Standing Council on Health

National Blood Authority Australia

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

Second Edition
July 2012

Quick Reference Guide

INTRODUCTION

This quick reference guide (QRG) is an abbreviated version of *the Criteria for the Clinical Use of Intravenous Immunoglobulin in Australia Second Edition* (*the Criteria* second edition) approved by all Australian Health Ministers in June 2012.

The second editions of both *the Criteria* and QRG have been produced to assist clinicians and transfusion medicine professionals identify the conditions and circumstances for which the use of intravenous immunoglobulin (IVIg) can be accessed under the National Blood Arrangements. The complete *Criteria* second edition should be referred to in the first instance.

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

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

IVIg is a precious biological product for which demand continues to grow. This growth prompted action by Australian governments to ensure it is reserved for use in those patients with the greatest need. As such, its use should be consistent with the evidence base and prescribed for the treatment of patients who are likely to benefit from IVIg therapy and for whom there are no safe and effective alternative treatments.

The conditions listed in *the Criteria* second edition are categorised according to the evidence identified through systematic reviews of the literature and the advice of clinical experts (see *Level of Evidence Categories* table on page 3). Governments have agreed to provide funded IVIg for the indications described in *the Criteria* second edition in chapter 5 (established therapeutic role), chapter 6

(emerging therapeutic role) and chapter 7 (exceptional circumstances only). IVIg is **not** funded under the National Blood Agreement to treat conditions listed in Chapter 8.

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

The Jurisdictional Blood Committee would like to acknowledge and thank those who contributed to the compilation of *the Criteria* including the members of the National IVIg Criteria Review Working Group:

Associate Professor Andrew Kornberg – neurology expert

Associate Professor John Gibson - haematology expert

Associate Professor Sean Riminton - clinical immunology expert

Dr Jane Peake - Australasian Society of Clinical Immunology and Allergy Representative

Dr Marija Borosak - Australian Red Cross Blood Service (Blood Service) Representative

Associate Professor Lyn Kiers - Australian and New Zealand Association of Neurologists

Dr Philip Crispin - Haematology Society of Australia and New Zealand Representative

Ms Joan Bedford and Ms Carolyn Duck - JBC Representatives

Dr Chris Hogan - National Blood Authority Principal Medical Officer (to January 2012)

Professor Henry Ekert - Department of Health and Ageing (DoHA) Clinical Representative

The following colleges and societies provided additional expert advice

Australasian College of Dermatologists

Australian & New Zealand Intensive Care Society

Bone Marrow Transplant Society of Australia and New Zealand

National Asthma Council Australia

Perinatal Society of Australia and New Zealand

Thoracic Society of Australia and New Zealand

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

Governments recognise the need for *the Criteria* to be regularly reviewed to take account of the evolving processes of disease diagnosis, treatment and outcome evaluation.

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

LEVEL OF EVIDENCE CATEGORIES

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

ALPHABETICAL INDEX OF CONDITIONS

CONDITIONS –ROLE IN THERAPY INDEX

The following index lists the same medical conditions as in the Alphabetical Index above, but by therapeutic role as they appear in Chapters 5 through to 8 of the full Criteria as follows:

Chapter 5	Established Therapeutic Role
Chapter 6	Emerging Therapeutic Role
Chapter 7	Use in Exceptional Circumstance Only
Chapter 8	Use of IVIg is **not** supported

The above colour coding has been applied throughout the remainder of the QRG to identify relevant role in therapy

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Amegakaryocytic thrombocytopenia	Linear IgA disease
Antiphospholipid syndrome (non-obstetric)	Lupus cerebritis
Aplastic anaemia/pancytopenia	Lupus nephritis
Asthma	Motor neuron disease/amyotrophic lateral sclerosis
Atopic dermatitis/eczema — adult	Myalgic encephalomyelitis
Autism	Narcolepsy/cataplexy
Autologous haemopoietic stem cell transplantation	Nephrotic syndrome
Behçet's disease	Obsessive compulsive disorders
Cardiac surgery with bypass — prophylaxis	Polyneuropathy of critical illness
Congestive cardiac failure	Recurrent foetal loss (with or without antiphospholipid syndrome)
Crohn's disease	Rheumatoid arthritis
Diamond Blackfan syndrome	Sepsis
Female infertility	Sickle cell disease
Glomerulonephritis — IgA nephritis	Systemic lupus erythematosus
Haemolytic uraemic syndrome	Ulcerative colitis

Conditions

Medical condition	ACQUIRED HYPOGAMMAGLOBULINAEMIA SECONDARY TO HAEMATOLOGICAL MALIGNANCIES (Condition for which IVIg has an *established* therapeutic role)
Indication for IVIg use	Prevention of recurrent bacterial infections due to antibody failure associated with haematological malignancies. Prevention of recurrent bacterial infections in patients undergoing haemopoietic stem cell transplantation (HSCT) for haematological malignancies.
Level of evidence	Evidence of probable benefit (Category 2a).
Description and diagnostic criteria	The manifestations of haematological malignancies can include a wide range of symptoms and physical and laboratory abnormalities in an individual patient. For diagnostic criteria, refer to the current World Health Organization classification criteria.
Qualifying criteria for IVIg therapy	Diagnosis of acquired hypogammaglobulinaemia secondary to haematological malignancies or stem cell transplantation with: • Recurrent or severe bacterial infection(s) and evidence of hypogammaglobulinaemia (excluding paraprotein); OR • Hypogammaglobulinaemia with IgG ‹4 g/L (excluding paraprotein). **Note:** For data tracking purposes, the type of malignancy being treated should be recorded with each request for IVIg.

Medical condition	ACQUIRED HYPOGAMMAGLOBULINAEMIA SECONDARY TO HAEMATOLOGICAL MALIGNANCIES (Condition for which IVIg has an *established* therapeutic role)
Exclusion criteria	The following conditions should not be approved under this indication: 1. HIV in children (see page 59); 2. Transplantation-related immunomodulation (solid organ transplantation; (see page 121); 3. Secondary hypogammaglobulinaemia (including iatrogenic immunodeficiency (see page 116).
Review criteria for assessing the effectiveness of IVIg use	Six-monthly review to assess clinical benefit. Cessation of IVIg should be considered, at least after each 12 months of therapy, extended as required to enable cessation of therapy in September/October, with repeat clinical and/or immunological evaluation before re-commencement of therapy. Written confirmation from the treating physician that: • an annual review has been undertaken; • the patient had demonstrated clinical benefit; • a trial period of cessation of IVIg for the purpose of immunological evaluation is medically contraindicated on safety grounds. In principle, IVIg should be continued or renewed only if there is a demonstrated clinical benefit.

Medical condition	ACQUIRED HYPOGAMMAGLOBULINAEMIA SECONDARY TO HAEMATOLOGICAL MALIGNANCIES (Condition for which IVIg has an *established* therapeutic role)
Dose	**Maintenance dose:** 0.4 g/kg every four weeks, modified to achieve an IgG trough level of at least the lower limit of the age-specific serum IgG reference range. **Loading dose:** One additional dose of 0.4 g/kg in the first month of therapy is permitted if the serum IgG level is <4 g/L. Subcutaneous administration of immunoglobulin can be considered as an alternative to IVIg. A suggested dose is 0.1 g/kg lean body mass every week modified to achieve an IgG trough level of at least the lower limit of the age-specific serum IgG reference range. **Refer to the current product information sheet for further information.** **The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.**

Medical condition	ACUTE DISSEMINATED ENCEPHALOMYELITIS (ADEM) (Condition for which IVIg has an *emerging* therapeutic role)
Indication for IVIg use	1. ADEM unresponsive to steroid therapy or where steroids are contraindicated (e.g. suspicion of CNS infection). 2. Recurrent or multiphasic ADEM unresponsive to steroid therapy or where steroid therapy has become intolerable or is contraindicated.
Level of evidence	Evidence of probable benefit (Category 2a).
Description and diagnostic criteria	ADEM is a monophasic inflammatory condition of the central nervous system that usually presents in children and young adults. It typically occurs following a viral prodrome with multifocal neurological disturbance and altered conscious state. ADEM usually follows a monophasic course, but patients may experience recurrence of the initial symptom complex (recurrent ADEM) or a second episode of ADEM (multiphasic ADEM). The majority make a full recovery. ADEM is thought to have an autoimmune basis. Pathologic similarities to experimental allergic encephalomyelitis (EAE), an animal model of inflammatory demyelination, support this theory. It is postulated that a common antigen shared by an infectious agent and a myelin epitope results in an autoimmune response.

Medical condition	ACUTE DISSEMINATED ENCEPHALOMYELITIS (ADEM) (Condition for which IVIg has an *emerging* therapeutic role)
Description and diagnostic criteria continued	Patients show multiple demyelinating lesions on magnetic resonance imaging (MRI) in the deep and subcortical white matter. The differential diagnosis includes other inflammatory demyelinating disorders, such as multiple sclerosis, optic neuritis and transverse myelitis. High-dose corticosteroids are first-line treatment of ADEM. IVIg has been used for patients who fail to respond to steroid therapy or in patients where steroids are contraindicated. Most patients with ADEM recover completely over a period of six weeks from onset. There is no biological marker for ADEM. Diagnosis is by clinical recognition of the multifocal neurological disturbance and altered conscious state, with the typical MRI findings of demyelination.
Qualifying criteria for IVIg therapy	1. ADEM unresponsive to steroid therapy or where steroids are contraindicated (e.g. suspicion of CNS infection). **Note:** Assessment by a neurologist is recommended, but not mandatory. OR 2. Recurrent or multiphasic ADEM unresponsive to steroid therapy, or where steroid therapy has become intolerable or is contraindicated, with assessment by a neurologist mandatory.
Review criteria for assessing the effectiveness of IVIg use	Objective evidence of improvement in relapse rate in comparison to pre-treatment levels. Six-monthly review by a neurologist is required for recurrent or multiphasic ADEM.

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

Medical condition	ACUTE LEUKAEMIA IN CHILDREN (Condition for which IVIg use is in *exceptional* circumstances only)
Indication for IVIg use	[Includes acute lymphoblastic or lymphoid leukaemia (ALL) and acute myeloblastic leukaemia (AML)]. IVIg may be considered in cases of ALL or AML with neutropenic sepsis in patients aged ≤15 years in whom conventional antimicrobial therapy has been ineffective and who have life-threatening infection. **Refer to the current product information sheet for further information.** **The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.**
Level of evidence	Evidence of probable benefit (Category 2a).

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

Medical condition	ANTI-NEUTROPHIL CYTOPLASMIC ANTIBODY (ANCA)-POSITIVE SYSTEMIC NECROTISING VASCULITIS (Condition for which IVIg has an *emerging* therapeutic role)
Qualifying criteria for IVIg therapy	MPO or PR3 ANCA-positive systemic necrotising vasculitis with both of the following: 1. Current (or within the previous six months) standard cytotoxic immunosuppressive ANCA-vasculitis regimens; AND 2. Persisent active disease.
Exclusion criteria for IVIg therapy	Initial therapy
Review criteria for assessing the effectiveness of IVIg use	• Six-month review assessing evidence of clinical benefit. • Reduction in the Birmingham vasculitis activity score of more than 50% after three months. • Erythrocyte sedimentation rate and C-reactive protein concentration. • ANCA titre.
Dose	2 g/kg in single or divided doses. **Dosing above 1 g/kg per day is contraindicated for some IVIg products.** **Refer to the current product information sheet for further information.** **The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.**

Medical condition	AUTOIMMUNE CONGENITAL HEART BLOCK (Condition for which IVIg use is in *exceptional* circumstances only)
Indication for IVIg use	IVIg therapy may be indicated during pregnancy when there is a history of autoimmune congenital heart block in at least one previous pregnancy and maternal SS-A and/or SS-B antibodies are present. **Refer to the current product information sheet for further information.** **The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.**
Level of evidence	Small case studies only - insufficient data (Category 4a).

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

Medical condition	AUTOIMMUNE HAEMOLYTIC ANAEMIA (AIHA) (Condition for which IVIg has an *emerging* therapeutic role)
Qualifying criteria for IVIg therapy	1. Symptomatic or severe AIHA (Hb <60 g/L, except patients with co-morbidities) refractory to conventional therapy with corticosteroids; OR 2. As a temporising measure before splenectomy; OR 3. As initial and maintenance therapy in AIHA in patients unsuitable for splenectomy or immunosuppression.
Exclusion criteria for IVIg therapy	Patients in whom a trial of corticosteroids has not been undertaken.
Review criteria for assessing the effectiveness of IVIg use	• Resolution of haemolytic anaemia (rising haemoglobin concentrations, falling bilirubin and LDH). • Clinical improvement in symptoms and signs.
Dose	Up to 2 g/kg as a single or divided dose. **Dosing above 1 g/kg per day is contraindicated for some IVIg products.** **Refer to the current product information sheet for further information.** **The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.**

Medical condition	AUTOIMMUNE NEUTROPENIA (Condition for which IVIg use is in *exceptional* circumstances only)
Indication for IVIg use	Autoimmune neutropenia is a rare disorder caused by peripheral destruction of antibody-sensitised neutrophils by cells of the reticuloendothelial system. IVIg may be considered among treatment options in rare circumstances when the standard treatment of G-CSF fails. **Refer to the current product information sheet for further information.** **The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.**
Level of evidence	Small case studies only - insufficient data (Category 4a).

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

Medical condition	BULLOUS PEMPHIGOID (BP) (Condition for which IVIg has an *emerging* therapeutic role)
Indication for IVIg use	Bullous pemphigoid resistant to topical and systemic glucocorticoids and immunosuppressive therapy.
Level of evidence	Small case studies only; insufficient data (Category 4a).
Description and diagnostic criteria	BP is a rare disease of elderly people characterised by tense blisters and vesicles with a prominent inflammatory component. The cause is unknown. Lesions result from a failure of basal keratinocytes to adhere to the epidermal basement membrane. The course of BP is characterised by exacerbations and remissions. Pruritis is a common feature and an increase in pruritis may herald an exacerbation. In most patients, BP is not a life-threatening disease. The side effects of systemic immunosuppressive therapy need to be managed. In most patients, the disease spontaneously clears within six years and all medication can be stopped. In a small group, the disease recurs after treatment is stopped. Skin infection is the most common complication. A submission by the Australasian College of Dermatologists recommends IVIg use in BP only in severe cases where improvement with conventional therapy is not readily achieved.

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

Medical condition	CATASTROPHIC ANTIPHOSPHOLIPID SYNDROME (Condition for which IVIg use is in *exceptional* circumstances only)
Indication for IVIg use	IVIg may be appropriate therapy for catastrophic antiphospholipid syndrome, a term that describes the accelerated form of antiphospholipid syndrome characterised by widespread small vessel thrombosis leading to multiorgan failure. It is not indicated for the treatment of antiphospholipid syndrome in other cases. Please see *Antiphospholipid syndrome (non-obstetric)* (page 14) and *Recurrent foetal loss (with or without antiphospholipid syndrome)* (page 14). **Qualifying criteria for IVIg therapy** A patient will qualify for IVIg when *all* the following criteria are met: 1. Evidence of rapidly evolving thrombosis involving two or more organs; 2. Unequivocal laboratory evidence of antiphospholipid antibodies (lupus anticoagulant and/or anticardiolipin antibodies and/or beta 2 glycoprotein I antibodies); and 3. Other causes of thrombotic microangiopathy are considered less likely. Confirmation by histopathology of thrombotic small vessel occlusion in at least one organ or tissue is desirable but should not delay IVIg therapy if indicated. A single treatment is usually sufficient, based on a dose of 2 g/kg divided over 2–5 days. The potential pro-thrombotic effect of IVIg should be considered in this indication.

Medical condition	CATASTROPHIC ANTIPHOSPHOLIPID SYNDROME (Condition for which IVIg use is in *exceptional* circumstances only)
Indication for IVIg use continued	**Refer to the current product information sheet for further information.** **The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.**
Level of evidence	Small case studies only - insufficient data (Category 4a).

Medical condition	CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY (CIDP) (Condition for which IVIg has an *established* therapeutic role)
Indication for IVIg use	First-line treatment for CIDP with treatment initiated when progression is rapid, or walking is compromised, or there is significant functional impairment.
Level of evidence	Clear evidence of benefit (Category 1).
Description and diagnostic criteria	CIDP is an acquired sensorimotor polyneuropathy characterised by a progressive or relapsing/ remitting course with evidence of demyelination on electrophysiological or pathological studies and response to immunomodulating therapies. There is no specific diagnostic test, but characteristic clinical and laboratory findings help distinguish this disorder from other immune mediated neuropathic syndromes. Serum protein electrophoresis with immunofixation may be indicated to search for monoclonal gammopathy and associated conditions.
Qualifying criteria for IVIg therapy	1. Diagnosis of CIDP verified by a neurologist; AND 2. Significant functional impairment of activities of daily living.

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

Medical condition	CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY (CIDP) (Condition for which IVIg has an *established* therapeutic role)
Dose	**Induction:** 2 g/kg in 2 to 5 divided doses. **Maintenance:** 0.4–1 g/kg, 2–6 weekly. The amount per dose should be titrated to the individual's response. Aim for minimum dose to maintain optimal functional status. **Refer to the current product information sheet for further information.** **The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.**

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

Medical condition	CICATRICIAL PEMPHIGOID (CP) or MUCOUS MEMBRANE PEMPHIGOID (MMP) (Condition for which IVIg has an *emerging* therapeutic role)
Qualifying criteria for IVIg therapy	Moderate to severe disease diagnosed by a dermatologist; AND 1. Corticosteroids or immunosuppressive agents are contraindicated; OR 2. Condition is unresponsive to corticosteroids and immunosuppressive agents; OR 3. Presenting with severe side effects of therapy.
Review criteria for assessing the effectiveness of IVIg use	• Response demonstrated at review at six months. Improvement to be demonstrated for continuation of supply. • Disease recurrence or relapse and duration of clinical remission. • Ability to reduce dose or discontinue other therapies. • Resolution of conjunctival inflammation. • Reduction of drug-related side effects.

Medical condition	CICATRICIAL PEMPHIGOID (CP) or MUCOUS MEMBRANE PEMPHIGOID (MMP) (Condition for which IVIg has an *emerging* therapeutic role)
Dose	Efficacy demonstrated with doses of at least 2 g/kg per monthly treatment cycle. **Dosing above 1 g/kg per day is contraindicated for some IVIg products.** **Refer to the current product information sheet for further information.** **The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.**

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

Medical condition	COAGULATION FACTOR INHIBITORS (Condition for which IVIg use is in *exceptional* circumstances only)
Indication for IVIg use continued	3. Acquired haemophilia A for: a. Support of correction of FVIII level for the management of bleeding, and before invasive procedures in individuals in whom steroid or immunosuppressive therapy is contraindicated or has failed to eradicate the inhibitor (2 g/kg over 2–5 days); or b. Support of correction of FVIII level following failure of first line therapies (steroids and immunosuppressants) and poor response to recombinant factor VIIa or FEIBA when used as part of the Bonn–Malmö protocol. 4. Other acquired (autoimmune) coagulation inhibitors (e.g. acquired Factor V inhibitors) to correct factor level for the management of bleeding and before invasive procedures in cases where other therapeutic approaches have failed or are contraindicated (2 g/kg over 2 to 5 days). Dosing above 1 g/kg per day is contraindicated for some IVIg products. **Refer to the current product information sheet for further information.** **The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.**
Level of evidence	Evidence of probable benefit (Category 2a).

Medical condition	DEVIC DISEASE (neuromyelitis optica) (Condition for which IVIg use is in *exceptional* circumstances only)
Indication for IVIg use	Devic disease is an idiopathic inflammatory demyelinating disorder of the central nervous system characterised by recurrent bouts of optic neuritis and myelitis. It is distinct from multiple sclerosis and evidence of B-cell autoimmunity has been found. A circulatory antibody to aquaporin-4 is found in many patients providing further evidence of B-cell autoimmunity in its pathogenesis and suggestive of a role for IVIg therapy. Single case reports of various therapies, including IVIg, have shown variable benefit in this otherwise devastating disorder. **Refer to the current product information sheet for further information.** **The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.**
Level of evidence	Small case studies only - insufficient data (Category 4a).

Medical condition	DIABETIC AMYOTROPHY (Condition for which IVIg use is in *exceptional* circumstances only)
Indication for IVIg use	IVIg may be considered in exceptional circumstances for intractable pain or progressive muscle weakness in patients in whom steroids are ineffective or cannot be tolerated. This condition is monophasic and usually self-limiting. A single treatment may be sufficient, although monthly infusions for up to six months may be required for recurrent pain. **Refer to the current product information sheet for further information.** **The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.**
Level of evidence	Small case studies only - insufficient data (Category 4a).

Medical condition	EPIDERMOLYSIS BULLOSA ACQUISITA (Condition for which IVIg use is in *exceptional* circumstances only)
Indication for IVIg use	IVIg should be considered for severe cases refractory to conventional immunosuppressive therapy. **Refer to the current product information sheet for further information.** **The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.**
Level of evidence	Small case studies only - insufficient data (Category 4a).

Medical condition	EPILEPSY (Condition for which IVIg use is in *exceptional* circumstances only)
Indication for IVIg use	• Landau–Kleffner syndrome • Lennox–Gastaut syndrome IVIg should be considered in childhood cases only after failure of all conventional therapies and full assessment by a paediatric neurologist. **Refer to the current product information sheet for further information.** **The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.**
Level of evidence	Evidence of probable benefit (Category 2a).

Medical condition	EVANS SYNDROME (Condition for which IVIg has an *emerging* therapeutic role)
Indication for IVIg use	To reduce platelet destruction and improve haemolysis in patients not responding to corticosteroid therapy.
Level of evidence	Small case studies only; insufficient data (Category 4a).
Description and diagnostic criteria	Evans syndrome is a rare but serious autoimmune disease defined by the simultaneous or sequential occurrence of autoimmune haemolytic anaemia (AIHA) and immune thrombocytopenia purpura (ITP) without underlying aetiology. As such, it is a diagnosis of exclusion and other disorders, such as collagen vascular diseases, especially systemic lupus erythematosus (SLE) and scleroderma should be ruled out. The 2005 review by Norton and Roberts provided perspective on diagnosis, clinical features and management.
Qualifying criteria for IVIg therapy	1. Refractory to conventional therapy with corticosteroids; OR 2. Where corticosteroids are contraindicated; OR 3. As a temporising measure before splenectomy.
Exclusion criteria for IVIg therapy	Patients in whom a trial of corticosteroids has not been undertaken (providing corticosteroids are not contra-indicated and can be tolerated at the required doses).

Medical condition	EVANS SYNDROME (Condition for which IVIg has an *emerging* therapeutic role)
Review criteria for assessing the effectiveness of IVIg use	• Maintenance therapy rarely required. • Resolution of haemolytic anaemia. • Improvement in platelet count. • Clinical improvement in symptoms and signs.
Dose	Up to 2 g/kg in divided dose. Dosing above 1 g/kg per day is contraindicated for some IVIg products. **Refer to the current product information sheet for further information.** **The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.**

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

Medical condition	FOETO-MATERNAL/NEONATAL ALLOIMMUNE THROMBOCYTOPENIA (FMAIT/NAIT) (Condition for which IVIg has an *emerging* therapeutic role)
Description and diagnostic criteria continued	Management of this condition is a specialised area and may include administration of HPA-compatible intrauterine and/or neonatal platelet transfusions. Further information regarding specialised platelet support is available from the Blood Service. Random (non-HPA-matched) platelets may be of benefit in the neonatal setting when matched platelets are not available (Kiefel 2006).
Qualifying criteria for IVIg therapy	Clinical suspicion of FMAIT in antenatal or neonatal setting based on clinical and laboratory features, including: 1. Thrombocytopenia or spontaneous haemorrhage in the foetus; OR 2. Thrombocytopenia with or without haemorrhage in the neonate; OR 3. Unexplained foetal death in a previous pregnancy and the presence of maternal platelet-specific alloantibodies that are known or suspected to cause this condition (most commonly HPA-1a or HPA-5b).

Medical condition	FOETO-MATERNAL/NEONATAL ALLOIMMUNE THROMBOCYTOPENIA (FMAIT/NAIT) (Condition for which IVIg has an *emerging* therapeutic role)
Review criteria for assessing the effectiveness of IVIg use	• Foetal or neonatal morbidity and mortality in the context of maternal alloantibodies. • Occurrence and severity of thrombocytopenia in the neonate. • Maternal HPA-1a antibody level (if assay is available). Note that the strength/titre of maternal antibody level, even if available, is not proven clinically relevant and not able to be compared readily between laboratories at this time.
Dose	Maternal dose: 1 g/kg weekly throughout pregnancy, with starting time tailored to individual risk profile and history if relevant. Other doses and schedules have been used and some studies have used IVIg in conjunction with steroids. Treatment of the neonate: 1 g/kg. Occasionally more than one dose is required if thrombocytopenia persists. **Refer to the current product information sheet for further information.** **The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.**

Medical condition	GRAVES OPHTHALMOPATHY (Condition for which IVIg use is in *exceptional* circumstances only)
Indication for IVIg use	IVIg may be indicated in select cases. Tagami et al, *Endocrinology* **43**:6, 689-99 have shown that IVIg is effective in this condition. Other studies have shown IVIg to be as effective as corticosteroids with fewer side effects. May be indicated where steroids have failed or are contraindicated. **Refer to the current product information sheet for further information.** **The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.**
Level of evidence	Evidence of probable benefit (Category 2a).

Medical condition	GUILLAIN–BARRÉ SYNDROME (GBS) (Condition for which IVIg has an *established* therapeutic role)
Indication for IVIg use	GBS and its variants with significant disability and progression.
Level of evidence	Clear evidence of benefit (Category 1).
Description and diagnostic criteria	GBS is the commonest cause of acute flaccid paralysis in the West. The syndrome typically presents with rapidly progressive, relatively symmetrical ascending limb weakness consistent with a polyradiculoneuropathy and often with associated cranial nerve involvement. Motor signs and symptoms usually predominate over sensory signs and symptoms. Loss of tendon reflexes occurs in most cases. Major complications include respiratory failure and autonomic dysfunction. The disease is monophasic, reaching its nadir usually within two weeks, although arbitrary definition accepts a limit of four weeks. A plateau phase of variable duration follows the nadir before gradual recovery. Although recovery is generally good or complete in the majority of patients, persistent disability has been reported to occur in about 20% and death in 4 to 15% of patients. IVIg has been shown to have the same efficacy as plasma exchange. The choice is based on availability, practicality, convenience, cost, and ease or safety of administration (Asia–Pacific IVIg Advisory Group).

Medical condition	GUILLAIN–BARRÉ SYNDROME (GBS) (Condition for which IVIg has an *established* therapeutic role)
Description and diagnostic criteria continued	*Investigations* There is no biological marker for GBS. It is diagnosed by clinical recognition of rapidly evolving paralysis with areflexia. Investigations include the following: • Cerebrospinal fluid (CSF) protein elevation, although the level may be normal in the first two weeks of illness. The CSF white cell count may rise transiently, but a sustained pleocytosis suggests an alternative diagnosis or association with an underlying illness (e.g. HIV). • Electrophysiological studies may show changes after the first or second week of the illness, including conduction block, conduction slowing or abnormalities in F waves.
Qualifying criteria for IVIg therapy	Patients with GBS (or variant) with significant disability and disease progression. **Note:** Assessment by a neurologist is recommended, but not mandatory.
Review criteria for assessing the effectiveness of IVIg use	Primary outcome measures: improvement in disability grade four weeks after treatment: 0. healthy 1. minor symptoms or signs of neuropathy but capable of manual work 2. able to walk without support of a stick but incapable of manual work 3. able to walk with a stick, appliance or support 4. confined to bed or chair bound 5. requiring assisted ventilation 6. dead

Medical condition	GUILLAIN–BARRÉ SYNDROME (GBS) (Condition for which IVIg has an *established* therapeutic role)
Review criteria for assessing the effectiveness of IVIg use continued	Secondary outcome measures: 1. time until recovery of unaided walking 2. time until recovery of walking with aid 3. time until discontinuation of ventilation (for those ventilated) 4. death or disability (inability to walk without aid after 12 months) 5. treatment-related fluctuation
Dose	2 g/kg in 2 to 5 divided doses. Approximately 10% of patients relapse, which may require a second treatment with IVIg. A second dose of IVIg must only be on the advice of and after assessment by a neurologist. **Refer to the current product information sheet for further information.** **The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.**

Medical condition	HAEMOLYTIC DISEASE OF THE NEWBORN (HDN) (Condition for which IVIg use is in *exceptional* circumstances only)
Indication for IVIg use	HDN arises from foetomaternal antigen incompatibility and can result in clinically significant foetal/neonatal haemolysis, severe anaemia and hyperbilirubinaemia. Although prophylaxis programs have reduced the frequency of Rhesus (Rh) D HDN, antibodies to RhD remain the most common cause in Australia. Antibodies to other antigens in the Rh system (e.g. Rhc, E), ABO and other antigens (e.g. K) may also cause disease ranging from mild to life-threatening. IVIg may be used in selected cases in consultation with experts in foetomaternal medicine and transfusion medicine. **Refer to the current product information sheet for further information.** **The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.**
Level of evidence	Small case studies only - insufficient data (Category 4a).

Medical condition	HAEMOLYTIC TRANSFUSION REACTION (Condition for which IVIg use is in *exceptional* circumstances only)
Indication for IVIg use	IVIg may be considered in the management or prevention of severe haemolytic transfusion reaction not responding to other interventions (e.g. corticosteroids). **Refer to the current product information sheet for further information.** **The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.**
Level of evidence	Small case studies only - insufficient data (Category 4a).

Medical condition	HAEMOPHAGOCYTIC SYNDROME (Condition for which IVIg has an *emerging* therapeutic role)
Indication for IVIg use	Management of severe haemophagocytic syndrome not responding to other treatments.
Description and diagnostic criteria	Haemophagocytic syndrome is characterised by fever, splenomegaly, jaundice, rash and the pathologic finding of haemophagocytosis (phagocytosis by macrophages of erythrocytes, leukocytes, platelets and their precursors) in bone marrow and other tissues with peripheral blood cytopenias. Haemophagocytic syndrome has been associated with a wide range of infectious, autoimmune, malignant and other disorders (modified from Fisman 2000). Mortality is high.
Level of evidence	Small case studies only; insufficient data (Category 4a).
Qualifying criteria for IVIg therapy	Bone marrow diagnosis or other biopsy evidence of haemophagocytosis in the characteristic clinical setting. **Note:** Since other therapies (cytotoxic agents) have major potential side effects, optimal therapy is not yet defined.
Review criteria for assessing the effectiveness of IVIg use	• Amelioration of cytopenia(s), hepato/splenomegaly and lymphadenopathy if present. • Survival or death.

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

Medical condition	HASHIMOTO ENCEPHALOPATHY (Condition for which IVIg use is in *exceptional* circumstances only)
Indication for IVIg use	IVIg is not supported as first-line treatment, because preferable alternative treatments are available. IVIg may be considered in exceptional circumstances where there is progressive neurologic decline despite appropriate steroid therapy. **Refer to the current product information sheet for further information.** **The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.**
Level of evidence	Small case studies only - insufficient data (Category 4a).

Medical condition	HIV IN CHILDREN (Condition for which IVIg use is in *exceptional* circumstances only)
Indication for IVIg use	The need for IVIg in paediatric HIV has been substantially reduced with the advent of highly active antiretroviral therapy (HAART). A trial of therapy may however be considered in children with significant recurrent bacterial infections despite HAART. **Refer to the current product information sheet for further information.** **The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.**
Level of evidence	Evidence of probable benefit (Category 2a).

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

Medical condition	IDIOPATHIC THROMBOCYTOPENIC PURPURA (ITP) — ADULT (Condition for which IVIg has an *established* therapeutic role)
Description and diagnostic criteria	ITP is a reduction in platelet count (thrombocytopenia) resulting from shortened platelet survival due to anti-platelet antibodies. When counts are very low (<30x10^9/L), bleeding into the skin (purpura) and mucous membranes can occur. Bone marrow platelet production (megakaryopoiesis) is morphologically normal. In some cases, there is additional impairment of platelet function related to antibody binding to glycoproteins on the platelet surface. ITP is divided into chronic and acute forms. It is a common finding in patients with HIV, and while it may be found at any stage of the infection, its prevalence increases as HIV disease advances. Around 80% of adults with ITP have the chronic form of disease. The highest incidence of chronic ITP is in women aged 15–50 years, although some reports suggest increasing incidence with age. Chronic ITP may relapse and remit spontaneously and the course may be difficult to predict. If the platelet count can be maintained at a level that prevents spontaneous bleeding or bruising, the outlook is good.

Medical condition	IDIOPATHIC THROMBOCYTOPENIC PURPURA (ITP) — ADULT (Condition for which IVIg has an *established* therapeutic role)
Qualifying criteria for IVIg therapy	**1. Refractory acute ITP:** a. Patients qualify for initial IVIg therapy when conventional doses of corticosteroids (0.5-2.0 mg/kg prednisolone, or equivalent) have failed to improve the platelet count or stop bleeding within a clinically appropriate time frame, as assessed by a clinical haematologist. The objective of therapy is to induce a prompt increase in the platelet count (to ›30x10^9/L) while other therapies are introduced. b. Patients qualify for continuing doses when splenectomy has failed or is contraindicated AND where therapy with at least one second-line agent has been unsuccessful in maintaining a platelet count ›30x10^9/L. With ongoing therapy, IVIg may be administered to achieve a platelet count ›30x10^9/L. Further doses may be administered in responsive patients for up to 6 months (thereafter see *Chronic refractory ITP).* The frequency and dose should be titrated to maintain a platelet count of at least 30x10^9/L. The objective of therapy is to maintain a safe platelet count while other therapeutic options are explored. **2. ITP with life-threatening haemorrhage or the potential for life-threatening haemorrhage:** IVIg therapy may be given when conventional doses of corticosteroids have failed or in conjunction with steroids when a rapid response is required.

Medical condition	IDIOPATHIC THROMBOCYTOPENIC PURPURA (ITP) — ADULT (Condition for which IVIg has an *established* therapeutic role)
Qualifying criteria for IVIg therapy continued	**3. ITP in pregnancy:** a. Platelets <30x10^9/L: IVIg therapy may be used to avoid corticosteroids, immunosuppressive agents and splenectomy. Further doses titrated to maintain a platelet count >30x10^9/L may be administered every three to four weeks throughout the pregnancy. b. Impending delivery: IVIg therapy may be used to achieve a platelet count considered safe for delivery (80–100x10^9/L). **4. Specific circumstances:** *a. Planned surgery:* IVIg may be used to achieve a platelet count considered safe for surgery. The safe threshold will vary with the nature of the surgery *(Recommended platelet counts for patients without concurrent risks of bleeding: minor dental work >30x10^9/L, minor surgery >50x10^9/L, major surgery >80x10^9/L, major neurosurgery >100x10^9/L.* *b. Severe ITP:* IVIg may be used where corticosteroids and immunosuppression are contraindicated. *c. Chronic refractory ITP unresponsive to all other available therapies:* These patients may be considered for long-term maintenance therapy with IVIg, subject to regular review by a haematologist. **5. HIV-associated ITP:** a. Failure of antiretroviral therapy with platelet count <30x10^9/L; OR b. Life-threatening haemorrhage secondary to thrombocytopenia.

Medical condition	IDIOPATHIC THROMBOCYTOPENIC PURPURA (ITP) — ADULT (Condition for which IVIg has an *established* therapeutic role)
Review criteria for assessing the effectiveness of IVIg use	• In chronic refractory ITP, six-month review assessing evidence of clinical benefit • Resolution of bleeding • Increment in platelet count.
Dose	**Initial therapy:** 1–2 g/kg as a single or divided dose. **Ongoing therapy:** When indicated, 1–2 g/kg in single or divided dose at 4 to 6 weekly intervals titrated to symptoms and platelet count. **Dosing above 1 g/kg per day is contraindicated for some IVIg products.** **Refer to the current product information sheet for further information.** **The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.**

Medical condition	IDIOPATHIC THROMBOCYTOPENIC PURPURA (ITP) — CHILDREN 15 years and younger (Condition for which IVIg has an *emerging* therapeutic role)
Indication for IVIg use	ITP with platelet count <30x10^9/L with significant bleeding.
Level of evidence	Clear evidence of benefit (Category 1).
Description and diagnostic criteria	ITP is a reduction in platelet count (thrombocytopenia) resulting from shortened platelet survival due to anti-platelet antibodies. When counts are very low (<30x10^9/L) bleeding into the skin (purpura) and mucous membranes can occur. Bone marrow morphology is normal. In some cases, there is additional impairment of platelet function related to antibody binding to glycoproteins on the platelet surface. ITP is divided into chronic and acute forms. In children, the acute form is the most common. The disease tends to present abruptly with dramatic evidence of bleeding into the skin (petechiae and purpura) and mucous membranes (gum bleeding, nose bleeds, blood blisters). **Occurrence** Girls and boys are affected equally. In 75% of patients, the episode follows vaccination or a viral infection such as varicella or infectious mononucleosis. **Prognosis** At least 80–90% of children will have spontaneous remission of their disease within 6–12 months. In 5–10% of cases, the disease may become chronic (lasting >6 months). Morbidity and mortality from acute ITP is very low.

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

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

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

Medical condition	IgM PARAPROTEINAEMIC NEUROPATHY (Condition for which IVIg has an *emerging* therapeutic role)
Qualifying criteria for IVIg therapy	Diagnosis by a neurologist of IgM paraproteinaemic neuropathy with: 1. Functional impairment of activities of daily living; AND 2. Other therapies have failed or are contraindicated or undesirable.
Review criteria for assessing the effectiveness of IVIg use	IVIg should be used for three to six months (three to six courses) before determining whether the patient has responded. If there is no benefit after three to six courses, IVIg therapy should be abandoned. **Review** Regular review by neurologist is required; frequency as determined by clinical status of patient. For stable patients on maintenance treatment review by a neurologist is required at least annually. **Effectiveness** Clinical documentation of effectiveness is necessary for continuation of IVIg therapy. Effectiveness can be demonstrated by objective findings of either: 1. Improvement in functional scores (activities of daily living — ADLs) or quantitative muscle scores, or Medical Research Council (MRC) muscle assessment or neuropathy score; or 2. Stabilisation of disease as defined by stable functional scores (ADLs) or quantitative muscle scores, or MRC muscle assessment or neuropathy score after previous evidence of deterioration in one of these scores.

Medical condition	IgM PARAPROTEINAEMIC NEUROPATHY (Condition for which IVIg has an *emerging* therapeutic role)
Dose	**Induction:** 2 g/kg in 2–5 divided doses. **Maintenance:** 0.4–1 g/kg, 2 to 6 weekly. Maintenance treatment only with clear, objective improvement. Aim for minimum dose to maintain optimal functional status. **Refer to the current product information sheet for further information.** **The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.**

Medical condition	INFLAMMATORY MYOPATHIES (Condition for which IVIg has an *established* therapeutic role)
Indication for IVIg use	1. Patients with polymyositis (PM) or dermatomyositis (DM) with significant muscle weakness unresponsive to corticosteroids and other immunosuppressive agents. 2. Patients with inclusion body myositis (IBM) who have dysphagia affecting function. 3. Patients with rapidly progressive IBM.
Level of evidence	Evidence of probable benefit (Category 2a).
Description and diagnostic criteria	The inflammatory myopathies are a group of three discrete disorders of skeletal muscle: DM, PM and IBM. These disorders are acquired and have in common the occurrence of significant muscle weakness and the presence of an inflammatory response within the muscle. The diagnosis of DM, PM or IBM is usually made by neurologists or rheumatologists, and relies on the combination of careful clinical evaluation, an elevated creatine kinase level, electromyography and muscle biopsy.
Qualifying criteria for IVIg therapy	Diagnosis made by a neurologist, rheumatologist or immunologist of: 1. Patients with PM or DM who have significant muscle weakness or dysphagia and have not responded to corticosteroids and other immunosuppressive agents; OR 2. Patients with IBM who have dysphagia affecting function; OR 3. Patients with rapidly progressive IBM.

Medical condition	INFLAMMATORY MYOPATHIES (Condition for which IVIg has an *established* therapeutic role)
Exclusion criteria for IVIg therapy	Expert consensus does not recommend IVIg to treat the limb weakness of IBM.
Review criteria for assessing the effectiveness of IVIg use	IVIg should be used for three to six months (three to six courses) before determining whether the patient has responded. If there is no benefit after three to six courses, IVIg therapy should be abandoned. **Review** Regular review by a neurologist, rheumatologist, or clinical immunologist is required; frequency as determined by clinical status of patient. For stable patients on maintenance treatment, review by a specialist is required at least annually. **Effectiveness** Clinical documentation of effectiveness is necessary for continuation of IVIg therapy. Effectiveness can be demonstrated by objective findings of either: 1. Improvement in functional scores (ADLs) or quantitative muscle scores or MRC muscle assessment; OR 2. Stabilisation of disease as defined by stable functional scores (ADLs) or quantitative muscle scores or MRC muscle assessment after previous evidence of deterioration in one of these scores.

Medical condition	INFLAMMATORY MYOPATHIES (Condition for which IVIg has an *established* therapeutic role)
Dose	**Induction:** 2 g/kg in 2 to 5 divided doses. **Maintenance:** 0.4–1 g/kg, 4–6 weekly. Aim for the minimum dose to maintain optimal functional status. **Dosing above 1 g/kg per day is contraindicated for some IVIg products.** **Refer to the current product information sheet for further information.** **The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.**

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

Medical condition	KAWASAKI DISEASE (Condition for which IVIg has an *established* therapeutic role)
Description and diagnostic criteria continued	• changes of the extremities, including peripheral erythema, peripheral oedema, and subsequent periungual or more generalised desquamation; • polymorphous rash; • cervical lymphadenopathy. A diagnosis of Kawasaki disease may be made if fever and fewer than four of the changes listed above are present where there is strong clinical suspicion of Kawasaki disease (refer to Newburger 2004). Between 10% and 20% of cases, particularly in younger infants, present with fever and fewer than four of the listed criteria. Expert advice should be sought. Data support the use of IVIg while there is ongoing inflammation (usually taken as ongoing fever or raised acute inflammatory markers). Prognosis is worse if IVIg is used 10 days post-onset, but should be used at any time if there is evidence of inflammation. Up to 15% of patients do not respond to initial IVIg therapy. Consensus is for re-treatment with 2 g/kg of IVIg before considering steroids.
Qualifying criteria for IVIg therapy	Clinical diagnosis of Kawasaki disease by a paediatrician or immunologist.
Dose	2 g/kg in a single dose over 10–12 hours unless cardiac function necessitates the administration of a prolonged or divided treatment dose, usually once only. Re-treatment with 2 g/kg in a single dose may be given when there is ongoing inflammation.

Medical condition	KAWASAKI DISEASE (Condition for which IVIg has an *established* therapeutic role)
Dose continued	**Dosing above 1 g/kg per day is contraindicated for some IVIg products.** **Refer to the current product information sheet for further information.** **The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.**

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

Medical condition	KIDNEY TRANSPLANTATION (Condition for which IVIg has an *emerging* therapeutic role)
Description and diagnostic criteria continued	Antibody mediated rejection (AbMR) occurs in 5–10% of renal transplants that have been performed with a compatible cross match. Before the use of IVIg and plasma exchange, AbMR failed to respond adequately to therapy in most cases. Additionally, complications from therapy were severe and sometimes fatal. AbMR responds to IVIg with or without plasma exchange in more than 85% of patients.
Qualifying criteria for IVIg therapy	**Pre-transplantation** Patients in whom an antibody or antibodies prevent transplantation (donor-specific anti-HLA antibody/ies or anti-blood group antibody). **Post-transplantation** 1. Biopsy proven cellular rejection unresponsive to steroids with clinical evidence of graft dysfunction; OR 2. Acute antibody mediated rejection with clinical evidence of graft dysfunction; OR 3. As treatment or prophylaxis for rejection where conventional immunosuppressive therapy is contraindicated, for example: • in a patient with life-threatening infection in whom conventional immunosuppression will place the patient at even greater risk; • when the transplant is at risk (e.g. due to BK virus infection).

Medical condition	KIDNEY TRANSPLANTATION (Condition for which IVIg has an *emerging* therapeutic role)
Review criteria for assessing the effectiveness of IVIg use	• Allograft organ function tests. • Biopsy response. • Laboratory monitoring of anti-HLA antibody and/or anti-blood group antibody responses. • Duration of graft and patient survival. • Reversal of clinical graft dysfunction.
Dose	**IVIg with plasma exchange:** 0.1 to 0.5 g/kg post exchange. **IVIg alone:** 2 g/kg to a maximum of 140 g as a single dose, or 2 to 3.5 g/kg in a divided dose. When IVIg is used alone, further doses may be warranted two to four weeks after initial therapy depending on clinical response and/or biopsy findings. **Dosing above 1 g/kg per day is contraindicated for some IVIg products.** **Refer to the current product information sheet for further information.** **The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.**

Medical condition	LAMBERT–EATON MYASTHENIC SYNDROME (LEMS) (Condition for which IVIg has an *established* therapeutic role)
Indication for IVIg use	Short-term therapy for severely affected nonparaneoplastic LEMS patients.
Level of evidence	Evidence of probable benefit (Category 2a).
Description and diagnostic criteria	LEMS is a disorder of neuromuscular transmission first recognised clinically in association with lung cancer and subsequently in cases in which no neoplasm was detected. Patients with LEMS have a presynaptic neuromuscular junction defect. The clinical picture is characterised by proximal muscle weakness with augmentation of strength after exercise, mild oculomotor signs, depressed deep tendon reflexes and autonomic dysfunction (dry mouth, constipation, erectile failure).
Qualifying criteria for IVIg therapy	1. Mandatory assessment by a neurologist; AND 2. Severely affected nonparaneoplastic LEMS patients in whom other therapy (e.g. with 3,4-diaminopyridine) has failed.
Review criteria for assessing the effectiveness of IVIg use	IVIg should be used for three to six months (three to six courses) before determining whether the patient has responded. If there is no benefit after three to six courses, IVIg therapy should be abandoned. **Review** Regular review by neurologist is required: frequency as determined by clinical status of patient. Initial review three to six monthly. For stable patients on maintenance treatment review by a neurologist is required at least annually.

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

Medical condition	LIMBIC ENCEPHALITIS — NONPARANEOPLASTIC (Condition for which IVIg use is in *exceptional* circumstances only)
Indication for IVIg use	There appears to be a role for IVIg in nonparaneoplastic limbic encephalitis associated with neuronal antibodies to cell surface antigens. This includes VGKC antibodies, as well as NMDA receptor antibodies and AMPA receptor antibodies. **Refer to the current product information sheet for further information.** **The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.**
Level of evidence	Small case studies only - insufficient data (Category 4a).

Medical condition	LIMBIC ENCEPHALITIS —PARANEOPLASTIC (Condition for which IVIg use is in *exceptional* circumstances only)
Indication for IVIg use	IVIg may be indicated in select cases, in combination with tumour therapy (tumour resection and/or oncological treatment) where the latter has not led to an improvement in the neurologic syndrome; where other immunomodulatory therapies are contraindicated or have failed; or if the neurologic features warrant urgent intervention. **Refer to the current product information sheet for further information.** **The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.**
Level of evidence	Small case studies only - insufficient data (Category 4a).

Medical condition	MULTIFOCAL MOTOR NEUROPATHY (MMN) (Condition for which IVIg has an *established* therapeutic role)
Indication for IVIg use	First-line therapy for MMN.
Level of evidence	Clear evidence of benefit (Category 1).
Description and diagnostic criteria	MMN is a relatively rare disorder characterised by slowly progressive, asymmetric, predominately distal limb weakness without sensory impairment. Weakness often begins in the arms and the combination of weakness, wasting, cramps and fasciculations may suggest a diagnosis of motor neuron disease. However, clinical examination may demonstrate that the pattern of weakness follows the distribution of individual nerves rather than a spinal segmental pattern. Investigations will typically show conduction block on nerve conduction studies. IgM anti-GM-1 antibodies have been reported in a large number of patients with MMN and provide confirmatory evidence but are not essential for the diagnosis.
Qualifying criteria for IVIg therapy	Patients who have multifocal motor neuropathy, with a typical clinical phenotype, with or without persistent conduction block, as diagnosed by a neurologist.
Exclusion criteria for IVIg therapy	• Presence of upper motor neuron signs. • Significant sensory impairment without an adequate alternative explanation.

Medical condition	MULTIFOCAL MOTOR NEUROPATHY (MMN) (Condition for which IVIg has an *established* therapeutic role)
Review criteria for assessing the effectiveness of IVIg use	IVIg should be used for three to six months (three to six courses) before determining whether the patient has responded. Most individuals will respond within three months unless there is significant axonal degeneration whereby a six-month course will be necessary. If there is no benefit after three to six courses, IVIg therapy should be abandoned. **Review** Regular review by neurologist is required: frequency as determined by clinical status of patient. For stable patients on maintenance treatment, review by a neurologist is required at least annually. **Effectiveness** Clinical documentation of effectiveness is necessary for continuation of IVIg therapy. Effectiveness can be demonstrated by objective findings of either: 1. Improvement in functional scores activities of daily living (ADL) or quantitative muscle scores or Medical Research Council (MRC) muscle assessment or neuropathy score; OR 2. Stabilisation of disease as defined by stable functional scores (ADLs) or quantitative muscle scores or MRC muscle assessment or neuropathy score after previous evidence of deterioration in one of these scores.

Medical condition	MULTIFOCAL MOTOR NEUROPATHY (MMN) (Condition for which IVIg has an *established* therapeutic role)
Dose	**Induction:** 2 g/kg in 2 to 5 divided doses. **Maintenance:** 0.4–2 g/kg, 2–6 weekly. The amount per dose should be titrated to the individual's response. Aim for the minimum dose to maintain optimal functional status. **Dosing above 1 g/kg per day is contraindicated for some IVIg products.** **Refer to the current product information sheet for further information.** **The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.**

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

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

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

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

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

Medical condition	MYASTHENIA GRAVIS (MG) (Condition for which IVIg has an *established* therapeutic role)
Review criteria for assessing the effectiveness of IVIg use continued	• Quantitative Myasthenia gravis score (Duke); • respiratory function (e.g. forced vital capacity); • quantitative dynamometry of proximal limb muscles; • variation of a myasthenic muscular score (MSS).
Dose	**Maintenance:** 0.4–1 g/kg, 4–6 weekly. **Induction or before surgery, or during myasthenic crisis:** 1–2 g/kg in 2 to 5 divided doses. Aim for minimum dose to maintain optimal functional status. **Note:** smaller dosage may be of greater efficacy. **Refer to the current product information sheet for further information.** **The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.**

Medical condition	MYOCARDITIS IN CHILDREN (Condition for which IVIg use is in *exceptional* circumstances only)
Indication for IVIg use	There is some evidence that IVIg improves cardiac function in children with proven or likely viral myocarditis. **Refer to the current product information sheet for further information.** **The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.**
Level of evidence	Small case studies only - insufficient data (Category 4a).

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

Medical condition	NEONATAL HAEMOCHROMATOSIS (NH) (Condition for which IVIg has an *established* therapeutic role)
Description and diagnostic criteria continued	In addition to extensive iron deposition (siderosis), liver biopsy would show cirrhosis with diffuse fibrosis, bile duct proliferation, and giant cells. Siderosis is also present in other tissues and viscera (e.g. epithelial tissues and the heart) but not in reticuloendothelial cells. **Occurrence** NH is a rare disease but the rate of recurrence after the index case in a sibship is up to 80%. **Prognosis** About 20% survival with medical treatment.
Qualifying criteria for IVIg therapy	Women who are pregnant or attempting to conceive and their most recent pregnancy ended in delivery of a foetus shown to have had NH.
Review criteria for assessing the effectiveness of IVIg use	• Occurrence of NH, or evidence of liver disease (serum ferritin and a-fetoprotein levels, coagulopathy) in the offspring of women who have previously given birth to an NH-affected neonate. • Requirement for liver transplantation in these neonates. • Survival and development of infants following maternal IVIg therapy during pregnancy.
Dose	1 g/kg body weight weekly from the 18th week until the end of gestation. **Refer to the current product information sheet for further information.** **The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.**

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

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

Medical condition	PAEDIATRIC AUTOIMMUNE NEUROPSYCHIATRIC DISORDER ASSOCIATED WITH STREPTOCOCCAL INFECTION (PANDAS) (Condition for which IVIg use is in *exceptional* circumstances only)
Indication for IVIg use	PANDAS was first described in the early 1990s. PANDAS is characterised by rapid-onset tics associated with obsessive-compulsive disorder (OCD) in the context of recovery from streptococcal infection. Molecular mimicry between streptococcal antigens and the central nervous system is thought to underlie the cause. Symptomatic therapy is used with variable response. A single randomised placebo-controlled trial using IVIg for PANDAS showed very prolonged and significant improvement in obsessive-compulsive symptoms, anxiety, depression, emotional lability and overall function compared with placebo. Improvements in symptoms were still evident at one-year follow-up. **Refer to the current product information sheet for further information.** **The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.**
Level of evidence	Evidence of probable benefit (Category 2a).

Medical condition	PARANEOPLASTIC CEREBELLAR DEGENERATION (Condition for which IVIg use is in *exceptional* circumstances only)
Indication for IVIg use	IVIg may be indicated in select cases, in combination with tumour therapy (tumour resection and/or oncological treatment) where the latter has not led to an improvement in the neurologic syndrome; where other immunomodulatory therapies are contraindicated or have failed; or if the neurologic features warrant urgent intervention. **Refer to the current product information sheet for further information.** **The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.**
Level of evidence	Small case studies only; insufficient data (Category 4a).

Medical condition	PARANEOPLASTIC SUBACUTE SENSORY NEUROPATHY (Condition for which IVIg use is in *exceptional* circumstances only)
Indication for IVIg use	IVIg may be indicated in select cases, in combination with tumour therapy (tumour resection and/or oncological treatment) where the latter has not led to an improvement in the neurologic syndrome; where other immunomodulatory therapies are contraindicated or have failed; or if the neurologic features warrant urgent intervention. **Refer to the current product information sheet for further information.** **The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.**
Level of evidence	Small case studies only; insufficient data (Category 4a).

Medical condition	PEMPHIGUS FOLIACEUS (PF) (Condition for which IVIg has an *emerging* therapeutic role)
Indication for IVIg use	PF resistant to corticosteroids and immunosuppressive therapy or when these agents are contra-indicated.
Level of evidence	Small case studies only; insufficient data (Category 4a).
Description and diagnostic criteria	PF is a rare autoimmune blistering skin disease characterised by loss of cohesion of cells (acantholysis) in the superficial (subcorneal) layers of the epidermis. The lesions are generally well demarcated and do not coalesce to form large eroded areas (as seen in pemphigus vulgaris). It is mediated by an autoantibody that targets desmoglein 1, a cell-to-cell protein molecule that binds the desmosomes of neighbouring keratinocytes in the epidermis. The disease has a long-term course with patients maintaining satisfactory health. Spontaneous remissions occasionally occur.
Qualifying criteria for IVIg therapy	Severe widespread PF, defined as disease involving 30% or more of body surface area, diagnosed by a dermatologist; AND 1. Corticosteroids or immunosuppressive agents are contraindicated; OR 2. Condition is unresponsive to corticosteroids and immunosuppressive agents; OR 3. Presenting with severe side effects of therapy.

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

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

Medical condition	PEMPHIGUS VULGARIS (PV) (Condition for which IVIg has an *emerging* therapeutic role)
Qualifying criteria for IVIg therapy	Moderate to severe disease diagnosed by a dermatologist; AND 1. Corticosteroids or immunosuppressive agents are contraindicated; OR 2. Condition is unresponsive to corticosteroids and immunosuppressive agents; OR 3. Presenting with severe side effects of therapy.
Review criteria for assessing the effectiveness of IVIg use	• Response demonstrated at review at six months. Improvement to be demonstrated for continuation of supply. • Titres of serum antibodies against keratinocytes. • Whether systemic corticosteroids can be gradually discontinued. • Total dose and duration of corticosteroid therapy, and number of relapses before and after the initiation of IVIg therapy.

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

Medical condition	POST-TRANSFUSION PURPURA (PTP) (Condition for which IVIg has an *emerging* therapeutic role)
Indication for IVIg use	Treatment of profound thrombocytopenia associated with bleeding.
Level of evidence	Small case studies only; insufficient data (Category 4a).
Description and diagnostic criteria	PTP is caused by antibodies to platelet-specific antigens, usually anti-HPA1a. PTP may result in profound thrombocytopenia with associated life-threatening bleeding. While the platelet count typically recovers spontaneously, this can take several weeks or more. Specialised investigations (antibody screening, patient/donor genotyping) and antigen-matched platelet and/or red cell transfusion support may be required — contact the Blood Service for more information.
Qualifying criteria for IVIg therapy	Clinical diagnosis/suspicion of PTP with thrombocytopenia associated with life-threatening bleeding. **Note:** Laboratory confirmation is desirable where possible in the time frame (usually an urgent, life-threatening clinical situation).
Review criteria	• Platelet counts in the days and weeks following IVIg. • Resolution of bleeding.
Dose	1 g/kg as a total dose, repeated if necessary. **Refer to the current product information sheet for further information.** **The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.**

Medical condition	POTASSIUM CHANNEL ANTIBODY-ASSOCIATED ENCEPHALOPATHY (Condition for which IVIg use is in *exceptional* circumstances only)
Indication for IVIg use	Potassium channel antibody-associated neurologic syndromes include limbic encephalitis/subacute amnesic encephalopathy, Morvan syndrome, peripheral nerve hyperexcitability and autonomic ganglionopathy. Potassium channel antibody-associated encephalopathy is considered to be an autoimmune, nonparaneoplastic, potentially treatable syndrome, but may respond to a variety of immunomodulatory agents, including IVIg. **Refer to the current product information sheet for further information.** **The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.**
Level of evidence	Small case studies only; insufficient data (Category 4a).

Medical condition	PRIMARY IMMUNODEFICIENCY DISEASES (PID) WITH ANTIBODY DEFICIENCY This excludes: 1. specific antibody deficiency (see page 122); 2. IgG subclass deficiency (not funded see page 124). (Condition for which IVIg has an *established* therapeutic role)
Indication for IVIg use	Management of infection related to antibody deficiency.
Level of evidence	Evidence of probable benefit (Category 2a).
Description and diagnostic criteria	PID comprise a group of more than 120 separate conditions. Many of these are manifest by failure of protective antibody production. Key diagnoses include common variable immunodeficiency (CVID), severe combined immunodeficiencies, transient hypogammaglobulinaemia of infancy, Wiskott Aldrich syndrome and X-linked agammaglobulinaemia. In certain conditions, such as Wiskott Aldrich syndrome, antibody failure may not be manifest as hypogammaglobulinaemia but functional antibody responses will be impaired. Some PID does not involve antibody failure, such as chronic granulomatous disease and deficiencies of complement components. In these cases, antibody replacement therapy is not justified.
Qualifying criteria for IVIg therapy	In each case, a specific PID diagnosis must be established under the supervision of a specialist clinical immunologist and the diagnosis must be advised for IVIg to be approved.

Medical condition	PRIMARY IMMUNODEFICIENCY DISEASES (PID) WITH ANTIBODY DEFICIENCY **This excludes:** **1. specific antibody deficiency (see page 122);** **2. IgG subclass deficiency (not funded see page 124).** **(Condition for which IVIg has an *established* therapeutic role)**
Exclusion criteria for IVIg therapy	The following conditions should not be approved under this indication: 1. Miscellaneous hypogammaglobulinaemia (see *Secondary hypogammaglobulinaemia*, page 116) 2. Specific antibody deficiency (see page 122) 3. IgG subclass deficiency (not funded; see page 124).
Review criteria for assessing the effectiveness of IVIg use	Review criteria for primary immunodeficiency diseases with antibody deficiency are not mandated. Nevertheless, the following may be of value to the clinician: • frequency of clinical episodes of infection; • trough levels; and • renal function.

Medical condition	PRIMARY IMMUNODEFICIENCY DISEASES (PID) WITH ANTIBODY DEFICIENCY This excludes: 1. specific antibody deficiency (see page 122); 2. IgG subclass deficiency (not funded see page 124). (Condition for which IVIg has an *established* therapeutic role)
Dose	Maintenance dose: 0.4 g/kg every four weeks, modifying dose and schedule to achieve IgG trough level of at least the lower limit of the age-specific serum IgG reference range. Loading dose: One additional dose of 0.4 g/kg in the first month of therapy is permitted if the serum IgG level is markedly reduced. Chronic suppurative lung disease: Dosing to achieve IgG trough level of up to 9 g/L is permitted if chronic suppurative lung disease is not adequately controlled at an IgG trough level at the lower limit of the age-specific serum IgG reference range. Subcutaneous administration of immunoglobulins is a suitable alternative to IVIg in this disease. **Refer to the current product information sheet for further information.** **The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.**

Medical condition	PURE RED CELL APLASIA (PRCA) (Condition for which IVIg use is in *exceptional* circumstances only)
Indication for IVIg use	PRCA is a rare syndrome of severe anaemia, reticulocytopenia and a selective deficiency of erythroid progenitors. IVIg should be considered as first-line therapy for viral PRCA associated with parvovirus B19 in immunocompromised patients. IVIg is a reasonable option for patients with immunological PRCA who have failed other therapies (e.g. prednisone or cyclosporine). **Refer to the current product information sheet for further information.** **The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.**
Level of evidence	No included studies (Category 4b).

Medical condition	PURE WHITE CELL APLASIA (PWCA) (Condition for which IVIg use is in *exceptional* circumstances only)
Indication for IVIg use	PWCA is a rare syndrome of severe neutropenia and a selective deficiency of granulocyte progenitors. IVIg is a reasonable option for patients with immunological PWCA who have failed other therapies (e.g. prednisone or cyclosporine). **Refer to the current product information sheet for further information.** **The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.**
Level of evidence	No included studies (Category 4b).

Medical condition	PYODERMA GANGRENOSUM (Condition for which IVIg use is in *exceptional* circumstances only)
Indication for IVIg use	Use of IVIg is limited to patients with significant pyoderma gangrenosum, diagnosed by a dermatologist, unresponsive to corticosteroids and other immunosuppressive agents. **Induction dose:** 2 g/kg divided over 3 days. **Maintenance therapy:** 1–2 g/kg divided over 2 days, monthly for 4–6 months. IVIg should be ceased in patients who fail to respond after three cycles. **Refer to the current product information sheet for further information.** **The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.**
Level of evidence	Small case studies only; insufficient data (Category 4a).

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

Medical condition	SCLEROMYXEDEMA (Condition for which IVIg use is in *exceptional* circumstances only)
Indication for IVIg use	IVIg may be indicated in select cases not responding to steroids, or when steroids and other alternative treatments (e.g. thalidomide) are contraindicated. **Refer to the current product information sheet for further information.** **The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.**
Level of evidence	Small case studies only; insufficient data (Category 4a).

Medical condition	SECONDARY HYPOGAMMAGLOBULINAEMIA (Condition for which IVIg has an *emerging* therapeutic role)
Indication for IVIg use	Replacement therapy for life-threatening infection due to hypogammaglobulinaemia related to other diseases or medical therapy. The following secondary causes of hypogammaglobulinaemia are considered elsewhere: 1. Acquired hypogammaglobulinaemia secondary to haematological malignancies or stem cell transplantation (see page 17) 2. HIV in children (see page 59) 3. Solid organ transplantation (see page 121)
Level of evidence	No included studies (Category 4b).
Description and diagnostic criteria	Recurrent and/or severe bacterial infections may arise from hypogammaglobulinaemia of diverse causes. Hypogammaglobulinaemia may arise from protein losing states, malnutrition and medical immunosuppression. In most cases, successful management of the underlying condition will reverse the immunodeficiency, restoring immunocompetence. In some cases, recurrent or severe infection may arise from secondary immunodeficiency where the underlying cause cannot be reversed, or where there are unwanted effects of removing or reducing immunosuppressive therapy. New immunosuppressive regimens such as monoclonal B-cell depletion with Rituximab or similar agents do not generally induce hypogammaglobulinaemia at standard doses.

Medical condition	SECONDARY HYPOGAMMAGLOBULINAEMIA (Condition for which IVIg has an *emerging* therapeutic role)
Description and diagnostic criteria continued	However, repeated cycles of B-cell depletion in combination with other agents used to treat life-threatening immune-mediated diseases may increase rates of infection related to hypogammaglobulinaemia.
Qualifying criteria for IVIg therapy	Hypogammaglobulinaemia secondary to underlying disease or medical therapy (including haemopoietic stem cell transplantation [HCST]) with all the following: 1. Serum IgG less than the lower limit of the reference range on two separate occasions; AND 2. Underlying cause of hypogammaglobulinaemia cannot be reversed or reversal is contraindicated; AND 3. At least one of the following: a. One invasive or life-threatening bacterial infection (e.g. pneumonia, meningitis, sepsis) in the previous year; or b. Clinically active bronchiectasis confirmed by radiology.
Exclusion criteria for IVIg therapy	Reversible underlying cause of hypogammaglobulinaemia. The following conditions should not be approved under this indication: 1. Acquired hypogammaglobulinaemia secondary to haematological malignancies or stem cell transplantation (see page 17); 2. HIV in children (see page 59); 3. Transplantation related immunomodulation (solid organ transplantation; see page 121).

Medical condition	SECONDARY HYPOGAMMAGLOBULINAEMIA (Condition for which IVIg has an *emerging* therapeutic role)
Review criteria for assessing the effectiveness of IVIg use	Six-monthly review to assess clinical benefit. Cessation of IVIg should be considered, at least after each 12 months of therapy, extended as required to enable cessation of therapy in September/October, with repeat clinical and/or immunological evaluation before re-commencement of therapy. Written confirmation from the treating physician that: • an annual review has been undertaken; • the patient had demonstrated clinical benefit; • a trial period of cessation of IVIg for the purpose of immunological evaluation is medically contraindicated on safety grounds. In principle, IVIg should be continued or renewed only if there is a demonstrated clinical benefit.

Medical condition	SECONDARY HYPOGAMMAGLOBULINAEMIA (Condition for which IVIg has an *emerging* therapeutic role)
Dose	**Maintenance dose:** 0.4 g/kg every four weeks, modified to achieve IgG trough level of at least the lower limit of the age-specific serum IgG reference range. **Loading dose:** One additional dose of 0.4 g/kg in the first month of therapy is permitted if the serum IgG level is markedly reduced. **Chronic suppurative lung disease:** Dosing to achieve IgG trough level of up to 9 g/L is permitted if chronic suppurative lung disease is not adequately controlled at an IgG trough level at the lower limit of the age-specific serum IgG reference range. Subcutaneous administration of immunoglobulins is a suitable alternative to IVIg in this disease. **Dosing above 1 g/kg per day is contraindicated for some IVIg products.** **Refer to the current product information sheet for further information.** **The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.**

Medical condition	SJOGREN'S SYNDROME (Condition for which IVIg use is in *exceptional* circumstances only)
Indication for IVIg use	IVIg may be indicated in certain highly selected cases where other treatments have not been effective. **Refer to the current product information sheet for further information.** **The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.**
Level of evidence	Small case studies only; insufficient data (Category 4a).

Medical condition	SOLID ORGAN TRANSPLANTATION (other than kidney) (Condition for which IVIg use is in *exceptional* circumstances only)
Indication for IVIg use	IVIg may be indicated in: • highly sensitised patients awaiting transplantation; • transplant recipients with acute antibody-mediated rejection with clinical evidence of graft dysfunction; and • transplant recipients as treatment or prophylaxis for rejection where conventional immunosuppressive therapy is contraindicated; for example, in a patient with life-threatening infection in whom conventional immunosuppression will place the patient at greater risk, or when the transplant is at risk. **Refer to the current product information sheet for further information.** **The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.**
Level of evidence	Small case studies only; insufficient data (Category 4a).

Medical condition	SPECIFIC ANTIBODY DEFICIENCY (Condition for which IVIg has an *emerging* therapeutic role)
Indication for IVIg use	Prevention of infections in individuals with frequent infections who have demonstrated failure to mount protective IgG antibody responses to vaccine antigen challenge despite normal total serum IgG levels.
Level of evidence	Small case studies only, insufficient data (Category 4a).
Description and diagnostic criteria	The term 'specific antibody deficiency' describes failure of specific antibody response to an antigen challenge, and is most often used in the more restrictive sense of applying to polysaccharide antibody responses only. Patients who have normal total IgG levels but impaired production of specific antibodies, including those with isolated deficient responses to numerous polysaccharide antigens after vaccination, can present a diagnostic challenge. IgG replacement therapy should be provided when there is well-documented severe polysaccharide non-responsiveness and evidence of recurrent infections with a documented requirement for antibiotic therapy and ongoing recurrent infections despite antibiotic prophylaxis (Orange *et al. J Allergy Clin Immunol*, 2006; **117**: S525-53). It is now generally agreed that IgG subclass level estimation in serum is relatively poorly predictive of infectious risk and is of limited value in the definition of those patients most likely to benefit from IVIg therapy. Further research investigating clinical and laboratory features of this disorder is required.

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

Medical condition	SPECIFIC ANTIBODY DEFICIENCY (Condition for which IVIg has an *emerging* therapeutic role)
Review criteria for assessing the effectiveness of IVIg use continued	Cessation of IVIg should be considered, at least after each 12 months of therapy extended as required to enable cessation of therapy in September/October. This should particularly be considered in patients who do not have suppurative lung disease or bronchiectasis. An immunoglobulin washout period of four to six months is necessary to enable an accurate assessment. Prophylactic antibiotics may be considered to cover the period of IVIg cessation. Patients may qualify for further IVIg therapy: • under other immunodeficiency criteria (e.g. common variable immunodeficiency [CVID]) depending on the results of subsequent immune evaluation; or • rarely under specific antibody deficiency following re-emergence of severe significant infection requiring hospitalisation. In principle, IVIg should only be continued or renewed if there is a demonstrated clinical benefit. Note that re-vaccination with pneumococcal polysaccharide vaccine is not recommended because of safety concerns, and the potential for specific hyporesponsiveness induced by repeated vaccination (O'Brien *et al. Lancet Infect Dis* 2007; **7**: 597-606). **IgG subclass deficiency** 1. <u>*New patients*</u> IVIg is not funded for new patients diagnosed with IgG subclass deficiency.

Medical condition	SPECIFIC ANTIBODY DEFICIENCY (Condition for which IVIg has an *emerging* therapeutic role)
Review criteria for assessing the effectiveness of IVIg use continued	2. *Patients who were receiving IVIg for IgG subclass deficiency before initial publication of the Criteria (December 2007)* Without clinically active bronchiectasis or suppurative lung disease: 3. These patients should have ceased IVIg and had their immunological status re-evaluated. Patients with a confirmed IgG deficiency have become eligible under another indication (e.g. primary immunodeficiency with antibody deficiency). Patients without a confirmed IgG deficiency have ceased IVIg therapy. *Patients who were receiving IVIg for IgG subclass deficiency before initial publication of the Criteria (December 2007)* Without clinically active bronchiectasis or suppurative lung disease: • These patients should have ceased IVIg and had their immunological status re-evaluated. Patients with a confirmed IgG deficiency have become eligible under another indication (e.g. primary immunodeficiency with antibody deficiency). Patients without a confirmed IgG deficiency have ceased IVIg therapy. With clinically active bronchiectasis or suppurative lung disease over the previous 12 months: To be eligible to receive IVIg for a further 12 months, the following is required: 1. Written confirmation from the treating clinical immunologist that : - an annual review has been undertaken; - the patient has demonstrated clinical benefit; and

Medical condition	SPECIFIC ANTIBODY DEFICIENCY (Condition for which IVIg has an *emerging* therapeutic role)
Review criteria for assessing the effectiveness of IVIg use continued	- a trial period of cessation of IVIg for the purpose of immunological evaluation is medically contraindicated on safety grounds. AND Written confirmation by a second physician that cessation of IVIg for the purpose of immunological evaluation is medically contraindicated on safety grounds. Cessation of IVIg should be considered, at least after each 12 months of therapy extended as required to enable cessation of therapy in September/October. **Note:** The above criteria for initial and ongoing access to IVIg funded by all governments under the National Blood Arrangements will be reviewed in light of emerging evidence at the next review of *the Criteria*.
Dose	**Maintenance dose:** 0.4 g/kg every 4 weeks. **Loading dose:** not approved. Subcutaneous administration of immunoglobulins (SCIg) is a suitable alternative to IVIg in this setting. **Refer to the current product information sheet for further information.** **The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.**

Medical condition	STIFF PERSON SYNDROME (Condition for which IVIg has an *established* therapeutic role
Indication for IVIg use	Treatment of significant functional impairment in patients who have a verified diagnosis of stiff person syndrome.
Level of evidence	Evidence of probable benefit (Category 2a).
Description and diagnostic criteria	Patients with stiff person syndrome present with symptoms related to muscular rigidity and superimposed episodic spasms. The rigidity insidiously spreads involving axial muscles, primarily abdominal and thoracolumbar, as well as proximal limb muscles. Typically, co-contraction of truncal agonist and antagonistic muscles leads to a board-like appearance with hyperlordosis. Less frequently, respiratory muscle involvement leads to breathing difficulty and facial muscle involvement to a mask-like face. Investigations that may be useful for diagnosis include auto-antibodies to GAD-65 or GAD-67, EMG recordings from stiff muscles that may show continuous discharges of motor unit, and CSF oligoclonal bands.
Qualifying criteria for IVIg therapy	Significant functional impairment in patients who have a verified diagnosis of stiff person syndrome made by a neurologist.

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

Medical condition	SUSAC SYNDROME (Condition for which IVIg use is in *exceptional* circumstances only)
Indication for IVIg use	Susac syndrome is a rare, microangiopathic disorder characterised by encephalopathy, hearing loss and retinal artery branch occlusions. Case reports show benefit of IVIg therapy in combination with corticosteroids, with or without other immunosuppressive agents. Dose: 1–2 g/kg/month for one year providing documented clinical improvement. Dosing above 1 g/kg per day is contraindicated for some IVIg products. **Note:** Effectiveness of IVIg therapy may be difficult to determine due to the fluctuating course of disease. **Refer to the current product information sheet for further information.** **The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.**
Level of evidence	Small case studies only; insufficient data (Category 4a).

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

Medical condition	TOXIC EPIDERMAL NECROLYSIS (TEN)/ STEVENS–JOHNSON SYNDROME (SJS) (Condition for which IVIg has an *emerging* therapeutic role)
Indication for IVIg use	To limit progression of TEN or SJS/TEN when administered in early stages.
Level of evidence	Small case studies only; insufficient data (Category 4a).
Description and diagnostic criteria	TEN is a rare, life-threatening hypersensitivity reaction to certain medications, such as sulphonamides, antibiotics, non-steroidal anti-inflammatory drugs and anti-convulsants. Drug-induced epidermal apoptosis has been proposed as possible pathogenesis. SJS is a less extensive manifestation of the same phenomenon. TEN and SJS are characterised by severe bullous reaction with extensive destruction of the epidermis, and morphologically by ongoing apoptotic keratinocyte cell death that results in the separation of the epidermis from the dermis. The term SJS is now used to describe patients with blistering and skin detachment involving a total body surface area of ‹10%. SJS/TEN describes patients with 10–30% detachment, and TEN describes patients with ›30% skin detachment.
Qualifying criteria for IVIg therapy	TEN or SJS/TEN overlap with *all* the following: 1. Diagnosis by a dermatologist; AND 2. Body surface area (erythema and/or erosions) of 10% or more; AND 3. Evidence of rapid evolution.

Medical condition	TOXIC EPIDERMAL NECROLYSIS (TEN)/ STEVENS–JOHNSON SYNDROME (SJS) (Condition for which IVIg has an *emerging* therapeutic role)
Qualifying criteria for IVIg therapy continued	**Notes:** • IVIg should be initiated as early as possible, preferably within 24 hours of diagnosis. • Urgent skin biopsy should be performed for confirmation but should not delay IVIg therapy if indicated. • The Adverse Drug Reactions Advisory Committee should be notified of the inciting medication.
Exclusion criteria for IVIg therapy	SJS alone
Dose	2 g/kg, preferably as a single dose, or divided over three consecutive days. **Dosing above 1 g/kg per day is contraindicated for some IVIg products.** **Refer to the current product information sheet for further information.** **The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.**

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

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

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

Medical condition	TOXIC SHOCK SYNDROME (TSS) (Condition for which IVIg has an *emerging* therapeutic role)
Description and diagnostic criteria continued	**Prognosis** Streptococcal TSS has a mortality rate of 30–80% in adults and 5–10% in children, with most deaths secondary to shock and respiratory failure. Staphylococcal TSS can also be fatal but mostly has a better prognosis.
Qualifying criteria for IVIg therapy	1. Diagnosis of streptococcal or staphylococcal TSS in accordance with criteria listed above, preferably with isolation of organism; AND 2. Failure to achieve rapid improvement with fluid resuscitation, inotropes, surgery, antibiotic therapy and other supportive measures.
Dose	2 g/kg as a single dose. Schrage *et al. Clin Infect Dis* **43**: 6, 743-6 reported differences between various preparations of IVIg and their ability to neutralise streptococcal superantigens. They commented that 'the variations between IVIg preparations from different manufacturers are most likely caused by the different geographical regions from which the plasma samples were collected and might reflect differences in ... group A streptococcal ... exposure.' The clinical significance of these findings is not yet known. Darenburg *et al. Clin Infect Dis* **38**: 836-42 suggested that higher doses of IVIg might be required for staphylococcal TSS than streptococcal TSS, based on in vitro neutralisation of superantigens.

Medical condition	TOXIC SHOCK SYNDROME (TSS) (Condition for which IVIg has an *emerging* therapeutic role)
Dose continued	**Dosing above 1 g/kg per day is contraindicated for some IVIg products.** **Refer to the current product information sheet for further information.** **The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.**