Perez Dieppa, I.; Ortiz, L., and Fernandez, M. [Experience with the use of immune intravenous immunoglobulin in symptomatic children with human immunodeficiency virus infection]. [Spanish]. Boletin - Asociacion Medica De Puerto Rico. 1991 Dec; 83(12):538-42.

Study design:	RCT	**Length of follow-up:**	
Sample size:	A sample of 33 children (participating in a wider study of 372 children).	**Population:**	Symptomatic children infected with HIV.
Intervention:	Gamma immunoglobulin in n = 15.		
Comparison / control:	Placebo in n = 16.		
Outcome(s) measured:	Number of serious infections; hospitalisations.		

Quality assessment (internal validity)

Placebo:	Yes
Follow-up:	

Results

Intervention groups:	Four out of15 children developed 5 episodes of serious infection; 6 hospitalisations.	**Control / comparison group(s):**	Nine out of 16 (56%) developed 23 episodes of serious infection; 24 hospitalisations.
P-value:			
Adverse events:	No adverse reactions were registered from the infusions.		
Conclusions / Comments:	IIVIG effective in preventing bacterial infections and decreasing the number of hospitalizations in a subgroup of children infected with HIV.		

Condition studies:	HIV/AIDS: Paediatric

113	Mofenson, L. M.; Bethel, J.; Moye, J. Jr; Flyer, P., and Nugent, R. (Adolescent and Maternal AIDS Branch, National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD 20892). Effect of intravenous immunoglobulin (IVIG) on CD4+ lymphocyte decline in HIV-infected children in a clinical trial of IVIG infection prophylaxis. The National Institute of Child Health and Human Development Intravenous Immunoglobulin Clinical Trial Study Group. Journal of Acquired Immune Deficiency Syndromes. 1993 Oct; 6(10):1103-13.

Study design:	RCT	**Length of follow-up:**	18 months
Sample size:	Sample of 277 children from a total of 313 participating in another trial.	**Population:**	Group of 277 children with three or more CD4+ counts (measured during a trial).
Intervention:	Dose of 400 mg per kilogram of IVIG every 28 days.		
Comparison / control:	A 0.1% albumin placebo.		
Outcome(s) measured:	Rates of CD4+ count decline.		

Quality assessment (internal validity)

Placebo:

Follow-up:

Results

Intervention groups:	Age-adjusted slope analysis showed slowing of CD4+ count decline by 13.5 cells/mm3 per month in IVIG compared with placebo recipients . Modeling log change between measurements documented a beneficial effect of IVIG that was cumulative over time and independent of other therapies.	**Control / comparison group(s):**	
P-value:	A 95% confidence interval, 3.1-23.9, p = 0.012.		

Adverse events:

Conclusions / Comments:	IVIG slow decline in CD4+ count, no effect on mortality.

Condition studies:	HIV/AIDS: Paediatric

114	Mofenson, L. M.; Korelitz, J.; Pelton, S.; Moye, J. Jr; Nugent, R., and Bethel, J. (Pediatric, Adolescent, and Maternal AIDS Branch, National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, Maryland 20892-7510, USA). Sinusitis in children infected with human immunodeficiency virus: clinical characteristics, risk factors, and prophylaxis. National Institute of Child Health and Human Development Intravenous Immunoglobulin Clinical Trial Study Group. Clinical Infectious Diseases. 1995 Nov; 21(5):1175-81.

Study design:	Cohort	**Length of follow-up:**	
Sample size:	Sample of 60 patients with 95 episodes of sinusitis.	**Population:**	Group of 60 patients with 95 episodes of sinusitis; one-third of the patients had two or more episodes.
Intervention:	Monthly IVIG prophylaxis.		
Comparison / control:	Placebo/ three times weekly trimethoprim sulfamethoxazole prophylaxis for Pneumocystis carinii pneumonia.		
Outcome(s) measured:	The clinical presentation, radiological and laboratory evaluation, treatment, and risk factors of sinusitis.		

Quality assessment (internal validity)

Placebo:	Yes
Follow-up:	

Results

Intervention groups:	Neither monthly IVIG prophylaxis nor three times weekly trimethoprim sulfamethoxazole prophylaxis for Pneumocystis carinii pneumonia decreased the risk of sinusitis.	**Control / comparison group(s):**	
P-value:			
Adverse events:			
Conclusions / Comments:	IVIG is not effective as prophylaxis for sinusitis in HIV-infected children.		

Condition studies:	HIV/AIDS: Paediatric

115	Mofenson, L. M.; Moye, J. J. r.; Bethel, J.; Hirschhorn, R.; Jordan, C., and Nugent, R. Prophylactic intravenous immunoglobulin in HIV-infected children with CD4+ counts of 0.20 x 109/L or more: Effect on viral, opportunistic, and bacterial infections. J AM MED ASSOC. 1992; 268(4):483-488.

Study design:	RCT	**Length of follow-up:**	
Sample size:	A sample of 376, 313 of whom had entry CD4+ counts of at least 0.20 x 109/L (greater than or equal to200/mm3).	**Population:**	Children infected with HIV.
Intervention:	400 mg of IVIG per kilogram of body weight every 28 days.		
Comparison / control:	Albumin placebo.		
Outcome(s) measured:	Incidence of laboratory-proven and clinically diagnosed viral, opportunistic, and bacterial infections.		

Quality assessment (internal validity)

Placebo:	Yes
Follow-up:	

Results

Intervention groups:	36.0 episodes of viral infection per 100 patient-years; 115.1 episodes of minor bacterial infection per 100 patient-years; 26.4 serious bacterial infections per 100 patient-years ; no apparent difference in rate of opportunistic infections between treatment arms.	**Control / comparison group(s):**	54.0 episodes of viral infection per 100 patient-years, 159.7 episodes of minor bacterial infection per 100 patient-years; 48.2 serious bacterial infections per 100 patient-years.
P-value:	P = 0.01 (viral infection); P = 0.202 (minor bacterial infection); P = 0.002 (serious bacterial infection).		
Adverse events:	None reported.		
Conclusions / Comments:	Beneficial effect of IVIG seen across multiple infectious outcome measures, in children with entry CD4+ counts of at least 0.20 x 109/L.		

Condition studies: HIV/AIDS: Paediatric

116

Mofenson, L. M. and Moye, J. Jr (Pediatric, Adolescent and Maternal AIDS Branch, National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, Maryland 20852). Intravenous immune globulin for the prevention of infections in children with symptomatic human immunodeficiency virus infection. [Review] [52 refs]. Pediatric Research. 1993 Jan; 33(1 Suppl):S80-7; discussion S87-9.

Study design: RCT **Length of follow-up:**

Sample size: 376 **Population:** HIV infected children under 13 years of age.

Intervention: IVIG 400 mg per kilogram of body weight) every 28 days.

Comparison / control: Placebo (0.1 percent albumin) every 28 days.

Outcome(s) measured: Rates of infection.

Quality assessment (internal validity)

Placebo: Yes

Follow-up:

Results

Intervention groups:

Control / comparison group(s):

P-value:

Adverse events:

Conclusions / Comments: In children with an entry CD4+ count of 200/mm3 or higher, IVIG significantly increased the time free from serious bacterial infections and significantly decreased the rates of minor bacterial infections and viral infections.

Condition studies:	HIV/AIDS: Paediatric

127	Spector, S. A.; Gelber, R. D.; McGrath, N.; Wara, D.; Barzilai, A.; Abrams, E.; Bryson, Y. J.; Dankner, W. M.; Livingston, R. A., and Connor, E. M. (University of California, San Diego, La Jolla 92093-0672). A controlled trial of intravenous immune globulin for the prevention of serious bacterial infections in children receiving zidovudine for advanced human immunodeficiency virus infection. Pediatric AIDS Clinical Trials Group.[see comment]. New England Journal of Medicine. 1994 Nov 3; 331(18):1181-7.

Study design:	RCT	**Length of follow-up:**	median 30.6 months
Sample size:	255 (129 in IVIG arm; 126 placebo arm)	**Population:**	Children between 3 months and 12 years of age who had acquired immunodeficiency syndrome (AIDS) or AIDS-related complex.
Intervention:	IVIG 400 mg per kilogram of body weight) every 28 days + zidovudine 180 mg per square meter of body-surface area orally four times daily.		
Comparison / control:	Placebo (0.1 percent albumin) every 28 days + zidovudine 180 mg per square meter of body-surface area orally four times daily.		
Outcome(s) measured:	Estimated two-year rates of serious bacterial infections with confirmed pathogens.		

Quality assessment (internal validity)

Placebo:	Yes
Follow-up:	

Results

Intervention groups:	Estimated two-year rate of serious bacterial infections with confirmed pathogens: 16.9 %; in the 174 children not receiving trimethoprim-sulfamethoxazole prophylaxis at entry the estimated two-year rate of infection was 11.3%; for the 81 children who were receiving trimethoprim-sulfamethoxazole prophylaxis initially, the estimated two-year rate of infection was 27.7%; 2-year survival 79.2% (similar to placebo).	**Control / comparison group(s):**	Estimated 2-year rate of serious bacterial infections with confirmed pathogens: 4.3 %; In the 174 children not receiving trimethoprim-sulfamethoxazole prophylaxis at entry the estimated two-year rate of infection was 26.8 %; for the 81 children who were receiving trimethoprim-sulfamethoxazole prophylaxis initially, the estimated two-year rate of infection was 17.7%; 2-year survival 75.4%.
P-value:	Serious bacterial infections - RR, 0.60; 95 % CI, 0.35 to 1.04; P = 0.07; 2-year rate of infection - RR, 0.45; 95 % CI, 0.22 to 0.91; P = 0.03; trimethoprim-sulfamethoxazole prophylaxis initially, 2-year rate of infection - RR, 1.26; 95 % CIl, 0.44 to 3.66; P = 0.67; 2-year survival P = 0.41.		

Adverse events:

Conclusions / Comments:	In children with advanced HIV disease who are receiving zidovudine, IVIG decreases the risk of serious bacterial infections, but only in children not receiving trimethoprim-sulfamethoxazole as prophylaxis; overall survival rate not significantly different.

Condition studies:	HIV/AIDS: Paediatric

134	Wintergerst, U.; Niinivaara-Kreuzer, K.; Notheis, G.; Auberger, K.; Bruckmann, C.; Gandenberger, S., and Belohradsky, B. H. (Universitats-Kinderkliniken, Ludwig-Maximilians-Universitat, Munchen, Germany). High-dose intravenous immunoglobulins in the treatment of adolescent and adult HIV-infected hemophiliacs. Clinical Investigator. 1994 Jan; 72(2):122-6.

Study design:	Cohort	**Length of follow-up:**	average treatment period 32 months
Sample size:	17	**Population:**	HIV-infected hemophiliacs aged 9-30 years.
Intervention:	Monthly intravenous immunoglobulins for an average of 32 months.		
Comparison / control:	Nil.		
Outcome(s) measured:	Manifestation rate of AIDS and prognostic markers.		

Quality assessment (internal validity)

Placebo:	No
Follow-up:	

Results

Intervention groups:	At the end of the study, 8 years after the HIV infection, three patients (18%) had progressed to AIDS. The average decrease in CD4 cells was 81 cells/microliter per year. No patients developed severe bacterial infections during the study period.	**Control / comparison group(s):**	The natural history of HIV infection in hemophiliacs in this age group shows a manifestation rate of AIDS between 11% and 26% 6-8 years after seroconversion and an average yearly decrease in CD4 lymphocytes of 68-110 cells/microliters.
P-value:			
Adverse events:			
Conclusions / Comments:	No difference in the manifestation rate of AIDS or in prognostic markers in this small cohort of HIV-infected hemophiliacs treated for more than 30% of their latency period with IVIG compared to the well-documented natural history of HIV-infected hemophiliacs.		

Immunological

Condition summary	Transplantations: Heart/Lung/Pancreas
Category:	IVb

Immunological

Condition summary	Transplantations: kidney - infection (eg BK virus)
Reference list:	142 Conti DJ, Freed BM, Gruber SA, Lempert N. Prophylaxis of primary cytomegalovirus disease in renal transplant recipients. A trial of ganciclovir vs immunoglobulin. Arch Surg 1994; 129(4):443-7. 140 Peraldi MN, Akposso K, Haymann JP et al. Long-term benefit of intravenous immunoglobulins in cadaveric kidney retransplantation. Transplantation 1996; 62(11):1670-3.
Types of study:	Case control (prospective randomised with historical control).
Total sample size:	51
Quality:	Low
Result:	Both IVIG and ganciclovir significantly reduced incidence of CMV infection P=<0.5 compared to control.
Adverse events:	Not mentioned for IVIG.
Conclusion:	Some benefit with IVIG based on 1 low quality case control study.
Category:	IIa

Condition studies:	Transplantations: kidney - infection (eg BK virus)

142	Conti DJ, Freed BM, Gruber SA, Lempert N. Prophylaxis of primary cytomegalovirus disease in renal transplant recipients. A trial of ganciclovir vs immunoglobulin. Arch Surg 1994; 129(4):443-7.

Study design:	Case-control, prospective, randomised, historical control.	**Length of follow-up:**	
Sample size:	51	**Population:**	CMV-seronegative patients who received renal allografts from seropositive donors.
Intervention:	Cytomegalovirus prophylaxis with 7 doses of IVIG for 6 weeks.		
Comparison / control:	Comparison: Cytomegalovirus prophylaxis with IV ganciclovir for 3 weeks. Control: 23 patients who received renal allografts from CMV-seropositive donors and who did not receive prophylaxis.		
Outcome(s) measured:	Patient and allograft survival, incidence and severity of CMV disease.		

Quality assessment (internal validity)

Placebo:

Follow-up:

Results

Intervention groups:	Both IVIG and ganciclovir significantly reduced incidence of CMV infection P=<0.5 compared to control.	**Control / comparison group(s):**	

P-value:

Adverse events:

Conclusions / Comments:	Ganciclovir cost $350/patient whereas IVIG cost $4000/patient.

Condition studies: Transplantations: kidney - infection (eg BK virus)

140

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

Study design:	Case-series, randomised.	**Length of follow-up:**	5 years
Sample size:	41	**Population:**	Patients who received a second cadaveric transplant between 1989-1994.
Intervention:	IVIG 0.4 g/kg/day for 5 days after transplant.		
Comparison / control:			
Outcome(s) measured:	Patient and graft survival.		

Quality assessment (internal validity)

Placebo:

Follow-up:

Results

Intervention groups:	5 year graft survival rate was higher (68% vs 50%) (P = 0.0017) in IVIG compared to control. Shorter delay of graft function (3.4 days vs 9.9 days) in IVIG group.	**Control / comparison group(s):**	

P-value:

Adverse events:

Conclusions / Comments: Poor quality study, because some patients were also treated with additional immunosuppressive treatments and 3 different IVIG preparations used during trial.

Immunological

Condition summary	Transplantations: kidney - rejection
Reference list:	139 Casadei DH, del C Rial M, Opelz G et al. A randomized 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.
Types of study:	One RCT.
Total sample size:	30
Quality:	Moderate
Result:	There were 46% (5/11) rejections in IVIG vs 75% (9/11) rejections in OKT3 group. Patient survival in IVIG was 87%, vs 92% patient survival in OKT3 group after 2 years. There was 80% graft survival in both groups.
Adverse events:	IVIG was better tolerated than OKT3. Cytokine release symptoms only occurred in OKT3 group. Data not shown in paper.
Conclusion:	IVIG was as effective as OKT3 treatment.
Category:	IIa

Condition studies:	Transplantations: kidney - rejection

139	Casadei DH, del C Rial M, Opelz G et al. A randomized 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.

Study design:	RCT	**Length of follow-up:**	2 years (patient survival rates)
Sample size:	30	**Population:**	Patients with kidney grafts with steroid-resistant rejection. Demographic factors and HLA mismatch were taken into account.
Intervention:	IVIG 500mg/kg for 7 days.		
Comparison / control:	Anti-CD3 antibody (OKT3) for 14 days.		
Outcome(s) measured:	Graft and patient survival.		

Quality assessment (internal validity)

Placebo:

Follow-up:

Results

Intervention groups:	Five out of 11 rejections (46%), 87% patient survival after 2 years, 80% graft survival.	**Control / comparison group(s):**	Nine out of 12 rejections (75%), 92% patient survival after 2 years, 80% graft survival.

P-value:

Adverse events:

Conclusions / Comments:	More side effects associated with OKT3 treatment.

Immunological

Condition summary	Transplantations: liver
Reference list:	
Types of study:	
Total sample size:	
Quality:	
Result:	
Adverse events:	
Conclusion:	
Category:	See: Transplantations: kidney - infection (eg BK virus)

Immunological

Condition summary	Untransplantability due to anti-HLA antibodies
Reference list:	
Types of study:	
Total sample size:	
Quality:	
Result:	
Adverse events:	
Conclusion:	
Category:	See: Transplantations: kidney - infection (eg BK virus)

Miscellaneous

Condition summary	Acute rheumatic fever
Reference list:	56 Cilliers AM, Manyemba J, Saloojee H. Anti-inflammatory treatment for carditis in acute rheumatic fever (Cochrane Review). In: The Cochrane Library, Issue 3, 2004. Chichester, UK: John Wiley & Sons, Ltd.
Types of study:	One systematic review.
Total sample size:	61
Quality:	Moderate
Result:	IVIG did not reduce the risk of developing heart lesions at one year (relative risk 0.87; 95% CI 0.55-1.39).
Adverse events:	None reported.
Conclusion:	Appears to be no significant effect, based on one moderate-level RCT in Cochrane review.
Category:	IIb

Condition studies:	Acute rheumatic fever

56	Cilliers AM, Manyemba J, Saloojee H. Anti-inflammatory treatment for carditis in acute rheumatic fever (Cochrane Review). In: The Cochrane Library, Issue 3, 2004. Chichester, UK: John Wiley & Sons, Ltd.

Study design:	Eight RCTs in total, including 1 for IVIG (Voss, 2001) (6 trials conducted from 1950-1965 and 2 in the last 10 years).	**Length of follow-up:**	1 year
Sample size:	Sample of 61 for IVIG (2 withdrawals).	**Population:**	Children aged < 12 years, with first episode of rheumatic fever.
Intervention:	IVIG 1 g/kg on days 0 and 1, then 0.4 mg/kg on days 14 and 28.		
Comparison / control:	Placebo infusion of dextrose/saline.		
Outcome(s) measured:	Presence of carditis at 1 year.		

Quality assessment (internal validity)

Placebo:

Follow-up:

Results

Intervention groups:	Fourteen out of 27 IVIG with carditis at 1 year.	**Control / comparison group(s):**	Nineteen out of 32 placebo with carditis at 1 year.
P-value:	NS		

Adverse events:

Conclusions / Comments:	Cochrane review concludes that IVIG did not reduce the risk of developing heart lesions at one year, based on one moderate-level RCT. More research needed.

Miscellaneous

Condition summary	Asthma
Reference list:	69 Kishiyama JL, Valacer D, Cunningham-Rundles C et al. A multicenter, randomized, double-blind, placebo-controlled trial of high-dose intravenous immunoglobulin for oral corticosteroid-dependent asthma.[see comment]. Clin Immunol 1999; 91(2):126-33.Got pdf 75 Niggemann B, Leupold W, Schuster A et al. Prospective, double-blind, placebo-controlled, multicentre study on the effect of high-dose, intravenous immunoglobulin in children and adolescents with severe bronchial asthma. Clinical & Experimental Allergy 1998; 28(2):205-10. 78 Salmun LM, Barlan I, Wolf HM et al. Effect of intravenous immunoglobulin on steroid consumption in patients with severe asthma: a double-blind, placebo-controlled, randomized trial. Journal of Allergy & Clinical Immunology 1999; 103(5 Pt 1):810-5.
Types of study:	Three RCTs.
Total sample size:	109
Quality:	Low-Moderate
Result:	One RCT -some decrease in duration of upper respiratory tract infections in children/adolescents; 1 RCT - steroid-sparing in adults with severe asthma requiring high doses of oral steroids; 1 RCT - no clinically or statistically significant advantage over placebo in children/adults.
Adverse events:	Three patients in IVIG (2g/kg) group hospitalised with symptoms consistent with aseptic meningitis; significantly more headaches in IVIG groups, some severe headaches (lasting over 24 h, some requiring narcotic analgesics).
Conclusion:	Possible benefit in steroid-sparing or reducing duration of infection, based on 2 RCTs; appears to be no signficant effect, based on 1 RCT.
Category:	IIc

Condition studies:	Asthma

69	Kishiyama JL, Valacer D, Cunningham-Rundles C et al. A multicenter, randomized, double-blind, placebo-controlled trial of high-dose intravenous immunoglobulin for oral corticosteroid-dependent asthma.[see comment]. Clin Immunol 1999; 91(2):126-33.Got pdf

Study design:	RCT (double-blind).	**Length of follow-up:**	7 months of treatment
Sample size:	Sample of 40 total - 16 (IVIG-2g), 9 (IVIG-1g) and 15 (albumin).	**Population:**	Severe, steroid-dependent asthma in patients between 6 and 68 years of age.
Intervention:	IVIG (1 or 2g/kg/month).		
Comparison / control:	Albumin (placebo) 2g/kg/month.		
Outcome(s) measured:	Primary - mean dailty prednisone-equivalent dose requirements; secondary - pulmonary function, frequency of emergency room visits or hospitalisations, days off from school and work.		

Quality assessment (internal validity)

Placebo:	Yes
Follow-up:	Premature termination following adverse events; 30/54 completed study.

Results

Intervention groups:	Dose rates fell by 33% (IVIG 1g/kg), 39% (IVIG 2g/kg).	**Control / comparison group(s):**	Fell by 39% in placebo group.
P-value:	NS		
Adverse events:	Three patients in IVIG (2g/kg) group hospitalised with symptoms consistent with aseptic meningitis; significantly more headaches in IVIG groups, some severe headaches (lasting over 24 h, some requiring narcotic analgesics).		
Conclusions / Comments:	No clinically or statistically significant advantage over placebo.		

Condition studies:	Asthma

75	Niggemann B, Leupold W, Schuster A et al. Prospective, double-blind, placebo-controlled, multicentre study on the effect of high-dose, intravenous immunoglobulin in children and adolescents with severe bronchial asthma. Clinical & Experimental Allergy 1998; 28(2):205-10.

Study design:	RCT	**Length of follow-up:**	1 month after end of treatment period
Sample size:	31	**Population:**	Children and adolescents, 9-22 years (median 14) with severe bronchial asthma.
Intervention:	IVIG (1g/kg). Two doses on consecutive days, 2 at 4-week intervals.		
Comparison / control:	Albumin (1g/kg).		
Outcome(s) measured:	Symptom score, bronchial hyperactivity and peak-flow variability.		

Quality assessment (internal validity)

Placebo:	Yes
Follow-up:	All those enrolled completed the study.

Results

Intervention groups:	Fewer total days of upper respiratory tract infections and symptom scores; less protracted infections.	**Control / comparison group(s):**	
P-value:	P < 0.03 for patients in IVIG group with more than or equal to 7 days less of upper resp tract infections.		
Adverse events:	Mild short-term symptoms (eg headache), no allergic reactions.		
Conclusions / Comments:	No significant reduction in incidence of upper respiratory tract infections, but patients who did have such infections appear to have less protracted infections.		

Condition studies:	Asthma

78	Salmun LM, Barlan I, Wolf HM et al. Effect of intravenous immunoglobulin on steroid consumption in patients with severe asthma: a double-blind, placebo-controlled, randomized trial. Journal of Allergy & Clinical Immunology 1999; 103(5 Pt 1):810-5.

Study design:	RCT (double-blind).	**Length of follow-up:**	
Sample size:	38	**Population:**	Immunocompetent patients with severe asthma.
Intervention:	IVIG		
Comparison / control:	Placebo.		
Outcome(s) measured:	Reduction in steroid use.		

Quality assessment (internal validity)

Placebo:	Yes
Follow-up:	28/38

Results

Intervention groups:	Significant reduction in oral steroid use; significant reduction in oral steroid requirement in patients requiring >2000 mg in previous year.	**Control / comparison group(s):**	Significant reduction in oral steroid use; no significant reduction in oral steroid requirement in patients requiring >2000 mg in previous year.
P-value:	P ≤0.01 in subgroup of patients requiring >2000mg (but not change in objective or subjective parameters of asthma).		
Adverse events:			
Conclusions / Comments:	IVIG may be a useful steroid-sparing agent in patients with severe asthma requiring high doses of oral steroids.		

Miscellaneous

Condition summary	Autism - young adults
Category:	IVb

Miscellaneous

Condition summary	Burns
Reference list:	74 Munster AM, Moran KT, Thupari J, Allo M, Winchurch RA. Prophylactic intravenous immunoglobulin replacement in high-risk burn patients. Journal of Burn Care & Rehabilitation 1987; 8(5):376-80.
Types of study:	One RCT.
Total sample size:	20
Quality:	Low
Result:	IVIG caused no significant difference in mortality rates; mortality from sepsis; positive cultures from wound, urine or IV lines; immune cell function. Significantly reduced polymicrobial blood cultures, CMV titres and blood endotoxin concentration.
Adverse events:	None reported.
Conclusion:	Possible benefit, based on 1 small RCT.
Category:	IIa

Condition studies: Burns

74 Munster AM, Moran KT, Thupari J, Allo M, Winchurch RA. Prophylactic intravenous immunoglobulin replacement in high-risk burn patients. Journal of Burn Care & Rehabilitation 1987; 8(5):376-80.

Study design: RCT (double blind).

Length of follow-up:

Sample size: Sample of 20 total (10 in each arm).

Population: Patients with extensive thermal injury.

Intervention: IVIG

Comparison / control: Albumin

Outcome(s) measured:

Quality assessment (internal validity)

Placebo: Yes

Follow-up: Eight patients died.

Results

Intervention groups: No sign diff in mortality rates, mortality from sepsis, positive cultures from wound, urine or IV lines, or immune cell function. Significantly less polymicrobial blood cultures, CMV titres and blood endotoxin concentration.

Control / comparison group(s):

P-value:

Adverse events:

Conclusions / Comments: Numbers small - do not follow up.

Miscellaneous

Condition summary	Cardiac surgery with bypass-prophylaxis
Reference list:	15 Friedrich I, Silber RE, Baumann B, Fischer C, Holzheimer RG. IgM-enriched immunoglobulin preparation for immunoprophylaxis in cardiac surgery. Eur J Med Res 2002; 7(12):544-9. 23 Kress HG, Scheidewig C, Schmidt H, Silber R. Reduced incidence of postoperative infection after intravenous administration of an immunoglobulin A- and immunoglobulin M-enriched preparation in anergic patients undergoing cardiac surgery.[see comment]. Crit Care Med 1999; 27(7):1281-7.
Types of study:	Two RCTs.
Total sample size:	80
Quality:	Moderate
Result:	IVIG increased endotoxin neutralizing capacity and significantly reduced number of patients with fever, leukocytosis, hypotension p=<0.05. IVIG significantly reduced the incidence of postoperative infections in anergic patients p=0.007.
Adverse events:	allergy (skin rash, dizziness) in 1 study.
Conclusion:	Possible benefit of IVIG although patient numbers low.
Category:	IIa

Condition studies:	Cardiac surgery with bypass-prophylaxis

15	Friedrich I, Silber RE, Baumann B, Fischer C, Holzheimer RG. IgM-enriched immunoglobulin preparation for immunoprophylaxis in cardiac surgery. Eur J Med Res 2002; 7(12):544-9.

Study design:	RCT	**Length of follow-up:**	
Sample size:	Sample of 41 patients in total: Intervention n=21, Comparison n=20.	**Population:**	Cardiac surgical patients.
Intervention:	IgM-enriched IVIG+antibiotic prophylaxis.		
Comparison / control:	Antibiotic prophylaxis plus placebo.		
Outcome(s) measured:	APACHE II score, comorbidity, coronary risk, operating time, clamp, ischemic time, endotoxin and endotoxin neutralizing capacity (ENC), Serum levels of interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF)-alpha, soluble TNF-Receptor I (sTNF-R1), and interleukin-10 (IL-10).		

Quality assessment (internal validity)

Placebo:

Follow-up:

Results

Intervention groups:	No mortality. Endotoxin plasma levels were generally higher in IVIG group. there was a significant difference in endotoxin neutralising capacity between groups, there was no difference between groups with respect to IL-6, TNF-alpha, IL-10 and TNF-R1; There were significantly less patients with signs of inflammation (fever, leukocytosis, hypotension) and slightly reduced hospitalization period in IVIG group.	**Control / comparison group(s):**	No mortality.

P-value:

Adverse events:

Conclusions / Comments:	IgM-enriched IVIG reduced signs of inflammation when used prophylactically in patients undergoing procedures with cardiopulmonary bypass. Numbers small.

Condition studies:	Cardiac surgery with bypass-prophylaxis

23	Kress HG, Scheidewig C, Schmidt H, Silber R. Reduced incidence of postoperative infection after intravenous administration of an immunoglobulin A- and immunoglobulin M-enriched preparation in anergic patients undergoing cardiac surgery.[see comment]. Crit Care Med 1999; 27(7):1281-7.

Study design:	RCT	**Length of follow-up:**	2 weeks
Sample size:	Sample of 19 patients in treatment group & 21 patients in control group.	**Population:**	Patients awaiting elective open heart surgery with cardiac bypass.
Intervention:	Commercial immunoglobulin IgA- and IgM-enriched immunoglobulin preparation (pentaglobin).		
Comparison / control:	Physiologic saline.		
Outcome(s) measured:	Postoperative infections.		

Quality assessment (internal validity)

Placebo:	Yes
Follow-up:	There were 19 patients followed up in the treatment group and 21 in the control group.

Results

Intervention groups:	Post operative infections were detected in 1/19 (5%) in treatment group compared to 9/21 (43%) in control group P = 0.007.	**Control / comparison group(s):**	Postoperative infections detected in 9/21 patients (43%) in the placebo group; 3/20 patients (15%) with normal immune response who received standard postoperative treatment developed postoperative infections.
P-value:			
Adverse events:	Two unrelated deaths reported due to septic shock (placebo group) and cardiac complication (IVIG group).		
Conclusions / Comments:	IVIG significantly reduced the incidence of postoperative infections in anergic patients P = 0.007.		

Miscellaneous

Condition summary	Congestive cardiac failure
Reference list:	52 Aukrust P, Gullestad L, Lappegard KT et al. Complement activation in patients with congestive heart failure: effect of high-dose intravenous immunoglobulin treatment. Circulation 2001; 104(13):1494-500. 65 Gullestad L, Aass H, Andreassen AK et al. [Immunomodulating treatment in advanced heart failure--effect of intravenous immunoglobulin].[see comment]. [Norwegian]. Tidsskr Nor Laegeforen 2001; 121(16):1902-7.
Types of study:	Two RCT.
Total sample size:	99
Quality:	Moderate
Result:	IVIG resulted in improved left ventricle ejection fraction.
Adverse events:	Not reported.
Conclusion:	Possible benefit, although no statistical analysis done.
Category:	IIa

Condition studies:	Congestive cardiac failure

52	Aukrust P, Gullestad L, Lappegard KT et al. Complement activation in patients with congestive heart failure: effect of high-dose intravenous immunoglobulin treatment. Circulation 2001; 104(13):1494-500.

Study design:	RCT	**Length of follow-up:**	6 months
Sample size:	Sample of 39 patients with congestive heart failure & 20 healthy control subjects.	**Population:**	
Intervention:	High-dose intraenous immunoglobulin.		
Comparison / control:	Placebo treatment not specified.		
Outcome(s) measured:	Complement activation.		

Quality assessment (internal validity)

Placebo:	Yes
Follow-up:	Group of 39 patients in treatment group and 20 in control group.

Results

Intervention groups:	Systemic complement activation was enhanced by IVIG which negatively correlated with improved left ventricle ejection fraction.	**Control / comparison group(s):**	No quantative data reported in abstract.
P-value:			
Adverse events:			
Conclusions / Comments:	Systemic complement activation was further enhanced during IVIG but not during placebo therapy.		

Condition studies:	Congestive cardiac failure

65	Gullestad L, Aass H, Andreassen AK et al. [Immunomodulating treatment in advanced heart failure--effect of intravenous immunoglobulin].[see comment]. [Norwegian]. Tidsskr Nor Laegeforen 2001; 121(16):1902-7.

Study design:	RCT	**Length of follow-up:**	26 weeks
Sample size:	Sample of 40 patients total. No information on size of study groups.	**Population:**	Patients with symptomatic chronic heart failure & left ventricular ejection fraction < 40 %.
Intervention:	Intravenous immunoglobulin.		
Comparison / control:	Placebo not specified.		
Outcome(s) measured:	Measurement of cytokines, left ventricular ejection fraction, functional capacity & haemodynamic variables.		

Quality assessment (internal validity)

Placebo:	Yes
Follow-up:	Group of 40 patients followed up.

Results

Intervention groups:	IVIG shifted cytokine balance resulting in improved left ventricle ejection fraction.	**Control / comparison group(s):**	
P-value:			
Adverse events:			
Conclusions / Comments:	Abstract supports the hypothesis that immunomodulating variables play a role in the pathogenesis of heart failure.		

Miscellaneous

Condition summary	Grave's ophthalmopathy
Reference list:	51 Antonelli A, Saracino A, Alberti B et al. High-dose intravenous immunoglobulin treatment in Graves' ophthalmopathy.[see comment]. Acta Endocrinol (Copenh) 1992; 126(1):13-23. 54 Baschieri L, Antonelli A, Nardi S et al. Intravenous immunoglobulin versus corticosteroid in treatment of Graves' ophthalmopathy. Thyroid 1997; 7(4):579-85. 68 Kahaly G, Pitz S, Muller-Forell W, Hommel G. Randomized trial of intravenous immunoglobulins versus prednisolone in Graves' ophthalmopathy. Clinical & Experimental Immunology 1996; 106(2):197-202.
Types of study:	One RCT, 1 RCT/historical control, 1 cohort.
Total sample size:	Sample of 4 in RCT.
Quality:	Low
Result:	Similar effect to corticosteroids in improvements in ocular function.
Adverse events:	Less with IVIG than with corticosteroids.
Conclusion:	Possible benefit (equivalent to corticosteroids), based on three small trials, none using placebo.
Category:	IIa

Condition studies:	Grave's ophthalmopathy

51	Antonelli A, Saracino A, Alberti B et al. High-dose intravenous immunoglobulin treatment in Graves' ophthalmopathy.[see comment]. Acta Endocrinol (Copenh) 1992; 126(1):13-23.

Study design:	RCT/Historical control.	**Length of follow-up:**	See paper
Sample size:	Seven per group and 12 in historical group.	**Population:**	
Intervention:	IVIG only.		
Comparison / control:	IVIG and orbital therapy (and historical group, treated with systemic steroids and orbital irradiation).		
Outcome(s) measured:	Ophthalmopathy index (OI), confirmed by computerised tomography (CT).		

Quality assessment (internal validity)

Placebo:	No
Follow-up:	

Results

Intervention groups:	Significant reduction between mean initial and final OI.	**Control / comparison group(s):**	Significant reduction between mean initial and final OI (for current and historical control group).
P-value:	?P = 0.005 in all 3 groups.		
Adverse events:	Corticosteroids - major and minor side effects.		
Conclusions / Comments:	Similar effect, fewer side effects with IVIG. Numbers small.		

Condition studies:	Grave's ophthalmopathy

54	Baschieri L, Antonelli A, Nardi S et al. Intravenous immunoglobulin versus corticosteroid in treatment of Graves' ophthalmopathy. Thyroid 1997; 7(4):579-85.

Study design:	Cohort	**Length of follow-up:**	21 months average for 27 of IVIG, 6 months for rest
Sample size:	Sample of 35 IVIG, 27 steroids (not clear).	**Population:**	
Intervention:	High-dose IVIG.		
Comparison / control:	Systemic corticosteroids.		
Outcome(s) measured:	Endocrine evaluation and blinded ophthalmological and orbital computed tomography (CT).		

Quality assessment (internal validity)

Placebo:	No
Follow-up:	Group of 27 IVIG patients followed up after end of treatment (12-48 months, average 21 months), rest 6 months.

Results

Intervention groups:	Improved or disappeared: soft tissue involvement (NOSPECS) - 32/35 (90%), diplopia - 22/29 (75%), orbital CT score in 30 patients - significant reduction of extraocular muscle thickness, proptosis- 20 of 31 (65%), responder patients defined in relation to the decrease in the highest NOSPECS class or grade - 26 of 34 (76%).	**Control / comparison group(s):**	Improved or disappeared: NOSPECS - 25 of 27 (92.5%), diplopia - 16 of 20 (80%), proptosis - 15 of 24 (62%) responder patients - 18 of 27 (66%).
P-value:	NS		
Adverse events:	Four out of 15 osteoporosis and three out of 15 less bone mineral content in steroid group. Moderate and minor adverse events more common in steroid group.		
Conclusions / Comments:	Similar effect, fewer side effects with IVIG. Numbers small.		

Condition studies:	Grave's ophthalmopathy

68	Kahaly G, Pitz S, Muller-Forell W, Hommel G. Randomized trial of intravenous immunoglobulins versus prednisolone in Graves' ophthalmopathy. Clinical & Experimental Immunology 1996; 106(2):197-202.

Study design:	RCT	**Length of follow-up:**	To end of therapy (20 weeks)
Sample size:	Sample of 21 IVIG, 19 steroids.	**Population:**	
Intervention:	IVIG (1g/kg bodyweight), 2 consecutive days every 3 weeks, for 20 weeks.		
Comparison / control:	Oral prednisolone (100mg/day).		
Outcome(s) measured:	Ophthalmological investigation and quantitative magnetic resonance (MR) imaging.		

Quality assessment (internal validity)

Placebo:	No
Follow-up:	

Results

Intervention groups:	Improvements for both groups in proptosis (median from 24.5 to 21.5 mm; P < 0.005), visual acuity (from 0.6 to 0.85; P < 0.001), intraocular pressure (from 25 to 20 mmHg; P < 0.0001), lid aperture (from 14 to 12 mm: P < 0.01) and a decrease in eye muscle area (inferior, from 44 to 33 mm2; medial, from 43 to 34 mm2; both P < 0.0005).	**Control / comparison group(s):**	
P-value:	? 0.01		
Adverse events:	Side effects were more frequent and severe during steroid than during immunoglobulin therapy.		
Conclusions / Comments:	Similar effect, fewer side effects with IVIG. Numbers small.		

Miscellaneous

Condition summary	Idiopathic dilated cardiomyopathy
Reference list:	73 McNamara DM, Holubkov R, Starling RC et al. Controlled trial of intravenous immune globulin in recent-onset dilated cardiomyopathy. Circulation 2001; 103(18):2254-9.
Types of study:	RCT
Total sample size:	62
Quality:	Moderate
Result:	IVIG did not augment the improvement in left ventricular ejection fraction in patients with recent onset dilated cardiomyopathy.
Adverse events:	Events in 6 IVIG patients (3 deaths, 2 transplants, 1 LVAD placement with transplant), 3 control patients (1 death, 1 transplant, 1 LVAD placement).
Conclusion:	Appears to be no signficant effect, based on one moderate-quality RCT.
Category:	IIb

Condition studies:	Idiopathic dilated cardiomyopathy

73	McNamara DM, Holubkov R, Starling RC et al. Controlled trial of intravenous immune globulin in recent-onset dilated cardiomyopathy. Circulation 2001; 103(18):2254-9.

Study design:	RCT	**Length of follow-up:**	2 years
Sample size:	Sample of 62 patients (37 men, 25 women).	**Population:**	Adults with recent onset of idiopathic dilated cardiomopathy or myocarditis, left ventricular ejection fraction (LVEF) of less than or equal to 0.40, and no more than 6 months of cardiac symptoms.
Intervention:	IVIG		
Comparison / control:	Placebo not specified.		
Outcome(s) measured:	Change in LVEF at 6 and 12 months.		

Quality assessment (internal validity)

Placebo:	Yes
Follow-up:	55 (at 1 year)

Results

Intervention groups:	Six months IVIG, LVEF = 0.14 +/- 0.12; 12 months IVIG = 0.16 +/-0.12.	**Control / comparison group(s):**	Six months IVIG, LVEF = 0.14 +/- 0.14; 12 months IVIG = 0.15 +/- 0.16.
P-value:	NS		
Adverse events:	Events in 6 IVIG patients (3 deaths, 2 transplants, 1 LVAD placement with transplant), 3 control patients (1 death, 1 transplant, 1 LVAD placement).		
Conclusions / Comments:	IVIG did not augment the improvement in LVEF in patients with recent onset dilated cardiomyopathy.		

Miscellaneous

Condition summary	Non-obstetric antiphospholipid syndrome
Category:	IVb

Miscellaneous

Condition summary	Other conditions (not listed elsewhere): IVF failure
Reference list:	81 Sher G, Matzner W, Feinman M et al. The selective use of heparin/aspirin therapy, alone or in combination with intravenous immunoglobulin G, in the management of antiphospholipid antibody-positive women undergoing in vitro fertilization. American Journal of Reproductive Immunology (Copenhagen) 1998; 40(2):74-82. 83 Stephenson MD, Fluker MR. Treatment of repeated unexplained in vitro fertilization failure with intravenous immunoglobulin: a randomized, placebo-controlled Canadian trial.[see comment]. Fertility & Sterility 2000; 74(6):1108-13.
Types of study:	One RCT, 1 case-control.
Total sample size:	173
Quality:	High/Low
Result:	No significant effect on birth rate in RCT, but significantly improves birth rate in women with antiphospholipid antibodies directed against PE or PS.
Adverse events:	Not reported.
Conclusion:	No benefit in high quality RCT and significant benefit in low quality case control.
Category:	IIc

Condition studies:	Other conditions (not listed elsewhere): IVF failure

81	Sher G, Matzner W, Feinman M et al. The selective use of heparin/aspirin therapy, alone or in combination with intravenous immunoglobulin G, in the management of antiphospholipid antibody-positive women undergoing in vitro fertilization. American Journal of Reproductive Immunology (Copenhagen) 1998; 40(2):74-82.

Study design:	Case-control	**Length of follow-up:**	
Sample size:	121	**Population:**	Women seropositive for antiphospholipid antibodies, younger than 40 years, completed up to 2 consecutive IVF-ET cycles within 12 months, did not achieve live births with H/A alone.
Intervention:	Heparin aspirin and IVIG.		
Comparison / control:	Heparin and aspirin.		
Outcome(s) measured:	Live births.		

Quality assessment (internal validity)

Placebo:	No
Follow-up:	

Results

Intervention groups:	Birth rate 41% when anti-PE or anti-PS involved IgG or IgM isotypes.	**Control / comparison group(s):**	With heparin/aspirin alone, birth rate 17% when anti-PE or anti-PS involved IgG or IgM isotypes.
P-value:			
Adverse events:			
Conclusions / Comments:	IVIG with heparin/aspirin therapy improves IVF birth rate in women (P = 0.0001) with antiphospholipid antibodies directed against PE or PS.		

Condition studies:	Other conditions (not listed elsewhere): IVF failure

83	Stephenson MD, Fluker MR. Treatment of repeated unexplained in vitro fertilization failure with intravenous immunoglobulin: a randomized, placebo-controlled Canadian trial.[see comment]. Fertility & Sterility 2000; 74(6):1108-13.

Study design:	RCT	**Length of follow-up:**	
Sample size:	51	**Population:**	Couples with a history of repeated unexplained IVF failure.
Intervention:	IVIG 500mk/kg on day of ET or preceding 72 hours and 4 weeks later if pregnancy confirmed by ultrasound.		
Comparison / control:	Normal saline.		
Outcome(s) measured:	Live births.		

Quality assessment (internal validity)

Placebo:	Yes
Follow-up:	

Results

Intervention groups:	Had a 19% live birth rate.	**Control / comparison group(s):**	Had a 17% live birth rate.
P-value:			
Adverse events:			
Conclusions / Comments:	No sign difference between IVIG and placebo.		

Miscellaneous

Condition summary	Other conditions (not listed elsewhere): obsessive compulsive/tic disorders
Reference list:	76 Perlmutter SJ, Leitman SF, Garvey MA et al. Therapeutic plasma exchange and intravenous immunoglobulin for obsessive-compulsive disorder and tic disorders in childhood.[see comment]. Lancet 1999; 354(9185):1153-8. 82 Hoekstra PJ, Minderaa RB, Kallenberg CG.Lack of effect of intravenous immunoglobulins on tics: a double-blind placebo-controlled study. J Clin Psychiatry. 2004 Apr;65(4):537-42.
Types of study:	Two RCTs.
Total sample size:	60
Quality:	Low
Result:	As effective as plasma-exchange in lessening severity of symptoms in children with infection-triggered OCD and tic disorders; no signficant effect in unselected tic disorder.
Adverse events:	Nausea and vomiting, mild to moderately severe headaches, low-grade fever.
Conclusion:	Possible benefit in children with infection-triggered OCD and tic disorders, based on 1 small RCT.
Category:	IIa

Condition studies:	Other conditions (not listed elsewhere): obsessive compulsive/tic disorders

76	Perlmutter SJ, Leitman SF, Garvey MA et al. Therapeutic plasma exchange and intravenous immunoglobulin for obsessive-compulsive disorder and tic disorders in childhood.[see comment]. Lancet 1999; 354(9185):1153-8.

Study design:	RCT	**Length of follow-up:**	1 and 12 months after treatment
Sample size:	Sample of 10 in each of 3 arms (30 total).	**Population:**	Children with sever, infection-triggered exacerbations of OCD or tic disorders.
Intervention:	IVIG (1g/kg/day, 2 days).		
Comparison / control:	Plasma exchange (5 single-volume exchanges over 2 weeks) or placebo (saline solution).		
Outcome(s) measured:	Standard assessment scales for OCD, tics, anxiety, depression, global function.		

Quality assessment (internal validity)

Placebo:	Yes
Follow-up:	9 in IVIG, 10 in control/comparison groups.

Results

Intervention groups:	At 1 month, mean improvements of 31-58% of assessment scales. At 1 year, 7/9 children 'much' or 'very much' improved over baseline.	**Control / comparison group(s):**	Improvements in most symptoms in IVIG and PE groups at 1 month, mostly maintained at 1 year (7/9 IVIG; 7/8 PE).
P-value:	$P < 0.05$, from baseline for obsessions and compulsions; sum of obsessions, compulsions, tics; psychosocial funtioning and global severity at 1 year.		
Adverse events:	Nausea and vomiting (5), mild to moderately severe headaches (3), low-grade fever (4).		
Conclusions / Comments:	IVIG and PE both effective in lessening severity of symptoms in children with infection-triggered OCD and tic disorders.		

Condition studies: Other conditions (not listed elsewhere): obsessive compulsive/tic disorders

82 Hoekstra PJ, Minderaa RB, Kallenberg CG.Lack of effect of intravenous immunoglobulins on tics: a double-blind placebo-controlled study. J Clin Psychiatry. 2004 Apr;65(4):537-42.

Study design:	RCT	**Length of follow-up:**	14 weeks post-treatment
Sample size:	30	**Population:**	Patients with a DSM-IV tic disorder.

Intervention: IVIG 1g/kg on 2 consecutive days.

Comparison / control: Placebo.

Outcome(s) measured: Symptoms rated using Yale Global Tic Severity Scale and Yale-Brown Obsessive Compulsive Scale.

Quality assessment (internal validity)

Placebo: Yes

Follow-up:

Results

Intervention groups:	Severity of obsessions and compulsions significantly decreased compared to placebo group at 6 weeks; improvement maintained to week 14, but no longer statistically different from control group.	**Control / comparison group(s):**	

P-value:

Adverse events: Significantly more than placebo; notably, headaches.

Conclusions / Comments: IVIG not recommended for unselected tic disorder patients.

Miscellaneous

Condition summary	Paediatric head injury
Reference list:	64 Gooding AM, Bastian JF, Peterson BM, Wilson NW. Safety and efficacy of intravenous immunoglobulin prophylaxis in pediatric head trauma patients: a double-blind controlled trial. J Crit Care 1993; 8(4):212-6.
Types of study:	One RCT.
Total sample size:	32
Quality:	Low
Result:	No significant difference between groups in incidence of pneumonia, sepsis, presumed sepsis, other infections, number of days on mechanical ventilation, number of hospital days.
Adverse events:	None noted.
Conclusion:	Appears to be no significant effect, based on one small RCT.
Category:	IIb

Condition studies:	Paediatric head injury

64	Gooding AM, Bastian JF, Peterson BM, Wilson NW. Safety and efficacy of intravenous immunoglobulin prophylaxis in pediatric head trauma patients: a double-blind controlled trial. J Crit Care 1993; 8(4):212-6.

Study design:	RCT	**Length of follow-up:**	28 days
Sample size:	Sample of 18 in treatment group & 14 in control group. 1 excluded.	**Population:**	Children with severe head injuries.
Intervention:	IVIG (400mg/kg).		
Comparison / control:	5% albumin		
Outcome(s) measured:	Clinical determination of infections. Determination of death.		

Quality assessment (internal validity)

Placebo:	Yes
Follow-up:	18 in treatment group and 14 in control group (1 death in treatment group, 2 in control, all due to non-infectious causes).

Results

Intervention groups:	No significant difference between groups in incidence of pneumonia, sepsis, presumed sepsis, other infections, number of days on mechanical ventilation, number of hospital days.	**Control / comparison group(s):**	
P-value:			
Adverse events:	None noted.		
Conclusions / Comments:	No effect of IVIG on the incidence of secondary infections in severly injured children.		

Miscellaneous

Condition summary	Recurrent fetal loss with or without antiphospholipid syndrome
Reference list:	79 Scott JR. Immunotherapy for recurrent miscarriage.[update of Cochrane Database Syst Rev. 2000;(2):CD000112; PMID: 10796135]. [Review] [54 refs]. Cochrane Database of Systematic Reviews 2003; (1):CD000112. 7 Branch DW, Peaceman AM, Druzin M et al. A multicenter, placebo-controlled pilot study of intravenous immune globulin treatment of antiphospholipid syndrome during pregnancy. The Pregnancy Loss Study Group. American Journal of Obstetrics & Gynecology 2000; 182(1 Pt 1):122-7. 84 Triolo G, Ferrante A, Ciccia F et al. Randomized study of subcutaneous low molecular weight heparin plus aspirin versus intravenous immunoglobulin in the treatment of recurrent fetal loss associated with antiphospholipid antibodies. Arthritis & Rheumatism 2003; 48(3):728-31. 262 Daya S, Gunby J, Clark DA. Intravenous immunoglobulin therapy for recurrent spontaneous abortion: a meta-analysis. Am J Reprod Immunol. 1998 Feb;39(2):69-76.
Types of study:	One systemic review (7 RCTs), 1 meta-analysis, 1 RCT.
Total sample size:	Not reported in systemic review, 16 in single RCT.
Quality:	High/Low
Result:	IVIG did not improve live birth rate.
Adverse events:	
Conclusion:	No benefit based on 1 Cochrane review, 1 meta-analysis and 1 low quality RCT.
Category:	III

Condition studies: Recurrent fetal loss with or without antiphospholipid syndrome

79 Scott JR. Immunotherapy for recurrent miscarriage.[update of Cochrane Database Syst Rev. 2000;(2):CD000112; PMID: 10796135]. [Review] [54 refs]. Cochrane Database of Systematic Reviews 2003; (1):CD000112.

Study design: Reviewed 19 RCTs in total, 7 for IVIG.

Length of follow-up:

Sample size:

Population: Women with recurrent miscarriages.

Intervention: IVIG

Comparison / control: Placebo or no intervention.

Outcome(s) measured: Live birth rate.

Quality assessment (internal validity)

Placebo:

Follow-up:

Results

Intervention groups: IVIG did not significant improvement in live birth rate.

Control / comparison group(s):

P-value:

Adverse events:

Conclusions / Comments: No significant improvement in live birth rate.

Condition studies:	Recurrent fetal loss with or without antiphospholipid syndrome

7	Branch DW, Peaceman AM, Druzin M et al. A multicenter, placebo-controlled pilot study of intravenous immune globulin treatment of antiphospholipid syndrome during pregnancy. The Pregnancy Loss Study Group. American Journal of Obstetrics & Gynecology 2000; 182(1 Pt 1):122-7.

Study design:	RCT - multicentre, double blind.	**Length of follow-up:**	
Sample size:	Sample of 16 (7 IVIG, 9 placebo).	**Population:**	Women 12 week or less gestation and antiphospholipid syndrome.
Intervention:	Dose of 1gm/kg IVIG 2 days per month until 36 weeks gestation with heparin and low dose aspirin.		
Comparison / control:	Placebo 2 days per month until 36 weeks gestation with heparin and low dose aspirin.		
Outcome(s) measured:	Live birth rate.		

Quality assessment (internal validity)

Placebo:	Yes
Follow-up:	

Results

Intervention groups:	All had live born infants after 32 weeks gestation. Antepartum complications - similar. Gestational age at delivery: 34.6+/-1.1wks, Birth weights: 2249.7+/-186.1g. Fetal growth restriction: 0%, ICU admission: 20%.	**Control / comparison group(s):**	All had live born infants after 32 weeks gestation. Antepartum complications similar. Gestational age at delivery: 36.7+/-2.1wks, Birth weights: 2604.4+/-868.9. Fetal growth restriction: 33%, ICU admission: 44%.
P-value:			
Adverse events:			
Conclusions / Comments:	IVIG did not improve outcome in IVIG compared to control, although there were no fetal deaths in any group. Larget study needed.		

Condition studies: Recurrent fetal loss with or without antiphospholipid syndrome

84 Triolo G, Ferrante A, Ciccia F et al. Randomized study of subcutaneous low molecular weight heparin plus aspirin versus intravenous immunoglobulin in the treatment of recurrent fetal loss associated with antiphospholipid antibodies. Arthritis & Rheumatism 2003; 48(3):728-31.

Study design: RCT **Length of follow-up:**

Sample size: 40 **Population:** Pregnant women with recurrent pregnancy loss (at least 3 occurences) and antiphospholipid antibodies.

Intervention: IVIG

Comparison / control: Heparin plus low dose aspirin.

Outcome(s) measured: Live birth rate.

Quality assessment (internal validity)

Placebo: No

Follow-up:

Results

Intervention groups: Had 57% live births. **Control / comparison group(s):** Had 84% live births.

P-value:

Adverse events:

Conclusions / Comments: More live births in heparin/aspirin control group. No effect of IVIG.

Condition studies: Recurrent fetal loss with or without antiphospholipid syndrome

262

Daya S, Gunby J, Clark DA. Intravenous immunoglobulin therapy for recurrent spontaneous abortion: a meta-analysis. Am J Reprod Immunol. 1998 Feb;39(2):69-76.

Study design: Four RCTs.

Length of follow-up:

Sample size:

Population:

Intervention:

Comparison / control:

Outcome(s) measured:

Quality assessment (internal validity)

Placebo:

Follow-up:

Results

Intervention groups: Two of the trials showed an increase in successful pregnancy outcome with IVIG treatment and two did not. The overall OR was 1.48 (95% CI, 0.84-2.60) in favor of IVIG, with an absolute treatment effect of 10.1% (95% CI, -4.8-24.6).

Control / comparison group(s):

P-value:

Adverse events:

Conclusions / Comments: This meta-analysis suggests that IVIG may have a role in the treatment of recurrent abortion, but as yet no conclusive evidence is available.

Miscellaneous

Condition summary	Trauma
Reference list:	27 Mao P, Enrichens F, Olivero G et al. Early administration of intravenous immunoglobulins in the prevention of surgical and post-traumatic sepsis: a double blind randomized clinical trial. SURG RES COMMUN 1989; 5(2):93-8. 61 Douzinas EE, Pitaridis MT, Louris G et al. Prevention of infection in multiple trauma patients by high-dose intravenous immunoglobulins.[see comment]. Crit Care Med 2000; 28(1):8-15. 63 Glinz W, Grob PJ, Nydegger UE et al. Polyvalent immunoglobulins for prophylaxis of bacterial infections in patients following multiple trauma. A randomized, placebo-controlled study. Intensive Care Med 1985; 11(6):288-94.
Types of study:	Three RCTs.
Total sample size:	230
Quality:	Low-Moderate
Result:	All 3 studies showed fewer septic complications and improved serum bacteriocidal activity in patients with severe trauma.
Adverse events:	None reported.
Conclusion:	Possible benefit, based on 3 small RCTs.
Category:	IIa

Condition studies:	Trauma

27	Mao P, Enrichens F, Olivero G et al. Early administration of intravenous immunoglobulins in the prevention of surgical and post-traumatic sepsis: a double blind randomized clinical trial. SURG RES COMMUN 1989; 5(2):93-8.

Study design:	RCT	**Length of follow-up:**	2 weeks
Sample size:	40	**Population:**	Post-traumatic and post-surgery patients, under 70 years, major surgery or trauma during pervious 24 hr, no primary infection at start of trial, no PID.
Intervention:	IVIG (10g, days 1, 3, 5, 10).		
Comparison / control:	Placebo (DW 5%).		
Outcome(s) measured:	Clinical and hemodynamic signs of sepsis, blood analyses.		

Quality assessment (internal validity)

Placebo:

Follow-up:

Results

Intervention groups:	Body temperature significantly lower in IVIG group, complement fractions C3 and C4 higher, no bacteremia, 3 with signs of clinical sepsis; overall mortality 6.7%.	**Control / comparison group(s):**	Six patients with bacteremia, 6 with signs of clinical sepsis; overall mortality 23.5%.
P-value:	? P = 0.05 for bacteremia.		
Adverse events:	None noted.		
Conclusions / Comments:	IVIG reduces sepsis in severely traumatised patients.		

Condition studies:	Trauma

61	Douzinas EE, Pitaridis MT, Louris G et al. Prevention of infection in multiple trauma patients by high-dose intravenous immunoglobulins.[see comment]. Crit Care Med 2000; 28(1):8-15.

Study design:	RCT	**Length of follow-up:**	7 days
Sample size:	Sample of 21 subjects & 19 controls.	**Population:**	Trauma patients with injury severity score of 16-50.
Intervention:	IVIG (250 mg/kg per day), 3 consecutive days and on day 6.		
Comparison / control:	Human albumin at 1g/kg.		
Outcome(s) measured:	Clinical variables related to infection were recorded. Complement components C3c, C4 & CH50, IgG & IgG fractions & serum bacteriocidal activity were measured.		

Quality assessment (internal validity)

Placebo:	Yes
Follow-up:	21 in treatment group and 18 in control group.

Results

Intervention groups:	IVIG patients had fewer pneumonias (p = 0.003) & fewer total non-catheter-related infections (P = 0.04). A significant increased trend in IgG and its subclasses was observed for days 4 & 7 (P < 0.000001). The SBA was significantly higher on days 4 & 7 (P < 0.000001). SBA was higher at 40 degrees C compared with 37 degrees C (P < 0.001). Low SBA was associated with increased risk of pneumonia (P < 0.01) and non-catheter-related infections (P = 0.06 for day 1 and P < 0.01 for days 4 and 7).	**Control / comparison group(s):**	
P-value:	See above.		
Adverse events:	None noted.		

Conclusions / Comments:	In trauma patients receiving high doses of IVIG, fewer septic complications and improved serum bacteriocidal activity.

Condition studies:	Trauma

63	Glinz W, Grob PJ, Nydegger UE et al. Polyvalent immunoglobulins for prophylaxis of bacterial infections in patients following multiple trauma. A randomized, placebo-controlled study. Intensive Care Med 1985; 11(6):288-94.

Study design:	RCT	**Length of follow-up:**	42 days
Sample size:	Sample of 76 in treatment group and 74 in control group.	**Population:**	Severly injured patients requiring long-term artificial ventilation.
Intervention:	IVIG (36g/patient over 3 days).		
Comparison / control:	Albumin.		
Outcome(s) measured:	Clinical determination of infections. Determination of death.		

Quality assessment (internal validity)

Placebo:	Yes
Follow-up:	76 in treatment group and74 in control group.

Results

Intervention groups:	In treatment group, incidence of pneumonia =28 cases, sepsis =14 cases, other infections =11 cases.	**Control / comparison group(s):**	In control group, incidence of pneumonia =43 cases, sepsis =19 cases, other infections =10 cases.
P-value:	Reduction in incidence of pneumonia (P = 0.0111).		
Adverse events:	None observed.		
Conclusions / Comments:	Intravenous immunoglobulin reduced the incidence of pneumonia in severly injured patients.		

Neurological

Condition summary	Acute idiopathic dysautonomia
Reference list:	
Types of study:	
Total sample size:	
Quality:	
Result:	
Adverse events:	
Conclusion:	
Category:	See: Guillain Barre syndrome

Neurological

Condition summary	Autoimmune diabetic neuropathy
Category:	IVb

Neurological

Condition summary	Chronic inflammatory demyelinating polyneuropathy
Reference list:	158 van Sheik IN, Winer JB, de Haan R, Vermeulen M. Intravenous immunoglobulin for chronic inflammatory demyelinating polyradiculoneuropathy (Cochrane Review). In: The Cochrane Library, Issue 2, 2004. Chichester, UK: John Wiley & Sons, Ltd.
Types of study:	One systematic review (6 RCTs).
Total sample size:	170
Quality:	Low-Moderate
Result:	IVIG improves disability for at least 2-6 weeks compared to placebo (RR 2.47; 95% CI 1.02-6.01); effect similar to plasma exchange and prednisolone.
Adverse events:	Not significantly different from other treatments (PE and prednisolone).
Conclusion:	Clear evidence of benefit based on 1 systematic review of 6 RCTs.
Category:	I

Condition studies:	Chronic inflammatory demyelinating polyneuropathy

158	van Sheik IN, Winer JB, de Haan R, Vermeulen M. Intravenous immunoglobulin for chronic inflammatory demyelinating polyradiculoneuropathy (Cochrane Review). In: The Cochrane Library, Issue 2, 2004. Chichester, UK: John Wiley & Sons, Ltd.
Study design:	Six RCTs.
Length of follow-up:	
Sample size:	170
Population:	Patients with definite or probable chronic inflammatory demyelinating polyradiculoneuropathy.
Intervention:	IVIG vs placebo (n = 113), IVIG vs plasma exchange (n = 17), IVIG vs prednisolone (n = 32).
Comparison / control:	
Outcome(s) measured:	Proportion of patients with significant improvement in disability within 1 month of treatment.

Quality assessment (internal validity)

Placebo:	
Follow-up:	

Results

Intervention groups:	IVIG improves disability for at least 2-6 weeks compared to placebo (RR 2.47; 95% CI 1.02-6.01); effect similar to plasma exchange and prednisolone.	**Control / comparison group(s):**	
P-value:			
Adverse events:	Not significantly different from other treatments (PE and prednisolone).		
Conclusions / Comments:	As effective as plasma exchange and prednisolone, cost-effectiveness studies comparing treatments are needed.		

Neurological

Condition summary	Encephalomyelitis and sensory neuropathy associated with anti- HU antibodies
Reference list:	186 Shahar E, Andraus J, Savitzki D, Pilar G, Zelnik N. Outcome of severe encephalomyelitis in children: effect of high-dose methylprednisolone and immunoglobulins. J Child Neurol 2002; 17(11):810-4.
Types of study:	One case-series.
Total sample size:	16
Quality:	Low
Result:	One child responded to IVIG but not methylprednisolone. 10 children recovered after high-dose methylprednisolone. Two fifths of the patients responded to combined treatment.
Adverse events:	None reported.
Conclusion:	Possible benefit, based on 1 small uncontrolled study (less effective than methylprednisolone, may be useful in combination).
Category:	IIa

Condition studies:	Encephalomyelitis and sensory neuropathy associated with anti- HU antibodies

186	Shahar E, Andraus J, Savitzki D, Pilar G, Zelnik N. Outcome of severe encephalomyelitis in children: effect of high-dose methylprednisolone and immunoglobulins. J Child Neurol 2002; 17(11):810-4.

Study design:	Case-series.	**Length of follow-up:**	
Sample size:	16	**Population:**	Children. Indications for treatment: severe acute disseminated encephalomyelitis, visual loss, or severe flaccid weakness with bladder and bowel incontinence.
Intervention:	IVIG alone.		
Comparison / control:	High-dose methylprednisolone alone or in combination with IVIG.		
Outcome(s) measured:	Recovery.		

Quality assessment (internal validity)

Placebo:

Follow-up:

Results

Intervention groups:	One child responded to IVIG but not methylprednisolone.	**Control / comparison group(s):**	Ten children recovered after high-dose methylprednisolone. Two out of vive patients responded to combined treatment.

P-value:

Adverse events:

Conclusions / Comments:	Either high-dose methylprednisolone or IVIG, given separately or combined, may be efficacious in severe debilitating pediatric-onset acute encephalomyelitis. In children with the most severe form of encephalomyeloradiculoneuropathy, suggest initially administering high-dose methylprednisolone and IVIG combined.

Neurological

Condition summary	Epilepsy
Reference list:	205 van Rijckevorsel-Harmant K, Delire M, Schmitz-Moorman W, Wieser HG. Treatment of refractory epilepsy with intravenous immunoglobulins. Results of the first double-blind/dose finding clinical study. International Journal of Clinical & Laboratory Research 1994; 24(3):162-6.
Types of study:	One RCT.
Total sample size:	61
Quality:	Low-Moderate
Result:	In partial epilepsy, significant improvement (reduced number of seizures) over placebo.
Adverse events:	Vomiting (1 patient).
Conclusion:	Possible benefit in patients with partial seizures, based on 1 RCT.
Category:	IIa

Condition studies:	Epilepsy

205	van Rijckevorsel-Harmant K, Delire M, Schmitz-Moorman W, Wieser HG. Treatment of refractory epilepsy with intravenous immunoglobulins. Results of the first double-blind/dose finding clinical study. International Journal of Clinical & Laboratory Research 1994; 24(3):162-6.

Study design:	RCT	**Length of follow-up:**	6 months
Sample size:	61	**Population:**	Patients with West, Lennox-Gastaut syndrome (LGS) or early myoclonic encephalopathy (only 4/61 with LGS).
Intervention:	IVIG, 100, 250 or 400 mg/kg. 4 doses in week 1, 1 dose in week 2, 3 and 6.		
Comparison / control:	Placebo.		
Outcome(s) measured:	Mean number of seizures per day, responder = 50% decrease of daily seizure frequency.		

Quality assessment (internal validity)

Placebo:	Yes
Follow-up:	Three patients excluded from evaluation.

Results

Intervention groups:	Positive trend in favour of IVIG, not significant P = 0.095. No relationship between dose and efficacy P = 0.31; in subgroup of patients with partial epilepsy, significant improvement compared to placebo (P = 0.041).	**Control / comparison group(s):**	
P-value:	See above.		
Adverse events:	Vomiting (1).		
Conclusions / Comments:	In patients with partial epilepsy, significant improvement over placebo.		

Neurological

Condition summary	Epilepsy: childhood epilepsy resistant
Reference list:	204 Munn R, Doucette J, Connolly M et al. Controlled study of intravenous immunoglobulin in children with intractable generalized epilepsy. Epilepsia 1995; 36 Suppl 4:106.
Types of study:	One RCT.
Total sample size:	27
Quality:	Low
Result:	IVIG: 1/13 - complete control of myoclonic seizures (other seizure types continued); 2/13 - >50% improvement in seizure control. Best available therapy: 2/14 seizure free; 5/14 - >50% improvement in seizure control.
Adverse events:	Three out of 13 IVIG patients (rash in 2, behaviour in 1); 13/14 BAT patients.
Conclusion:	Possible benefit, based on 1 small RCT.
Category:	IIa

Condition studies:	Epilepsy: childhood epilepsy resistant

204	Munn R, Doucette J, Connolly M et al. Controlled study of intravenous immunoglobulin in children with intractable generalized epilepsy. Epilepsia 1995; 36 Suppl 4:106.

Study design:	RCT	**Length of follow-up:**	
Sample size:	Sample of 27 (13 on IVIG).	**Population:**	Children 7 months - 15 years of age with intractable infantile spasm or myoclonic seizures.
Intervention:	IVIG (600mg/kg at 4-week intervals, for 12 weeks).		
Comparison / control:	Best available therapy.		
Outcome(s) measured:	Seizure control.		

Quality assessment (internal validity)

Placebo:	No
Follow-up:	

Results

Intervention groups:	One out of 13 - complete control of myoclonic seizures (other seizure types continued); 2/13 - >50% improvement in seizure control.	**Control / comparison group(s):**	Two out of 14 seizure free; 5/14 - >50% improvement in seizure control.
P-value:			
Adverse events:	Three out of 13 IVIG patients (rash in 2, behaviour in 1); 13/14 BAT patients.		
Conclusions / Comments:	IVIG less effective than BAT in control of seizures, but IVIG associated with less adverse effects.		

Neurological

Condition summary	Epilepsy: Landau-Kleffner syndrome
Reference list:	203 Mikati MA, Saab R, Fayad MN, Choueiri RN. Efficacy of intravenous immunoglobulin in Landau-Kleffner syndrome. Pediatr Neurol 2002; 26(4):298-300.
Types of study:	One case-series.
Total sample size:	5
Quality:	Low
Result:	Significant drop in severity score P=0.025, 2/5 patients completely recovered.
Adverse events:	None reported.
Conclusion:	Possible benefit, based on 1 small uncontrolled study.
Category:	IIa

Condition studies:	Epilepsy: Landau-Kleffner syndrome		
203	Mikati MA, Saab R, Fayad MN, Choueiri RN. Efficacy of intravenous immunoglobulin in Landau-Kleffner syndrome. Pediatr Neurol 2002; 26(4):298-300.		
Study design:	Case-series.	**Length of follow-up:**	
Sample size:	5	**Population:**	Landau-Kleffner syndrome patients.
Intervention:	Dose of 2 mg/kg IVIG for 4 days.		
Comparison / control:	I month baseline.		
Outcome(s) measured:	Severity score: speech, comprehension, behaviour, seizures, electroencephalography.		

Quality assessment (internal validity)

Placebo:

Follow-up:

Results

Intervention groups:	Significant drop in severity score P=0.025, 2/5 patients completely recovered.	**Control / comparison group(s):**	
P-value:	See above.		
Adverse events:	None reported.		
Conclusions / Comments:	Possible benefit, but study small and uncontrolled.		

Neurological

Condition summary	Epilepsy: Lennox-Gastaut syndrome
Reference list:	205 van Rijckevorsel-Harmant K, Delire M, Schmitz-Moorman W, Wieser HG. Treatment of refractory epilepsy with intravenous immunoglobulins. Results of the first double-blind/dose finding clinical study. International Journal of Clinical & Laboratory Research 1994; 24(3):162-6. 206 Illum N, Taudorf K, Heilmann C et al. Intravenous immunoglobulin: a single-blind trial in children with Lennox-Gastaut syndrome. Neuropediatrics 1990; 21(2):87-90. 207 van Engelen BG, Renier WO, Weemaes CM, Strengers PF, Bernsen PJ, Notermans SL. High-dose intravenous immunoglobulin treatment in cryptogenic West and Lennox-Gastaut syndrome; an add-on study. Eur J Pediatr 1994; 153(10):762-9.
Types of study:	One add on, placebo controlled, single-blind trial, 1 case series.
Total sample size:	25
Quality:	Low
Result:	One study - 2/10 patients showed a reduction in high-frequency and invariable seizure activity; 1 study - average of 70% reduction in clinical seizures, 40% reduction in epileptic discharges, acceleration of EEG background activity, improved psychomotor development.
Adverse events:	None observed.
Conclusion:	Possible benefit of IVIG in reducing seizures, particularly where other treatments have failed, based on 2 small studies (not RCTs).
Category:	IIa

Condition studies:	Epilepsy: Lennox-Gastaut syndrome

205	van Rijckevorsel-Harmant K, Delire M, Schmitz-Moorman W, Wieser HG. Treatment of refractory epilepsy with intravenous immunoglobulins. Results of the first double-blind/dose finding clinical study. International Journal of Clinical & Laboratory Research 1994; 24(3):162-6.

Study design:	RCT	**Length of follow-up:**	6 months
Sample size:	61	**Population:**	Patients with West, Lennox-Gastaut syndrome (LGS) or early myoclonic encephalopathy (only 4/61 with LGS).
Intervention:	IVIG, 100, 250 or 400 mg/kg. 4 doses in week 1, 1 dose in week 2, 3 and 6.		
Comparison / control:	Placebo.		
Outcome(s) measured:	Mean number of seizures per day, responder = 50% decrease of daily seizure frequency.		

Quality assessment (internal validity)

Placebo:	Yes
Follow-up:	Three patients excluded from evaluation.

Results

Intervention groups:	Positive trend in favour of IVIG, not significant P = 0.095. No relationship between dose and efficacy P = 0.31; in subgroup of patients with partial epilepsy, significant improvement compared to placebo (P = 0.041).	**Control / comparison group(s):**	
P-value:	See above.		
Adverse events:	Vomiting (1).		
Conclusions / Comments:	In patients with partial epilepsy, significant improvement over placebo.		

Condition studies:	Epilepsy: Lennox-Gastaut syndrome

206

Illum N, Taudorf K, Heilmann C et al. Intravenous immunoglobulin: a single-blind trial in children with Lennox-Gastaut syndrome. Neuropediatrics 1990; 21(2):87-90.

Study design:	Case-control, add on, placebo controlled, single blind trial.	**Length of follow-up:**	14 week observation period
Sample size:	10	**Population:**	Patients aged 4-14 with Lennox-Gastaut syndrome with insufficient response to conventional anticonvulsive therapy.
Intervention:	IVIG 400 mg/kg twice with interval of 2 weeks followed by 4 week washout period.		
Comparison / control:	Placebo.		
Outcome(s) measured:	Number and type of seizures, EEG, in vitro lympgocyte transformation tests, IG levels before and after treatment.		

Quality assessment (internal validity)

Placebo:

Follow-up:

Results

Intervention groups:	Two out of 10 patients showed a reduction in high-frequency and invariable seizure activity (42% to 100%), a more normal EEG, improved well-being and intellectual performance. 8/10 patients showed no change .	**Control / comparison group(s):**	

P-value:

Adverse events:

Conclusions / Comments:	Possible benefit in some patients with high, constant seizural activity not further reducible by optimal conventional therapy.

Condition studies:	Epilepsy: Lennox-Gastaut syndrome

207	van Engelen BG, Renier WO, Weemaes CM, Strengers PF, Bernsen PJ, Notermans SL. High-dose intravenous immunoglobulin treatment in cryptogenic West and Lennox-Gastaut syndrome; an add-on study. Eur J Pediatr 1994; 153(10):762-9.

Study design:	Case-series - pilot study	**Length of follow-up:**	Tested before IVIG and 3 months later (14 days after final IVIG)
Sample size:	15	**Population:**	Children with cryptogenic and intractable West syndrom (3) and Lennox-Gastaut syndrome (12).

Intervention:	IVIG, 0.4 g/kg per day for 5 days, then every 2 weeks for 3 months.
Comparison / control:	
Outcome(s) measured:	Clinical seizures, mean epileptic discharges (EEG recordings), psychomotor development, serum and CSF IG concentration.

Quality assessment (internal validity)

Placebo:	No
Follow-up:	

Results

Intervention groups:	Average of 70% reduction in clinical seizures, 40% reduction in epileptic discharges, acceleration of EEG background activity, improved psychomotor development. On average serum IG and CSF IG increased by 76% and 44% respectively.	**Control / comparison group(s):**	

P-value:	
Adverse events:	None observed.
Conclusions / Comments:	Possible benefit in treatment of West syndrome and Lennox-Gastaut syndrome, particularly where other treatments (eg ACTH) have failed.

Neurological

Condition summary	Epilepsy: mixed seizures of early onset associated with IgG
Reference list:	
Types of study:	
Total sample size:	
Quality:	
Result:	
Adverse events:	
Conclusion:	
Category:	See: Other epilepsy categories

Neurological

Condition summary	Epilepsy: Rasmussen syndrome
Reference list:	
Types of study:	
Total sample size:	
Quality:	
Result:	
Adverse events:	
Conclusion:	
Category:	See: Other epilepsy categories

Neurological

Condition summary	Epilepsy: subclass deficiency
Reference list:	
Types of study:	
Total sample size:	
Quality:	
Result:	
Adverse events:	
Conclusion:	
Category:	See: Other epilepsy categories

Neurological

Condition summary	Guillain Barre syndrome
Reference list:	[157] Hughes RAC, RaphaÙl JC, Swan AV, van Doorn PA. Intravenous immunoglobulin for Guillain-BarrÚ syndrome (Cochrane Review). In: The Cochrane Library, Issue 3, 2004. Chichester, UK: John Wiley & Sons, Ltd.
Types of study:	One systemic review (9 RCTs).
Total sample size:	536
Quality:	Moderate
Result:	IVIG hastens recovery in adults to the same degree as plasma exchange.
Adverse events:	Inadequately reported.
Conclusion:	IVIG appears to hasten recovery as much as plasma exchange (based on 9 RCTs, without adequate comparisons with placebo), more research needed to decide effect in children, adults with mild disease and adults who start treatment after more than 2 weeks.
Category:	IIa

Condition studies:	Guillain Barre syndrome

157	Hughes RAC, RaphaÙl JC, Swan AV, van Doorn PA. Intravenous immunoglobulin for Guillain-BarrÚ syndrome (Cochrane Review). In: The Cochrane Library, Issue 3, 2004. Chichester, UK: John Wiley & Sons, Ltd.
Study design:	Nine RCTs. **Length of follow-up:**
Sample size:	**Population:**
Intervention:	1) IVIG vs supportive treatment alone, 2) IVIG vs plasma exchange, 3) IVIG+plasma exchange vs plasma exchange alone, 4) IVIG+immunoabsorption vs immunoabsorption alone, 5) IVIG dose study.
Comparison / control:	
Outcome(s) measured:	Improvement in disability grade.

Quality assessment (internal validity)

Placebo:

Follow-up:

Results

Intervention groups:	IVIG hastens recovery in adults to the same degree as plasma exchange.	**Control / comparison group(s):**	
P-value:			
Adverse events:	Inadequately reported.		
Conclusions / Comments:	IIa - No adequate comparisons to placebo. IVIG has similar efficacy as plasma exchange so choice of treatment may depend on cost.		

Neurological

Condition summary	IgM paraproteinaemic neuropathy
Reference list:	181 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. 182 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. 183 Mariette X, Chastang C, Clavelou P, Louboutin JP, Leger JM, Brouet JC. A randomised clinical trial comparing interferon-alpha and intravenous immunoglobulin in polyneuropathy associated with monoclonal IgM. The IgM-associated Polyneuropathy Study Group. Journal of Neurology, Neurosurgery & Psychiatry 1997; 63(1):28-34.
Types of study:	One case-control, prospective, randomised, open.
Total sample size:	20
Quality:	Low
Result:	At 6 months: 1/10 patients on IVIG had CNDS improvement, mean CNDS worsened by 8% (patient improved at 6 months returned to baseline at 12 months). Anti-MAG activity continued.
Adverse events:	Self-limited erythroderma in 1 patient 5 days after IVIG.
Conclusion:	Appears to be no significant benefit, based on 1 small case-control study.
Category:	IIb

Condition studies:	IgM paraproteinaemic neuropathy

181	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.

Study design:	Case-control, multicentre, randomised double blind crossover.	**Length of follow-up:**	
Sample size:	22	**Population:**	Demyelating neuropathy (by INCAT criteria) + MGUS and serum M <20g/l, significant disability in limb function, stable or worsening condition.
Intervention:	IVIG 2.0 g/kg over 24 or 48 hours.		
Comparison / control:			
Outcome(s) measured:	Primary outcome: disability grade. Secondary outcomes: Rankin scale, time to walk 10 metres, grip strength, sensory symptoms score.		

Quality assessment (internal validity)

Placebo:	Yes
Follow-up:	

Results

Intervention groups:	Disability grade decreased after 4 weeks P=0.001. Mean difference between treatment effects was significant P=0.05. 10 patients improved, 11 stable, 1 deteriorated. Secondary outcome measures better than placebo.	**Control / comparison group(s):**	Disability grade unmodified after 4 weeks. 4 patients improved, 14 stable, 4 deteriorated.
P-value:	Disability grade decreased after 4 weeks P = 0.001. Mean difference between treatment effects was significant P = 0.05.		
Adverse events:	Two adverse events in placebo group.		
Conclusions / Comments:	Some benefit to some patients with IGM paraproteinaemic demyelinating neuropathy. Authors suggest a single trial of IVIG justified in any PDN patient.		

Condition studies:	IgM paraproteinaemic neuropathy

182 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.

Study design:	Case-series, randomised, double blind crossover.	**Length of follow-up:**	
Sample size:	11	**Population:**	IgM paraproteinemic demyelinating neuropathy.
Intervention:	IVIG monthly for 3 months then washout period.		
Comparison / control:	Placebo.		
Outcome(s) measured:	Muscle strength, sensation, neurmuscular symptoms at baseline, 3 months and treatment's end.		

Quality assessment (internal validity)

Placebo:

Follow-up:

Results

Intervention groups:	Strength improved 2/11 patients (by 28 and 38.5 points) and declined after placebo. 1/11 patients sensory score improved by 13 points.	**Control / comparison group(s):**	

P-value:

Adverse events:	None reported.
Conclusions / Comments:	IVIG gave modest, short-lived benefit to 18% of patients.

Condition studies:	IgM paraproteinaemic neuropathy

183 Mariette X, Chastang C, Clavelou P, Louboutin JP, Leger JM, Brouet JC. A randomised clinical trial comparing interferon-alpha and intravenous immunoglobulin in polyneuropathy associated with monoclonal IgM. The IgM-associated Polyneuropathy Study Group. Journal of Neurology, Neurosurgery & Psychiatry 1997; 63(1):28-34.

Study design:	Case-control, multicentre, prospective, randomised, open.	**Length of follow-up:**	12 months
Sample size:	20	**Population:**	Patients with stable or progressive neuropathy for at least 3 months, monoclonal IgM to MAG.

Intervention: IVIG 2 g/kg, then 1 g/kg every 3 weeks.

Comparison / control: Recombinant interferon-alpha 3 MU/m2 SC X3 weekly.

Outcome(s) measured: Clinical neuropathy disability score (CNDS).

Quality assessment (internal validity)

Placebo:

Follow-up:

Results

Intervention groups:	At 6 months: 1/10 patients on IVIG had CNDS improvement, mean CNDS worsened by 8% (patient improved at 6 months returned to baseline at 12 months). Anti-MAG activity continued.	**Control / comparison group(s):**	At 6 months: 8/10 CNDS improvement P=0.005, mean CNDS improved by 31%. Improved sensory component P=0.02 but not motor component P = 0.39.

P-value:

Adverse events: Self-limited erythroderma in 1 patient 5 days after IVIG.

Conclusions / Comments: IFN-alpha showed benefits whereas IVIG did not.

Neurological

Condition summary	Multifocal motor neuropathy with persistent conduction block
Reference list:	174 Federico P, Zochodne DW, Hahn AF, Brown WF, Feasby TE. Multifocal motor neuropathy improved by IVIg: randomized, double-blind, placebo-controlled study.[comment]. Neurology 2000; 55(9):1256-62. 175 Leger JM, Chassande B, Musset L, Meininger V, Bouche P, Baumann N. Intravenous immunoglobulin therapy in multifocal motor neuropathy: a double-blind, placebo-controlled study. Brain 2001; 124(Pt 1):145-53. 176 Van den Berg, L. H, Franssen H, Oey PL, and Wokke JHJ. The effect of intravenous immunoglobulin treatment in patients with multifocal motor neuropathy or lower motor neurone disease. J Neurol 1995; 242:149. 177 Van den Berg LH, Franssen H, Wokke JH. The long-term effect of intravenous immunoglobulin treatment in multifocal motor neuropathy. Brain 1998; 121 (Pt 3):421-8. 178 Van den Berg LH, Kerkhoff H, Oey PL et al. Treatment of multifocal motor neuropathy with high dose intravenous immunoglobulins: a double blind, placebo controlled study. Journal of Neurology, Neurosurgery & Psychiatry 1995; 59(3):248-52. 179 Van den Berg-Vos RM, Franssen H, Wokke JH, Van den Berg LH. Multifocal motor neuropathy: long-term clinical and electrophysiological assessment of intravenous immunoglobulin maintenance treatment. Brain 2002; 125(Pt 8):1875-86.
Types of study:	One sytematic review (no relevant RCTs), 6 case studies or cross-over RCTs.
Total sample size:	68
Quality:	Low
Result:	Some improvement in condition seen in 6 studies.
Adverse events:	Headache, rash, fatigue, malaise, anorexia, chills, fever, transient hypertension.
Conclusion:	Possible benefit based on 6 small studies (5 uncontrolled).
Category:	IIa

Condition studies:	Multifocal motor neuropathy with persistent conduction block

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

Study design:	RCT-cross-over.	**Length of follow-up:**	28 days
Sample size:	16	**Population:**	Patients with multifocal motor neuropathy with conduction block in motor nerves, normal sensory nerve conduction.
Intervention:	Dose of 0.4 g/kg per day for 5 days, 28 day washout, cross to other group.		
Comparison / control:	Placebo, dextrose or saline.		
Outcome(s) measured:	Functional improvement, neurologic disability score, grip strength, distal and proximal compound muscle action potential amplitude, conduction block, before and 28 days after treatment.		

Quality assessment (internal validity)

Placebo:	Yes
Follow-up:	

Results

Intervention groups:	Subjective functional improvement was: very good in 9 patients, moderate in 1, mild in 1, absent in 5. Neurologic disability score improved P=0.038, grip strength increased P=0.00021, conduction block improved P=0.037 and was reversed in 5 patients.	**Control / comparison group(s):**	No subjective functional improvement. Neurologic disability score, grip strength and conduction block deteriorated.
P-value:	See intervention groups.		
Adverse events:	Headache (5), headache + rash (3), rash (2), headache + malaise (1), anorexia, chills, fever (1), transient hypertension (1).		
Conclusions / Comments:	Improvement in weakness, disability and conduction block, based on small cross-over study.		

Condition studies:	Multifocal motor neuropathy with persistent conduction block

175	Leger JM, Chassande B, Musset L, Meininger V, Bouche P, Baumann N. Intravenous immunoglobulin therapy in multifocal motor neuropathy: a double-blind, placebo-controlled study. Brain 2001; 124(Pt 1):145-53.

Study design:	Case-control, double-blind.	**Length of follow-up:**	7 months
Sample size:	19	**Population:**	Patients with multifocal motor neuropathy with conduction block; 2 groups - Gp 1 (10 patients) never treated with IVIG, Gp2 (9 patients) previously successfully treated with IVIG.
Intervention:	IVIG 500 mg/kg/day for 5 days once a month for 3 months (responders continued, non-responders switched).		
Comparison / control:	Placebo, dextrose or saline.		
Outcome(s) measured:	MRC score in 28 muscles, self-evaluation scale (5 daily motor activities scored 0-5), electrophysiological studies.		

Quality assessment (internal validity)

Placebo:	
Follow-up:	18/19 completed.

Results

Intervention groups:	Seven out of 9 IVIG patients and two out of 9 placebo patients were responders at month 4 P = 0.03. Significant difference in self-evaluation score, no difference in MRC score or electrophysiological examination at month 4 between IVIG and placebo.	**Control / comparison group(s):**	See above.
P-value:	See intervention groups.		
Adverse events:	Some minor adverse events.		
Conclusions / Comments:	Possible benefit in MMN.		

Condition studies:	Multifocal motor neuropathy with persistent conduction block

176	Van den Berg, L. H, Franssen H, Oey PL, and Wokke JHJ. The effect of intravenous immunoglobulin treatment in patients with multifocal motor neuropathy or lower motor neurone disease. J Neurol 1995; 242:149.

Study design:	Open trial then follow-up trial (single patient, double blind, pacebo controlled).	**Length of follow-up:**	
Sample size:	9	**Population:**	Six patients with multifocal motor neuropathy, 3 patients with lower motor neuron disease (associated with elevated anti-GM 1 antibodies).
Intervention:	Open trial: IVIG 0.4 g/kg for 5 days.		
Comparison / control:			
Outcome(s) measured:	Muscle strength.		

Quality assessment (internal validity)

Placebo:	
Follow-up:	Two IVIG treatments and 2 placebo treatments.

Results

Intervention groups:	Open trial: 6/6 MMN and 1/3 LMND patients responded to IVIG. Follow-up: 5/6 MMN and same LMND patient responded to IVIG but not placebo and 1/6 MMN responded equallly to treatment and placebo.	**Control / comparison group(s):**	See above.
P-value:			
Adverse events:	None reported.		
Conclusions / Comments:	Some apparent benefit, but small uncontrolled study.		

Condition studies:	Multifocal motor neuropathy with persistent conduction block

177	Van den Berg LH, Franssen H, Wokke JH. The long-term effect of intravenous immunoglobulin treatment in multifocal motor neuropathy. Brain 1998; 121 (Pt 3):421-8.

Study design:	Case-series.	**Length of follow-up:**	up to 4 years
Sample size:	7	**Population:**	Patients with multifocal motor neuropathy.
Intervention:	Full treatment: IVIG 0.4 g/kg for 5 days. Maintenance treatment: one infusion every week for 2-4 years.		
Comparison / control:			
Outcome(s) measured:	Muscle strength, electrophysiological follow-up.		

Quality assessment (internal validity)

Placebo:

Follow-up:

Results

Intervention groups:	Full treatment: improved muscle strength (for up to 12 weeks) in 6/7 patients. Maintenance treatment: deteriorated muscle strength in 3/7 patients, improved conduction block, appearance of new conduction block sites, ongoing axonal degeneration. IVIG had beneficial effect on muscle groups during follow-up period.	**Control / comparison group(s):**	

P-value:

Adverse events: None reported.

Conclusions / Comments: Some apparent benefit, but small uncontrolled study.

Condition studies:	Multifocal motor neuropathy with persistent conduction block

178	Van den Berg LH, Kerkhoff H, Oey PL et al. Treatment of multifocal motor neuropathy with high dose intravenous immunoglobulins: a double blind, placebo controlled study. Journal of Neurology, Neurosurgery & Psychiatry 1995; 59(3):248-52.

Study design:	Open trial then follow-up trial (single patient, double blind, pacebo controlled).	**Length of follow-up:**	
Sample size:	6	**Population:**	Patients with multifocal motor neuropathy.
Intervention:	Open trial: 0.4 g/kg for 5 days. Follow-up trial: 4 patients received 2 IVIG and 2 pacebo treatments, 2 patients received 1 IVIG and 1placebo treatment.		
Comparison / control:	Placebo in follow-up trial.		
Outcome(s) measured:	Muscle strength.		

Quality assessment (internal validity)

Placebo:

Follow-up:

Results

Intervention groups:	Six out of 6 patients responded to IVIG in the open trial, 5/6 patients responded to IVIG but not placebo in follow-up trial, 1/6 responded equally to IVIG and placebo.	**Control / comparison group(s):**	See above.

P-value:

Adverse events:	None reported.
Conclusions / Comments:	Some apparent benefit, but small study.

Condition studies:	Multifocal motor neuropathy with persistent conduction block

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

Study design:	Case-series, initial treatment then follow-up treatment.	**Length of follow-up:**	4-8 years
Sample size:	11	**Population:**	Patients with multifocal motor neuropathy.
Intervention:	Initial treament: IVIG 0.4 g/kg for 5 days followed by 1 IVIg infusion 0.4 g/kg per week. Follow-up: Frequency and dosage determined per patient (frequency range - one infusion every 1-7 weeks, dose range - 7-48 g IVIG/week).		
Comparison / control:			
Outcome(s) measured:	Muscle strength: MRC sumscore of 20 muscle groups, hand-held dynamometry on weak muscle groups. Electrophysiological studies. Disability: upper limb and lower limb subscales of Guy's Neurological Disability Scale.		

Quality assessment (internal validity)

Placebo:

Follow-up:

Results

Intervention groups:	Muscle strength improved after initial treatment but decreased during follow-up. Upper limb disability better after initial treatment. Conduction block disappeared in 6 nerve segments but new sites appeared during follow-up. Remyelination or reinnervation occured in 13 nerves and demyelination or axon loss occurred in 14 nerves during follow-up.	**Control / comparison group(s):**	

P-value:

Adverse events:	Headache, rash, fatigue.
Conclusions / Comments:	Possible benefit of IVIG in muscle strength.

Neurological

Condition summary	Multiple sclerosis: progressive/relapsing or remitting
Reference list:	214 Gray OM, McDonnell GV, Forbes RB. Intravenous immunoglobulins for multiple sclerosis. 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. 217 Barak Y, Gabbay U, Gilad R, Sarova-Pinhas I, Achiron A. Neuropsychiatric assessment as a secondary outcome measure in a multiple sclerosis intravenous immunoglobulin (IVIg) trial. International Journal of Psychiatry in Clinical Practice 1999; 3(1):31-4. 218 Deisenhammer F, Fazekas F, Strasser-Fuchs S et al. Intravenous immunoglobulins in multiple sclerosis: Results of the Austrian Immunoglobulin in Multiple Sclerosis (AIMS) trial. Infusionsther Transfusionsmed 1999; 26(Suppl 2):42-7. 224 Lewanska, M., Siger-Zajdel, M., and 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. 226 Oztekin, N. and Oztekin M. F. Intravenous immunoglobulin tratment in relapsing-remitting multiple sclerosis: a double blind cross over study. Mult Scler 1998; 4:391. 232 Soelberg-Sorebsen, P. Wanscher B. Schreiber K. Blinkenberg M. Jensen C. V. and Ravnborg M. Effect of intravenous immunoglobulin (IVIG) 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. 238 Stangel M, Boegner F, Klatt CH, Hofmeister C, Seyfert S. Placebo controlled pilot trial to study the remyelinating potential of intravenous immunoglobulins in multiple sclerosis. Journal of Neurology, Neurosurgery & Psychiatry 2000; 68(1):89-92. 239 Strasser-Fuchs S, Fazekas F, Deisenhammer F, Nahler G, Mamoli B. The Austrian Immunoglobulin in MS (AIMS) study: final analysis. Multiple Sclerosis. 6 Suppl 2:S9-13, 2000 Oct . 250 Noseworthy JH, O'Brien PC, Weinshenker BG, Weis JA, Petterson TM, Erickson BJ, Windebank AJ, Whisnant JP, Stolp-Smith KA, Harper CM Jr, Low PA, Romme LJ, Johnson M, An KN, Rodriguez M. IV immunoglobulin does not reverse established weakness in MS. Neurology. 2000 Oct 24;55(8):1135-43.
Types of study:	One sytemic review (2 RCTs), 6 RCTs, 3 case-controls, 1 case-series.
Total sample size:	849
Quality:	High/Moderate/Low
Result:	Reduction in relapse rate, and increased time to first relapse, reduction in neurological disability.
Adverse events:	Fatigue, headaches, rash, low-grade fever, rash, eosinophilia, eczema, uticaria, depression, nausea, hepatitis C, severe ezcema, depression. 25 serious adverse events occurred requiring hospitalisation - not drug related.
Conclusion:	Some evidence of benefit in the systemic review (n=168), no benefit in 2 RCTs (n=107) and significant benefit in 2 RCTs (n=197).
Category:	IIc

Condition studies:	Multiple sclerosis: progressive/relapsing or remitting

214	Gray OM, McDonnell GV, Forbes RB. Intravenous immunoglobulins for multiple sclerosis. 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.
Study design:	Two RCTs- all IVIG. **Length of follow-up:**
Sample size:	168 **Population:**
Intervention:	IVIG
Comparison / control:	
Outcome(s) measured:	Primary outcomes: EDSS score, relapse rate, proportion of patients remaining relapse free. Secondary outcomes: Time to disease progression, time to first relapse, number of new or enlarging brain lesions, number of gadolinium enhancing lesions, total MRI lesion burden, number treated relapses, side-effects.

Quality assessment (internal validity)

Placebo:

Follow-up:

Results

Intervention groups:	Evidence that IVIG may reduce relapse rate over 2 years and increase probability of remaining relapse free. No conclusive MRI data to back-up view that IVIG is disease modifying.	**Control / comparison group(s):**

P-value:

Adverse events:	Well tolerated by majority of patients.
Conclusions / Comments:	Two high-quality trials excluded from this review and 4 current trials running. Future trials for RR-MS should include MRI data and sustained EDSS worsening as outcomes. For progressive MS awaiting results of pending trials.

Condition studies: Multiple sclerosis: progressive/relapsing or remitting

217 Barak Y, Gabbay U, Gilad R, Sarova-Pinhas I, Achiron A. Neuropsychiatric assessment as a secondary outcome measure in a multiple sclerosis intravenous immunoglobulin (IVIg) trial. International Journal of Psychiatry in Clinical Practice 1999; 3(1):31-4.

Study design: RCT **Length of follow-up:**

Sample size: 40 **Population:** RR-MS

Intervention: IVIG for 2 years.

Comparison / control: Placebo.

Outcome(s) measured: Neuropsychological function evaluation at baseline, 1 year and 2 years.

Quality assessment (internal validity)

Placebo:

Follow-up:

Results

Intervention groups: No difference in anxiety, depression, and general psychopathology. Pathological laughing and crying in 1 patient and overt depression in 1 patient.

Control / comparison group(s): Two patients with hypomanic episode and pathological laughing and crying in two patients.

P-value:

Adverse events:

Conclusions / Comments: No effect on cognitive changes.

Condition studies: Multiple sclerosis: progressive/relapsing or remitting

218 Deisenhammer F, Fazekas F, Strasser-Fuchs S et al. Intravenous immunoglobulins in multiple sclerosis: Results of the Austrian Immunoglobulin in Multiple Sclerosis (AIMS) trial. Infusionsther Transfusionsmed 1999; 26(Suppl 2):42-7.

Study design:

Length of follow-up:

Sample size:

Population:

Intervention:

Comparison / control:

Outcome(s) measured:

Quality assessment (internal validity)

Placebo:

Follow-up:

Results

Intervention groups:

Control / comparison group(s):

P-value:

Adverse events:

Conclusions / Comments: Same trial as Fazekas 1997

Condition studies:	Multiple sclerosis: progressive/relapsing or remitting

224	Lewanska, M., Siger-Zajdel, M., and 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.

Study design:	RCT	**Length of follow-up:**	
Sample size:	49	**Population:**	
Intervention:	IVIG low dose 0.2 g/kg or high dose 0.04 g/kg.		
Comparison / control:	Placebo.		
Outcome(s) measured:	Clinical data assessed monthly, MRI performed every 3 months, annual relapse rate, change of expanded disability status scale, neurological rating scale score. For MRI activity total lesion volume, new lesions and gadolinium-enhanced lesions were measured.		

Quality assessment (internal validity)

Placebo:

Follow-up:

Results

Intervention groups:	ARR reduced, neurological disability (P=0.0117) and neurological impairment decreased, compared tp placebo in low and h igh dose groups. Total lesion volume, Gd-enhancing lesions and new lesions was less in IVIG than in placebo.	**Control / comparison group(s):**	

P-value:

Adverse events:

Conclusions / Comments:	Neurological disability (P = 0.0117) and neurological impairment decreased in IVIG group compared to placebo. IVIG dose 0.2 g/kg and 0.4 g/kg are equally effective at reducing MS activity.

Condition studies: Multiple sclerosis: progressive/relapsing or remitting

226

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

Study design:

Length of follow-up:

Sample size:

Population:

Intervention:

Comparison / control:

Outcome(s) measured:

Quality assessment (internal validity)

Placebo:

Follow-up:

Results

Intervention groups:

Control / comparison group(s):

P-value:

Adverse events:

Conclusions / Comments: This is listed in the Cochrane register of trials but no abstract and not in Medline or Science Direct.

Condition studies: Multiple sclerosis: progressive/relapsing or remitting

232 Soelberg-Sorebsen, P. Wanscher B. Schreiber K. Blinkenberg M. Jensen C. V. and Ravnborg M. Effect of intravenous immunoglobulin (IVIG) 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.

Study design:

Length of follow-up:

Sample size:

Population:

Intervention:

Comparison / control:

Outcome(s) measured:

Quality assessment (internal validity)

Placebo:

Follow-up:

Results

Intervention groups:

Control / comparison group(s):

P-value:

Adverse events:

Conclusions / Comments: This is listed in the Cochrane register of trials but no abstract and not in Medline or Science Direct

Condition studies:	Multiple sclerosis: progressive/relapsing or remitting

238	Stangel M, Boegner F, Klatt CH, Hofmeister C, Seyfert S. Placebo controlled pilot trial to study the remyelinating potential of intravenous immunoglobulins in multiple sclerosis. Journal of Neurology, Neurosurgery & Psychiatry 2000; 68(1):89-92.

Study design:	Case-control, pilot trial.	**Length of follow-up:**	6 weeks
Sample size:	10	**Population:**	
Intervention:	IVIG 0.4 g/kg on 5 consecutive days.		
Comparison / control:	Placebo.		
Outcome(s) measured:	Change in central motor conduction time to measure central myelination, neurological examinations including EDSS, neurological rating scale, manual muscle testing.		

Quality assessment (internal validity)

Placebo:

Follow-up:

Results

Intervention groups:	Slight clinical improvement, no difference in central motor conduction times.	**Control / comparison group(s):**	

P-value:

Adverse events:

Conclusions / Comments:	Data do not support role for IVIG in remyelination of stable multiple sclerosis lesions. Excluded efficacy data due to low numbers.

Condition studies: Multiple sclerosis: progressive/relapsing or remitting

239 Strasser-Fuchs S, Fazekas F, Deisenhammer F, Nahler G, Mamoli B. The Austrian Immunoglobulin in MS (AIMS) study: final analysis. Multiple Sclerosis. 6 Suppl 2:S9-13, 2000 Oct .

Study design: RCT **Length of follow-up:**

Sample size: 148 **Population:**

Intervention: IVIG 0.15-0.2 g/kg given monthly over 2 years.

Comparison / control: Placebo.

Outcome(s) measured: EDSS, frequency of relapsespatient self-rating (incapacity status and environmental status scales).

Quality assessment (internal validity)

Placebo:

Follow-up:

Results

Intervention groups: More favourable course of disability by EDSS P = 0.008 and reduced frequency of relapses P = 0.011. Positive effect on daily and social living associated with less days spent in hospital.

Control / comparison group(s):

P-value:

Adverse events:

Conclusions / Comments: Significant beneficial effect of IVIG. Further studies required.

Condition studies:	Multiple sclerosis: progressive/relapsing or remitting

250	Noseworthy JH, O'Brien PC, Weinshenker BG, Weis JA, Petterson TM, Erickson BJ, Windebank AJ, Whisnant JP, Stolp-Smith KA, Harper CM Jr, Low PA, Romme LJ, Johnson M, An KN, Rodriguez M. IV immunoglobulin does not reverse established weakness in MS. Neurology. 2000 Oct 24;55(8):1135-43.

Study design:	RCT	**Length of follow-up:**	
Sample size:	67	**Population:**	MS patients with persistent muscle weakness for 4-18 months.
Intervention:	IVIG 0.4 g/kg daily for 5 days, then single infusions every 2 weeks for 3 months.		
Comparison / control:	Placebo.		
Outcome(s) measured:	Isometric muscle strength.		

Quality assessment (internal validity)

Placebo:

Follow-up:

Results

Intervention groups:	Interim analysis showed no difference in change of muscle strength between groups at 6 months. No benefit in relapse behaviour or impairment measures.	**Control / comparison group(s):**	

P-value:

Adverse events:	IVIG well tolerated.
Conclusions / Comments:	Trial was terminated after 6 months. IVIG does not reverse established muscle weakness.

Neurological

Condition summary	Muscle diseases: dermatomyositis
Reference list:	188 Dalakas MC, Illa I, Dambrosia JM et al. A controlled trial of high-dose intravenous immune globulin infusions as treatment for dermatomyositis.[see comment]. N Engl J Med 1993; 329(27):1993-2000.
Types of study:	One double blind, placebo-controlled.
Total sample size:	15
Quality:	Low
Result:	Significant improvement in muscle strength P=<0.018 and neuromuscular symptoms P=<0.035 of 8/8 patients.
Adverse events:	None reported.
Conclusion:	IVIG appears to be beneficial, based on one small double-blind, placebo controlled trial.
Category:	IIa

Condition studies:	Muscle diseases: dermatomyositis

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

Study design:	Double blind, placebo-controlled.	**Length of follow-up:**	3 months after completion of infusions
Sample size:	15	**Population:**	Patients (aged 18-55) with biopsy-proved, treatment-resistant dermatomyositis (10 women and 5 men).
Intervention:	Prednisone (25 mg/day) and IVIG 2g/kg per month for 3 months.		
Comparison / control:	Prednisone (25 mg/day) and placebo (dextrose in saline) for 3 months.		
Outcome(s) measured:	Muscle strength, neuromuscular symptoms and changes in rash. Changes in immune-mediated abnormalities were determined by repeated muscle biopsy.		

Quality assessment (internal validity)

Placebo:

Follow-up:

Results

Intervention groups:	Significant improvement in muscle strength P =< 0.018 and neuromuscular symptoms P =< 0.035 of 8/8 patients.	**Control / comparison group(s):**	No improvement in muscle strength or neuromuscular symptoms in 7/7 patients.
P-value:	Significant improvement in muscle strength P =< 0.018 and neuromuscular symptoms P =< 0.035 of 8/8 patients.		
Adverse events:	None reported.		
Conclusions / Comments:	High dose IVIG appears to be effective in treatment of refractory dermatomyositis.		

Neurological

Condition summary	Muscle diseases: inclusion body myositis
Reference list:	273 Dalakas MC, Koffman B, Fujii M, Spector S, Sivakumar K, Cupler E. A controlled study of intravenous immunoglobulin combined with prednisone in the treatment of IBM. Neurology. 2001 Feb 13;56(3):323-7. 274 Walter MC, Lochmuller H, Toepfer M, Schlotter B, Reilich P, Schroder M, Muller-Felber W, Pongratz D. High-dose immunoglobulin therapy in sporadic inclusion body myositis: a double-blind, placebo-controlled study. J Neurol. 2000 Jan;247(1):22-8. 275 Dalakas MC, Sonies B, Dambrosia J, Sekul E, Cupler E, Sivakumar K. Treatment of inclusion-body myositis with IVIg: a double-blind, placebo-controlled study. Neurology. 1997 Mar;48(3):712-6.
Types of study:	Three controlled studies (2 cross-over).
Total sample size:	77
Quality:	Low
Result:	Studies show possible slight benefit in reducing endomysial inflammation, disease progression and severity.
Adverse events:	No adverse events reported.
Conclusion:	Possible benefit based on three small studies showing minor improvements.
Category:	IIa

Condition studies:	Muscle diseases: inclusion body myositis

273	Dalakas MC, Koffman B, Fujii M, Spector S, Sivakumar K, Cupler E. A controlled study of intravenous immunoglobulin combined with prednisone in the treatment of IBM. Neurology. 2001 Feb 13;56(3):323-7.

Study design:	RCT	**Length of follow-up:**	4 months
Sample size:	36	**Population:**	Patients with biopsy-proven IBM, treated with high-dose prednisone for 3 months.
Intervention:	IVIG		
Comparison / control:	Placebo		
Outcome(s) measured:	Muscle strength, inflammation.		

Quality assessment (internal validity)

Placebo:	Yes
Follow-up:	

Results

Intervention groups:	#Deleted	**Control / comparison group(s):**	No significant change in muscle strength from baseline to 4 months. Fewer necrotic fibres and CD2+ cells.
P-value:	P = 0.001 (necrotic fibres), P = 0.0001 (CD2+ cells) (in both groups compared to baseline).		
Adverse events:			
Conclusions / Comments:	IVIG combined with prednisone for a 3-month period was not effective in IBM. Endomysial inflammation was significantly reduced after treatment, but the reduction was not of clinical significance.		

Condition studies: Muscle diseases: inclusion body myositis

274

Walter MC, Lochmuller H, Toepfer M, Schlotter B, Reilich P, Schroder M, Muller-Felber W, Pongratz D. High-dose immunoglobulin therapy in sporadic inclusion body myositis: a double-blind, placebo-controlled study. J Neurol. 2000 Jan;247(1):22-8.

Study design:	Controlled cross-over (double blind, placebo controlled).	**Length of follow-up:**	12 months
Sample size:	22	**Population:**	Adults with IBM (mean duration 5.2 years).

Intervention: IVIG 2g/kg bodyweight 6 months, then switched groups for 6 months.

Comparison / control: Placebo for 6 months, then IVIG for 6 months.

Outcome(s) measured:

Quality assessment (internal validity)

Placebo: Yes

Follow-up:

Results

Intervention groups:	No progression of disease in 90% of patients, improvement (11%) by neuromuscular symptom score.	**Control / comparison group(s):**	

P-value:

Adverse events: None.

Conclusions / Comments: IVIG may have a slight benefit in preventing disease progression or causing improvement in sporadic IBM. Further research is needed.

Condition studies:	Muscle diseases: inclusion body myositis

275	Dalakas MC, Sonies B, Dambrosia J, Sekul E, Cupler E, Sivakumar K. Treatment of inclusion-body myositis with IVIg: a double-blind, placebo-controlled study. Neurology. 1997 Mar;48(3):712-6.

Study design:	Controlled cross-over (double blind, placebo controlled).	**Length of follow-up:**	6 months
Sample size:	19	**Population:**	Patients with IBM.

Intervention:	IVIG 2g/kg bodyweight 3 months, then switched groups for 3 months (after washout period).
Comparison / control:	Placebo for 3 months, then IVIG for 3 months.
Outcome(s) measured:	Muscle strenght, swallowing functions.

Quality assessment (internal validity)

Placebo:	Yes
Follow-up:	

Results

Intervention groups:	Muscle strength improved in lower limbs, decreased in other limbs compared with placebo.	**Control / comparison group(s):**	

P-value:	Less than 0.05 for limb improvement, same for swallowing function.
Adverse events:	
Conclusions / Comments:	Possible benefit of IVIG in IBM (functionally important improvement in 6/19 patients).

Neurological

Condition summary	Muscle diseases: polymyositis
Reference list:	190 Cherin P, Pelletier S, Teixeira A et al. Results and long-term followup of intravenous immunoglobulin infusions in chronic, refractory polymyositis: an open study with thirty-five adult patients. Arthritis & Rheumatism 2002; 46(2):467-74.
Types of study:	Case-series, open, prospective.
Total sample size:	35
Quality:	Low
Result:	IVIG may be of benefit in chronic, refractory polymyositis, and may allow reduction in dose of corticosteroid.
Adverse events:	Side effects in 6 patients (4 mild headaches, 3 fever and sweating).
Conclusion:	Possible benefit based on one small, uncontrolled study. Further studies are needed to confirm the findings and to determine dose, duration of treatment and number of infusions.
Category:	IIa

Condition studies:	Muscle diseases: polymyositis

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

Study design:	Case-series, open, prospective.	**Length of follow-up:**	over 3 years
Sample size:	Sample of 35 adults.	**Population:**	20 female, 15 male, mean age 43.5 years with chronic refractory polymyositis.
Intervention:	IVIG 1 gm/kg for 2 days per month for up to months, as third-line therapy.		
Comparison / control:			
Outcome(s) measured:	Evaluation of proximal muscle power, muscle disability scale score and esophageal disorders, creatinine kinase levels.		

Quality assessment (internal validity)

Placebo:	No
Follow-up:	Mean of 51 months for 25 patients who responded to IVIG.

Results

Intervention groups:	Clinical improvement seen in 15/35 patients. Mean muscle power improved P=<0.01, creatinine kinase levels decreased before 4th IVIG dose P=<0.01. 12/25 patients remained in full remission following treatment. After discontinuation of IVIG, efficacy remained at 50%. 7/25 patients relapsed at average of 17.1 months.	**Control / comparison group(s):**	
P-value:	Mean muscle power improved P = <0.01, creatinine kinase levels decreased before 4th IVIG dose P = <0.01.		
Adverse events:	Side effects in 6 patients (4 mild headaches, 3 fever and sweating).		
Conclusions / Comments:	IVIG may be of benefit in chronic, refractory polymyositis, and may allow reduction in dose of corticosteroid. Further studies are needed to confirm the findings and to determine dose, duration of treatment and number of infusions.		

Neurological

Condition summary	Muscle diseases: polymyositis and systemic connective tissue disease
Reference list:	
Types of study:	
Total sample size:	
Quality:	
Result:	
Adverse events:	
Conclusion:	
Category:	See: Muscle diseases: polymyositis

Neurological

Condition summary	Myalgic encephalomyelitis
Reference list:	244 Vollmer-Conna U, Hickie I, Hadzi-Pavlovic D et al. Intravenous immunoglobulin is ineffective in the treatment of patients with chronic fatigue syndrome. Am J Med 1997; 103(1):38-43. 243 Peterson PK, Shepard J, Macres M et al. A controlled trial of intravenous immunoglobulin G in chronic fatigue syndrome.[comment]. Am J Med 1990; 89(5):554-60.
Types of study:	Three RCTs.
Total sample size:	178
Quality:	Low-Moderate
Result:	1 RCT found benefit in 43% of IVIG group; 2 RCTs found no significant effect.
Adverse events:	Phlebitis, headaches, fatigue, concentration impairment.
Conclusion:	Appears to be either no benefit, or possible benefit in some patients, based on 3 RCTs.
Category:	IIc

Condition studies: Myalgic encephalomyelitis

244 Vollmer-Conna U, Hickie I, Hadzi-Pavlovic D et al. Intravenous immunoglobulin is ineffective in the treatment of patients with chronic fatigue syndrome. Am J Med 1997; 103(1):38-43.

Study design:	RCT	**Length of follow-up:**	6 months
Sample size:	99	**Population:**	Adults with CFS.

Intervention: IVIG (0.5-2g/kg), monthly for 3 months.

Comparison / control: Placebo (albumin).

Outcome(s) measured: Karnofsy performance score, degree of involvement in work, school, sport or social activities.

Quality assessment (internal validity)

Placebo: Yes

Follow-up:

Results

Intervention groups:	No significant therapeutic effect.	**Control / comparison group(s):**	

P-value:

Adverse events: Not sign diff between placebo and IVIG group.

Conclusions / Comments: No apparent benefit.

Condition studies: Myalgic encephalomyelitis

243 Peterson PK, Shepard J, Macres M et al. A controlled trial of intravenous immunoglobulin G in chronic fatigue syndrome.[comment]. Am J Med 1990; 89(5):554-60.

Study design:	RCT	**Length of follow-up:**	~ 20 weeks
Sample size:	30	**Population:**	Patients with chronic fatigue syndrome.

Intervention: IVIG 1 g/kg every 30 days for 6 months.

Comparison / control: Dose of 1% albumin every 30 days for 6 months.

Outcome(s) measured: Severity of symptoms, functional status, health perceptions, adverse experiences.

Quality assessment (internal validity)

Placebo: Yes

Follow-up: Two patients withdrew (adverse effects).

Results

Intervention groups:	No significant therapeutic effect.	**Control / comparison group(s):**	

P-value:

Adverse events: Significantly more headaches in IVIG group.

Conclusions / Comments: No apparent benefit.

Neurological

Condition summary	Neuromuscular disorders: Lambert Eaton Syndrome
Reference list:	199 Maddison P, Newsom-Davis J. Treatment for Lambert-Eaton myasthenic syndrome. Maddison P, Newsom-Davis J. Treatment for Lambert-Eaton Myasthenic Syndrome (Cochrane Review). In: The Cochrane Library, Issue 1, 2004. Chichester, UK: John Wiley & Sons, Ltd. 200 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. 201 Motomura M, Bain, P. G et al. Effects of intravenous immunoglobulin (IVIG) treatment on anti-calcium channel antibody titres in the Lambert-Eaton myasthenic syndrome. J Neurol 1995; 242:S44.
Types of study:	One systematic review, with 1 RCT.
Total sample size:	9
Quality:	Low
Result:	Significant improvement of myometric muscle strength scores and compound muscle action potential amplitudes, insufficient data to quantify treatment.
Adverse events:	Acute meningism in 1 patient, self-limiting headache in 4 patients.
Conclusion:	Possible slight benefit, based on 1 small RCT.
Category:	IIa

Condition studies:	Neuromuscular disorders: Lambert Eaton Syndrome

199	Maddison P, Newsom-Davis J. Treatment for Lambert-Eaton myasthenic syndrome. Maddison P, Newsom-Davis J. Treatment for Lambert-Eaton Myasthenic Syndrome (Cochrane Review). In: The Cochrane Library, Issue 1, 2004. Chichester, UK: John Wiley & Sons, Ltd.

Study design:	1 IVIG RCT (cross-over design)	**Length of follow-up:**	Two 8-week study periods
Sample size:	Sample of 9 in IVIG trial.	**Population:**	Patients with Lambert-eaton myasthenic syndrome.
Intervention:	IVIG 2g/kg/day for 2 days, cross-over, with 8 weeks inbetween.		
Comparison / control:	Placebo - 0.3% albumin.		
Outcome(s) measured:	Muscle strength.		

Quality assessment (internal validity)

Placebo:

Follow-up:

Results

Intervention groups:	Significant improvement of myometric muscle strength scores and compound muscle action potential amplitudes.	**Control / comparison group(s):**	

P-value:

Adverse events:	Acute meningism in 1 patient, self-limiting headache in 4 patients.
Conclusions / Comments:	Treatment appears to be provide slight benefit, based on 1 small RCT.

Condition studies: Neuromuscular disorders: Lambert Eaton Syndrome

200 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.

Study design:

Length of follow-up:

Sample size:

Population:

Intervention:

Comparison / control:

Outcome(s) measured:

Quality assessment (internal validity)

Placebo:

Follow-up:

Results

Intervention groups:

Control / comparison group(s):

P-value:

Adverse events:

Conclusions / Comments: Included in Cochrane review

Condition studies: Neuromuscular disorders: Lambert Eaton Syndrome

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

Study design:	Case-series, double blind, placebo controlled, crossover.	**Length of follow-up:**	8 weeks following each treatment
Sample size:	7	**Population:**	Lambert-Eaton syndrome.

Intervention: IVIG 1 g/kg/day for 2 days.

Comparison / control: Dose of 0.3% abumin.

Outcome(s) measured: Serum antibodies were measured to voltage-gated calcium channels (VGCC) at motor nerve terminals, performance measures.

Quality assessment (internal validity)

Placebo:

Follow-up:

Results

Intervention groups:	Fall in mean serum anti-VGCC antibody levels at 2-8 weeks (P = < 0.05 < 0.01) associated with improvement in performance measures.	**Control / comparison group(s):**	

P-value:

Adverse events:

Conclusions / Comments: Potential benefit from IVIG, but cross-over trial with small numbers.

Neurological

Condition summary	Neuromuscular disorders: myasthenia gravis
Reference list:	192 Gajdos P, Chevret S, Toyka K. Intravenous immunoglobulin for myasthenia gravis. Gajdos P, Chevret S, Toyka K. Intravenous Immunoglobulin for Myasthenia Gravis (Cochrane Review). In: The Cochrane Library, Issue 2, 2004. Chichester, UK: John Wiley & Sons, Ltd.
Types of study:	One systematic review (4 RCTs).
Total sample size:	147
Quality:	Low
Result:	One RCT, no significant difference between IVIG and plasma exchange (PE) after 2 weeks; 1 RCT, no sign diff between IVIG and PE after 4 weeks; 1 RCT, no sign diff between IVIG and placebo; 1 RCT, no sign diff between IVIG and methylprednisolone.
Adverse events:	Fever, nausea, headache - self limiting.
Conclusion:	Either no significant effect or possible benefit, based on 4 low-quality RCTs.
Category:	IIc

Condition studies:	Neuromuscular disorders: myasthenia gravis

192	Gajdos P, Chevret S, Toyka K. Intravenous immunoglobulin for myasthenia gravis. Gajdos P, Chevret S, Toyka K. Intravenous Immunoglobulin for Myasthenia Gravis (Cochrane Review). In: The Cochrane Library, Issue 2, 2004. Chichester, UK: John Wiley & Sons, Ltd.

Study design:	Four RCTs.	**Length of follow-up:**	
Sample size:	147	**Population:**	Children and adults with myasthenia gravis.
Intervention:	IVIG		
Comparison / control:	Plasma exchange, other treatments or placebo.		
Outcome(s) measured:	Short-term benefit.		

Quality assessment (internal validity)

Placebo:

Follow-up:

Results

Intervention groups:	One RCT, no significant difference between IVIG and plasma exchange (PE) after 2 weeks; 1 RCT, no sign diff between IVIG and PE after 4 weeks; 1 RCT, no sign diff between IVIG and placebo; 1 RCT, no sign diff between IVIG and methylprednisolone.	**Control / comparison group(s):**	
P-value:	NS		
Adverse events:	Fever, nausea, headache - self limiting.		
Conclusions / Comments:	Poorly designed RCTs, further research needed.		

Neurological

Condition summary	Neuromuscular disorders: stiff man syndrome
Reference list:	202 Dalakas MC, Fujii M, Li M, Lutfi B, Kyhos J, McElroy B. High-dose intravenous immune globulin for stiff-person syndrome.[see comment]. N Engl J Med 2001; 345(26):1870-6.
Types of study:	One randomised, double blind, placebo-controlled cross over.
Total sample size:	16
Quality:	Low
Result:	Stiffness scores decreased, heightened-sensitivity scores decreased during IVIG, beneficial effects lasted 6 weeks to 1 year.
Adverse events:	One in 16 had severe, long-lasting blistering rash after each infusion.
Conclusion:	Possible benefit in treatment of stiff-person syndrome, based on one small cross-over study.
Category:	IIa

Condition studies:	Neuromuscular disorders: stiff man syndrome		
202	Dalakas MC, Fujii M, Li M, Lutfi B, Kyhos J, McElroy B. High-dose intravenous immune globulin for stiff-person syndrome.[see comment]. N Engl J Med 2001; 345(26):1870-6.		
Study design:	Randomised, double blind, placebo-controlled cross over.	**Length of follow-up:**	
Sample size:	16	**Population:**	Patients with stiff-person syndrome and anti-GAD65 antibodies.
Intervention:	IVIG 2g/kg bodyweight/month (2 doses of 1g/kg) for 3 months followed by 1 month washout.		
Comparison / control:	Placebo (saline) for 3 months followed by 1 month washout.		
Outcome(s) measured:	Scores on the distribution-of-stiffness index and heightened-sensitivity scale (baseline to 2nd and 3rd month).		

Quality assessment (internal validity)

Placebo:	Yes
Follow-up:	

Results

Intervention groups:	Stiffness scores decreased, heightened-sensitivity scores decreased during IVIG, beneficial effects lasted 6 weeks to 1 year.	**Control / comparison group(s):**	Scores did not change significantly during 3 mo of placebo, decreased during IVIG therapy.
P-value:	IVIG had significant direct treatment effect (P = 0.001).		
Adverse events:	1 person had severe, long-lasting blistering rash after each infusion.		
Conclusions / Comments:	IVIG shows some benefit in treatment of stiff-person syndrome, based on one small cross-over study.		

Neurological

Condition summary	Other disorders: adrenoleukodystrophy
Category:	IVb

Neurological

Condition summary	Other disorders: amyotrophic lateral sclerosis
Category:	IVb

Neurological

Condition summary	Other disorders: motor neuron disease
Reference list:	208 Azulay JP, Blin O, Pouget J et al. Intravenous immunoglobulin treatment in patients with motor neuron syndromes associated with anti-GM1 antibodies: a double-blind, placebo-controlled study. Neurology 1994; 44(3 Pt 1):429-32. 210 Van den Berg, L. H, Franssen H, Oey PL, and Wokke JHJ. The effect of intravenous immunoglobulin treatment in patients with multifocal motor neuropathy or lower motor neurone disease. J Neurol 1995; 242:149. 212 Van den Berg-Vos RM, Franssen H, Wokke JH, Van Es HW, Van den Berg LH. Multifocal motor neuropathy: diagnostic criteria that predict the response to immunoglobulin treatment. Ann Neurol 2000; 48(6):919-26.
Types of study:	One RCT.
Total sample size:	12
Quality:	Low
Result:	Significant increase in muscle strength in patients with conduction blocks.
Adverse events:	Cutaneous rash, transient fever.
Conclusion:	Possible benefit in patients with conduction blocks, based on 1 small RCT.
Category:	IIa

Condition studies:	Other disorders: motor neuron disease

208	Azulay JP, Blin O, Pouget J et al. Intravenous immunoglobulin treatment in patients with motor neuron syndromes associated with anti-GM1 antibodies: a double-blind, placebo-controlled study. Neurology 1994; 44(3 Pt 1):429-32.

Study design:	Case-series, double blind, crossover.	**Length of follow-up:**	56 days
Sample size:	12	**Population:**	Patients with motor neuron syndrome with high titres anti-GMI antibodies (5 had conduction blocks).

Intervention:	IVIG 0.4 g/kg per day for 5 days.
Comparison / control:	Placebo.
Outcome(s) measured:	Muscle strength (using computer analyser), Norris scale for disability, motor nerve conduction velocities (for patients with conduction blocks), immunologic markers. All measure at 5, 28 and 56 days.

Quality assessment (internal validity)

Placebo:

Follow-up:

Results

Intervention groups:	Increase in muscle strength in patients with conduction blocks.	**Control / comparison group(s):**	

P-value:

Adverse events:

Conclusions / Comments:	Compared with placebo, IVIg induced a significant increase in muscle strength only in the patients with conduction blocks.

Condition studies: Other disorders: motor neuron disease

210 Van den Berg, L. H, Franssen H, Oey PL, and Wokke JHJ. The effect of intravenous immunoglobulin treatment in patients with multifocal motor neuropathy or lower motor neurone disease. J Neurol 1995; 242:149.

Study design: Case-series, open-trial then follow-up double-blind trial.

Length of follow-up:

Sample size: 9

Population: Six multifocal motor neuropathy (MMN) patients, 3 lower motor neuron disease (LMND) patients.

Intervention: Open trial = IVIG 0.4 g/kg for 5 days. Follow-up trial = 2 IVIG treatments and 2 placebo treatments in random order.

Comparison / control:

Outcome(s) measured: Muscle strength.

Quality assessment (internal validity)

Placebo:

Follow-up:

Results

Intervention groups: Open trial: 6/6 MMN patients and 1/3 LMND responded. Double-blind trial: 5/6 MMN and the same LMND patient responded .

Control / comparison group(s): One MMN patient responded equally to placebo and IVIG.

P-value:

Adverse events:

Conclusions / Comments:

Condition studies:	Other disorders: motor neuron disease

212	Van den Berg-Vos RM, Franssen H, Wokke JH, Van Es HW, Van den Berg LH. Multifocal motor neuropathy: diagnostic criteria that predict the response to immunoglobulin treatment. Ann Neurol 2000; 48(6):919-26.

Study design:	Case-control, randomised, double blind, placebo controlled.	**Length of follow-up:**	3 months
Sample size:	40	**Population:**	Patients with chronic fatigue syndrome (40 with abnormal cell-mediated immunity).
Intervention:	IVIG 3 doses 2 g/kg/month.		
Comparison / control:	Placebo.		
Outcome(s) measured:	Severity of symptoms and associated disability, change of physical symptoms and functional capacity using visual analogue scales. Psychologic morbidity using patient-rated indices of depression. Cell-mediated immunity evaluated by T-cell subset analysis, delayed hypersensitivity skin testing, lymphocyte transformation with phytohemagglutinin.		

Quality assessment (internal validity)

Placebo:

Follow-up:

Results

Intervention groups:	Ten out of 23 (43%) responded (improved physical, psychologic and immunologic measures).	**Control / comparison group(s):**	Three out of 26 (12%) responded.
P-value:	IVIG more effective P =< 0.01.		
Adverse events:			
Conclusions / Comments:			

Neurological

Condition summary	Other disorders: opsiclonus myoclonus
Category:	IVb

Neurological

Condition summary	Other disorders: paraneoplastic cerebellar degeneration with N0 antibodies
Category:	IVb

Neurological

Condition summary	Polyneuropathy of critical illness
Reference list:	185 Mohr M, Englisch L, Roth A, Burchardi H, Zielmann S. Effects of early treatment with immunoglobulin on critical illness polyneuropathy following multiple organ failure and gram-negative sepsis. Intensive Care Med 1997; 23(11):1144-9.
Types of study:	Case-series, retrospective study.
Total sample size:	8
Quality:	Moderate
Result:	IVIG appeared to reduce the development of CIP in survivors of MOF and sepsis.
Adverse events:	
Conclusion:	Possible benefit based on one uncontrolled study with small numbers (based on retrospective chart analysis).
Category:	IIa

Condition studies:	Polyneuropathy of critical illness		
185	Mohr M, Englisch L, Roth A, Burchardi H, Zielmann S. Effects of early treatment with immunoglobulin on critical illness polyneuropathy following multiple organ failure and gram-negative sepsis. Intensive Care Med 1997; 23(11):1144-9.		
Study design:	Case-series, retrospective study.	**Length of follow-up:**	
Sample size:	8	**Population:**	Patients who survived multiple organ failure.
Intervention:	IVIG 0.3 g/kg for 3 days within 24 hours of diagnosis of sepsis (enriched for IgM, with high titres against bacterial antigens and lipid A of endotoxin.		
Comparison / control:			
Outcome(s) measured:	Electrophysical studies for the diagnosis of critical illness polyneuropathy. Factors relating to development of critical illness polyneuropathy were noted.		

Quality assessment (internal validity)

Placebo:

Follow-up:

Results

Intervention groups:	The 8 patients who survived multiple organ failure (MOF) with sepsis, treated with IVIG, did not develop critical illness polyneuropathy (CIP).	**Control / comparison group(s):**	Four out of seven patients with MOF and sepsis, without IVIG, developed CIP.
P-value:			
Adverse events:			
Conclusions / Comments:	IVIG appeared to reduce the development of CIP in survivors of MOF and sepsis, but the one study had small numbers and was based on retrospective chart analysis. More research is needed.		

Primary immunodeficiencies

Condition summary

B-cell tumours

Reference list:	155 Griffiths H, Brennan V, Lea J, Bunch C, Lee M, Chapel H. Crossover study of immunoglobulin replacement therapy in patients with low-grade B-cell tumors. Blood 1989; 73(2):366-8.
Types of study:	One Case-series (randomised cross-over).
Total sample size:	12
Quality:	Low
Result:	Less bacterial infections with IVIG treatment P=0.001 (Mainland's cross-over method).
Adverse events:	Not specifically reported. No serious adverse occurred.
Conclusion:	Statistically significant effect of IVIG based on 1 small case series trial.
Category:	IIa

Condition studies:	B-cell tumours

155	Griffiths H, Brennan V, Lea J, Bunch C, Lee M, Chapel H. Crossover study of immunoglobulin replacement therapy in patients with low-grade B-cell tumors. Blood 1989; 73(2):366-8.

Study design:	Case-series, randomised cross-over.	**Length of follow-up:**	
Sample size:	12	**Population:**	Chronic lymphocytic leukaemia or non-Hodgkin'slymphoma patients with hypogammaglobulinemia or history of recurrent infection.
Intervention:	IVIG every 3 weeks for 1 year.		
Comparison / control:	Placebo every 3 weeks for 1 year.		
Outcome(s) measured:	Number of serious bacterial infections.		

Quality assessment (internal validity)

Placebo:

Follow-up:

Results

Intervention groups:	Less bacterial infections with IVIG treatment P=0.001 (Mainland's cross-over method).	**Control / comparison group(s):**	Serious bacterial infections associated with IgG level of >6.4 g/L (P = 0.046 Fisher's exact test).

P-value:

Adverse events:

Conclusions / Comments:

Primary immunodeficiencies

Condition summary	Combined immune deficiency including specific syndromes (eg. Wiskott-Aldrich syndrome)
Reference list:	
Types of study:	
Total sample size:	
Quality:	
Result:	
Adverse events:	
Conclusion:	
Category:	See: Common variable immunodeficiency; Primary hypogammaglobulinaemia

Primary immunodeficiencies

Condition summary

Common variable immunodeficiency

Reference list:	30 Martinez Garcia MA, de Rojas MD, Nauffal Manzur MD et al. Respiratory disorders in common variable immunodeficiency. Respir Med 2001; 95(3):191-5. 40 Pruzanski W, Sussman G, Dorian W, Van T, Ibanez D, Redelmeier D. Relationship of the dose of intravenous gammaglobulin to the prevention of infections in adults with common variable immunodeficiency. Inflammation 1996; 20(4):353-9. 146 Roifman CM, Levison H, Gelfand EW. High-dose versus low-dose intravenous immunoglobulin in hypogammaglobulinaemia and chronic lung disease. Lancet 1987; 1(8541):1075-7.
Types of study:	Two cross-over double blind; 2 case series.
Total sample size:	92
Quality:	Low
Result:	Case series found less pneumonic episodes after IVIG; in cross-over studies (comparing dosages), 1 found higher dose more effective, the other no significant difference between doses.
Adverse events:	Polyarthralgia, transient fever, pruritic skin rash, shortness of breath or watery eyes and flushing; headache, pyrexia, repeated reactions (controlled by hydrocortisone).
Conclusion:	Possible benefit of IVIG; conflicting results on effect of dose, based on 4 small studies.
Category:	IIa

Condition studies: Common variable immunodeficiency

30 Martinez Garcia MA, de Rojas MD, Nauffal Manzur MD et al. Respiratory disorders in common variable immunodeficiency. Respir Med 2001; 95(3):191-5.

Study design: Case-series.

Length of follow-up:

Sample size: 19

Population: Patients with previous diagnosis of common variable immunodeficiency and treatment with IVIG replacement. Twelve men, mean age 33.1.

Intervention: IVIG

Comparison / control:

Outcome(s) measured: Lower respiratory tract infections.

Quality assessment (internal validity)

Placebo:

Follow-up:

Results

Intervention groups: Pneumonic episodes decreased from 0.28 per patient per year before treatment to 0.16 per patient per year after treatment.

Control / comparison group(s):

P-value:

Adverse events: None noted.

Conclusions / Comments: IVIG appears to reduce pneumonic episodes in CVID.

Condition studies:	Common variable immunodeficiency

40	Pruzanski W, Sussman G, Dorian W, Van T, Ibanez D, Redelmeier D. Relationship of the dose of intravenous gammaglobulin to the prevention of infections in adults with common variable immunodeficiency. Inflammation 1996; 20(4):353-9.

Study design:	Cross-over double blind cohort.	**Length of follow-up:**	Average 34 months
Sample size:	21	**Population:**	A group of 21 adults with common variable immunodeficiency and past history of frequent and severe sino-pulmonary infections.
Intervention:	IVIG		
Comparison / control:	Three doses of IVIG were compared: 200 mg/kg, 400 mg/kg and 600 given monthly, switching dose at 6-mo intervals.		
Outcome(s) measured:	Number and severity of infections.		

Quality assessment (internal validity)

Placebo:

Follow-up:

Results

Intervention groups:	No significant differences in severity of infections or duration of infection-free intervals between dosage groups.	**Control / comparison group(s):**	
P-value:	NS		
Adverse events:	Of 722 infusions, 26 adverse reactions (10 polyarthralgia, 7 transient fever, 2 pruritic skin rash, 7 shortness of breath or watery eyes and flushing).		
Conclusions / Comments:	No significant difference in the severity of infections or duration of infection-free intervals on the 3 dosages; therefore, high dosages of IVIG do not confer better protection against infections in such patients.		

Condition studies:	Common variable immunodeficiency

146	Roifman CM, Levison H, Gelfand EW. High-dose versus low-dose intravenous immunoglobulin in hypogammaglobulinaemia and chronic lung disease. Lancet 1987; 1(8541):1075-7.

Study design:	Case-series, randomised, cross-over study.	**Length of follow-up:**	
Sample size:	12	**Population:**	Ten patients with CVID, 2 with X-linked agammaglobulinaemia (4 females, 8 males).
Intervention:			
Comparison / control:	Two doses of IVIG were compared: 0.6 g/kg and 0.2 g/kg given monthly for 6 months, switched to alternative dose.		
Outcome(s) measured:	Incidence of infections, frequency of acute infections, pulmonary function.		

Quality assessment (internal validity)

Placebo:

Follow-up:

Results

Intervention groups:	Pulmonary function worsened on 0.2 g/kg dose, improved on 0.6 g/kg dose; no significant difference between doses in incidence of infection; frequency of acute infection reduced when serum IgG level was <500 mg/dl.	**Control / comparison group(s):**	

P-value:

Adverse events:	Three out of 12 had repeated reactions, controlled by hydrocortisone; other reactions were headache and pyrexia.
Conclusions / Comments:	High-dose IVIG may be more effective than low dose.

Primary immunodeficiencies

Condition summary	Hyperimmunoglobulin M Syndrome (Type 1-4) immune deficiency with normal or elevated IgM
Reference list:	
Types of study:	
Total sample size:	
Quality:	
Result:	
Adverse events:	
Conclusion:	
Category:	See: Common variable immunodeficiency; Primary hypogammaglobulinaemia

Primary immunodeficiencies

Condition summary	IgG subclass deficiencies including isolated IgG2 deficiency and isolated IgG3 deficiency
Reference list:	
Types of study:	
Total sample size:	
Quality:	
Result:	
Adverse events:	
Conclusion:	
Category:	See: Common variable immunodeficiency; Primary hypogammaglobulinaemia

Primary immunodeficiencies

Condition summary

Lymphocytic leukaemia with hypogammaglobulinaemia

Reference list:	89 Anonymous. Intravenous immunoglobulin for the prevention of infection in chronic lymphocytic leukemia. A randomized, controlled clinical trial. Cooperative Group for the Study of Immunoglobulin in Chronic Lymphocytic Leukemia. N Engl J Med 1988; 319(14):902-7. 90 Boughton BJ, Jackson N, Lim S, Smith N. Randomized trial of intravenous immunoglobulin prophylaxis for patients with chronic lymphocytic leukaemia and secondary hypogammaglobulinaemia. Clinical & Laboratory Haematology 1995; 17(1):75-80. 102 Gamm H, Huber C, Chapel H, Lee M, Ries F, Dicato MA. Intravenous immune globulin in chronic lymphocytic leukaemia. Clinical & Experimental Immunology. 97 Suppl 1:17-20, 1994 Jul. 150 Chapel H, Dicato M, Gamm H et al. Immunoglobulin replacement in patients with chronic lymphocytic leukaemia: a comparison of two dose regimes. Br J Haematol 1994; 88(1):209-12.
Types of study:	Three RCTs, 1 cross-over.
Total sample size:	204
Quality:	Low-Moderate
Result:	Decrease in incidence of bacterial infections (significant in some studies), no significant difference between doses.
Adverse events:	Minor - chills, fever, back pain.
Conclusion:	Some benefit of IVIG in reducing incidence of bacterial infections, based on 4 small studies (3 RCTs); studies comparing IVIG with prophylactic antibiotics would be useful.
Category:	IIa

Condition studies: Lymphocytic leukaemia with hypogammaglobulinaemia

89 Anonymous. Intravenous immunoglobulin for the prevention of infection in chronic lymphocytic leukemia. A randomized, controlled clinical trial. Cooperative Group for the Study of Immunoglobulin in Chronic Lymphocytic Leukemia. N Engl J Med 1988; 319(14):902-7.

Study design: Case-control, double blind, randomised.

Length of follow-up:

Sample size: 84

Population: Chronic lymphocytic leukemia with hypogammaglobulinemia and/or history of infection.

Intervention: IVIG 400 mg/kg every 3 weeks for 1 year.

Comparison / control: Placebo every 3 weeks for 1 year.

Outcome(s) measured: Number of bacterial infections.

Quality assessment (internal validity)

Placebo:

Follow-up:

Results

Intervention groups: Fewer bacterial infections for patients who completed a full year P = 0.001. Length to first infection longer P = 0.026.

Control / comparison group(s):

P-value: See above.

Adverse events: No nonbacterial infections.

Conclusions / Comments:

Condition studies:	Lymphocytic leukaemia with hypogammaglobulinaemia

90	Boughton BJ, Jackson N, Lim S, Smith N. Randomized trial of intravenous immunoglobulin prophylaxis for patients with chronic lymphocytic leukaemia and secondary hypogammaglobulinaemia. Clinical & Laboratory Haematology 1995; 17(1):75-80.

Study design:	Case-control, randomised.	**Length of follow-up:**	12 months
Sample size:	42	**Population:**	Chronic lymphocytic leukemia with hypogammaglobulinemia and history of infection.
Intervention:	IVIG 18 g every 3 weeks for 1 year. If 3 or more infections occurred IVIG dose was increased to 24 g.		
Comparison / control:	Human albumin placebo every 3 weeks. If 3 or more infections occurred IVIG treatment was given.		
Outcome(s) measured:	Number of infections.		

Quality assessment (internal validity)

Placebo:

Follow-up:

Results

Intervention groups:	Decrease in infections.	**Control / comparison group(s):**	

P-value:

Adverse events:

Conclusions / Comments:	Possible benefit of prophylactic IVIG in CLL patients with hypogammaglobulinaemia, with recurrent infections and serum IgG levels < 3 milligrams.

Condition studies: Lymphocytic leukaemia with hypogammaglobulinaemia

102 Gamm H, Huber C, Chapel H, Lee M, Ries F, Dicato MA. Intravenous immune globulin in chronic lymphocytic leukaemia. Clinical & Experimental Immunology. 97 Suppl 1:17-20, 1994 Jul.

Study design: Case-series, double blind, randomised.

Length of follow-up:

Sample size: 36

Population: Chronic lymphocytic leukemia with hypogammaglobulinemia.

Intervention: IVIG 500 or 250 mg/kg every 4 weeks.

Comparison / control: None.

Outcome(s) measured: Rate of infections.

Quality assessment (internal validity)

Placebo:

Follow-up:

Results

Intervention groups: No significant difference in infection rates.

Control / comparison group(s):

P-value:

Adverse events:

Conclusions / Comments: Possible benefit of IVIG as prophylaxis against infection in patients with CLL, effect; no significant difference between 2 doses.

Condition studies:	Lymphocytic leukaemia with hypogammaglobulinaemia

150	Chapel H, Dicato M, Gamm H et al. Immunoglobulin replacement in patients with chronic lymphocytic leukaemia: a comparison of two dose regimes. Br J Haematol 1994; 88(1):209-12.

Study design:	Case-series, double blind, randomised.	**Length of follow-up:**	1 year
Sample size:	34	**Population:**	Chronic lymphocytic leukemia with hypogammaglobulinemia.
Intervention:	IVIG 500 or 250 mg/kg every 4 weeks for 1 year.		
Comparison / control:	None.		
Outcome(s) measured:	Rate of infections.		

Quality assessment (internal validity)

Placebo:

Follow-up:

Results

Intervention groups:	No significant difference in infection rates.	**Control / comparison group(s):**	

P-value:

Adverse events:

Conclusions / Comments:	Possible benefit of IVIG as prophylaxis against infection in patients with secondary hypogammaglobulinaemia due to a low-grade lymphoproliferative disease; no significant difference between 2 doses.

Primary immunodeficiencies

Condition summary

Nephrotic syndrome

Reference list:	156 Ogi M, Yokoyama H, Tomosugi N et al. Risk factors for infection and immunoglobulin replacement therapy in adult nephrotic syndrome. Am J Kidney Dis 1994; 24(3):427-36.
Types of study:	Case series.
Total sample size:	18
Quality:	Low
Result:	Following IVIG treatment, infections decreased to a rate equal to patients with endogenous <600 mg/dL.
Adverse events:	
Conclusion:	Possible benefit of IVIG in reducing risk of infection, based on 1 small case series.
Category:	IIa

Condition studies: Nephrotic syndrome

156 Ogi M, Yokoyama H, Tomosugi N et al. Risk factors for infection and immunoglobulin replacement therapy in adult nephrotic syndrome. Am J Kidney Dis 1994; 24(3):427-36.

Study design: Case-series **Length of follow-up:**

Sample size: 18 **Population:** Adult patients with nephrotic syndrome but no diabetic nephropathy with serum IG >600 mg/dL.

Intervention: IVIG 10-15 g every 4 weeks until serum IG was <600 mg/dL.

Comparison / control:

Outcome(s) measured: Rate of bacterial infections.

Quality assessment (internal validity)

Placebo:

Follow-up:

Results

Intervention groups: Decreased infections to a rate equal to patients with endogenous <600 mg/dL.

Control / comparison group(s):

P-value:

Adverse events:

Conclusions / Comments: The effects of intravenous immunoglobulin suggest that maintenance of serum IgG levels over 600 mg/dL may reduce the risk of infection.

Primary immunodeficiencies

Condition summary	Other primary (inherited) immunodeficiency diseases with defective B cell function
Reference list:	
Types of study:	
Total sample size:	
Quality:	
Result:	
Adverse events:	
Conclusion:	
Category:	See: Common variable immunodeficiency; Primary hypogammaglobulinaemia

Primary immunodeficiencies

Condition summary	Paraneoplastic cerebellar degeneration with NO antibodies
Category:	IVb

Primary immunodeficiencies

Condition summary

Primary hypogammaglobulinaemia

Reference list:	152 Eijkhout HW, van Der Meer JW, Kallenberg CG et al. The effect of two different dosages of intravenous immunoglobulin on the incidence of recurrent infections in patients with primary hypogammaglobulinemia. A randomized, double-blind, multicenter crossover trial. Ann Intern Med 2001; 135(3):165-74. 154 Gaspar J, Gerritsen B, Jones A. Immunoglobulin replacement treatment by rapid subcutaneous infusion. Arch Dis Child 1998; 79(1):48-51.
Types of study:	Case-series, randomised, cross-over study.
Total sample size:	43
Quality:	Low
Result:	High dose IVIG significantly reduced the number (3.5 vs 2.5 per patient P=0.004) and duration (median 33 days vs 21 days P=0.015) of infections compared to standard dose IVIG.
Adverse events:	No difference in adverse events between high and standard dose IVIG.
Conclusion:	High dose IVIG more effective than standard dose IVIG in reducing number and duration of infections, based on one randomised cross-over study.
Category:	IIa

Condition studies:	Primary hypogammaglobulinaemia

152	Eijkhout HW, van Der Meer JW, Kallenberg CG et al. The effect of two different dosages of intravenous immunoglobulin on the incidence of recurrent infections in patients with primary hypogammaglobulinemia. A randomized, double-blind, multicenter crossover trial. Ann Intern Med 2001; 135(3):165-74.

Study design:	Case-series, multicenter, double-blind, randomised, cross-over study (15 outpatient clinics).	**Length of follow-up:**	
Sample size:	Sample of 43 (41 completed protocol).	**Population:**	Patients (adults and children) with primary hypogammaglobulinemia.
Intervention:	IVIG high dose (600 mg/kg in adults, 800 mg/kg in children) every 4 weeks for 9 months.		
Comparison / control:	IVIG standard dose 300 mg/kg in adults, 400 mg/kg in children) every 4 weeks for 9 months. 3 month washout period between treatments.		
Outcome(s) measured:	Total number and duration of infections, periods of fever, hospital admissions, use of antibiotics, adsence from school or work and trough levels of serum IG.		

Quality assessment (internal validity)

Placebo:

Follow-up:

Results

Intervention groups:	High dose IVIG significantly reduced the number (3.5 vs 2.5 per patient P = 0.004) and duration (median 33 days vs 21 days P = 0.015) of infections compared to standard dose IVIG.	**Control / comparison group(s):**	

P-value:

Adverse events:	Incidence and type of side effects did not differ significantly between standard and high dose IVIG groups.

Conclusions / Comments:

Condition studies:	Primary hypogammaglobulinaemia		
154	Gaspar J, Gerritsen B, Jones A. Immunoglobulin replacement treatment by rapid subcutaneous infusion. Arch Dis Child 1998; 79(1):48-51.		
Study design:	Case-series, retrospective comparative treatment in some patients.	**Length of follow-up:**	
Sample size:	26	**Population:**	Children with immunodeficiencies.
Intervention:	SCIG for median period of 2 years (range 6 months to 3.5 years).		
Comparison / control:	A group of 15 patients in SCIG group had previously been treated with IVIG.		
Outcome(s) measured:	IG concentrations, quality of life.		

Quality assessment (internal validity)

Placebo:

Follow-up:

Results

Intervention groups:	**Control / comparison group(s):**

P-value:

Adverse events: No systemic adverse reaction or severe reactions requiring hospitalisation in SCIG group.

Conclusions / Comments:

Primary immunodeficiencies

Condition summary

Severe combined immunodeficiency

Reference list:

Types of study:

Total sample size:

Quality:

Result:

Adverse events:

Conclusion:

Category: See: Common variable immunodeficiency; Primary hypogammaglobulinaemia

Primary immunodeficiencies

Condition summary	Specific antibody deficiency (with deficiency of IgG subclasses and/or IgA)
Reference list:	
Types of study:	
Total sample size:	
Quality:	
Result:	
Adverse events:	
Conclusion:	
Category:	See: Common variable immunodeficiency; Primary hypogammaglobulinaemia

Primary immunodeficiencies

Condition summary

Specific antibody deficiency (with normal IgG subclasses and IgA)

Reference list:	10 Chapel HM, Spickett GP, Ericson D, Engl W, Eibl MM, Bjorkander J. The comparison of the efficacy and safety of intravenous versus subcutaneous immunoglobulin replacement therapy. J Clin Immunol 2000; 20(2):94-100. 10 Chapel HM, Spickett GP, Ericson D, Engl W, Eibl MM, Bjorkander J. The comparison of the efficacy and safety of intravenous versus subcutaneous immunoglobulin replacement therapy. J Clin Immunol 2000; 20(2):94-100.
Types of study:	1 case series
Total sample size:	40
Quality:	Low
Result:	No significant effect.
Adverse events:	Not significantly different between groups.
Conclusion:	Appears to be no significant effect, based on one small case series study.
Category:	See: Common variable immunodeficiency; Primary hypogammaglobulinaemia

Condition studies:	Specific antibody deficiency (with normal IgG subclasses and IgA)

10	Chapel HM, Spickett GP, Ericson D, Engl W, Eibl MM, Bjorkander J. The comparison of the efficacy and safety of intravenous versus subcutaneous immunoglobulin replacement therapy. J Clin Immunol 2000; 20(2):94-100.

Study design:	Case-series, multicentre, randomised, cross over.	**Length of follow-up:**	1 year
Sample size:	40	**Population:**	Primary antibody deficiency syndrome (common variable immunodeficiency or IgG subclass deficiency or specific antibody deficiency) who required IG therapy.
Intervention:	IVIG for 1 year.		
Comparison / control:	Subcutaneous IG for 1 year.		
Outcome(s) measured:	Primary end point: number of infections and their severity during the 2 treatment periods. Secondary end point: adverse reactions, length of infections, days lost from school or work due to infections, acceptability of treatment regimens.		

Quality assessment (internal validity)

Placebo:

Follow-up:

Results

Intervention groups:	No significant differences in efficacy between treatments.	**Control / comparison group(s):**	
P-value:			
Adverse events:	No significant differences in adverse events between treatments.		
Conclusions / Comments:	No significant effect of IVIG.		

Condition studies:	Specific antibody deficiency (with normal IgG subclasses and IgA)

10	Chapel HM, Spickett GP, Ericson D, Engl W, Eibl MM, Bjorkander J. The comparison of the efficacy and safety of intravenous versus subcutaneous immunoglobulin replacement therapy. J Clin Immunol 2000; 20(2):94-100.

Study design:	Case-series, multicentre, randomised, cross over.	**Length of follow-up:**	1 year
Sample size:	40	**Population:**	Primary antibody deficiency syndrome (common variable immunodeficiency or IgG subclass deficiency or specific antibody deficiency) who required IG therapy.
Intervention:	IVIG for 1 year.		
Comparison / control:	Subcutaneous IG for 1 year.		
Outcome(s) measured:	Primary end point: number of infections and their severity during the 2 treatment periods. Secondary end point: adverse reactions, length of infections, days lost from school or work due to infections, acceptability of treatment regimens.		

Quality assessment (internal validity)

Placebo:

Follow-up:

Results

Intervention groups:	No significant differences in efficacy between treatments.	**Control / comparison group(s):**	
P-value:			
Adverse events:	No significant differences in adverse events between treatments.		
Conclusions / Comments:			

Primary immunodeficiencies

Condition summary

Transient hypogammaglobulinemia of infancy

Reference list:

Types of study:

Total sample size:

Quality:

Result:

Adverse events:

Conclusion:

Category: See: Primary hypogammaglobulinaemia

Primary immunodeficiencies

Condition summary	X-linked hypogammaglobulinaemia
Reference list:	
Types of study:	
Total sample size:	
Quality:	
Result:	
Adverse events:	
Conclusion:	
Category:	See: Primary hypogammaglobulinaemia

Skin diseases

Condition summary	Autoimmune blistering diseases: atopic dermatitis
Reference list:	36 Paul C, Lahfa M, Bachelez H, Chevret S, Dubertret L. A randomized controlled evaluator-blinded trial of intravenous immunoglobulin in adults with severe atopic dermatitis. Br J Dermatol 2002; 147(3):518-22.
Types of study:	One RCT.
Total sample size:	10
Quality:	Low
Result:	No significant improvement in clinical condition with IVIG.
Adverse events:	One in ten urticaria and mild dyspnoea, persisted after reduction in infusion speed. IVIG discontinued.
Conclusion:	Appears to be no significant effect, based on one small RCT.
Category:	IIb

Condition studies:	Autoimmune blistering diseases: atopic dermatitis

36	Paul C, Lahfa M, Bachelez H, Chevret S, Dubertret L. A randomized controlled evaluator-blinded trial of intravenous immunoglobulin in adults with severe atopic dermatitis. Br J Dermatol 2002; 147(3):518-22.

Study design:	RCT - evaluator blinded.	**Length of follow-up:**	90 days
Sample size:	10	**Population:**	Adults with severe atopic dermatitis (AD).
Intervention:	IVIG 2g/kg (1g/kg, 8 hr infusion, 2 consecutive days).		
Comparison / control:	Delay by 1 month.		
Outcome(s) measured:	AD severity score at day 30.		

Quality assessment (internal validity)

Placebo:	No
Follow-up:	Assessed at 15, 30, 60 and 90 days.

Results

Intervention groups:	15% decrease in SCORAD at 30 days and 22% (95% CI, 5-39%) at 60 days post IVIG compared to baseline.	**Control / comparison group(s):**	No difference between groups at 30 days.
P-value:			
Adverse events:	One out 10 urticaria and mild dyspnoea, persisted after reduction in infusion speed. IVIG discontinued.		
Conclusions / Comments:	No clinically significant improvement.		

Skin diseases

Condition summary	Autoimmune blistering diseases: bullous pemphigoid
Reference list:	
Types of study:	
Total sample size:	
Quality:	
Result:	
Adverse events:	
Conclusion:	
Category:	See: Autoimmune blistering diseases: cicatricial pemphigoid, pemphigoid – oral, pemphigus vulgaris and foliaceus

Skin diseases

Condition summary	Autoimmune blistering diseases: cicatricial pemphigoid
Reference list:	45 Sami N, Bhol KC, Razzaque Ahmed A. Intravenous immunoglobulin therapy in patients with multiple mucosal involvement in mucous membrane pemphigoid. Clin Immunol 2002; 102(1):59-67.
Types of study:	One systematic review; 1 case-series.
Total sample size:	15 (case series)
Quality:	Low
Result:	Reduction in side effects, recurrences and relapses, duration and dose of prednisone; improved quality of life. Able to discontinue other systemic therapies, prolonged clinical remission.
Adverse events:	No serious side effects seen.
Conclusion:	Cochrane review found only 1 IVIG trial, uncontrolled, n=2 (therefore excluded); possible benefit, based on one small case-series study.
Category:	IIa

Condition studies: Autoimmune blistering diseases: cicatricial pemphigoid

45 Sami N, Bhol KC, Razzaque Ahmed A. Intravenous immunoglobulin therapy in patients with multiple mucosal involvement in mucous membrane pemphigoid. Clin Immunol 2002; 102(1):59-67.

Study design: Case-series.

Length of follow-up:

Sample size: 15

Population: Patients with sever mucous membrane pemphigoid (MMP) non-responsive to systemic corticosteroids and immunosuppressive agents, multiple side-effects.

Intervention: IVIG 1-2g/kg.

Comparison / control:

Outcome(s) measured: Side effects, recurrences and relapses, duration and dose of prednisone, quality of life.

Quality assessment (internal validity)

Placebo: No

Follow-up:

Results

Intervention groups: Reduction in side effects, recurrences and relapses, duration and dose of prednisone; improved quality of life. Able to discontinue other systemic therapies, prolonged clinical remission.

Control / comparison group(s):

P-value:

Adverse events: No serious side effects seen.

Conclusions / Comments: Small numbers and not RCT.

Skin diseases

Condition summary	Autoimmune blistering diseases: epidermolysis bullosa acquisita
Reference list:	
Types of study:	1 systematic review
Total sample size:	2
Quality:	
Result:	
Adverse events:	
Conclusion:	Cochrane review found only 1 IVIG trial, uncontrolled, n=2 (therefore excluded).
Category:	IVa

Skin diseases

Condition summary	Autoimmune blistering diseases: linear IgA disease
Category:	IVb

Skin diseases

Condition summary	Autoimmune blistering diseases: pemphigoid - oral
Reference list:	43 Sami N, Bhol KC, Ahmed AR. Treatment of oral pemphigoid with intravenous immunoglobulin as monotherapy. Long-term follow-up: influence of treatment on antibody titres to human alpha6 integrin.[comment]. Clinical & Experimental Immunology 2002; 129(3):533-40.
Types of study:	Case-control
Total sample size:	14
Quality:	Low
Result:	Prolonged and sustained clinical remission in 7/7 on IVIG, after mean period of 26.9 months; statistically significant difference in quality of life pre and post IVIG; faster rate of antibody decline in IVIG group.
Adverse events:	
Conclusion:	Possible benefit of IVIG, based on one small case-control study.
Category:	IIa

Condition studies:	Autoimmune blistering diseases: pemphigoid - oral

43	Sami N, Bhol KC, Ahmed AR. Treatment of oral pemphigoid with intravenous immunoglobulin as monotherapy. Long-term follow-up: influence of treatment on antibody titres to human alpha6 integrin.[comment]. Clinical & Experimental Immunology 2002; 129(3):533-40.

Study design:	Case-control.	**Length of follow-up:**	Mean of 26.9 months
Sample size:	14	**Population:**	Patients with severe OP, in whom systemic conventional treatment was contraindicated.
Intervention:	IVIG		
Comparison / control:	Conventional therapy.		
Outcome(s) measured:	Quality of life, antibodies to human alpha 6 integrin.		

Quality assessment (internal validity)

Placebo:	No
Follow-up:	

Results

Intervention groups:	Prolonged and sustained clinical remission in 7/7 on IVIG, after mean period of 26.9 months; statistically significant difference in quality of life pre and post IVIG; faster rate of antibody decline in IVIG group.	**Control / comparison group(s):**	
P-value:	?P = 0.01 (quality of life); P = 0.03 (decline in antibody levels at 6 months).		
Adverse events:			
Conclusions / Comments:	Reduction in antialpha 6 integrin antibody titres; sustained, clinical and serological remission.		

Skin diseases

Condition summary	Autoimmune blistering diseases: pemphigoid gestationes
Reference list:	
Types of study:	
Total sample size:	
Quality:	
Result:	
Adverse events:	
Conclusion:	
Category:	See: Autoimmune blistering diseases: cicatricial pemphigoid, pemphigoid – oral, pemphigus vulgaris and foliaceus

Skin diseases

Condition summary	Autoimmune blistering diseases: pemphigus vulgaris and foliaceus
Reference list:	46 Sami N, Qureshi A, Ruocco E, Ahmed AR. Corticosteroid-sparing effect of intravenous immunoglobulin therapy in patients with pemphigus vulgaris. Arch Dermatol 2002; 138(9):1158-62.
Types of study:	Case-series, retrospective analysis.
Total sample size:	15
Quality:	Low
Result:	Intravenous immunoglobulin therapy appears to have corticosteroid-sparing effect.
Adverse events:	None reported.
Conclusion:	Possible benefit based on one small uncontrolled study.
Category:	IIa

Condition studies:	Autoimmune blistering diseases: pemphigus vulgaris and foliaceus

46	Sami N, Qureshi A, Ruocco E, Ahmed AR. Corticosteroid-sparing effect of intravenous immunoglobulin therapy in patients with pemphigus vulgaris. Arch Dermatol 2002; 138(9):1158-62.

Study design:	Case-series, retrospective analysis.	**Length of follow-up:**	6.2 years
Sample size:	15	**Population:**	Patients with moderate to severe PV, corticosteroid dependent.
Intervention:	IVIG 1-2g/kg.		
Comparison / control:			
Outcome(s) measured:	Dose of prednisone, Duration of prednisone therapy, Number of relapses.		

Quality assessment (internal validity)

Placebo:	No
Follow-up:	

Results

Intervention groups:	Decrease in total dose of prednisone.	**Control / comparison group(s):**	
P-value:	Reduction in dose of prednisone (0.004), duration of prednisone (0.003) and number of relapses (<0.001).		
Adverse events:			
Conclusions / Comments:	Intravenous immunoglobulin therapy appears to have corticosteroid-sparing effect, but numbers small and study uncontrolled.		

Skin diseases

Condition summary	Stevens Johnson syndrome
Reference list:	4 Bachot N, Revuz J, Roujeau JC. Intravenous immunoglobulin treatment for Stevens-Johnson syndrome and toxic epidermal necrolysis: a prospective noncomparative study showing no benefit on mortality or progression.[see comment]. Arch Dermatol 2003; 139(1):33-6. 9 Campione E, Marulli GC, Carrozzo AM, Chimenti MS, Costanzo A, Bianchi L. High-dose intravenous immunoglobulin for severe drug reactions: efficacy in toxic epidermal necrolysis. Acta Derm Venereol 2003; 83(6):430-2. 39 Prins C, Vittorio C, Padilla RS et al. Effect of high-dose intravenous immunoglobulin therapy in Stevens-Johnson syndrome: a retrospective, multicenter study. Dermatology 2003; 207(1):96-9.
Types of study:	One cohort, 2 case-series.
Total sample size:	36
Quality:	Low
Result:	2 case-series showed apparent benefit, cohort no benefit.
Adverse events:	None reported.
Conclusion:	Possible benefit or possible lack of significant effect, based on three small, uncontrolled studies.
Category:	IIc

Condition studies:	Stevens Johnson syndrome

4	Bachot N, Revuz J, Roujeau JC. Intravenous immunoglobulin treatment for Stevens-Johnson syndrome and toxic epidermal necrolysis: a prospective noncomparative study showing no benefit on mortality or progression.[see comment]. Arch Dermatol 2003; 139(1):33-6.

Study design:	Cohort.	**Length of follow-up:**	
Sample size:	A total of 34 patients admitted for; (n=9 Stevens-Johnson syndrome (SJS); n=20 toxic epidermal necrolysis (TEN); n=5 SJS-TEN).	**Population:**	
Intervention:	A dose of 2 g/kg of IVIG adminisered within 2 days of admission.		
Comparison / control:	Comparisons between conditions.		
Outcome(s) measured:	Detached plus detachable proportions of the total body surface area measured before and after treatment and predicted death rate estimated on admission with a validated prognostic score.		

Quality assessment (internal validity)

Placebo:	No
Follow-up:	

Results

Intervention groups:	Epidermal detachment involved a mean +/- SD 19% +/- 16% of the total body surface area on admission and 32% +/- 26% after IVIG treatment (progression in 22 of 34 cases, including most patients referred early).	**Control / comparison group(s):**	See intervention.
P-value:			
Adverse events:	No adverse events were reported.		
Conclusions / Comments:	No measurable effect was observed on the progression of detachment or on the speed of reepidermalization. These results do not support the routine use of IVIG treatment for patients with SJS or TEN, especially in cases of impaired renal function.		

Condition studies:	Stevens Johnson syndrome

9	Campione E, Marulli GC, Carrozzo AM, Chimenti MS, Costanzo A, Bianchi L. High-dose intravenous immunoglobulin for severe drug reactions: efficacy in toxic epidermal necrolysis. Acta Derm Venereol 2003; 83(6):430-2.

Study design:	Case-series.	**Length of follow-up:**	5 days
Sample size:	A total of 10 patients affected by toxic epidermal necrolysis.	**Population:**	
Intervention:	A dose of 400 mg/kg per day of intravenous immunoglobulin on 5 consecutive days.		
Comparison / control:	None.		
Outcome(s) measured:	Predicted mortality.		

Quality assessment (internal validity)

Placebo:	No
Follow-up:	

Results

Intervention groups:	A mortality rate of 10% and a survival rate of 90% were reached; nine patients improved dramatically after only one infusion at an early stage of the disease.	**Control / comparison group(s):**	N/A
P-value:			
Adverse events:	No adverse events were reported.		
Conclusions / Comments:	Apparent benefit, but small numbers, not RCT.		

Condition studies:	Stevens Johnson syndrome

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

Study design:	Case-series.	**Length of follow-up:**	45 days post onset
Sample size:	Sample of 12 patients with SJS.	**Population:**	
Intervention:	IVIG at a mean dose of 0.6g/kg/day for an average of 4 days.		
Comparison / control:	None.		
Outcome(s) measured:	Tolerance, survival at 45 days after onset and total healing time were assessed.		

Quality assessment (internal validity)

Placebo:	No
Follow-up:	All patients were followed up.

Results

Intervention groups:	Overall survival rate was 100%; Total skin healing occurred, on average, within 8.3 days; Time to total healing was shorter in a group of patients with fewer severe underlying diseases who had received IVIG infusion rapidly after the onset of skin lesions.	**Control / comparison group(s):**	N/A
P-value:	Other		
Adverse events:	No adverse events were reported.		
Conclusions / Comments:	High-dose IVIG may be effective in blocking the progression of SJS and reducing the time to complete skin healing, but small numbers and not RCT.		

Skin diseases

Condition summary	Toxic epidermal necrolysis
Reference list:	272 Bachot N, Revuz J, Roujeau JC. Intravenous immunoglobulin treatment for Stevens-Johnson syndrome and toxic epidermal necrolysis: a prospective noncomparative study showing no benefit on mortality or progression.[see comment]. Arch Dermatol 2003; 139(1):33-6.
Types of study:	One systematic review, 1 cohort study.
Total sample size:	20
Quality:	Low
Result:	No measurable effect seen, either on the progression of detachment or on the speed of re-epithelisation.
Adverse events:	Study suggests that the death rate among TEN patients treated with IVIG is even higher than expected from earlier epidemiological studies.
Conclusion:	Appears to be no signficant effect, based on one uncontrolled study.
Category:	IIb

Condition studies: Toxic epidermal necrolysis

272 Bachot N, Revuz J, Roujeau JC. Intravenous immunoglobulin treatment for Stevens-Johnson syndrome and toxic epidermal necrolysis: a prospective noncomparative study showing no benefit on mortality or progression.[see comment]. Arch Dermatol 2003; 139(1):33-6.

Study design: Cohort.

Length of follow-up:

Sample size: A total of 34 patients admitted for; (n = 9 Stevens-Johnson syndrome (SJS); n = 20 toxic epidermal necrolysis (TEN); n = 5 SJS-TEN).

Population:

Intervention: A dose of 2 g/kg of IVIG adminisered within 2 days of admission.

Comparison / control: Comparisons between conditions.

Outcome(s) measured: Detached plus detachable proportions of the total body surface area measured before and after treatment and predicted death rate estimated on admission with a validated prognostic score.

Quality assessment (internal validity)

Placebo: No

Follow-up:

Results

Intervention groups: Epidermal detachment involved a mean +/- SD 19% +/- 16% of the total body surface area on admission and 32% +/- 26% after IVIG treatment (progression in 22 of 34 cases, including most patients referred early).

Control / comparison group(s): See intervention.

P-value:

Adverse events: Death rate higher than expected.

Conclusions / Comments: Small numbers and not RCT.

Vasculitis/inflammatory

Condition summary	ANCA-positive vasculitis (including Wegener's)
Reference list:	18 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. 19 Jayne DR, Davies MJ, Fox CJ, Black CM, Lockwood CM. Treatment of systemic vasculitis with pooled intravenous immunoglobulin. Lancet 1991; 337(8750):1137-9.
Types of study:	One RCT, 1 case-series.
Total sample size:	A sample of 34 in RCT.
Quality:	Low
Result:	Fourteen out of 17 responders. Larger reduction of C-reactive protein levels at 2 weeks (P=0.02) and 1 month (P=0.04). No differences in C-reactive protein or disease activity after 3 months between groups; OR 8.56; 95% CI 1.74-42.2.
Adverse events:	There were 17 adverse events in 12 patients from the IVIG group (mostly mild); 4 reversible rises in serum creatinine; 6 adverse events in 4 from placebo group.
Conclusion:	Possible benefit in treatment of AASV if disease activity persists after standard therapy, based on one small RCT.
Category:	IIa

Condition studies:	ANCA-positive vasculitis (including Wegener's)

18	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.

Study design:	Randomised, placebo-controlled.	**Length of follow-up:**	12 months
Sample size:	34	**Population:**	Previously treated anti-neutrophil cytoplasmm antibody associated systemic vasculitis with persistent disease activity.
Intervention:	IVIG 2 g/kg single dose.		
Comparison / control:	Placebo.		
Outcome(s) measured:	Vasculitic activity monitored by Birmingham vasculitis activity score (BVAS), C-reactive protein, anti-neutrophil cytoplasm antibody levels. Treatment response defined as reduction in BVAS of >50% after 3 months.		

Quality assessment (internal validity)

Placebo:	Yes
Follow-up:	

Results

Intervention groups:	Fourteen out of 17 responders. Larger reduction of C-reactive protein levels at 2 weeks (P = 0.02) and 1 month (P = 0.04). No differences in C-reactive protein or disease activity after 3 months between groups.	**Control / comparison group(s):**	Six out of 17 responders.
P-value:	IVIG more effective P = 0.015.		
Adverse events:	Seventeen adverse events in 12 patients from IVIG group (mostly mild; 4 reversible rises in serum creatinine; 6 adverse events in 4 from placebo group.		
Conclusions / Comments:	IVIG is a possible treatment for AASV if disease activity persists after standard therapy.		

Condition studies: ANCA-positive vasculitis (including Wegener's)

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

Study design: Case-series. **Length of follow-up:**

Sample size: 7 **Population:** Patients with systemic vasculitis.

Intervention: IVIG

Comparison / control:

Outcome(s) measured: Disease activity, circulating anti-neutrophil cytoplasm antibodies.

Quality assessment (internal validity)

Placebo:

Follow-up:

Results

Intervention groups: Seven out of 7 showed clinical improvement, sustained in 6/7, transient in 1/7. Anti-neutrophil cytoplasm antibody and C-reactive protein levels dropped.

Control / comparison group(s):

P-value:

Adverse events:

Conclusions / Comments: Small numbers and not RCT.

Vasculitis/inflammatory

Condition summary	Churg-Strauss vasculitis
Category:	IVb

Vasculitis/inflammatory

Condition summary	Henoch-Schonlein pupura
Category:	IVb

Vasculitis/inflammatory

Condition summary	Inflamatory bowel disease: Crohn's disease
Category:	IVb

Vasculitis/inflammatory

Condition summary	Inflamatory bowel disease: ulcerative colitis
Category:	IVb

Vasculitis/inflammatory

Condition summary	Kawasaki's disease
Reference list:	136 Oates-Whitehead, R. M.; Baumer, J. H.; Haines, L.; Love, S.; Maconochie, I. K.; Gupta, A.; Roman, K.; Dua, J. S., and Flynn, I. Intravenous immunoglobulin for the treatment of Kawasaki disease in children. Oates-Whitehead RM, Baumer JH, Haines L, Love S, Maconochie IK, Gupta A, Roman K, Dua JS, Flynn I. Intravenous Immunoglobulin for the Treatment of Kawasaki Disease in Children (Cochrane Review). In: The Cochrane Library, Issue 2, 2004. Chichester, UK: John Wiley & Sons, Ltd.
Types of study:	One systemic review.
Total sample size:	16 RCT
Quality:	High
Result:	Significant decrease in new coronary artey abnormalities after IVIG treatment compared to placebo, at 30 days (RR=0.74, 95% CI (0.61 to 0.90). No significant difference after that. This effect was dose-dependent. No difference between different IVIG preparations.
Adverse events:	No difference in adverse events between intervention and control groups.
Conclusion:	IVIG (single dose, 2g/kg, within 10 days of onset of symptoms) recommended for children fulfilling criteria for Kawasaki disease. Further research needed for treatment of children with atypical and late presentation.
Category:	I

Condition studies:	Kawasaki's disease

136	Oates-Whitehead, R. M.; Baumer, J. H.; Haines, L.; Love, S.; Maconochie, I. K.; Gupta, A.; Roman, K.; Dua, J. S., and Flynn, I. Intravenous immunoglobulin for the treatment of Kawasaki disease in children. Oates-Whitehead RM, Baumer JH, Haines L, Love S, Maconochie IK, Gupta A, Roman K, Dua JS, Flynn I. Intravenous Immunoglobulin for the Treatment of Kawasaki Disease in Children (Cochrane Review). In: The Cochrane Library, Issue 2, 2004. Chichester, UK: John Wiley & Sons, Ltd.
Study design:	Reviewed 16 RCTs.
Length of follow-up:	
Sample size:	
Population:	Children with Kawasaki disease.
Intervention:	IVIG
Comparison / control:	Placebo or no treatment (aspirin).
Outcome(s) measured:	Death, coronary dilation and coronary artery aneurysms, myocardial function abnormalities, duration of fever, adverse effects, duration of hospital stay, longterm cardiac sequelae.

Quality assessment (internal validity)

Placebo:

Follow-up:

Results

Intervention groups:	Significant decrease in new coronary artey abnormalities after IVIG treatment compared to placebo, at 30 days (RR = 0.74, 95% CI (0.61 to 0.90). No significant difference after that. This effect was dose-dependent. No difference between different IVIG preparations.	**Control / comparison group(s):**	

P-value:

Adverse events:	No difference in adverse events between IVIG and placebo.
Conclusions / Comments:	No efficacy data for IVIG.

Vasculitis/inflammatory

Condition summary	Rheumatoid arthritis: adult
Reference list:	31 Muscat C, Bertotto A, Ercolani R et al. Long term treatment of rheumatoid arthritis with high doses of intravenous immunoglobulins: effects on disease activity and serum cytokines. Ann Rheum Dis 1995; 54(5):382-5. 47 Sany J, Clot J, Combe B et al. [Treatment of rheumatoid arthritis. Comparative study of the effect of immunoglobulins G eluted from the placenta and of venoglobulins]. [French]. Presse Med 1987; 16(15):723-4. 5 Bagge E, Geijer M, Tarkowski A. Intra-articular administration of polyclonal immunoglobulin G in rheumatoid arthritis. A double-blind, placebo-controlled pilot study. Scand J Rheumatol 1996; 25(3):174-6. 21 Kanik KS, Yarboro CH, Naparstek Y, Plotz PH, Wilder RL. Failure of low-dose intravenous immunoglobulin therapy to suppress disease activity in patients with treatment-refractory rheumatoid arthritis. Arthritis & Rheumatism 1996; 39(6):1027-9. 26 Maksymowych WP, Avina-Zubieta A, Luong M, Russell AS. High dose intravenous immunoglobulin (IVIg) in severe refractory rheumatoid arthritis: no evidence for efficacy. Clinical & Experimental Rheumatology 1996; 14(6):657-60.
Types of study:	One RCT, 2 uncontrolled.
Total sample size:	34
Quality:	Low
Result:	RCT terminated early, but suggests no significant therapeutic effect of IVIG in patients with treatment refractory RA; in uncontrolled studies, 1 found no significant effect and possible TNF alpha generation, 1 found improvement in symptoms and decrease in inflammatory cytokines.
Adverse events:	None reported - RCT terminated early due to reported contamination of IVIG with hepatitis C, no evidence of hepatitis C infection.
Conclusion:	No significant effect, based on 1 small, unfinished RCT and 1 small uncontrolled study; possible benefit, based on 1 small, uncontrolled study.
Category:	IIc

Condition studies: Rheumatoid arthritis: adult

31 Muscat C, Bertotto A, Ercolani R et al. Long term treatment of rheumatoid arthritis with high doses of intravenous immunoglobulins: effects on disease activity and serum cytokines. Ann Rheum Dis 1995; 54(5):382-5.

Study design:	Case-series.	**Length of follow-up:**	Clinical evaluation and lab analyses once per month
Sample size:	A sample of 10 patients.	**Population:**	Ten patients with active RA and prior unsuccessful treatment with at least one slow-acting anti-RA drug.

Intervention: A dose of 400mg/kg IVIG for 3days, then once a month for 12 months.

Comparison / control: None.

Outcome(s) measured: Serum TNF-alpha, solube IL-2 receptor, IL1-alpha, IL-1 beta, IL-6 and IFN gamma.

Quality assessment (internal validity)

Placebo: Yes

Follow-up:

Results

Intervention groups:	No effect on lab parameters (?), significant clinical improvement after 6 months, rapid, presistent decrease in TNF-alpha and sIL-2R.	**Control / comparison group(s):**	

P-value:

Adverse events:

Conclusions / Comments: Small numbers, not RCT.

Condition studies:	Rheumatoid arthritis: adult

47	Sany J, Clot J, Combe B et al. [Treatment of rheumatoid arthritis. Comparative study of the effect of immunoglobulins G eluted from the placenta and of venoglobulins]. [French]. Presse Med 1987; 16(15):723-4.

Study design:	RCT	**Length of follow-up:**	
Sample size:	A sample of 113 patients.	**Population:**	Hospitalised patients with RA (severe - 92 cases, definite - 21 cases), mean duration of disease 10 years.
Intervention:	Venoglobulins (IVIG).		
Comparison / control:	Placenta-eluted IgG .		
Outcome(s) measured:	Quantitative indices of RA, biological parameters.		

Quality assessment (internal validity)

Placebo:	No
Follow-up:	8 days?

Results

Intervention groups:	Decrease in all quantitative indices except for grip strength by day 8.	**Control / comparison group(s):**	More effective for swollen joints, Ritchie's index and some extra-articular manifestations.
P-value:	Statistically significant decrease of all quantitative indices except for grip strength, with IVIG and placenta-eluted IgG, on the 8th day of treatment.		
Adverse events:	Some cases of benign venulitis.		
Conclusions / Comments:	Possible benefit of IVIG in rheumatoid arthritis, placebo controlled studies needed.		

Condition studies: Rheumatoid arthritis: adult

5 Bagge E, Geijer M, Tarkowski A. Intra-articular administration of polyclonal immunoglobulin G in rheumatoid arthritis. A double-blind, placebo-controlled pilot study. Scand J Rheumatol 1996; 25(3):174-6.

Study design: RCT - double blind.

Length of follow-up:

Sample size: Six in study group, 5 in control.

Population: Patients with RA, with flare-up of knee joint synovitis.

Intervention: Intra-articular IgG (1g in 10ml saline) in knee joint.

Comparison / control: Saline only.

Outcome(s) measured: Clinical evaluation, magnetic resonance imaging.

Quality assessment (internal validity)

Placebo: Yes

Follow-up:

Results

Intervention groups: One out of 6 patients - modest decrease of synovial hypertrophy.

Control / comparison group(s): One out of 5 patients - modest decrease of synovial hypertrophy.

P-value:

Adverse events:

Conclusions / Comments: Delete - intra-articular not intravenous.

Condition studies:	Rheumatoid arthritis: adult

21	Kanik KS, Yarboro CH, Naparstek Y, Plotz PH, Wilder RL. Failure of low-dose intravenous immunoglobulin therapy to suppress disease activity in patients with treatment-refractory rheumatoid arthritis. Arthritis & Rheumatism 1996; 39(6):1027-9.

Study design:	RCT (pilot scale).	**Length of follow-up:**	18 weeks
Sample size:	A sample of 20 patients, 10 in each arm.	**Population:**	Patients with treatment-refractory RA.
Intervention:	IVIG (5mg/kg), 6 courses, once every 3 weeks.		
Comparison / control:	Albumin (5mg/kg).		
Outcome(s) measured:			

Quality assessment (internal validity)

Placebo:	Yes
Follow-up:	Five patients dropped out before 18-week follow up.

Results

Intervention groups:	No sign diff in global activity indices, joint swelling, pain or tenderness, erythrocyte sedimentation rate, C-reactive protein level, or rheumatoid factor.	**Control / comparison group(s):**	
P-value:			
Adverse events:	Trial terminated early because of reported contamination by hepatitis C, no evidence of hep C infection.		
Conclusions / Comments:	Small numbers, terminated early, check on evidence for hepatitis C contamination.		

Condition studies:	Rheumatoid arthritis: adult

26	Maksymowych WP, Avina-Zubieta A, Luong M, Russell AS. High dose intravenous immunoglobulin (IVIg) in severe refractory rheumatoid arthritis: no evidence for efficacy. Clinical & Experimental Rheumatology 1996; 14(6):657-60.

Study design:	Case-series.	**Length of follow-up:**	Up to 4 months after initiation of therapy
Sample size:	Four adults.	**Population:**	Four patients (3 male, 1 female) average age 58.25 (range 41-69) with sever refractory RA who failed at least 4 second-line drugs.
Intervention:	IVIG at 1g/day for days, once a month for 3 months.		
Comparison / control:	None.		
Outcome(s) measured:	Responders/non-responders according to Paulus criteria.		

Quality assessment (internal validity)

Placebo:	No
Follow-up:	4

Results

Intervention groups:	No patients worsened or improved by Paulus criteria.	**Control / comparison group(s):**	
P-value:			
Adverse events:	Increased TNF alpha production in LPS stimulated whole blood assays in 3/4 patients during treatment.		
Conclusions / Comments:	Small numbers and not RCT.		

Vasculitis/inflammatory

Condition summary	Rheumatoid arthritis: juvenile
Reference list:	49 Silverman ED, Cawkell GD, Lovell DJ et al. Intravenous immunoglobulin in the treatment of systemic juvenile rheumatoid arthritis: A randomized placebo controlled trial. J Rheumatol 1994; 21(12):2353-8. 17 Giannini EH, Lovell DJ, Silverman ED, Sundel RP, Tague BL, Ruperto N. Intravenous immunoglobulin in the treatment of polyarticular juvenile rheumatoid arthritis: a phase I/II study. Pediatric Rheumatology Collaborative Study Group.[comment]. J Rheumatol 1996; 23(5):919-24.
Types of study:	One RCT.
Total sample size:	25
Quality:	Low
Result:	About 75% of patients with poly-JRA showed clinical improvement with IVIG, but beneficial effect quickly lost when IVIG discontinued. IVIG may be more effective in those with JRA for less than 5 years. Effect sizes moderate to large, compared to placebo (number of active jointes, overall articular severity score, physician global assessment).
Adverse events:	None reported.
Conclusion:	Possible benefit, based on 1 small RCT.
Category:	IIa

Condition studies: Rheumatoid arthritis: juvenile

49 Silverman ED, Cawkell GD, Lovell DJ et al. Intravenous immunoglobulin in the treatment of systemic juvenile rheumatoid arthritis: A randomized placebo controlled trial. J Rheumatol 1994; 21(12):2353-8.

Study design: RCT **Length of follow-up:**

Sample size: 31 **Population:** Children with systemic JRA, not controlled adequately by standard therapy.

Intervention: IVIG (1.5g/kg)

Comparison / control: Placebo (0.1% albumin)

Outcome(s) measured: Rheuatologic and lab parameters, articular disease activity and extra-articular features.

Quality assessment (internal validity)

Placebo: Yes

Follow-up: Seven discontinued in each group (12 due to insufficient therapeutic effect, 1 logistical, 1 noninfection related hepatitis).

Results

Intervention groups: 50% of patients improved as assessed by physician's global assessment; less fever and other systemic manifestations, no significant changes in other factors (joint count, blood analyses).

Control / comparison group(s): 27% of patients improved as assessed by physician's global assessment.

P-value: NS

Adverse events: Ten events, in 4 patients (chills, fever, emesis or headache).

Conclusions / Comments: IVIG is not highly effective for patients with systemic JRA.

Condition studies:	Rheumatoid arthritis: juvenile

17	Giannini EH, Lovell DJ, Silverman ED, Sundel RP, Tague BL, Ruperto N. Intravenous immunoglobulin in the treatment of polyarticular juvenile rheumatoid arthritis: a phase I/II study. Pediatric Rheumatology Collaborative Study Group.[comment]. J Rheumatol 1996; 23(5):919-24.

Study design:	RCT (blinded withdrawal).	**Length of follow-up:**	6 months of treatment
Sample size:	25	**Population:**	A sample of 25 children with polyarticular juvenile RA.

Intervention:	All patients - IVIG at 1.5-2.0g/kg bimonthly for 2 months (open phase - OP), from month 3, those showing 'clinically important improvement' randomised to IVIG or placebo for 4 months (double blind - DB).
Comparison / control:	Placebo from months 3-6.
Outcome(s) measured:	Clinical improvement.

Quality assessment (internal validity)

Placebo:	Yes
Follow-up:	25 in initial group, 6 not included in DB (3 did not meet improvement criteria, 3 dropped out during OP).

Results

Intervention groups:		**Control / comparison group(s):**	Improvement due to IVIG in first 2 months rapidly lost on placebo; only 4/9 able to complete double-blind study without moving to IVIG or dropping out.
P-value:			

Adverse events:	None seen.
Conclusions / Comments:	About 75% of patients with poly-JRA showed clinical improvement with IVIG, but beneficial effect quickly lost when IVIG discontinued. IVIG may be more effective in those with JRA for less than 5 years.

Vasculitis/inflammatory

Condition summary

Sepsis: adult sepsis

Reference list:

1 Alejandria MM, Lansang MA, Dans LF, Mantaring JB. Intravenous immunoglobulin for treating sepsis and septic shock.[update of Cochrane Database Syst Rev. 2001;(2):CD001090; PMID: 11405973]. [Review] [87 refs]. Cochrane Database of Systematic Reviews 2002; (1):CD001090.

8 Cafiero F, Gipponi M, Bonalumi U, Piccardo A, Sguotti C, Corbetta G. Prophylaxis of infection with intravenous immunoglobulins plus antibiotic for patients at risk for sepsis undergoing surgery for colorectal cancer: results of a randomized, multicenter clinical trial. Surgery 1992; 112(1):24-31.

15 Friedrich I, Silber RE, Baumann B, Fischer C, Holzheimer RG. IgM-enriched immunoglobulin preparation for immunoprophylaxis in cardiac surgery. Eur J Med Res 2002; 7(12):544-9.

23 Kress HG, Scheidewig C, Schmidt H, Silber R. Reduced incidence of postoperative infection after intravenous administration of an immunoglobulin A- and immunoglobulin M-enriched preparation in anergic patients undergoing cardiac surgery.[see comment]. Crit Care Med 1999; 27(7):1281-7.

27 Mao P, Enrichens F, Olivero G et al. Early administration of intravenous immunoglobulins in the prevention of surgical and post-traumatic sepsis: a double blind randomized clinical trial. SURG RES COMMUN 1989; 5(2):93-8.

37 Pilz G, Appel R, Kreuzer E, Werdan K. Comparison of early IgM-enriched immunoglobulin vs polyvalent IgG administration in score-identified postcardiac surgical patients at high risk for sepsis. Chest 1997; 111(2):419-26.

37 Pilz G, Appel R, Kreuzer E, Werdan K. Comparison of early IgM-enriched immunoglobulin vs polyvalent IgG administration in score-identified postcardiac surgical patients at high risk for sepsis. Chest 1997; 111(2):419-26.

38 Pilz G, Kreuzer E, Kaab S, Appel R, Werdan K. Early sepsis treatment with immunoglobulins after cardiac surgery in score-identified high-risk patients.[erratum appears in Chest 1994 Jun;105(6):1924]. Chest 1994; 105(1):76-82.

Types of study:	One systemic review (22 RCTs), 5 RCTs, 1 case study (historical control).
Total sample size:	587
Quality:	High/Moderate
Result:	IVIG significantly reduced mortality in review and 1 RCT, and significantly reduced infections in 2 RCTs, beneficial effect seen in 3 RCT and case study.
Adverse events:	One patient with allergy (skin rash, dizziness).
Conclusion:	Beneficial effect of IVIG, although larger studies needed.
Category:	IIa

Condition studies: Sepsis: adult sepsis

1 Alejandria MM, Lansang MA, Dans LF, Mantaring JB. Intravenous immunoglobulin for treating sepsis and septic shock.[update of Cochrane Database Syst Rev. 2001;(2):CD001090; PMID: 11405973]. [Review] [87 refs]. Cochrane Database of Systematic Reviews 2002; (1):CD001090.

Study design: Reviewed 11 relevant RCTs (polyclonal) to IVIG for adult and neonates.

Length of follow-up:

Sample size: n = 251 for adult sepsis.

Population: Adults with sepsis.

Intervention: IVIG

Comparison / control: Placebo or no treatment.

Outcome(s) measured: Mortality.

Quality assessment (internal validity)

Placebo:

Follow-up:

Results

Intervention groups: Polyclonal IVIG significantly reduced mortality in adults (n = 251, RR = 0.62; 95% CI 0.42, 1.18).

Control / comparison group(s):

P-value:

Adverse events:

Conclusions / Comments: IVIG reduced mortality from sepsis but all trials were small. Larger studies needed.

Condition studies:	Sepsis: adult sepsis

8	Cafiero F, Gipponi M, Bonalumi U, Piccardo A, Sguotti C, Corbetta G. Prophylaxis of infection with intravenous immunoglobulins plus antibiotic for patients at risk for sepsis undergoing surgery for colorectal cancer: results of a randomized, multicenter clinical trial. Surgery 1992; 112(1):24-31.

Study design:	RCT	**Length of follow-up:**	
Sample size:	80	**Population:**	Patients at risk of sepsis undergoing colorectal surgery for colorectal cancer.
Intervention:	IVIG + antibiotic given 1 day before surgery and day 1 and 5 after surgery.		
Comparison / control:	Antibiotic alone.		
Outcome(s) measured:	Infections.		

Quality assessment (internal validity)

Placebo:

Follow-up:

Results

Intervention groups:	Reduction in infections 21 infections/20 patients (1.05 infections/patient) in IVIG compared to control P = 0.004.	**Control / comparison group(s):**	Had 37 infections/29 patients (1.27 infections/patient).

P-value:

Adverse events:

Conclusions / Comments:	Significantly reduced infections with IVIG.

Condition studies:	Sepsis: adult sepsis

15	Friedrich I, Silber RE, Baumann B, Fischer C, Holzheimer RG. IgM-enriched immunoglobulin preparation for immunoprophylaxis in cardiac surgery. Eur J Med Res 2002; 7(12):544-9.

Study design:	RCT	**Length of follow-up:**	
Sample size:	Sample of 20 subjects and 20 controls.	**Population:**	Cardiac surgical patients.
Intervention:	IgM enriched immunoglobulin (Pentaglobin).		
Comparison / control:	Placebo treatment not specified.		
Outcome(s) measured:	Endotoxin and endotoxin neutralising capacity (ENC) were determined by kinetic turbidimetric Limulus amebocyte lysate assay.Serum levels of IL-6, TNF-alpha, soluble TNFReceptor 1 and IL-10 were measured by ELISA.		

Quality assessment (internal validity)

Placebo:	Yes
Follow-up:	A group of 21 recruited and 20 followed up in treatment group, with 1 drop out. Twenty in control group followed up.

Results

Intervention groups:	Patients with signs of inflammation in treatment group = 2. Hospitalization period in treatment group = 12.05 +/- 3.66.	**Control / comparison group(s):**	Patients with signs of inflammation in control group = 9. Hospitalization period in control group = 13.45 +/- 3.72. See paper for details of other outcomes.
P-value:	$P < 0.05$ for reduction in signs of inflammation.		
Adverse events:	One patient with allergy (skin rash, dizziness).		
Conclusions / Comments:	IgM enriched IVIG shown to be effective when used prophylactically in patients undergoing bypass surgery.		

Condition studies: Sepsis: adult sepsis

23 Kress HG, Scheidewig C, Schmidt H, Silber R. Reduced incidence of postoperative infection after intravenous administration of an immunoglobulin A- and immunoglobulin M-enriched preparation in anergic patients undergoing cardiac surgery.[see comment]. Crit Care Med 1999; 27(7):1281-7.

Study design:	RCT	**Length of follow-up:**	2 weeks following surgery
Sample size:	40	**Population:**	Patients awaiting elective open heart surgery that were annergic to recall antigens by skin test.

Intervention: IVIG enriched with IgA and IgM (dose, 20 g). Infusion given 4 h after surgery over 53 h.

Comparison / control: Placebo-saline.

Outcome(s) measured: Postoperative infection.

Quality assessment (internal validity)

Placebo: Yes

Follow-up: All patients were followed up.

Results

Intervention groups:	Post operative infection in 1/19 patients (5%) IVIG patients. Much lower than control P = 0.007.	**Control / comparison group(s):**	Post operative infection was identified in 9/21 patients (43%) placebo patients.

P-value:

Adverse events:

Conclusions / Comments: IgA/IgM-enriched IVIG significantly reduced postoperative infections in anergic patients. Numbers small.

Condition studies: Sepsis: adult sepsis

27 Mao P, Enrichens F, Olivero G et al. Early administration of intravenous immunoglobulins in the prevention of surgical and post-traumatic sepsis: a double blind randomized clinical trial. SURG RES COMMUN 1989; 5(2):93-8.

Study design: RCT **Length of follow-up:**

Sample size: 40 **Population:** Patients with severe trauma or major surgery.

Intervention: IVIG on postoperative days 1, 3, 5 and 10.

Comparison / control: Placebo.

Outcome(s) measured: Body temperature, complement C3, and C4, blood cultures.

Quality assessment (internal validity)

Placebo:

Follow-up:

Results

Intervention groups: 6.7% mortality in IVIG group compared to 23.5% in placebo. **Control / comparison group(s):**

P-value:

Adverse events:

Conclusions / Comments: IVIG reduced mortality in severely traumatised patients ($p < 0.05$), small numbers.

Condition studies:	Sepsis: adult sepsis

37	Pilz G, Appel R, Kreuzer E, Werdan K. Comparison of early IgM-enriched immunoglobulin vs polyvalent IgG administration in score-identified postcardiac surgical patients at high risk for sepsis. Chest 1997; 111(2):419-26.

Study design:	RCT	**Length of follow-up:**	See paper
Sample size:	A sample of 14 patients on intravenous IgG & 13 patients on IgGMA.	**Population:**	Patients after elective open-heart surgery at high risk for sepsis.
Intervention:	Intravenous immunoglobulin (IgGMA).		
Comparison / control:	IV IgG		
Outcome(s) measured:	Clinical parameters: disease severity and in hospital mortality.		

Quality assessment (internal validity)

Placebo:	Yes
Follow-up:	Thirteen followed up in treatment group (IgGMA) & 14 in control group (IgG).

Results

Intervention groups:	Fall in APACHEII score 4 days (IgGMA) = -5.2. Score defined improvement rate (IgGMA) = 54%. In-hospital mortality = 31%.	**Control / comparison group(s):**	Fall in APACHEII score 4 days (IgG) = -6.9. Score defined improvement rate (IgG) = 57%. In-hospital mortality = 29 %.
P-value:	All findings non-significant. See paper for details.		
Adverse events:			
Conclusions / Comments:	IgG and IgGMA were associated with comparable improvement in disease severity. Appears to be a reasoneble study albeit with small numbers and a negative finding with respect to the effect of intravenous immunoglobulin.		

Condition studies:	Sepsis: adult sepsis

37	Pilz G, Appel R, Kreuzer E, Werdan K. Comparison of early IgM-enriched immunoglobulin vs polyvalent IgG administration in score-identified postcardiac surgical patients at high risk for sepsis. Chest 1997; 111(2):419-26.

Study design:	RCT	**Length of follow-up:**	
Sample size:	A sample of 27 total, n = 14 IV IgG, n = 13 IV IgGMA.	**Population:**	Post cardiac surgical at high risk for sepsis.
Intervention:	IV IgG (Polyglobin, 18 mL/kg).		
Comparison / control:	IV IgGMA (Pentaglobin, 15 mL/kg) group and placebo group.		
Outcome(s) measured:	Disease severity, mortality in hospital.		

Quality assessment (internal validity)

Placebo:

Follow-up:

Results

Intervention groups:	Score quantified improvement in disease severity, score-defined improvement rates and in-hospital mortality similar in both groups.	**Control / comparison group(s):**	

P-value:

Adverse events:

Conclusions / Comments:	Comparable improvement with IV IgG vs IV IgMA . Larger trials needed for independent validation. Numbers small.

Condition studies: Sepsis: adult sepsis

38 Pilz G, Kreuzer E, Kaab S, Appel R, Werdan K. Early sepsis treatment with immunoglobulins after cardiac surgery in score-identified high-risk patients.[erratum appears in Chest 1994 Jun;105(6):1924]. Chest 1994; 105(1):76-82.

Study design: Case-control. **Length of follow-up:**

Sample size: A sample of 108 total. **Population:**

Intervention: IV Ig (n = 41) or IgGMA (n = 25).

Comparison / control: Historical control population, equivalent in patient characteristics and disease severity, n = 21 risk group, n = 21 high risk group.

Outcome(s) measured: APACHE II scores.

Quality assessment (internal validity)

Placebo: No

Follow-up: Full information on follow up was not provided.

Results

Intervention groups: A marked fall in APACHE II scores, especially in the high-risk group (IgG, n = 26: $p < 0.05$; IgGMA, n = 13).

Control / comparison group(s):

P-value:

Adverse events:

Conclusions / Comments: Early Ig therapy improves disease severity and may improve prognosis in high risk patients. Numbers small.

Vasculitis/inflammatory

Condition summary	Sepsis: neonatal sepsis: prevention/treatment
Reference list:	33 Ohlsson A, Lacy JB. Intravenous immunoglobulin for preventing infection in preterm and/or low-birth-weight infants.[update of Cochrane Database Syst Rev. 2000;(2):CD000361; PMID: 10796199]. [Review] [74 refs]. Cochrane Database of Systematic Reviews 2004; (2):CD000361. 271 Alejandria MM, Lansang MA, Dans LF, Mantaring JB. Intravenous immunoglobulin for treating sepsis and septic shock.[update of Cochrane Database Syst Rev. 2001;(2):CD001090; PMID: 11405973]. [Review] [87 refs]. Cochrane Database of Systematic Reviews 2002; (1):CD001090.
Types of study:	Two systemic reviews.
Total sample size:	19 RCTs (5000), 1 RCT (241)
Quality:	High/Moderate
Result:	IVIG reduced sepsis by 3-4% (p=0.02) but no significant effect on mortality or other morbidities (Ohlsson). Reduced mortality from sepsis (not significant) (Alejandria).
Adverse events:	No major adverse effects reported in 19 RCTs. Adverse events not mentioned by Alejandria.
Conclusion:	IVIG has either no or marginal effect, based on 1 high and 1 moderate-level RCT.
Category:	III

Condition studies:	Sepsis: neonatal sepsis: prevention/treatment

33 Ohlsson A, Lacy JB. Intravenous immunoglobulin for preventing infection in preterm and/or low-birth-weight infants.[update of Cochrane Database Syst Rev. 2000;(2):CD000361; PMID: 10796199]. [Review] [74 refs]. Cochrane Database of Systematic Reviews 2004; (2):CD000361.

Study design:	Reviewed 19 RCTs.	**Length of follow-up:**	8 days or longer
Sample size:	Approximately 5000.	**Population:**	Pre-term or low birth weight babies.

Intervention: IVIG

Comparison / control: Placebo or no intervention.

Outcome(s) measured: Sepsis, any serious infection, necrotizing enterocolitis, mortality (all causes), mortality (infection), duration of hospital stay, bronchopulmonary dysplasia, intraventricular hemorrhage.

Quality assessment (internal validity)

Placebo:

Follow-up:

Results

Intervention groups:	3% reduction in 4% sepsis (p=0.02) and any serious infection. No reductions in mortality or other morbidities.	**Control / comparison group(s):**	

P-value:

Adverse events: No major adverse events.

Conclusions / Comments: Level III - Reviewers conclude the effect of IVIG is of marginal importance.

Condition studies:	Sepsis: neonatal sepsis: prevention/treatment

271	Alejandria MM, Lansang MA, Dans LF, Mantaring JB. Intravenous immunoglobulin for treating sepsis and septic shock.[update of Cochrane Database Syst Rev. 2001;(2):CD001090; PMID: 11405973]. [Review] [87 refs]. Cochrane Database of Systematic Reviews 2002; (1):CD001090.

Study design:	Cochrane review including 5 RCT specific to neonates.	**Length of follow-up:**	
Sample size:	241	**Population:**	Neonates with sepsis.
Intervention:	IVIG different doses.		
Comparison / control:	Placebo.		
Outcome(s) measured:	All-cause mortality.		

Quality assessment (internal validity)

Placebo:

Follow-up:

Results

Intervention groups:	**Control / comparison group(s):**

P-value:

Adverse events:

Conclusions / Comments:	Barely significant effect.

Vasculitis/inflammatory

Condition summary	Sepsis: paediatric sepsis
Reference list:	12 Ersahin Y, Mutluer S, Kocaman S. Immunoglobulin prophylaxis in shunt infections: a prospective randomized study. Childs Nerv Syst 1997; 13(10):546-9. 48 Scielzo R, Caramazza L, Circone R, Graziano DV. [Intravenous immunoglobulin in the prevention of infections in high-risk pediatric neurosurgery]. [Italian]. Minerva Anestesiol 1992; 58(4 Suppl 1):235-8.
Types of study:	One RCT, 1 case-control.
Total sample size:	60 (RCT), 64 (CC)
Quality:	Moderate/Low
Result:	IVIG reduced shunt infections (not significant) in RCT, reduced number of postoperative respiratory and urinary infective events in case-control study.
Adverse events:	None observed.
Conclusion:	Possible benefit of IVIG , based on 1 RCT and 1 case-control study.
Category:	IIa

Condition studies:	Sepsis: paediatric sepsis

12	Ersahin Y, Mutluer S, Kocaman S. Immunoglobulin prophylaxis in shunt infections: a prospective randomized study. Childs Nerv Syst 1997; 13(10):546-9.

Study design:	RCT	**Length of follow-up:**	6 months
Sample size:	A total of 60 infant patients (n = 30 intervention and n = 30 control).	**Population:**	Patients aged 7 days-12 months with diagnosis of hydrocephalus.
Intervention:	IVIG 1 g/kg in the night before surgery.		
Comparison / control:			
Outcome(s) measured:	Infection/patient, infection/procedure (shunts).		

Quality assessment (internal validity)

Placebo:	
Follow-up:	

Results

Intervention groups:	No infections.	**Control / comparison group(s):**	Had 5.1% infection rate/procedure (P = 0.494) and 6.6% infection rate/patient (0.492).
P-value:			
Adverse events:	No adverse events were reported.		
Conclusions / Comments:	IVIG reduced shunt infections, not significant because number of patients too small. More research needed.		

Condition studies:	Sepsis: paediatric sepsis

48	Scielzo R, Caramazza L, Circone R, Graziano DV. [Intravenous immunoglobulin in the prevention of infections in high-risk pediatric neurosurgery]. [Italian]. Minerva Anestesiol 1992; 58(4 Suppl 1):235-8.

Study design:	Case-control.	**Length of follow-up:**	
Sample size:	A sample of 64 (n=32 in each group).	**Population:**	Children undergoing "high risk" neurosurgery.
Intervention:	IVIG 0.2 g/kg on day 0, 2, 5, 12, 32 after surgery.		
Comparison / control:	Placebo.		
Outcome(s) measured:	Number of postoperative respiratory and urinary infective events.		

Quality assessment (internal validity)

Placebo:

Follow-up:

Results

Intervention groups:	Reduced number of postoperative respiratory and urinary infective events.	**Control / comparison group(s):**	
P-value:			
Adverse events:			
Conclusions / Comments:	Full paper in Italian, translation not possible. Summary based on abstract.		

Vasculitis/inflammatory

Condition summary	Sepsis: preterm sepsis: prevention/treatment
Reference list:	
Types of study:	
Total sample size:	
Quality:	
Result:	
Adverse events:	
Conclusion:	
Category:	See: Sepsis: neonatal, paediatric

Vasculitis/inflammatory

Condition summary	Systemic lupus erythematosus (SLE)
Reference list:	13 Flanc RS, Roberts MA, Strippoli GFM, Chadban SJ, Kerr PG, Atkins RC. Treatment for lupus nephritis. Flanc RS, Roberts MA, Strippoli GFM, Chadban SJ, Kerr PG, Atkins RC. Treatment for Lupus Nephritis (Cochrane Review). In: The Cochrane Library, Issue 1, 2004. Chichester, UK: John Wiley & Sons, Ltd.
Types of study:	One sytematic review.
Total sample size:	14
Quality:	Low
Result:	No significant difference between IVIG and cyclphosphamide.
Adverse events:	
Conclusion:	Possible benefit, based on 1 small RCT.
Category:	IIa

Condition studies:	Systemic lupus erythematosus (SLE)

13	Flanc RS, Roberts MA, Strippoli GFM, Chadban SJ, Kerr PG, Atkins RC. Treatment for lupus nephritis. Flanc RS, Roberts MA, Strippoli GFM, Chadban SJ, Kerr PG, Atkins RC. Treatment for Lupus Nephritis (Cochrane Review). In: The Cochrane Library, Issue 1, 2004. Chichester, UK: John Wiley & Sons, Ltd.

Study design:	Reviewed 25 RCTs in total, including 1 study on IVIG (Boletis 1999).	**Length of follow-up:**	
Sample size:	14	**Population:**	Patients with Class III or IV lupus nephritis.
Intervention:	In IVIG study: IVIG 400 mg/kg monthly for 18 months.		
Comparison / control:	Cyclophosphamide.		
Outcome(s) measured:	Creatinine, creatinine clearance or proteinuria, deaths.		

Quality assessment (internal validity)

Placebo:

Follow-up:

Results

Intervention groups:	No reported difference in creatinine, creatinine clearance or proteinuria at 12 weeks. No deaths after 18 months follow-up.	**Control / comparison group(s):**	

P-value:

Adverse events:

Conclusions / Comments:	For IVIG, only 1 small RCT, no difference found for IVIG.

Vasculitis/inflammatory

Condition summary	Systemic necrotizing vasculitis
Reference list:	
Types of study:	
Total sample size:	
Quality:	
Result:	
Adverse events:	
Conclusion:	
Category:	See: Systemic lupus erythematosus (SLE)

Appendix 3 — Safety of IVIG

General information

Condition summary	Safety of IVIG

Reference list:

252 Sekul EA, Cupler EJ, Dalakas MC. Aseptic meningitis associated with high-dose intravenous immunoglobulin therapy: frequency and risk factors. Ann Intern Med. 1994 Aug 15;121(4):259-62.

165 Wittstock M, Benecke R, Zettl UK. Therapy with intravenous immunoglobulins: complications and side-effects. Eur Neurol 2003; 50(3):172-5.

245 Grillo JA, Gorson KC, Ropper AH, Lewis J, Weinstein R. Rapid infusion of intravenous immune globulin in patients with neuromuscular disorders. Neurology. 2001 Nov 13;57(9):1699-701.

246 Caress JB, Cartwright MS, Donofrio PD, Peacock JE Jr.The clinical features of 16 cases of stroke associated with administration of IVIg.Neurology. 2003 Jun 10;60(11):1822-4.

247 Dalakas MC, Clark WM. Strokes, thromboembolic events, and IVIg: rare incidents blemish an excellent safety record. Neurology. 2003 Jun 10;60(11):1736-7.

248 Okuda D, Flaster M, Frey J, Sivakumar K. Arterial thrombosis induced by IVIg and its treatment with tPA. Neurology. 2003 Jun 10;60(11):1825-6.

251 Scribner CL, Kapit RM, Phillips ET, Rickles NM. Aseptic meningitis and intravenous immunoglobulin therapy. Ann Intern Med. 1994 Aug 15;121(4):305-6.

253 Schmaldienst S, Mullner M, Goldammer A, Spitzauer S, Banyai S, Horl WH, Derfler K. Intravenous immunoglobulin application following immunoadsorption: benefit or risk in patients with autoimmune diseases? Rheumatology (Oxford). 2001 May;40(5):513-21.

254 Schiavotto C, Ruggeri M, Rodeghiero F. Adverse reactions after high-dose intravenous immunoglobulin: incidence in 83 patients treated for idiopathic thrombocytopenic purpura (ITP) and review of the literature. Haematologica. 1993 Nov-Dec;78(6 Suppl 2):35-40.

255 Kattamis AC, Shankar S, Cohen AR. Neurologic complications of treatment of childhood acute immune thrombocytopenic purpura with intravenously administered immunoglobulin G. J Pediatr. 1997 Feb;130(2):281-3.

24 Levy JB, Pusey CD. Nephrotoxicity of intravenous immunoglobulin. QJM 2000; 93(11):751-5.

257 Pierce LR, Jain N. Risks associated with the use of intravenous immunoglobulin. Transfus Med Rev. 2003 Oct;17(4):241-51.

258 No authors listed. Renal insufficiency and failure associated with immune globulin intravenous therapy--United States, 1985-1998. MMWR Morb Mortal Wkly Rep. 1999 Jun 25;48(24):518-21.

	259 Yap PL. Intravenous immunoglobulin and hepatitis C virus: an overview of transmission episodes with emphasis on manufacturing data. Clin Ther. 1996;18 Suppl B:43-58. 260 Berger M, Pinciaro PJ. Safety, Efficacy, and Pharmacokinetics of Flebogamma(R) 5% [immune Globulin Intravenous (human)] for Replacement Therapy in Primary Immunodeficiency Diseases. J Clin Immunol. 2004 Jul;24(4):389-96. 256 Eibi MM 249 Dalakas MC. High-dose intravenous immunoglobulin and serum viscosity: risk of precipitating thromboembolic events. Neurology. 1994 Feb;44(2):223-6.
Types of study:	7 uncontrolled studies
Total sample size:	512
Quality:	Low
Result:	Varied from no adverse events, to mild adverse events (4-42.7%) to severe adverse events (3.5-8%)
Adverse events:	
Conclusion:	Conflicting results, generally appear to be few adverse events except in certain subpopulations
Category:	

Condition studies:	Safety of IVIG

252	Sekul EA, Cupler EJ, Dalakas MC. Aseptic meningitis associated with high-dose intravenous immunoglobulin therapy: frequency and risk factors. Ann Intern Med. 1994 Aug 15;121(4):259-62.

Study design:	Other	**Length of follow-up:**	N/A
Sample size:	54	**Population:**	
Intervention:	high-dose (2 g/kg) IVIG		
Comparison / control:	N/A		
Outcome(s) measured:	aseptic meningitis, associated risk factors, penetration of serum IgG into the cerebrospinal fluid, and clearance of cerebrospinal fluid IgG		

Quality assessment (internal validity)

Placebo:	No
Follow-up:	

Results

Intervention groups:	6/54 patients (11%; 95% CI, 4% to 23%) developed aseptic meningitis within 24 hours after completion of the infusions; Cerebrospinal fluid showed pleocytosis in 4 patients, eosinophilia in 3 patients, and IgG elevation in all patients	**Control / comparison group(s):**	
P-value:	See Col 29, 31		
Adverse events:	Symptoms, lasting 3 to 5 days, included severe headache, meningismus, photophobia, and fever		
Conclusions / Comments:	High rate of aseptic meningitis associated with high-dose IVIG. More likely to occur with history of migraine, appears not to be related to type of preparation or infusion rate. Could be related to IgG itself, stabilising products, cytokine release triggered by IVIG, cerebrovascular sensitivity in those with migraine.		

Condition studies:	Safety of IVIG

165	Wittstock M, Benecke R, Zettl UK. Therapy with intravenous immunoglobulins: complications and side-effects. Eur Neurol 2003; 50(3):172-5.

Study design:	Case-series	**Length of follow-up:**	No length of follow up was recorded
Sample size:	117	**Population:**	
Intervention:	IVIG		
Comparison / control:	N/A		
Outcome(s) measured:	Adverse effects including; headaches, DVT		

Quality assessment (internal validity)

Placebo:	No
Follow-up:	

Results

Intervention groups:	42.7% showed adverse events	**Control / comparison group(s):**	N/A
P-value:			
Adverse events:	Majority of patients presented with minor adverse effects, mostly asymptomatic laboratory changes including; Rash or mild headache; DVT complications		
Conclusions / Comments:	Side effects generally absent or minor. Patients with pre-existing disorders (eg heart or renal insufficiency, or immobilisation) may be at higher risk for complications		

Condition studies:	Safety of IVIG

245	Grillo JA, Gorson KC, Ropper AH, Lewis J, Weinstein R. Rapid infusion of intravenous immune globulin in patients with neuromuscular disorders. Neurology. 2001 Nov 13;57(9):1699-701.

Study design:	Case-series	**Length of follow-up:**	No length of follow up was recorded
Sample size:	50 patients with neuromuscular disorders	**Population:**	
Intervention:	Rapid infusion of IVIG		
Comparison / control:	N/A		
Outcome(s) measured:	Adverse effects		

Quality assessment (internal validity)

Placebo:	No
Follow-up:	

Results

Intervention groups:	There were 89 adverse events after 341 rapid infusions (26%), 3.5% of which were considered to be major (requiring hospitalization - chest pain, myocardial infarction, congestive heart failure, severe headache, pleurisy, tranfusion-related acute lung injury, allergic reaction) and 22.5% minor (mild or moderate headache, malaise, nausea, myalgia, hypertension, fever, chills, pedal edema, slight dyspnea).	**Control / comparison group(s):**	N/A
P-value:			
Adverse events:			
Conclusions / Comments:	Rate of adverse events slightly higher (26%) than for conventional-infusion regimens at slower rates.		

Condition studies:	Safety of IVIG

246	Caress JB, Cartwright MS, Donofrio PD, Peacock JE Jr.The clinical features of 16 cases of stroke associated with administration of IVIg.Neurology. 2003 Jun 10;60(11):1822-4.

Study design:	Case-series	**Length of follow-up:**	No length of follow up was recorded
Sample size:	16 stroke patients	**Population:**	
Intervention:	IVIG		
Comparison / control:	N/A		
Outcome(s) measured:	Adverse effects		

Quality assessment (internal validity)

Placebo:	No
Follow-up:	

Results

Intervention groups:	14 of the strokes occurred within 24 hours of an infusion; 9 patients had multifocal infarctions.	**Control / comparison group(s):**	N/A
P-value:			
Adverse events:	strokes, multifocal infarctions		
Conclusions / Comments:	Exclude due to small numbers and risk factors		

Condition studies: Safety of IVIG

247 Dalakas MC, Clark WM. Strokes, thromboembolic events, and IVIg: rare incidents blemish an excellent safety record. Neurology. 2003 Jun 10;60(11):1736-7.

Study design: Other **Length of follow-up:** N/A

Sample size: N/A **Population:**

Intervention: IVIG

Comparison / control: N/A

Outcome(s) measured: Adverse effects

Quality assessment (internal validity)

Placebo: No

Follow-up:

Results

Intervention groups: N/A **Control / comparison group(s):** N/A

P-value:

Adverse events:

Conclusions / Comments: Exclude - editorial

Condition studies:	Safety of IVIG

248	Okuda D, Flaster M, Frey J, Sivakumar K. Arterial thrombosis induced by IVIg and its treatment with tPA. Neurology. 2003 Jun 10;60(11):1825-6.

Study design:	Case-series	**Length of follow-up:**	No length of follow up was recorded
Sample size:	4 patients who developed cerebral and peripheral arterial thrombosis after treatment with IV immunoglobulin	**Population:**	
Intervention:	IVIG		
Comparison / control:	N/A		
Outcome(s) measured:	Use of tissue plasminogen activator		

Quality assessment (internal validity)

Placebo:	No
Follow-up:	

Results

Intervention groups:	No sufficient information is provided	**Control / comparison group(s):**	N/A
P-value:			
Adverse events:			
Conclusions / Comments:	Exclude - small sample		

Condition studies: Safety of IVIG

251 Scribner CL, Kapit RM, Phillips ET, Rickles NM. Aseptic meningitis and intravenous immunoglobulin therapy. Ann Intern Med. 1994 Aug 15;121(4):305-6.

Study design: Other **Length of follow-up:**

Sample size: N/A **Population:**

Intervention:

Comparison / control: N/A

Outcome(s) measured:

Quality assessment (internal validity)

Placebo: No

Follow-up:

Results

Intervention groups: N/A **Control / comparison group(s):**

P-value:

Adverse events:

Conclusions / Comments: Exclude - editorial

Condition studies:	Safety of IVIG

253	Schmaldienst S, Mullner M, Goldammer A, Spitzauer S, Banyai S, Horl WH, Derfler K. Intravenous immunoglobulin application following immunoadsorption: benefit or risk in patients with autoimmune diseases? Rheumatology (Oxford). 2001 May;40(5):513-21.
Study design:	RCT **Length of follow-up:**
Sample size:	35 **Population:**
Intervention:	n=17 combined immunoadsorption and intravenous immunoglobulins
Comparison / control:	n=18 control immunoadsorption alone
Outcome(s) measured:	infection rates, adverse effects

Quality assessment (internal validity)

Placebo:	No
Follow-up:	

Results

Intervention groups:	1.3 infections per patient-year	**Control / comparison group(s):**	0.9 infections per patient-year
P-value:			
Adverse events:	in patients in whom circulating immunoglobulins had been depleted was associated with a high incidence of serious side-effects		
Conclusions / Comments:	Exclude - not relevant to safety, looks at benefit of IVIG after immunoadsorption (outside the scope of this review)		

Condition studies: Safety of IVIG

254 Schiavotto C, Ruggeri M, Rodeghiero F. Adverse reactions after high-dose intravenous immunoglobulin: incidence in 83 patients treated for idiopathic thrombocytopenic purpura (ITP) and review of the literature. Haematologica. 1993 Nov-Dec;78(6 Suppl 2):35-40.

Study design: Other **Length of follow-up:**

Sample size: N/A **Population:**

Intervention: IVIG

Comparison / control:

Outcome(s) measured: adverse reactions

Quality assessment (internal validity)

Placebo:

Follow-up:

Results

Intervention groups: Major adverse reactions included aseptic meningitis (14 cases), hemolytic anemia (8 cases) and renal dysfunction (12 cases) **Control / comparison group(s):**

P-value:

Adverse events:

Conclusions / Comments: Exclude - editorial

Condition studies:	Safety of IVIG

255	Kattamis AC, Shankar S, Cohen AR. Neurologic complications of treatment of childhood acute immune thrombocytopenic purpura with intravenously administered immunoglobulin G. J Pediatr. 1997 Feb;130(2):281-3.

Study design:	Case-series	**Length of follow-up:**	
Sample size:	38 children with acute immune thrombocytopenic purpura (ITP)	**Population:**	
Intervention:	IVIG		
Comparison / control:	N/A		
Outcome(s) measured:	incidence, associated morbidity, and impact on health care charges of neurologic complications		

Quality assessment (internal validity)

Placebo:	No
Follow-up:	

Results

Intervention groups:	13/38 (34%) had transient neurologic complications, manifested by severe headache, nausea, and, rarely, aseptic meningitis	**Control / comparison group(s):**	
P-value:			
Adverse events:	12 patients were hospitalized longer than was required for their ITP alone		
Conclusions / Comments:	Frequency of significant acute side effects with IVIG may be higher than previously suggested, may substantially increase costs of treatment		

Condition studies:	Safety of IVIG

24	Levy JB, Pusey CD. Nephrotoxicity of intravenous immunoglobulin. QJM 2000; 93(11):751-5.

Study design:	Cohort	**Length of follow-up:**	
Sample size:	119	**Population:**	Variety of indications - thrombocytopaenia, SLE, neruopathy, Guillain-Barre syndrome, infections
Intervention:	IVIG (Vigam and Sandoglobulin)		
Comparison / control:			
Outcome(s) measured:	Renal function		

Quality assessment (internal validity)

Placebo:	No
Follow-up:	

Results

Intervention groups:	Renal function deteriorated in 8 patients (6.7%) and no renal recovery occurred in 2 (1.7%). The 3 patients with the most severe renal failure received Vigam IVIG.	**Control / comparison group(s):**	
P-value:			
Adverse events:	IVIG associated with renal impairment that may be irreversible (max incidence 6.7%)		
Conclusions / Comments:	Results suggest that any preparation of IVIG can cause renal impairment, therefore, IVIG should not be used with other potential nephrotoxins, renal function should be checked before and after administration of IVIG, especially in patients with pre-existing renal disease, and serum creatinine should be measured 4-5 days after starting high-dose IVIG therapy.		

Condition studies: Safety of IVIG

257 Pierce LR, Jain N. Risks associated with the use of intravenous immunoglobulin. Transfus Med Rev. 2003 Oct;17(4):241-51.

Study design: Other **Length of follow-up:**

Sample size: N/A **Population:**

Intervention: IVIG

Comparison / control:

Outcome(s) measured: Literature review

Quality assessment (internal validity)

Placebo:

Follow-up:

Results

Intervention groups: **Control / comparison group(s):**

P-value:

Adverse events:

Conclusions / Comments: Exclude - review

Condition studies: Safety of IVIG

258

No authors listed. Renal insufficiency and failure associated with immune globulin intravenous therapy--United States, 1985-1998. MMWR Morb Mortal Wkly Rep. 1999 Jun 25;48(24):518-21.

Study design: Other **Length of follow-up:**

Sample size: N/A **Population:**

Intervention: IVIG

Comparison / control:

Outcome(s) measured: Literature review/report on the epidemiology of IGIV-associated RAEs in the United States

Quality assessment (internal validity)

Placebo:

Follow-up:

Results

Intervention groups:

Control / comparison group(s):

P-value:

Adverse events:

Conclusions / Comments: Exclude - review

Condition studies: Safety of IVIG

259 Yap PL. Intravenous immunoglobulin and hepatitis C virus: an overview of transmission episodes with emphasis on manufacturing data. Clin Ther. 1996;18 Suppl B:43-58.

Study design: Other **Length of follow-up:**

Sample size: N/A **Population:**

Intervention: IVIG

Comparison / control:

Outcome(s) measured: Literature review

Quality assessment (internal validity)

Placebo:

Follow-up:

Results

Intervention groups: **Control / comparison group(s):**

P-value:

Adverse events:

Conclusions / Comments: Exclude - review

Condition studies:	Safety of IVIG

260	Berger M, Pinciaro PJ. Safety, Efficacy, and Pharmacokinetics of Flebogamma(R) 5% [immune Globulin Intravenous (human)] for Replacement Therapy in Primary Immunodeficiency Diseases. J Clin Immunol. 2004 Jul;24(4):389-96.

Study design:	cohort	**Length of follow-up:**	12 months
Sample size:	51 (aged 14-74)	**Population:**	Subjects aged14 and older, minimum weight of 27 kg, with well-defined primary immunodeficiency.
Intervention:	IVIG (Flebogamma) with well-defined primary immunodeficiency diseases at a dose of 300-600 mg/kg every 21-28 days		
Comparison / control:	N/A		
Outcome(s) measured:	safety, efficacy, and pharmacokinetics of Flebogamma(R)		

Quality assessment (internal validity)

Placebo:	No
Follow-up:	

Results

Intervention groups:	The calculated serious infection rate for the intent-to-treat population was 0.061/subject/year. The incidence of adverse events considered potentially related to Flebogamma(R) 5%, and occurring during or within 72 h after completing the infusion was approximately 8%.	**Control / comparison group(s):**	
P-value:			
Adverse events:			
Conclusions / Comments:	Flebogamma(R) 5% is efficacious, safe, and well-tolerated, and does not put subjects at increased risk of adverse events other than those that could be reasonably expected in primary immunodeficient subjects who are receiving any immune globulin product.		

Condition studies: Safety of IVIG

256 Eibi MM

Study design: Other **Length of follow-up:**

Sample size: N/A **Population:**

Intervention: IVIG

Comparison / control:

Outcome(s) measured: Literature review

Quality assessment (internal validity)

Placebo:

Follow-up:

Results

Intervention groups: **Control / comparison group(s):**

P-value:

Adverse events:

Conclusions / Comments: Exclude - review

Condition studies: Safety of IVIG

249

Dalakas MC. High-dose intravenous immunoglobulin and serum viscosity: risk of precipitating thromboembolic events. Neurology. 1994 Feb;44(2):223-6.

Study design: Case-series

Length of follow-up:

Sample size: 13 patients (5 with amyotrophic lateral sclerosis [ALS], 8 with IgM paraproteinemic polyneuropathy)

Population:

Intervention: IVIG

Comparison / control: N/A

Outcome(s) measured: measured serum viscosity

Quality assessment (internal validity)

Placebo: No

Follow-up:

Results

Intervention groups: Serum viscosity increased after IVIg in all the patients by 0.1 to 1.0 centipoise;

Control / comparison group(s):

P-value:

Adverse events:

Conclusions / Comments: Exclude - small sample

Appendix 4

Excluded references

Excluded - in Cochrane

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