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Criteria for the Clinical Use of Immune Globulin

First Edition

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Disclaimer: Important information about this document

This guideline reflects the best available data at the time the guideline was prepared. The recommendations are based, where possible, upon systematic review of the evidence. In the absence of published evidence, information and access criteria are based on clinical advice from the Guideline Development Group and individual clinical experts.

The information provided is not intended to be a definitive reference on any of the conditions. Patients and physicians should not use this document as a substitute for expert medical guidance and advice. The ultimate judgment regarding the propriety of any specific therapy must be made by the physician and the patient after considering all of the circumstances presented by the individual patient, the known variability and biological behavior of the disease, and other relevant factors in each case.

Expert clinical opinion about treatment regimens should always be sought. The aim in each case is to find the minimal effective dose and optimize the treatment for each individual.

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BACKGROUND

The Prairie Collaborative Immune Globulin (IG) Utilization Management Framework project was initiated to establish criteria for IG therapy as a means to increase accountability for the quality, safety, and sustainability of the blood supply system and to demonstrate stewardship for the use of public funds. This project is a trilateral agreement between the Alberta, Manitoba, and Saskatchewan ministries of health and is founded on the following principles:

- IG treatment is considered after exploring all other safe, effective, and affordable alternative therapies.
- When IG 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; IG should not be continued in patients with no demonstrable benefit.

An Inter-Provincial Medical Expert Committee (IMEC) was established, hereafter referred to as the Guideline Development Group (GDG), to review existing best practice evidence and guidelines on IG. A full description of the methods used to develop this evidence-based guideline is available from: http://www.ihe.ca.

Objectives

- Provide evidence-based recommendations on the effective, efficient, and clinically appropriate use of IG.
- Provide evidence-based guidance for identifying the conditions and circumstances for which for IG is clinically appropriate and funded within the National Blood Program.
- Provide review criteria for demonstrating the effectiveness of IG use, adherence to the guidance, and appropriate clinical follow up of IG therapy.

Target population

Pediatric and adult patients in any healthcare setting who require IG therapy.

Intended users

The Criteria are intended for:

- Transfusion medicine professionals and clinicians (e.g., dermatologists, hematologists, immunologists, infectious disease specialists, neurologists, rheumatologists, transplant specialists) treating patients with conditions that require intravenous, subcutaneous, or oral preparations of human IG.
- Administrators assessing and reviewing clinically appropriate access to IG preparations.

Conditions included

IG is used for prophylaxis and treatment of a range of diseases and conditions across various medical specialties. In this document, the conditions considered for IG therapy are listed under the following broad categories: dermatology; hematology; immunology; infectious disease; neurology and neuromuscular medicine; rheumatology; transplant medicine; and other indications. See the index for a full list of conditions included in this document.

Exclusions

- Review of criteria and utilization practices for fresh blood products and other plasma products, including hyperimmune globulins, albumin products, and coagulation factors.
- Although some advice is provided with regard to particular adverse effects of intravenous IG (IVIG) administration, the guideline does not provide detailed guidance on the safe use of IG.

Additional information

For additional information, please see the following indices:

- Appendix A – Categorization of Recommendations (i.e., explanations of ✓, ?, and ×)
- Appendix B – Evidence Sources
- Appendix C – Participants in the Guideline Development Process

References and the index of conditions included can be found at the end of this document.

SECTION 1: General Statements

Specialist assessment	
General	The use of immune globulin (IG) requires understanding of the diagnosis and pathophysiology of the disorder being treated. This includes monitoring and measuring outcomes to inform further treatment. A review by an appropriate specialist familiar with the product should occur prior to the initiation of IG therapy, whenever possible. Ongoing use of IG for chronic conditions should be done primarily by specialists with expertise in the particular disorder being treated, or in partnership with them. This is particularly important for recommendations in the "Do Not Know" category.
Dosing	
General	The dosing of IG will vary, depending on whether IG is for replacement therapy or immunomodulation and the individual patient's condition, clinical presentation, comorbidities, concurrent therapy and response.
Calculations	Unless otherwise indicated, use adjusted body weight for dosing calculations in overweight or obese adults as follows. **Dosing Weight** is an *adjusted* body weight (of overweight or obese patients): Dosing Weight = IBW + [0.5 x (Actual - IBW)] Note: If actual body weight is less than IBW, then Dosing Weight = actual body weight. **Ideal Body Weight (IBW)**,[1] Devine formula is: IBW (male) = 50.0 kg + 2.3 kg (each inch over 5 feet) IBW (female) = 45.5 kg + 2.3 kg (each inch over 5 feet) In most circumstances, dosing for children is calculated based on actual body weight. An online calculator is available from: https://www.albertahealthservices.ca/webapps/labservices/IVIG_Dosing_Calculator.htm. 1. Pai MP, Paloucek FP. *Annals of Pharmacotherapy* 2000;34(9):1066-9.
Maximum Dose	The maximum daily dose of intravenous immune globulin (IVIG) is typically 1 g/kg adjusted body weight, as the risk of some side effects may increase with higher doses or infusion rates. However, it is reasonable to use a maximum daily dose of 2 g/kg adjusted body weight in specific clinical circumstances when clinical judgement deems that the benefit of treatment outweighs the risk. Note that some experts endorse the use of 1.6 g/kg adjusted body weight as a single dose, *in lieu of* 2 g/kg adjusted body weight administered over 2 days, in selected patients requiring longer term treatment who have demonstrated good tolerance for this approach. Specific doses are provided in the guideline when supported by the evidence.
Maintenance Therapy	For most chronic conditions, efforts should be made to reduce the dose once the patient's condition has stabilized. Consider titrating the dose and/or the treatment interval to the lowest dose that continues to maintain the appropriate clinical effect for each patient. In some circumstances, the underlying condition may resolve completely and permit discontinuation of treatment.

Subcutaneous administration	
General	Subcutaneous administration of immune globulin (SCIG) should be considered as an alternative to IVIG in patients with primary and secondary immunodeficiencies.[1] Where appropriate, SCIG may also be considered in other patients receiving long-term therapy. 1. Health Quality Ontario. *Ontario Health Technology Assessment Series* 2017;17(16):1-86.
Off-label use, including very rare diseases	
General	In the event that a clinical decision is not covered by or in alignment with the guideline, the clinician shall notify the relevant provincial blood coordinating program, or similar provincial authority, and provide details of the treatment including indication and rationale for use outside of guidelines, the dose, and the duration. The provincial program or alternate may require additional outcome measures be reported as appropriate.
Immune globulin in combination with other therapies	
General	When IG will not be retained in circulation (e.g., massive bleeding or impending plasma exchange), the timing or sequencing of IG administration should be given due consideration. In general, IG administration should follow plasma exchange. Note that IG may increase the clearance of rituximab and other monoclonal antibodies.
Adverse effects	
General	It is important to assess individual patient risk for side effects when considering IG treatment. The GDG notes the following two specific areas of concern related to IVIG: • There is an increased risk of hemolysis in patients who have non-group O blood, receive a large cumulative IVIG dose, or have an underlying inflammatory or autoimmune disorder.[1, 2] • Some sucrose-stabilized formulations of IVIG have shown nephrotoxicity and are best avoided in patients with pre-existing kidney impairment.[3] ***Statements in italics in the recommendations relate to harm.*** Although some advice is provided with regard to particular adverse effects of IVIG administration, detailed guidance on the safe use of IG is beyond the scope of this document. Refer to the product monograph for more comprehensive guidance on the safe use of IG. 1. Branch DR, et al. *Blood* 2018;131(7):830-5. 2. Cherin P, et al. *Autoimmunity Reviews* 2016;15(1):71-81. 3. Dantal J. *American Journal of Nephrology* 2013;38:275-84.

SECTION 2: Dermatology Indications

? Atopic dermatitis

Do Not Know Recommendation	There is insufficient evidence to recommend for or against IVIG. IVIG may be considered in patients with atopic dermatitis who have: • the most severe forms of eczema; • underlying immunodeficiency; • contraindications to standard immunosuppressive therapies; and/or • recurrent or life-threatening infections.
Dose	2 g/kg adjusted body weight divided over 2 to 5 days. IVIG should be administered every 4 weeks initially, in addition to conventional immunosuppressive therapy, unless otherwise contraindicated. If clinical response is good, based on objective measures of effectiveness established at the outset of treatment, the interval between infusions can be gradually increased. IVIG should be administered for 3 to 6 months to assess efficacy. Some patients do not show a definitive sustained response until they have undergone up to 6 treatment cycles. In rare instances when longer term treatment is required (e.g., when disease recurs after withdrawal of IVIG and no other treatment options are available), regular washout periods should be attempted.
Review Criteria	If clinical effectiveness has not been achieved after 6 treatment cycles, IVIG should be discontinued. Continued use of IVIG should be based on objective measures of effectiveness established at the outset of treatment. These measures should be assessed no later than 6 months after initiation of long-term treatment and at least annually thereafter. If clinical effectiveness has not been achieved or sustained, IVIG should be discontinued.
Evidence Source	RCT (G8); EO (G6, GDG)

See Appendix A for category definitions

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✓ Autoimmune blistering diseases

Recommendation includes but is not limited to	o bullous pemphigoid o epidermolysis bullosa acquisita o IgA pemphigus o pemphigus herpetiformis o linear IgA disease o mucous membrane pemphigoid/cicatricial pemphigoid o paraneoplastic autoimmune multiorgan syndrome o pemphigus foliaceus o pemphigus vulgaris
Do Recommendation	IVIG is recommended in addition to standard corticosteroid and/or immunosuppressive therapy for all severe forms of autoimmune blistering diseases. It is not generally recommended as monotherapy, but this may be justified in isolated cases when other therapies are ineffective or contraindicated. The results are particularly good in pemphigus vulgaris, pemphigus foliaceus, mucous membrane pemphigoid, and epidermolysis bullosa acquisita. However, IVIG may also be indicated in severe forms of bullous pemphigoid, linear IgA disease, IgA pemphigus, and paraneoplastic autoimmune multiorgan syndrome.

LEGEND (see Appendix B for seed guideline references): CS – case series study; EO – expert opinion; G – guideline; GDG – guideline development group (IMEC); IVIG – intravenous immune globulin; NR – non-systematic/narrative review; RCT – randomized controlled trial; SR – systematic review

✓ Autoimmune blistering diseases

Dose	2 g/kg adjusted body weight divided over 2 to 5 days. IVIG should be administered every 4 weeks initially, usually in addition to conventional immunosuppressive therapy. If clinical response is good, based on objective measures of effectiveness established at the outset of treatment, the interval between infusions can be gradually increased. IVIG should be administered for 3 to 6 months to assess efficacy. Some patients do not show a definitive sustained response until they have undergone up to 6 treatment cycles. In rare instances when longer term treatment is required (e.g., when disease recurs after withdrawal of IVIG and no other treat options are available), regular washout periods should be attempted.
Review Criteria	If clinical effectiveness has not been achieved after 6 treatment cycles, IVIG should be discontinued. Continued use of IVIG should be based on objective measures of effectiveness established at the outset of treatment. These measures should be assessed no later than 6 months after initiation of long-term treatment and at least annually thereafter. If clinical effectiveness has not been achieved or sustained, IVIG should be discontinued.
Evidence Source	SR (G8); CS (G7)

? Chronic idiopathic urticaria

Do Not Know Recommendation	There is insufficient evidence to recommend for or against IVIG. IVIG may be considered as a last resort in patients with severe disease when conventional therapies are ineffective or contraindicated.
Dose	2 g/kg adjusted body weight divided over 2 to 5 days. IVIG should be administered every 4 weeks initially. If clinical response is good, based on objective measures of effectiveness established at the outset of treatment, the interval between infusions can be gradually increased. IVIG should be administered for 3 to 6 months to assess efficacy. Some patients do not show a definitive sustained response until they have undergone up to 6 treatment cycles. In rare instances when longer term treatment is required (e.g., when disease recurs after withdrawal of IVIG and no other treat options are available), regular washout periods should be attempted.
Review Criteria	If clinical effectiveness has not been achieved after 6 treatment cycles, IVIG should be discontinued. Continued use of IVIG should be based on objective measures of effectiveness established at the outset of treatment. These measures should be assessed no later than 6 months after initiation of long-term treatment and at least annually thereafter. If clinical effectiveness has not been achieved or sustained, IVIG should be discontinued.
Evidence Source	NR (G8); EO (GDG)

See Appendix A for category definitions

LEGEND (see Appendix B for seed guideline references): CS – case series study; EO – expert opinion; G – guideline; GDG – guideline development group (IMEC); IVIG – intravenous immune globulin; NR – non-systematic/narrative review; RCT – randomized controlled trial; SR – systematic review

? Livedoid vasculopathy

Do Not Know Recommendation	There is insufficient evidence to recommend for or against using IVIG. IVIG may be considered in exceptional circumstances when patients do not respond to primary standard therapy.
Dose	2 g/kg adjusted body weight divided over 2 to 5 days. IVIG should be administered every 4 weeks initially. If clinical response is good, based on objective measures of effectiveness established at the outset of treatment, the interval between infusions can be gradually increased. IVIG should be administered for 3 to 6 months to assess efficacy. Some patients do not show a definitive sustained response until they have undergone up to 6 treatment cycles. In rare instances when longer term treatment is required (e.g., when disease recurs after withdrawal of IVIG and no other treat options are available), regular washout periods should be attempted.
Review Criteria	If clinical effectiveness has not been achieved after 6 treatment cycles, IVIG should be discontinued. Continued use of IVIG should be based on objective measures of effectiveness established at the outset of treatment. These measures should be assessed no later than 6 months after initiation of long-term treatment and at least annually thereafter. If clinical effectiveness has not been achieved or sustained, IVIG should be discontinued.
Evidence Source	EO (G8, GDG)

✓ Pyoderma gangrenosum

Do Recommendation	IVIG may be considered in patients with significant pyoderma gangrenosum, diagnosed by a dermatologist, when other therapies are ineffective or contraindicated.
Dose	Induction: 2 g/kg adjusted body weight divided over 2 to 5 days. Maintenance: 1 to 2 g/kg adjusted body weight divided over 2 days, every 4 weeks for 4 to 6 cycles. If there is no clinical response after 3 to 6 treatment cycles, IVIG should be discontinued.
Review Criteria	Patient response should be documented according to objective measures of effectiveness established at the outset of treatment.
Evidence Source	CS (G1); EO (GDG)

✓ Scleromyxedema

Do Recommendation	IVIG may be considered in severe scleromyxedema when other therapies are ineffective or contraindicated.

See Appendix A for category definitions

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✓ Scleromyxedema	
Dose	2 g/kg adjusted body weight divided over 2 to 5 days. In the case of severe organ involvement, particularly kidney or heart, the treatment should be administered slowly (i.e., over 5 days). IVIG should be administered every 4 weeks initially. If clinical response is good, based on objective measures of effectiveness established at the outset of treatment, the interval between infusions can be gradually increased. IVIG should be administered for 6 months to assess efficacy.
Review Criteria	Long-term therapy is recommended when there is a severe relapse after discontinuing IVIG. Continued use of IVIG should be based on objective measures of effectiveness established at the outset of treatment. These measures should be assessed no later than 6 months after initiation of long-term treatment and at least annually thereafter. If clinical effectiveness has not been achieved, IVIG should be discontinued. Regular washout periods should be attempted.
Evidence Source	CS (G1, G8)

✓ Toxic epidermal necrolysis (TEN)/Stevens–Johnson syndrome (SJS)	
Do Recommendation	Early administration of IVIG is recommended as an option when other treatments are contraindicated and when the condition is life-threatening.
Dose	One dose of 2 g/kg adjusted body weight, or 1 g/kg/day for 3 consecutive days. IVIG should be initiated as early as possible, preferably within 24 hours of diagnosis.
Qualifying Criteria	TEN or SJS/TEN with <u>all</u> of the following: 1. Consultation with a dermatologist or an allergist; AND 2. Characteristic cutaneous and mucous membrane involvement; AND 3. Evidence of rapid evolution. Urgent skin biopsies for both routine histology and direct immunofluorescence should be performed, but should not delay IVIG therapy if indicated. The classification of disease is not always clear on initial presentation and the diagnosis may change during the first few days in hospital.
Review Criteria	Patient response should be documented according to objective measures of effectiveness established at the outset of treatment.
Evidence Source	SR (G1); G (G2); EO (G36, GDG-SR)

See Appendix A for category definitions

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SECTION 3: Hematology Indications

Autoimmune cytopenias secondary to chronic lymphocytic leukemia

See separate entries for immune thrombocytopenic purpura (ITP) and/or autoimmune hemolytic anemia (AIHA).

? Autoimmune hemolytic anemia (AIHA)

Do Not Know Recommendation	There is insufficient evidence to recommend for or against IVIG. IVIG is not recommended for routine use, but may be considered as one of several options in urgent situations.
Dose	1 to 2 g/kg adjusted body weight divided over 2 to 5 days.
Review Criteria	Patient response should be documented according to objective measures of effectiveness established at the outset of treatment.
Evidence Source	G (G2); EO (GDG)

? Autoimmune neutropenia

Do Not Know Recommendation	There is insufficient evidence to recommend for or against IVIG. IVIG may be considered as one of several options in rare circumstances when standard therapy fails.
Dose	There is insufficient evidence to recommend a dose.
Review Criteria	Patient response should be documented according to objective measures of effectiveness established at the outset of treatment.
Evidence Source	G (G1, G2); EO (GDG)

? Coagulation factor inhibitors

Recommendation includes but is not limited to	o acquired hemophilia o acquired von Willebrand disease o inhibitors to factor VIII in hemophilia A o inhibitors to factor IX in hemophilia B
Do Not Know Recommendation	There is insufficient evidence to recommend for or against IVIG.
Dose	Dosing regimens vary according to clinical context.
Review Criteria	Continued use of IVIG should be based on objective measures of effectiveness established at the outset of treatment. These measures should be assessed no later than 6 months after initiation of treatment and at least annually thereafter. If clinical effectiveness has not been achieved, IVIG should be discontinued.
Evidence Source	EO (GDG)

See Appendix A for category definitions

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LEGEND (see Appendix B for seed guideline references): CS – case series study; EO – expert opinion; G – guideline; GDG – guideline development group (IMEC); HPA – human platelet antigen; IVIG – intravenous immune globulin; NR – non-systematic/narrative review; NRCS – non-randomized comparative study; SR – systematic review

✓ Feto-maternal/neonatal alloimmune thrombocytopenia (FMAIT/NAIT)	
Do Recommendation	IVIG is recommended for preventing or treating fetal or neonatal thrombocytopenia or hemorrhage. Treatment should be under the direction of a specialist with expertise in high-risk obstetrics.
Dose	Maternal: 1 g/kg weekly throughout pregnancy, with starting time tailored to individual risk profile and history. Neonatal: Single dose of 1 g/kg. Occasionally more than one dose is required if thrombocytopenia persists.
Qualifying Criteria	Clinical suspicion of FMAIT/NAIT in the antenatal or neonatal setting based on clinical and laboratory features, including: 1. Thrombocytopenia or spontaneous hemorrhage in the fetus; OR 2. Thrombocytopenia with or without hemorrhage in the neonate; OR 3. Unexplained fetal death in a previous pregnancy and the presence of maternal platelet-specific alloantibodies that are known or suspected to cause this condition (most commonly anti-HPA-1a or anti-HPA-5b).
Review Criteria	Patient response should be documented according to objective measures of effectiveness established at the outset of treatment.
Evidence Source	SR (G1); G (G2); EO (G36)

✓ Hemolytic disease of the newborn (HDN)	
Do Recommendation	IVIG may be considered in selected cases in consultation with experts in feto-maternal medicine and transfusion medicine.
Dose	Single dose of 1 g/kg. Dose may be repeated if clinically indicated.
Review Criteria	Patient response should be documented according to objective measures of effectiveness established at the outset of treatment.
Evidence Source	SR (G1); EO (G36)

? Hemolytic uremic syndrome (HUS)	
Do Not Know Recommendation	There is insufficient evidence to recommend for or against IVIG.
Dose	There is insufficient evidence to recommend a dose.
Review Criteria	Patient response should be documented according to objective measures of effectiveness established at the outset of treatment.
Evidence Source	EO (GDG)

See Appendix A for category definitions

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✓ Heparin-induced thrombocytopenia (HIT)

Do Recommendation	IVIG may be considered as an option for severe HIT refractory to standard therapies.
Dose	2 g/kg adjusted body weight divided over 2 days.
Review Criteria	Patient response should be documented according to objective measures of effectiveness established at the outset of treatment.
Evidence Source	EO (GDG-CS)

Hypogammaglobulinemia, acquired secondary to hematological malignancies

Includes but is not limited to	o chronic lymphocytic leukemia o lymphoma o myeloma o post-hematopoietic stem cell transplant (HSCT)

See entry for secondary hypogammaglobulinemia in the Immunology Indications section.

✓ Immune thrombocytopenic purpura (ITP) – adult

Do Recommendation

IVIG is recommended for:

1. Refractory ITP on the recommendation of an appropriate clinical specialist

   Patients with severe thrombocytopenia (platelets less than $20x10^9$/L) in whom other therapies are ineffective or contraindicated.
2. Acute ITP with life-threatening hemorrhage or immediate high risk for life-threatening hemorrhage

   Patients with acute, severe ITP and clinical evidence of a hemostatic defect (e.g., mucous membrane hemorrhage) or active bleeding.
3. ITP in pregnancy

   Pregnant patients with ITP and 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 less than $20x10^9$/L) where corticosteroids and other immunosuppressives are contraindicated; and/or
   d. Chronic ITP under the guidance of a clinical hematologist, in addition to other therapies or where other therapies are ineffective or contraindicated.
5. HIV–associated ITP

   Patients unresponsive to antiviral therapy and:
   a. Platelet count less than 20 x 10^9/L; or
   b. Less than 50 x 10^9/L with bleeding.
6. Lupus–associated ITP

   See separate entry for systemic lupus erythematosus (SLE).

See Appendix A for category definitions

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✓ Immune thrombocytopenic purpura (ITP) – adult	
	For each of these indications, consultation with a clinical hematologist is strongly recommended.
Dose	Induction: 1 to 2 g/kg adjusted body weight divided over 2 to 5 days. Ongoing therapy: When indicated, 1 to 2 g/kg adjusted body weight in single or divided dose every 4 to 6 weeks, titrated as needed to achieve a clinical effect (it is unusual to give more than 1 g/kg in a single dose).
Review Criteria	For acute treatment, patient response should be documented according to objective measures of effectiveness established at the outset of treatment. In rare instances when longer term treatment is required, continued use of IVIG should be based on objective measures of effectiveness established at the outset of treatment. These measures should be assessed no later than 6 months after initiation of treatment and at least annually thereafter. If clinical effectiveness has not been achieved, IVIG should be discontinued.
Evidence Source	SR (G1); G (G2); EO (G36)

✓ Immune thrombocytopenic purpura (ITP) – pediatric	
Do Recommendation	Acute: IVIG may be considered in patients with a platelet count of less than 20 x 10^9/L as part of multimodal therapy when the patient has life-threatening bleeding or requires surgery. IVIG is not indicated for mild bleeding. While the effectiveness of IVIG is not disputed, clinical experts advise that most children with ITP do not require IVIG therapy. Consultation with a pediatric hematologist is advised. Chronic: IVIG may be considered.
Dose	Acute or chronic ITP: Single dose of 0.8 to 1 g/kg adjusted body weight, with a second dose within 48 hours if the platelet count has not increased above 20 x 10^9/L. Acute ITP with life-threatening bleeding: 2 g/kg adjusted body weight divided over 2 days.
Review Criteria	For acute treatment, patient response should be documented according to objective measures of effectiveness established at the outset of treatment. In rare instances when longer term treatment is required, continued use of IVIG should be based on objective measures of effectiveness established at the outset of treatment. These measures should be assessed no later than 6 months after initiation of treatment and at least annually thereafter. If clinical effectiveness has not been achieved, IVIG should be discontinued.
Evidence Source	SR (G1); G (G2); EO (G36)

? Neonatal hemochromatosis	
Do Not Know Recommendation	There is insufficient evidence to recommend for or against IVIG. IVIG may be considered for pregnant women who have had a previous pregnancy affected by neonatal hemochromatosis.

See Appendix A for category definitions

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? Neonatal hemochromatosis

Dose	There is insufficient evidence to recommend a dose.
Review Criteria	Patient response should be documented according to objective measures of effectiveness established at the outset of treatment.
Evidence Source	NRCS (G1); EO (GDG)

✓ Neonatal thrombocytopenia secondary to maternal autoimmune disorders

Do Recommendation	IVIG is recommended in addition to other therapies, in consultation with a neonatologist.
Dose	Neonatal: Single dose of 1 g/kg. Dose may be repeated if clinically indicated.
Review Criteria	Patient response should be documented according to objective measures of effectiveness established at the outset of treatment.
Evidence Source	CS (G29); EO (G36)

✓ Post-transfusion purpura (PTP)

Do Recommendation	IVIG is recommended as standard first-line therapy for suspected or confirmed PTP with life-threatening bleeding.
Dose	2 g/kg adjusted body weight divided over 2 days.
Review Criteria	Patient response should be documented according to objective measures of effectiveness established at the outset of treatment.
Evidence Source	G (G2); EO (G36)

✓ Pure red cell aplasia (PRCA)

Do Recommendation	IVIG is recommended for viral PRCA associated with proven parvovirus B19 in immunocompromised patients. IVIG may be considered for patients with immunological PRCA who have not responded to other therapies.
Dose	0.5 g/kg adjusted body weight weekly for 4 weeks.
Review Criteria	Patient response should be documented according to objective measures of effectiveness established at the outset of treatment.
Evidence Source	G (G1, G2)

? Sickle cell disease, hyperhemolysis syndrome

Do Not Know Recommendation	There is insufficient evidence to recommend for or against IVIG. IVIG may be considered as one of several options in urgent situations.
Dose	2 g/kg adjusted body weight divided over 2 to 5 days.

See Appendix A for category definitions

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? Sickle cell disease, hyperhemolysis syndrome	
Review Criteria	Patient response should be documented according to objective measures of effectiveness established at the outset of treatment.
Evidence Source	G (G2); EO (GDG-CS)

? Thrombotic thrombocytopenic purpura (TTP)	
Do Not Know Recommendation	There is insufficient evidence to recommend for or against IVIG.
Dose	There is insufficient evidence to recommend a dose.
Review Criteria	Patient response should be documented according to objective measures of effectiveness established at the outset of treatment.
Evidence Source	EO (GDG)

See Appendix A for category definitions

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SECTION 4: Immunology Indications

✓ Hypogammaglobulinemia, secondary

See separate entries for Kawasaki disease in the Rheumatology Indications section; for necrotizing fasciitis and toxic shock syndrome (TSS) in the Infectious Disease Indications section; and for transplant-related immunomodulation (solid organ transplant) in the Transplant Medicine Indications section.

Do Recommendation	Immunoglobulin replacement is recommended for preventing recurrent, severe infection due to hypogammaglobulinemia (excluding paraprotein) related to other diseases or medical therapy.
Dose	Aim to use the dose that achieves a significant reduction in the number of bacterial infections. Maintenance: 0.4 to 0.6 g/kg adjusted body weight IVIG every 4 weeks, or SCIG 0.1 to 0.5 g/kg adjusted body weight weekly, modified to achieve an IgG trough level of at least the lower limit of the age-specific serum IgG reference range, or as needed to achieve clinical effectiveness. Loading: One additional dose of 0.4 g/kg adjusted body weight may be given in the first month of therapy if the serum IgG level is markedly reduced. Chronic suppurative lung disease: 0.4 to 0.8 g/kg adjusted body weight IVIG or equivalent SCIG dose may be given 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.
Qualifying Criteria	Hypogammaglobulinemia secondary to underlying disease or medical therapy (including hematopoietic stem cell transplant [HCST]) with all of the following: 1. Serum IgG less than the lower limit of the reference range on two separate occasions AND 2. At least one of the following: a. One invasive or life-threatening bacterial infection (e.g., pneumonia, meningitis, sepsis) in the previous year; b. Recurrent, severe bacterial infections; c. Clinically active bronchiectasis confirmed by radiology; d. Assessment by a physician specializing in immunodeficiency indicating a significant antibody defect that would benefit from immunoglobulin replacement.
Review Criteria	Continued use of IG should be based on objective measures of effectiveness established at the outset of treatment. These measures should be assessed no later than 6 months after initiation of treatment and at least annually thereafter by a physician specializing in immunodeficiency disorders. If clinical effectiveness has not been achieved, IG treatment should be discontinued. Cessation of IG treatment may be possible depending on the status of the underlying disease.
Evidence Source	SR (G1); G (G2); EO (G36, GDG)

See Appendix A for category definitions

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LEGEND (see Appendix B for seed guideline references): EO – expert opinion; G – guideline; GDG – guideline development group (IMEC); IG – immune globulin; IgG – immunoglobulin G; IV – intravenous; IVIG – intravenous immune globulin; NR – non-systematic/narrative review; NRCS – non-randomized comparative study; SC – subcutaneous; SCIG – subcutaneous immune globulin; SR – systematic review

✓ Primary immunodeficiency (PID) disorders	
Do Recommendation	Immunoglobulin replacement is recommended for preventing bacterial infection.
Dose	Aim to use the dose that achieves a significant reduction in the number of bacterial infections. Maintenance: 0.4 to 0.6 g/kg adjusted body weight IVIG every 4 weeks or SCIG 0.1 to 0.5 g/kg adjusted body weight weekly, modified to achieve an IgG trough level of at least the lower limit of the age-specific serum IgG reference range, or as needed to achieve clinical effectiveness. Loading: One additional dose of 0.4 g/kg adjusted body weight may be given in the first month of therapy if the serum IgG level is markedly reduced. Chronic suppurative lung disease: 0.4 to 0.8 g/kg adjusted body weight IVIG or equivalent SCIG dose may be given 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. Specific antibody deficiency and IgG subclass deficiency: IVIG should be titrated based on clinical outcome alone as measurement of IgG trough levels is unhelpful in these conditions.
Qualifying Criteria	PID diagnosis must be established by a physician specializing in immunodeficiency disorders. Functional testing should be completed to establish diagnosis for: a. Common variable immunodeficiency (CVID) and associated disorders b. Specific antibody deficiency c. IgG subclass deficiency
Evidence Source	SR (G1); NRCS (G34); G (G2); EO (G36, GDG-SR)

See Appendix A for category definitions

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LEGEND (see Appendix B for seed guideline references): EO – expert opinion; G – guideline; GDG – guideline development group (IMEC); IG – immune globulin; IgG – immunoglobulin G; IV – intravenous; IVIG – intravenous immune globulin; NR – non-systematic/narrative review; NRCS – non-randomized comparative study; SC – subcutaneous; SCIG – subcutaneous immune globulin; SR – systematic review

SECTION 5: Infectious Disease Indications

× Clostridium difficile infection (CDI), recurrent

Do Not Do Recommendation	IVIG is not recommended in the absence of hypogammaglobulinemia (see separate entry for secondary hypogammaglobulinemia).
Evidence Source	SR (G17)

× HIV/AIDS

Do Not Do Recommendation	IVIG is not recommended in the absence of hypogammaglobulinemia (see separate entry for secondary hypogammaglobulinemia).
Evidence Source	EO (G1, GDG)

? Necrotizing fasciitis

For patients with hemodynamic compromise, see separate entry for toxic shock syndrome (TSS).

Do Not Know Recommendation	There is insufficient evidence to recommend for or against IVIG in patients without hemodynamic compromise.
Dose	There is insufficient evidence to recommend a dose.
Review Criteria	Patient response should be documented according to objective measures of effectiveness established at the outset of treatment.
Evidence Source	EO (GDG)

× Sepsis, neonatal prophylaxis

See separate entries for primary immunodeficiency (PID) disorders and secondary hypogammaglobulinemia in the Immunology Indications section.

Do Not Do Recommendation	IVIG is not recommended.
Evidence Source	RCT (G1)

✓ Toxic shock syndrome (TSS)

Do Recommendation	IVIG is recommended in addition to surgical intervention, antibiotic therapy, and other supportive measures for streptococcal TSS or staphylococcal TSS. Consultation with an infectious disease specialist is strongly recommended.
Dose	Single dose of 2 g/kg adjusted body weight.
Review Criteria	Patient response should be documented according to objective measures of effectiveness established at the outset of treatment.
Evidence Source	RCT (G1); G (G2); EO (GDG)

See Appendix A for category definitions

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LEGEND (see Appendix B for seed guideline references): AIDS – acquired immune deficiency syndrome; EO – expert opinion; G – guideline; GDG – guideline development group (IMEC); HIV – human immunodeficiency virus; IVIG – intravenous immune globulin; RCT – randomized controlled trial; SR – systematic review

×/✓ Varicella-zoster virus (VZV), prophylaxis	
When VZV immune globulin is available	
Do Not Do Recommendation	IVIG is not recommended for varicella-susceptible immunocompromised patients with primary exposure to VZV when VZV immune globulin is available.
Evidence Source	EO (G40)
When VZV immune globulin is unavailable	
Do Recommendation	IVIG is a suitable alternative for varicella-susceptible immunocompromised patients when VZV immune globulin is unavailable within 96 hours after exposure.
Dose	Single dose of 0.4 g/kg adjusted body weight, as soon as possible. Ideally the dose should be given within 96 hours after exposure, but administration up to 10 days post-exposure may be helpful. Patients who have received IVIG within the prior 3 weeks should be protected.
Evidence Source	EO (G40, G41)

See Appendix A for category definitions

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LEGEND (see Appendix B for seed guideline references): AIDS – acquired immune deficiency syndrome; EO – expert opinion; G – guideline; GDG – guideline development group (IMEC); HIV – human immunodeficiency virus; IVIG – intravenous immune globulin; RCT – randomized controlled trial; SR – systematic review

SECTION 6: Transplant Medicine Indications (including infectious diseases in transplant recipients)

✓/?/× Community-acquired respiratory virus (CARV), upper respiratory tract infection (URTI)

Proven respiratory syncytial virus (RSV) in high risk patients*	
Do Recommendation	IVIG may be considered in addition to antiviral therapy to prevent progression to lower respiratory tract infection.
Dose	0.5 g/kg adjusted body weight, daily, for 5 to 7 days.
Review Criteria	Patient response should be documented according to objective measures of effectiveness established at the outset of treatment.
Evidence Source	EO (GDG-G)
Non-RSV in high risk patients*	
Do Not Know Recommendation	There is insufficient evidence to recommend for or against IVIG. In some circumstances, IVIG may be considered in addition to antiviral therapy on a case-by-case basis to prevent progression to lower respiratory tract infection.
Dose	0.5 g/kg adjusted body weight, daily, for 5 to 7 days.
Review Criteria	Patient response should be documented according to objective measures of effectiveness established at the outset of treatment.
Evidence Source	EO (GDG-G)
All other patient groups, including solid organ transplant (other than lung)	
Do Not Do Recommendation	IVIG is not recommended.
Evidence Source	EO (GDG)
***Note**	The term "high risk patient"[1] signifies: • Lung transplant patients, especially children; • Leukemia and/or allogeneic hematopoietic stem cell transplant patients with: - Severe lymphopenia (absolute lymphocyte count less than 0.2 x 10^9/L); - Severe neutropenia (absolute neutrophil count less than 0.5 x 10^9/L); - Age greater than 60 years; - HLA mismatched or unrelated donor. 1. Beaird OE, et al. *Transplant Infectious Disease* 2016;18(2):210-5.

See Appendix A for category definitions

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LEGEND (see Appendix B for seed guideline references): CS – case series study; EO – expert opinion; G – guideline; GDG – guideline development group (IMEC); IG – immune globulin; IgG – immunoglobulin G; IVIG – intravenous immune globulin; NR – non-systematic/narrative review; NRCS – non-randomized comparative study; RCT – randomized controlled trial; SCIG – subcutaneous immune globulin; SR – systematic review

?/× Community-acquired respiratory virus (CARV), lower respiratory tract infection (LRTI)

High risk patients*	
Do Not Know Recommendation	There is insufficient evidence to recommend for or against IVIG. In some circumstances, IVIG may be considered in addition to antiviral therapy on a case-by-case basis.
Dose	0.5 g/kg adjusted body weight, daily, for 5 to 7 days.
Review Criteria	Patient response should be documented according to objective measures of effectiveness established at the outset of treatment.
Evidence Source	EO (GDG-G)

All other patient groups, including solid organ transplant (other than lung)	
Do Not Do Recommendation	IVIG is not recommended.
Evidence Source	EO (GDG)

***Note**	The term "high risk patient"[1] signifies: • Lung transplant patients, especially children; • Leukemia and/or allogeneic hematopoietic stem cell transplant patients with: - Severe lymphopenia (absolute lymphocyte count less than 0.2 x 10^9/L); - Severe neutropenia (absolute neutrophil count less than 0.5 x 10^9/L); - Age greater than 60 years; - HLA mismatched or unrelated donor. 1. Beaird OE, et al. *Transplant Infectious Disease* 2016;18(2):210-5.

See Appendix A for category definitions

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× Cytomegalovirus (CMV) infection, prophylaxis

Recommendation includes	o hematopoietic stem cell transplant (HSCT) o solid organ transplant
Do Not Do Recommendation	IVIG is not recommended.
Evidence Source	SR (G28); EO (GDG-NR)

× Epstein-Barr virus (EBV)-associated post-transplant lymphoproliferative disorders (PTLD)

Recommendation includes	o hematopoietic stem cell transplant (HSCT) o solid organ transplant
Do Not Do Recommendation	IVIG is not recommended for prophylaxis or treatment.
Evidence Source	EO (G33, GDG)

LEGEND (see Appendix B for seed guideline references): CS – case series study; EO – expert opinion; G – guideline; GDG – guideline development group (IMEC); IG – immune globulin; IgG – immunoglobulin G; IVIG – intravenous immune globulin; NR – non-systematic/narrative review; NRCS – non-randomized comparative study; RCT – randomized controlled trial; SCIG – subcutaneous immune globulin; SR – systematic review

?/× Gastrointestinal viruses in solid organ transplant

Refractory and persistent Norovirus or Rotavirus diarrhea	
Do Not Know Recommendation	There is insufficient evidence to recommend for or against IG. Oral IG should be considered for persistent, proven *Norovirus* or *Rotavirus* in immunosuppressed transplant recipients where reduction of immunosuppression is contraindicated.
Dose	Maximum dose of 360 mg, given as single oral doses of 25 mg to 45 mg, four times daily, for at least 2 days.
Review Criteria	Patient response should be documented according to objective measures of effectiveness established at the outset of treatment.
Evidence Source	EO (GDG-NR)

Refractory and persistent viral gastroenteritis syndromes (other than Norovirus or Rotavirus)	
Do Not Do Recommendation	IG is not recommended.
Evidence Source	EO (GDG)

✓ Hematopoietic stem cell transplant (HSCT), allogeneic, Cytomegalovirus (CMV)-induced pneumonitis

Do Recommendation	IVIG is recommended, in addition to appropriate antiviral chemotherapy, for proven or probable[1] CMV-induced pneumonitis following allogeneic HSCT. 1. Ljungman P, et al. *Clinical Infectious Diseases* 2017;64(1):87-91.
Dose	0.4 g/kg adjusted body weight, daily, for 7 to 14 days.
Evidence Source	G (G2); EO (GDG-NRCS)

× Hematopoietic stem cell transplant (HSCT), allogeneic, graft-versus-host disease

Do Not Do Recommendation	IVIG is not recommended for preventing graft-versus-host disease in allogeneic HSCT.
Evidence Source	EO (GDG-SR)

× Hematopoietic stem cell transplant (HSCT), autologous

Do Not Do Recommendation	IVIG is not recommended unless the patient has established humoral deficiency (see separate entry for secondary hypogammaglobulinemia).
Evidence Source	EO (G1)

See Appendix A for category definitions

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LEGEND (see Appendix B for seed guideline references): CS – case series study; EO – expert opinion; G – guideline; GDG – guideline development group (IMEC); IG – immune globulin; IgG – immunoglobulin G; IVIG – intravenous immune globulin; NR – non-systematic/narrative review; NRCS – non-randomized comparative study; RCT – randomized controlled trial; SCIG – subcutaneous immune globulin; SR – systematic review

✓ Hematopoietic stem cell transplant (HSCT) for primary immunodeficiency (PID) disorders

Do Recommendation	IVIG is recommended to reduce baseline community-acquired encapsulated Gram-positive bacterial infections.
Dose	0.4 to 0.6 g/kg adjusted body weight, every 4 weeks or SCIG 0.1 to 0.5 g/kg adjusted body weight weekly, modified to achieve an IgG trough level of at least the lower limit of the age-specific serum IgG reference range, or as needed to achieve clinical effectiveness. Requirements may change and IVIG should be titrated based on clinical outcome.
Evidence Source	G (G2); EO (GDG)

✓ Kidney, active antibody-mediated rejection (ABMR) prevention and management

Do Recommendation	Pre-transplant: IVIG is recommended when an antibody or antibodies might preclude transplantation (e.g., donor specific anti-human leukocyte antigen (HLA) antibody or anti-blood group antibody). IVIG may be continued for up to 3 months post-transplant. Post-transplant: IVIG may be used to treat active ABMR[1] when other therapies are ineffective. 1. Haas M, et al. *American Journal of Transplantation* 2018;18:293-307.
Dose	IVIG with plasma exchange: 0.1 g/kg adjusted body weight after each plasma exchange, to a maximum total dose of 2 g/kg. IVIG alone: 2 g/kg adjusted body weight divided over 2 to 5 days. When IVIG is used alone, further doses may be indicated every 4 weeks for a further 3 cycles, depending on clinical response or biopsy findings. Thereafter, additional treatment cycles (often together with other treatment modalities) may be indicated, but only when biopsy findings and/or clinical response demonstrate ongoing/recurrent active ABMR or chronic active ABMR.[1] Demonstration of ongoing/recurrent active ABMR or chronic active ABMR should precede each treatment cycle. *Note: Some sucrose-stabilized formulations of IVIG have shown nephrotoxicity and are best avoided in patients with pre-existing kidney impairment.[2] Some nephrologists recommend that IVIG infusions be capped at 140 g/day to reduce the risk of nephrotoxicity.* 1. Haas M, et al. *American Journal of Transplantation* 2018;18:293-307. 2. Dantal J. *American Journal of Nephrology* 2013;38:275-84.
Review Criteria	Patient response to each treatment cycle should be documented according to objective measures of effectiveness established at the outset of treatment.
Evidence Source	SR (G1); G (G2); EO (GDG)

See Appendix A for category definitions

LEGEND (see Appendix B for seed guideline references): CS – case series study; EO – expert opinion; G – guideline; GDG – guideline development group (IMEC); IG – immune globulin; IgG – immunoglobulin G; IVIG – intravenous immune globulin; NR – non-systematic/narrative review; NRCS – non-randomized comparative study; RCT – randomized controlled trial; SCIG – subcutaneous immune globulin; SR – systematic review

? Kidney, acute/active T-cell mediated rejection (TCMR) management	
Do Not Know Recommendation	There is insufficient evidence to recommend for or against using IVIG. It may be considered in exceptional cases when other therapies are ineffective or contraindicated.
Dose	There is insufficient evidence to recommend a particular dosing regimen. Most centres report short-term treatment (1 to 4 doses), rather than long-term administration. *Note: Some sucrose-stabilized formulations of IVIG have shown nephrotoxicity and are best avoided in patients with pre-existing kidney impairment.[1] Some nephrologists recommend that IVIG infusions be capped at 140 g/day to reduce the risk of nephrotoxicity.* 1. Dantal J. *American Journal of Nephrology* 2013;38:275-84.
Review Criteria	Patient response should be documented according to objective measures of effectiveness established at the outset of treatment.
Evidence Source	SR (G1); G (G2); EO (GDG)

? Kidney, non-active rejection management	
Do Not Know Recommendation	There is insufficient evidence to recommend for or against using IVIG. It may be considered in exceptional cases when other therapies are ineffective or contraindicated. However, it is generally discouraged due to the lack of evidence of effectiveness in the absence of active disease, weighed against the known toxicity (including nephrotoxicity), administrative burden to the patient, and cost. If used, it should be given according to an established protocol that enables subsequent evaluation of its overall efficacy as a management strategy.
Dose	There is insufficient evidence to recommend a particular dosing regimen. Most centres use short-term protocols (1 to 4 doses), often as part of a multi-modality treatment protocol, rather than long-term administration. In long-term protocols, once the patient's condition has stabilized, consider titrating the dose and/or the treatment interval to the lowest dose necessary to maintain clinical effectiveness. *Note: Some sucrose-stabilized formulations of IVIG have shown nephrotoxicity and are best avoided in patients with pre-existing kidney impairment.[1] Some nephrologists recommend that IVIG infusions be capped at 140 g/day to reduce the risk of nephrotoxicity.* 1. Dantal J. *American Journal of Nephrology* 2013;38:275-84.
Review Criteria	For short-term treatment, patient response should be documented according to objective measures of effectiveness established at the outset of treatment. In rare instances when long- or indefinite-term treatment is given, continued use of IVIG should be based on objective measures of effectiveness established at the outset of treatment. These measures should be assessed no later than 6 months after initiation of treatment and at least semi-annually thereafter. If clinical effectiveness has not been achieved, IVIG should be discontinued.

See Appendix A for category definitions

LEGEND (see Appendix B for seed guideline references): CS – case series study; EO – expert opinion; G – guideline; GDG – guideline development group (IMEC); IG – immune globulin; IgG – immunoglobulin G; IVIG – intravenous immune globulin; NR – non-systematic/narrative review; NRCS – non-randomized comparative study; RCT – randomized controlled trial; SCIG – subcutaneous immune globulin; SR – systematic review

? Kidney, non-active rejection management	
Evidence Source	SR (G1); G (G2); EO (GDG)

× Pulmonary graft-versus-host disease	
Do Not Do Recommendation	IVIG is not recommended.
Evidence Source	EO (GDG)

? Solid organ (other than kidney)	
Do Not Know Recommendation	There is insufficient evidence to recommend for or against IVIG. IVIG may be considered in: • highly sensitized patients awaiting transplantation; • transplant recipients with acute T-cell mediated rejection (TCMR) and clinical evidence of graft dysfunction; • transplant recipients as treatment or prophylaxis for rejection when conventional immunosuppressive therapy is contraindicated.
Dose	There is insufficient evidence to recommend a dose.
Review Criteria	Patient response should be documented according to objective measures of effectiveness established at the outset of treatment.
Evidence Source	CS (G1); EO (GDG-NR)

✓ Solid organ (other than kidney), antibody-mediated rejection (ABMR)	
Do Recommendation	IVIG is recommended in addition to plasma exchange. Where appropriate, biopsy evidence of rejection should be sought.
Dose	0.1 g/kg adjusted body weight after each plasma exchange, to a maximum dose of 2 g/kg total.
Review Criteria	Patient response should be documented according to objective measures of effectiveness established at the outset of treatment.
Evidence Source	CS (G1); EO (G36, GDG)

See Appendix A for category definitions

LEGEND (see Appendix B for seed guideline references): CS – case series study; EO – expert opinion; G – guideline; GDG – guideline development group (IMEC); IG – immune globulin; IgG – immunoglobulin G; IVIG – intravenous immune globulin; NR – non-systematic/narrative review; NRCS – non-randomized comparative study; RCT – randomized controlled trial; SCIG – subcutaneous immune globulin; SR – systematic review

SECTION 7: Neurology and Neuromuscular Indications

✓ Acute disseminated encephalomyelitis (ADEM)	
Do Recommendation	IVIG is recommended for: 1. ADEM unresponsive to steroid therapy or where steroids are contraindicated. 2. Recurrent or multiphasic ADEM unresponsive to steroid therapy or where steroid therapy has become intolerable or is contraindicated.
Dose	Induction: 2 g/kg adjusted body weight divided over 2 to 5 days. Maintenance (for recurrent or multiphasic ADEM only): 0.4 to 2 g/kg adjusted body weight every 4 to 6 weeks. Once the patient's condition has stabilized, consider titrating the dose and/or the treatment interval to the lowest dose necessary to maintain clinical effectiveness.
Review Criteria	Continued use of IVIG should be based on objective measures of effectiveness established at the outset of treatment. These measures should be assessed no later than 6 months after initiation of treatment and at least annually thereafter. If clinical effectiveness has not been achieved, IVIG should be discontinued.
Evidence Source	CS (G1)

? Acute flaccid myelitis	
Do Not Know Recommendation	There is insufficient evidence to recommend for or against IVIG.
Dose	There is insufficient evidence to recommend a dose.
Review Criteria	Patient response should be documented according to objective measures of effectiveness established at the outset of treatment.
Evidence Source	EO (GDG)

× Acute optic neuritis	
See separate entry for neuromyelitis optica (Devic disease).	
Do Not Do Recommendation	IVIG is not recommended.
Evidence Source	RCT (G1)

× Adrenoleukodystrophy	
Do Not Do Recommendation	IVIG is not recommended.
Evidence Source	EO (G1, G36)

See Appendix A for category definitions

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LEGEND (see Appendix B for seed guideline references): CR – case report; CS – case series study; EO – expert opinion; G – guideline; GDG – guideline development group (IMEC); IgA – immunoglobulin A; IgG – immunoglobulin G; IVIG – intravenous immune globulin; MAG - myelin-associated glycoprotein; NR – non-systematic/narrative review; qSR – quasi-systematic review; RCT – randomized controlled trial; SR – systematic review

? Aicardi-Goutières syndrome

Do Not Know Recommendation	There is insufficient evidence to recommend for or against IVIG.
Dose	There is insufficient evidence to recommend a dose.
Review Criteria	For acute treatment, patient response should be documented according to objective measures of effectiveness established at the outset of treatment. In rare instances when longer term treatment is required, continued use of IVIG should be based on objective measures of effectiveness established at the outset of treatment. These measures should be assessed no later than 6 months after initiation of treatment and at least annually thereafter. If clinical effectiveness has not been achieved, IVIG should be discontinued.
Evidence Source	EO (GDG-CR)

× Alzheimer disease

Do Not Do Recommendation	IVIG is not recommended.
Evidence Source	EO (G36)

✓ Anti-NMDA receptor encephalitis

Do Recommendation	IVIG may be considered as an option with expert consultation.
Dose	2 g/kg adjusted body weight divided over 2 to 5 days.
Review Criteria	Patient response should be documented according to objective measures of effectiveness established at the outset of treatment.
Evidence Source	EO (GDG-qSR)

× Autism

Do Not Do Recommendation	IVIG is not recommended.
Evidence Source	EO (G36)

See Appendix A for category definitions

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LEGEND (see Appendix B for seed guideline references): CR – case report; CS – case series study; EO – expert opinion; G – guideline; GDG – guideline development group (IMEC); IgA – immunoglobulin A; IgG – immunoglobulin G; IVIG – intravenous immune globulin; MAG - myelin-associated glycoprotein; NR – non-systematic/narrative review; qSR – quasi-systematic review; RCT – randomized controlled trial; SR – systematic review

? Childhood epilepsy, medically refractory/intractable

Recommendation includes but is not limited to	o Infantile spasms o Landau–Kleffner syndrome o Lennox–Gastaut syndrome
Do Not Know Recommendation	There is insufficient evidence to recommend for or against IVIG. IVIG should be considered only when conventional therapies are ineffective, with previous full assessment by a pediatric epileptologist. If IVIG is used, a therapeutic trial should be conducted, under the supervision of a pediatric epileptologist: • Infantile spasms: one dose only • Landau–Kleffner syndrome: one dose only • Lennox–Gastaut syndrome: one dose every 4 weeks, up to 6 cycles If the therapeutic trial is effective, IVIG can be used long term.
Dose	0.4 to 2 g/kg adjusted body weight divided over 2 to 5 days, every 4 weeks for 4 to 6 cycles.
Review Criteria	Continued use of IVIG should be based on objective measures of effectiveness established at the outset of treatment. These measures should be assessed no later than 6 months after initiation of treatment and at least annually thereafter. If clinical effectiveness has not been achieved, IVIG should be discontinued.
Evidence Source	EO (G1, G36, GDG-CS)

× Chronic fatigue syndrome (myalgic encephalomyelitis)

Do Not Do Recommendation	IVIG is not recommended.
Evidence Source	EO (G1, GDG-RCT)

✓ Chronic inflammatory demyelinating polyneuropathy (CIDP)

Recommendation includes but is not limited to	o Demyelinating neuropathy associated with IgG and IgA paraproteinemia
Do Recommendation	IVIG is recommended for first-line treatment, to be initiated when progression is rapid, walking is compromised, or there is significant functional impairment. The diagnosis of CIDP is complicated, particularly in patients with concurrent diabetes. Evaluation by a neurologist with expertise in neuromuscular disease is required.
Dose	2 g/kg adjusted body weight divided over 2 to 5 days, every 4 weeks. IVIG should be administered for 3 to 6 months to assess efficacy. Some patients do not show a definitive sustained response until they have undergone up to 6 treatment cycles. Once the patient's condition has stabilized, consider titrating the dose and/or the treatment interval to the lowest dose necessary to maintain clinical effectiveness.

See Appendix A for category definitions

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LEGEND (see Appendix B for seed guideline references): CR – case report; CS – case series study; EO – expert opinion; G – guideline; GDG – guideline development group (IMEC); IgA – immunoglobulin A; IgG – immunoglobulin G; IVIG – intravenous immune globulin; MAG - myelin-associated glycoprotein; NR – non-systematic/narrative review; qSR – quasi-systematic review; RCT – randomized controlled trial; SR – systematic review

✓ Chronic inflammatory demyelinating polyneuropathy (CIDP)

Review Criteria	Regular review by a neurologist is required: frequency as determined by the clinical status of the patient. If clinical effectiveness has not been achieved after 6 treatment cycles, IVIG should be discontinued. Continued use of IVIG should be based on objective measures of effectiveness established at the outset of treatment, in consultation with a neurologist. For stable patients, these measures should be assessed, in consultation with a neurologist, no later than 6 months after initiation of long-term treatment and at least annually thereafter. If clinical effectiveness has not been achieved or sustained, IVIG should be discontinued.
Evidence Source	SR (G1); EO (GDG)

× Critical illness polyneuropathy (CIP)

Do Not Do Recommendation	IVIG is not recommended.
Evidence Source	EO (G1, G36)

? Diabetic amyotrophy

Do Not Know Recommendation	There is insufficient evidence to recommend for or against IVIG. IVIG may be considered in exceptional circumstances with expert consultation.
Dose	There is insufficient evidence to recommend a dose.
Review Criteria	In rare instances when longer term treatment is required, continued use of IVIG should be based on objective measures of effectiveness established at the outset of treatment. These measures should be assessed no later than 6 months after initiation of treatment and at least annually thereafter. If clinical effectiveness has not been achieved, IVIG should be discontinued.
Evidence Source	EO (G1, GDG-SR)

✓ Guillain–Barré syndrome (GBS)

Do Recommendation	IVIG is recommended in patients with significant disability and progression.
Dose	2 g/kg adjusted body weight divided over 2 to 5 days. A second course of IVIG may be considered in patients with clearly demonstrated secondary deterioration, after assessment by a neurologist.
Evidence Source	SR (G1)

? Hashimoto encephalopathy

Do Not Know Recommendation	IVIG is not recommended as first-line treatment because preferable alternative treatment is available. IVIG may be considered in exceptional circumstances where there is progressive neurologic decline despite appropriate steroid therapy.

See Appendix A for category definitions

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LEGEND (see Appendix B for seed guideline references): CR – case report; CS – case series study; EO – expert opinion; G – guideline; GDG – guideline development group (IMEC); IgA – immunoglobulin A; IgG – immunoglobulin G; IVIG – intravenous immune globulin; MAG - myelin-associated glycoprotein; NR – non-systematic/narrative review; qSR – quasi-systematic review; RCT – randomized controlled trial; SR – systematic review

? Hashimoto encephalopathy	
Dose	Single dose of 2 g/kg adjusted body weight.
Review Criteria	Patient response should be documented according to objective measures of effectiveness established at the outset of treatment.
Evidence Source	CS (G1)

✓ Lambert–Eaton myasthenic syndrome (LEMS)	
Do Recommendation	IVIG is recommended as an option for initial treatment. IVIG may be considered in patients who show objective evidence of clinical improvement with IVIG therapy but have incomplete response to oral maintenance therapies.
Dose	Induction: 2 g/kg adjusted body weight divided over 2 to 5 days. Maintenance: Maximum dose of 2 g/kg adjusted body weight, every 4 weeks. Once the patient's condition has stabilized, consider titrating the dose and/or the treatment interval to the lowest dose necessary to maintain clinical effectiveness.
Review Criteria	Continued use of IVIG should be based on objective measures of effectiveness established at the outset of treatment. These measures should be assessed no later than 6 months after initiation of treatment and at least annually thereafter. If clinical effectiveness has not been achieved, IVIG should be discontinued.
Evidence Source	G (G2); EO (G36, GDG)

× Motor neuron disease	
See separate entry for multifocal motor neuropathy (MMN).	
Recommendation includes but is not limited to	o amyotrophic lateral sclerosis (ALS)
Do Not Do Recommendation	IVIG is not recommended.
Evidence Source	EO (G24, G36)

✓ Multifocal motor neuropathy (MMN)	
Do Recommendation	IVIG is recommended as first-line treatment. Diagnosis should be made by a neuromuscular specialist with specific electrodiagnostic expertise.
Dose	Induction: 2 g/kg adjusted body weight divided over 2 to 5 days. Maintenance: 0.4 to 2 g/kg adjusted body weight every 2 to 6 weeks. Once the patient's condition has stabilized, consider titrating the dose and/or the treatment interval to the lowest dose necessary to maintain clinical effectiveness.

See Appendix A for category definitions

LEGEND (see Appendix B for seed guideline references): CR – case report; CS – case series study; EO – expert opinion; G – guideline; GDG – guideline development group (IMEC); IgA – immunoglobulin A; IgG – immunoglobulin G; IVIG – intravenous immune globulin; MAG - myelin-associated glycoprotein; NR – non-systematic/narrative review; qSR – quasi-systematic review; RCT – randomized controlled trial; SR – systematic review

✓ Multifocal motor neuropathy (MMN)

Review Criteria	Continued use of IVIG should be based on objective measures of effectiveness established at the outset of treatment. These measures should be assessed no later than 6 months after initiation of treatment and at least annually thereafter. If clinical effectiveness has not been achieved, IVIG should be discontinued.
Evidence Source	SR (G1); G (G2)

✓/× Multiple sclerosis (MS)

Short-term therapy	
Do Recommendation	IVIG is recommended for short-term therapy in patients with clinically definite relapsing/remitting MS,[1,2] confirmed by a neurologist, and one of the following indications: 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 are ineffective; 3. Severe relapse with no response to high-dose methylprednisolone. 1. Thompson AJ, et al. *Lancet Neurology* 2018;17(2):162-73. 2. Krupp LB, et al. *Multiple Sclerosis* 2013;19(10):1261-7.
Dose	Induction: 1 to 2 g/kg adjusted body weight divided over 2 to 5 days. Maintenance for indications 1 and 2: 0.4 to 1 g/kg adjusted body weight every 4 to 6 weeks. Once the patient's condition has stabilized, consider titrating the dose and/or the treatment interval to the lowest dose necessary to maintain clinical effectiveness.
Review Criteria	Continued use of IVIG should be based on objective measures of effectiveness established at the outset of treatment. These measures should be assessed no later than 6 months after initiation of treatment and at least annually thereafter. If clinical effectiveness has not been achieved, IVIG should be discontinued.
Evidence Source	SR (G1)
Long-term therapy	
Do Not Do Recommendation	IVIG is not recommended.
Evidence Source	SR (G1)

✓ Myasthenia gravis (MG), moderate to severe generalized

Do Recommendation	IVIG is recommended as: 1. An alternative to plasma exchange in acute exacerbation (myasthenic crisis) or before surgery and/or thymectomy. 2. Maintenance therapy for moderate to severe generalized MG when other treatments are ineffective or have caused intolerable side effects.

See Appendix A for category definitions

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LEGEND (see Appendix B for seed guideline references): CR – case report; CS – case series study; EO – expert opinion; G – guideline; GDG – guideline development group (IMEC); IgA – immunoglobulin A; IgG – immunoglobulin G; IVIG – intravenous immune globulin; MAG - myelin-associated glycoprotein; NR – non-systematic/narrative review; qSR – quasi-systematic review; RCT – randomized controlled trial; SR – systematic review

✓ Myasthenia gravis (MG), moderate to severe generalized	
Dose	Induction, before surgery, or during myasthenic crisis: 1 to 2 g/kg adjusted body weight divided over 2 to 5 days. Maintenance: 0.4 to 1 g/kg adjusted body weight every 4 to 6 weeks. Once the patient's condition has stabilized, consider titrating the dose and/or the treatment interval to the lowest dose necessary to maintain clinical effectiveness.
Review Criteria	Continued use of IVIG should be based on objective measures of effectiveness established at the outset of treatment. These measures should be assessed no later than 6 months after initiation of treatment and at least annually thereafter. If clinical effectiveness has not been achieved, IVIG should be discontinued.
Evidence Source	SR (G1)

? Myasthenia gravis (MG), ocular and/or mild generalized	
Do Not Know Recommendation	There is insufficient evidence to recommend for or against IVIG.
Dose	There is insufficient evidence to recommend a dose. Once the patient's condition has stabilized, consider titrating the dose and/or the treatment interval to the lowest dose necessary to maintain clinical effectiveness.
Review Criteria	Continued use of IVIG should be based on objective measures of effectiveness established at the outset of treatment. These measures should be assessed no later than 6 months after initiation of treatment and at least annually thereafter. If clinical effectiveness has not been achieved, IVIG should be discontinued.
Evidence Source	SR (G38)

? Narcolepsy/cataplexy	
Do Not Know Recommendation	There is insufficient evidence to recommend for or against IVIG. IVIG may be considered in exceptional circumstances with expert consultation.
Dose	There is insufficient evidence to recommend a dose. Once the patient's condition has stabilized, consider titrating the dose and/or the treatment interval to the lowest dose necessary to maintain clinical effectiveness.
Review Criteria	In rare circumstances when long-term treatment is required, continued use of IVIG should be based on objective measures of effectiveness established at the outset of treatment. These measures should be assessed no later than 6 months after initiation of treatment and at least annually thereafter. If clinical effectiveness has not been achieved, IVIG should be discontinued.
Evidence Source	EO (G1, GDG-qSR)

? Neuromyelitis optica (Devic disease)	
Do Not Know Recommendation	There is insufficient evidence to recommend for or against IVIG.

See Appendix A for category definitions

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LEGEND (see Appendix B for seed guideline references): CR – case report; CS – case series study; EO – expert opinion; G – guideline; GDG – guideline development group (IMEC); IgA – immunoglobulin A; IgG – immunoglobulin G; IVIG – intravenous immune globulin; MAG - myelin-associated glycoprotein; NR – non-systematic/narrative review; qSR – quasi-systematic review; RCT – randomized controlled trial; SR – systematic review

? Neuromyelitis optica (Devic disease)	
Dose	There is insufficient evidence to recommend a dose.
Review Criteria	Continued use of IVIG should be based on objective measures of effectiveness established at the outset of treatment. These measures should be assessed no later than 6 months after initiation of treatment and at least annually thereafter. If clinical effectiveness has not been achieved, IVIG should be discontinued.
Evidence Source	NR (G1)

× Neuropathic pain	
Do Not Do Recommendation	IVIG is not recommended.
Evidence Source	EO (GDG)

✓/?/× Neuropathy associated with IgM paraproteinemia	
Demyelinating neuropathy without anti-MAG antibodies	
Do Recommendation	IVIG is recommended for neuropathy associated with IgM and features consistent with CIDP, in the absence of anti-MAG antibodies.
Dose	2 g/kg divided over 2 to 5 days, every 4 weeks. IVIG should be administered for 3 to 6 months to assess efficacy. Some patients do not show a definitive sustained response until they have undergone up to 6 treatment cycles. Once the patient's condition has stabilized, consider titrating the dose and/or the treatment interval to the lowest dose necessary to maintain clinical effectiveness.
Review Criteria	Regular review by a neurologist is required: frequency as determined by the clinical status of the patient. If clinical effectiveness has not been achieved after 6 treatment cycles, IVIG should be discontinued. Continued use of IVIG should be based on objective measures of effectiveness established at the outset of treatment, in consultation with a neurologist. For stable patients, these measures should be assessed, in consultation with a neurologist, no later than 6 months after initiation of long-term treatment and at least annually thereafter. If clinical effectiveness has not been achieved or sustained, IVIG should be discontinued.
Evidence Source	SR (G1, G2); EO (GDG)
Demyelinating neuropathy with anti-MAG antibodies	
Do Not Know Recommendation	There is insufficient evidence to recommend for or against IVIG.
Dose	There is insufficient evidence to recommend a dose. Once the patient's condition has stabilized, consider titrating the dose and/or the treatment interval to the lowest dose necessary to maintain clinical effectiveness.

See Appendix A for category definitions

LEGEND (see Appendix B for seed guideline references): CR – case report; CS – case series study; EO – expert opinion; G – guideline; GDG – guideline development group (IMEC); IgA – immunoglobulin A; IgG – immunoglobulin G; IVIG – intravenous immune globulin; MAG - myelin-associated glycoprotein; NR – non-systematic/narrative review; qSR – quasi-systematic review; RCT – randomized controlled trial; SR – systematic review

✓/?/× Neuropathy associated with IgM paraproteinemia	
Review Criteria	Continued use of IVIG should be based on objective measures of effectiveness established at the outset of treatment. These measures should be assessed no later than 6 months after initiation of treatment and at least annually thereafter. If clinical effectiveness has not been achieved, IVIG should be discontinued.
Evidence Source	EO (GDG)
Axonal neuropathy	
Do Not Do Recommendation	IVIG is not recommended.
Evidence Source	EO (GDG)

? Opsoclonus-myoclonus ataxia (OMA) – adult	
Do Not Know Recommendation	There is insufficient evidence to recommend for or against IVIG.
Dose	There is insufficient evidence to recommend a dose. Once the patient's condition has stabilized, consider titrating the dose and/or the treatment interval to the lowest dose necessary to maintain clinical effectiveness.
Review Criteria	Continued use of IVIG should be based on objective measures of effectiveness established at the outset of treatment. These measures should be assessed no later than 6 months after initiation of treatment and at least annually thereafter. If clinical effectiveness has not been achieved, IVIG should be discontinued.
Evidence Source	EO (GDG)

✓ Opsoclonus-myoclonus ataxia (OMA) – pediatric	
Do Recommendation	IVIG is recommended for acute and long-term treatment, in consultation with a neurologist, in addition to other tumour therapies, as applicable.
Dose	Induction: 1 to 2 g/kg adjusted body weight divided over 2 to 5 days. Maintenance: 0.4 to 1 g/kg adjusted body weight every 4 to 6 weeks. Once the patient's condition has stabilized, consider titrating the dose and/or the treatment interval to the lowest dose necessary to maintain clinical effectiveness.
Review Criteria	Continued use of IVIG should be based on objective measures of effectiveness established at the outset of treatment. These measures should be assessed no later than 6 months after initiation of treatment and at least annually thereafter. If clinical effectiveness has not been achieved, IVIG should be discontinued.
Evidence Source	CS (G1); EO (GDG)

? Paraneoplastic neurological syndromes	
Do Not Know Recommendation	There is insufficient evidence to recommend for or against IVIG for paraneoplastic neurological syndromes that are not otherwise specified.

See Appendix A for category definitions

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LEGEND (see Appendix B for seed guideline references): CR – case report; CS – case series study; EO – expert opinion; G – guideline; GDG – guideline development group (IMEC); IgA – immunoglobulin A; IgG – immunoglobulin G; IVIG – intravenous immune globulin; MAG - myelin-associated glycoprotein; NR – non-systematic/narrative review; qSR – quasi-systematic review; RCT – randomized controlled trial; SR – systematic review

? Paraneoplastic neurological syndromes

Dose	Dosing regimens vary according to clinical context. Once the patient's condition has stabilized, consider titrating the dose and/or the treatment interval to the lowest dose necessary to maintain clinical effectiveness.
Review Criteria	Continued use of IVIG should be based on objective measures of effectiveness established at the outset of treatment. These measures should be assessed no later than 6 months after initiation of treatment and at least annually thereafter. If clinical effectiveness has not been achieved, IVIG should be discontinued.
Evidence Source	EO (GDG)

✓ Paraneoplastic or sporadic autoimmune encephalitis

See separate entries for anti-NMDA receptor encephalitis and Rasmussen syndrome.

Recommendation includes but is not limited to	o potassium channel antibody-associated encephalopathy
Do Recommendation	IVIG should be considered for both paraneoplastic and sporadic autoimmune encephalitis. IVIG may play a role in maintenance therapy.
Dose	Induction: 2 g/kg adjusted body weight divided over 2 to 5 days. Maintenance: 0.5 to 2 g/kg adjusted body weight, every 4 weeks. Once the patient's condition has stabilized, consider titrating the dose and/or the treatment interval to the lowest dose necessary to maintain clinical effectiveness.
Review Criteria	Continued use of IVIG should be based on objective measures of effectiveness established at the outset of treatment. These measures should be assessed no later than 6 months after initiation of treatment and at least annually thereafter. If clinical effectiveness has not been achieved, IVIG should be discontinued.
Evidence Source	EO (G36; GDG-qSR)

See Appendix A for category definitions

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? Pediatric autoimmune neuropsychiatric disorder associated with streptococcal infection (PANDAS)

Do Not Know Recommendation	There is insufficient evidence to recommend for or against IVIG. The utility of IVIG appears to be limited to patients with a confirmed diagnosis, including evidence of recent streptococcal infection. Diagnosis of PANDAS requires expert consultation.
Dose	2 g/kg adjusted body weight divided over 2 days.
Review Criteria	Patient response should be documented according to objective measures of effectiveness established at the outset of treatment.
Evidence Source	G (G2); EO (G36, GDG-RCT)

LEGEND (see Appendix B for seed guideline references): CR – case report; CS – case series study; EO – expert opinion; G – guideline; GDG – guideline development group (IMEC); IgA – immunoglobulin A; IgG – immunoglobulin G; IVIG – intravenous immune globulin; MAG - myelin-associated glycoprotein; NR – non-systematic/narrative review; qSR – quasi-systematic review; RCT – randomized controlled trial; SR – systematic review

× Polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, skin changes (POEMS) syndrome

Do Not Do Recommendation	IVIG is not recommended.
Evidence Source	EO (G36)

? Postpolio syndrome

Do Not Know Recommendation	There is insufficient evidence to recommend for or against IVIG for routine treatment. While IVIG may be considered in exceptional circumstances for postpolio muscular atrophy, experts generally advise against the use of IVIG in this context.
Dose	There is insufficient evidence to recommend a dose. Once the patient's condition has stabilized, consider titrating the dose and/or the treatment interval to the lowest dose necessary to maintain clinical effectiveness.
Review Criteria	In rare instances when long-term treatment is required, continued use of IVIG should be based on objective measures of effectiveness established at the outset of treatment. These measures should be assessed no later than 6 months after initiation of treatment and at least annually thereafter. If clinical effectiveness has not been achieved, IVIG should be discontinued.
Evidence Source	RCT (G25); EO (GDG)

?/× Rasmussen syndrome

Short-term therapy	
Do Not Know Recommendation	There is insufficient evidence to recommend for or against IVIG. IVIG is an option as a short-term, temporizing measure.
Dose	2 g/kg adjusted body weight divided over 2 to 5 days.
Review Criteria	Patient response should be documented according to objective measures of effectiveness established at the outset of treatment.
Evidence Source	G (G2); EO (G36, GDG)
Long-term therapy	
Do Not Do Recommendation	IVIG is not recommended.
Evidence Source	G (G2)

✓ Stiff person syndrome (Moersch–Woltmann syndrome)

Do Recommendation	IVIG is recommended for treatment of significant functional impairment in patients who have stiff person syndrome, verified in consultation with a neurologist.

See Appendix A for category definitions

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LEGEND (see Appendix B for seed guideline references): CR – case report; CS – case series study; EO – expert opinion; G – guideline; GDG – guideline development group (IMEC); IgA – immunoglobulin A; IgG – immunoglobulin G; IVIG – intravenous immune globulin; MAG - myelin-associated glycoprotein; NR – non-systematic/narrative review; qSR – quasi-systematic review; RCT – randomized controlled trial; SR – systematic review

✓ Stiff person syndrome (Moersch–Woltmann syndrome)	
Dose	Induction: 2 g/kg adjusted body weight divided over 2 to 5 days. Maintenance: 1 to 2 g/kg adjusted body weight, every 4 to 6 weeks. Once the patient's condition has stabilized, consider titrating the dose and/or the treatment interval to the lowest dose necessary to maintain clinical effectiveness.
Review Criteria	Continued use of IVIG should be based on objective measures of effectiveness established at the outset of treatment. These measures should be assessed no later than 6 months after initiation of treatment and at least annually thereafter. If clinical effectiveness has not been achieved, IVIG should be discontinued.
Evidence Source	SR (G1)

✓/? Sydenham chorea	
Short-term therapy	
Do Recommendation	The use of a single dose of IVIG is reasonable to provide short-term improvement in symptoms for children with moderate to severe Sydenham chorea associated with significant impairment.
Dose	Single dose of 2 g/kg adjusted body weight.
Review Criteria	Patient response should be documented according to objective measures of effectiveness established at the outset of treatment.
Evidence Source	EO (GDG-qSR)
Long-term therapy	
Do Not Know Recommendation	There is insufficient evidence to recommend for or against IVIG in the long-term therapy of children with moderate to severe Sydenham chorea.
Dose	There is insufficient evidence to recommend a dose. Once the patient's condition has stabilized, consider titrating the dose and/or the treatment interval to the lowest dose necessary to maintain clinical effectiveness.
Review Criteria	Continued use of IVIG should be based on objective measures of effectiveness established at the outset of treatment. These measures should be assessed no later than 6 months after initiation of treatment and at least annually thereafter. If clinical effectiveness has not been achieved, IVIG should be discontinued.
Evidence Source	EO (GDG)

? Susac syndrome	
Do Not Know Recommendation	There is insufficient evidence to recommend for or against IVIG.
Dose	1 to 2 g/kg adjusted body weight divided over 2 to 5 days, every 4 weeks. Once the patient's condition has stabilized, consider titrating the dose and/or the treatment interval to the lowest dose necessary to maintain clinical effectiveness.

See Appendix A for category definitions

LEGEND (see Appendix B for seed guideline references): CR – case report; CS – case series study; EO – expert opinion; G – guideline; GDG – guideline development group (IMEC); IgA – immunoglobulin A; IgG – immunoglobulin G; IVIG – intravenous immune globulin; MAG - myelin-associated glycoprotein; NR – non-systematic/narrative review; qSR – quasi-systematic review; RCT – randomized controlled trial; SR – systematic review

? Susac syndrome	
Review Criteria	Continued use of IVIG should be based on objective measures of effectiveness established at the outset of treatment. These measures should be assessed no later than 6 months after initiation of treatment and at least annually thereafter. If clinical effectiveness has not been achieved, IVIG should be discontinued. Effectiveness of IVIG therapy may be difficult to determine due to the fluctuating course of disease.
Evidence Source	CS (G1); EO (GDG)

? Transverse myelitis	
Do Not Know Recommendation	There is insufficient evidence to recommend for or against IVIG.
Dose	There is insufficient evidence to recommend a dose.
Review Criteria	Patient response should be documented according to objective measures of effectiveness established at the outset of treatment.
Evidence Source	EO (GDG)

See Appendix A for category definitions

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LEGEND (see Appendix B for seed guideline references): CR – case report; CS – case series study; EO – expert opinion; G – guideline; GDG – guideline development group (IMEC); IgA – immunoglobulin A; IgG – immunoglobulin G; IVIG – intravenous immune globulin; MAG - myelin-associated glycoprotein; NR – non-systematic/narrative review; qSR – quasi-systematic review; RCT – randomized controlled trial; SR – systematic review

SECTION 8: Rheumatology Indications

× Antiphospholipid syndrome (other than catastrophic)

See separate entry for catastrophic antiphospholipid syndrome.

Do Not Do Recommendation	IVIG is not recommended.
Evidence Source	EO (G1, GDG-qSR)

✓ Antiphospholipid syndrome, catastrophic

See separate entry for antiphospholipid syndrome other than catastrophic.

Do Recommendation	IVIG is recommended for catastrophic antiphospholipid syndrome, characterized by widespread small vessel thrombosis leading to multiorgan failure.
Dose	2 g/kg adjusted body weight divided over 2 to 5 days. A single treatment is usually sufficient. *The potential pro-thrombotic effect of IVIG should be considered in this indication.*
Qualifying Criteria	All of the following criteria must be 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.
Evidence Source	G (G1)

See Appendix A for category definitions

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× Behçet disease

Do Not Do Recommendation	IVIG is not recommended.
Evidence Source	EO (G1)

? Congenital heart block, autoimmune (neonatal lupus)

Do Not Know Recommendation	There is insufficient evidence to recommend for or against IVIG.
Dose	There is insufficient evidence to recommend a dose.
Review Criteria	Patient response should be documented according to objective measures of effectiveness established at the outset of treatment.
Evidence Source	EO (GDG-CS)

LEGEND (see Appendix B for seed guideline references): CS – case series study; EO – expert opinion; G – guideline; GDG – guideline development group (IMEC); IVIG – intravenous immune globulin; NR – non-systematic/narrative review; qSR – quasi-systematic review; RCT – randomized controlled trial; SR: systematic review

✓ Dermatomyositis – adult	
Do Recommendation	IVIG should be considered for patients who do not respond to first-line therapies. In severe or life-threatening situations, e.g., dysphagia, it may be part of first line therapy.
Dose	2 g/kg adjusted body weight divided over 2 days, every 4 weeks. Once the patient's condition has stabilized, consider titrating the dose and/or the treatment interval to the lowest dose necessary to maintain clinical effectiveness.
Review Criteria	Continued use of IVIG should be based on objective measures of effectiveness established at the outset of treatment. These measures should be assessed no later than 6 months after initiation of treatment and at least annually thereafter. If clinical effectiveness has not been achieved, IVIG should be discontinued.
Evidence Source	EO (GDG-RCT)

✓ Dermatomyositis – pediatric	
Do Recommendation	IVIG should be considered: • in addition to corticosteroids and/or immunosuppressives: o at the outset of treatment; or o when the response is suboptimal; • for persistent skin disease when the muscle disease is otherwise well controlled.
Dose	2 g/kg adjusted body weight divided over 2 to 5 days, every 2 weeks for 3 to 5 cycles, and then every 4 weeks.[1] Once the patient's condition has stabilized, consider titrating the dose and/or the treatment interval to the lowest dose necessary to maintain clinical effectiveness. 1. Huber AM, et al. *Journal of Rheumatology* 2017;44(1):110-6.
Review Criteria	Continued use of IVIG should be based on objective measures of effectiveness established at the outset of treatment. These measures should be assessed no later than 6 months after initiation of treatment and at least annually thereafter. If clinical effectiveness has not been achieved, IVIG should be discontinued.
Evidence Source	EO (GDG-G)

✓ Eosinophilic granulomatosis with polyangiitis (EGPA) (Churg–Strauss disease)	
Do Recommendation	IVIG may be considered for patients with nervous system or cardiac disorders who do not respond to primary standard therapy.
Dose	2 g/kg adjusted body weight divided over 2 to 5 days, every 4 weeks. Once the patient's condition has stabilized, consider titrating the dose and/or the treatment interval to the lowest dose necessary to maintain clinical effectiveness.

See Appendix A for category definitions

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LEGEND (see Appendix B for seed guideline references): CS – case series study; EO – expert opinion; G – guideline; GDG – guideline development group (IMEC); IVIG – intravenous immune globulin; NR – non-systematic/narrative review; qSR – quasi-systematic review; RCT – randomized controlled trial; SR: systematic review

✓ Eosinophilic granulomatosis with polyangiitis (EGPA) (Churg–Strauss disease)	
Review Criteria	Continued use of IVIG should be based on objective measures of effectiveness established at the outset of treatment. These measures should be assessed no later than 6 months after initiation of treatment and at least annually thereafter. If clinical effectiveness has not been achieved, IVIG should be discontinued.
Evidence Source	EO (G31, GDG-NR)

? Immune-mediated uveitis	
Do Not Know Recommendation	There is insufficient evidence to recommend for or against IVIG. IVIG may be considered for exceptional cases of immune-mediated, sight-threatening uveitis with persistent activity despite corticosteroid and immunosuppressive therapy.
Dose	1 to 2 g/kg adjusted body weight, in single or divided dose, every 4 weeks for 3 months (it is unusual to give more than 1 g/kg in a single dose). In rare circumstances, longer term therapy may be required.
Review Criteria	In rare circumstances when long-term treatment is required, continued use of IVIG should be based on objective measures of effectiveness established at the outset of treatment. These measures should be assessed no later than 3 months after initiation of long-term treatment and at least annually thereafter. If clinical effectiveness has not been achieved, IVIG should be discontinued.
Evidence Source	CS (G1)

×/? Inclusion body myositis (IBM)	
IBM without dysphagia	
Do Not Do Recommendation	IVIG is not recommended.
Evidence Source	EO (G36)
IBM with dysphagia	
Do Not Know Recommendation	There is inconclusive evidence to recommend for or against IVIG in patients with IBM who have dysphagia affecting function. Given the modest effect identified in a small number of reported patients, expert opinion advises against the use of IVIG in this context.[1] 1. Dalakas MC, et al. *Neurology* 1997;48(3):712-6.
Dose	There is insufficient evidence to recommend a dose. Once the patient's condition has stabilized, consider titrating the dose and/or the treatment interval to the lowest dose necessary to maintain clinical effectiveness.
Review Criteria	Continued use of IVIG should be based on objective measures of effectiveness established at the outset of treatment. These measures should be assessed no later than 6 months after initiation of treatment and at least annually thereafter. If clinical effectiveness has not been achieved, IVIG should be discontinued.

See Appendix A for category definitions

LEGEND (see Appendix B for seed guideline references): CS – case series study; EO – expert opinion; G – guideline; GDG – guideline development group (IMEC); IVIG – intravenous immune globulin; NR – non-systematic/narrative review; qSR – quasi-systematic review; RCT – randomized controlled trial; SR: systematic review

×/? Inclusion body myositis (IBM)	
Evidence Source	EO (GDG-SR)

? Kawasaki disease – adult	
Do Not Know Recommendation	There is insufficient evidence to recommend for or against IVIG.
Dose	There is insufficient evidence to recommend a dose.
Review Criteria	Patient response should be documented according to objective measures of effectiveness established at the outset of treatment.
Evidence Source	EO (GDG)

✓ Kawasaki disease – pediatric	
Do Recommendation	IVIG is recommended early in Kawasaki disease to prevent coronary artery pathology.
Dose	2 g/kg adjusted body weight over 10 to 12 hours unless cardiac function necessitates the administration of a prolonged or divided treatment dose. A single treatment is usually sufficient. One additional dose may be given if there is ongoing inflammation. A third dose of IVIG is not recommended.
Qualifying Criteria	Clinical diagnosis of Kawasaki disease by a pediatrician, rheumatologist, or immunologist.
Evidence Source	SR (G1, G37)

Livedoid vasculopathy
See entry in the Dermatology Indications section.

✓ Macrophage activation syndrome (MAS)	
Do Recommendation	IVIG may be used in addition to other therapies.
Dose	Single dose of 2 g/kg adjusted body weight.
Review Criteria	Patient response should be documented according to objective measures of effectiveness established at the outset of treatment.
Evidence Source	EO (GDG-qSR)

✓ Polymyositis – adult	
Do Recommendation	IVIG is recommended for patients who do not respond to first-line therapies.

See Appendix A for category definitions

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LEGEND (see Appendix B for seed guideline references): CS – case series study; EO – expert opinion; G – guideline; GDG – guideline development group (IMEC); IVIG – intravenous immune globulin; NR – non-systematic/narrative review; qSR – quasi-systematic review; RCT – randomized controlled trial; SR: systematic review

✓ Polymyositis – adult	
Dose	2 g/kg adjusted body weight divided over 2 to 5 days, every 4 weeks. Once the patient's condition has stabilized, consider titrating the dose and/or the treatment interval to the lowest dose necessary to maintain clinical effectiveness.
Review Criteria	Continued use of IVIG should be based on objective measures of effectiveness established at the outset of treatment. These measures should be assessed no later than 6 months after initiation of treatment and at least annually thereafter. If clinical effectiveness has not been achieved, IVIG should be discontinued.
Evidence Source	G (G2)

? Polymyositis – pediatric	
Do Not Know Recommendation	There is insufficient evidence to recommend for or against IVIG.
Dose	There is insufficient evidence to recommend a dose. Once the patient's condition has stabilized, consider titrating the dose and/or the treatment interval to the lowest dose necessary to maintain clinical effectiveness.
Review Criteria	Continued use of IVIG should be based on objective measures of effectiveness established at the outset of treatment. These measures should be assessed no later than 6 months after initiation of treatment and at least annually thereafter. If clinical effectiveness has not been achieved, IVIG should be discontinued.
Evidence Source	EO (GDG)

× Rheumatoid arthritis	
Do Not Do Recommendation	IVIG is not recommended.
Evidence Source	EO (G1)

? Scleroderma	
Do Not Know Recommendation	There is insufficient evidence to recommend for or against IVIG. It may be considered in exceptional circumstances when patients do not respond to primary standard therapy.
Dose	There is insufficient evidence to recommend a dose. Once the patient's condition has stabilized, consider titrating the dose and/or the treatment interval to the lowest dose necessary to maintain clinical effectiveness.
Review Criteria	Continued use of IVIG should be based on objective measures of effectiveness established at the outset of treatment. These measures should be assessed no later than 6 months after initiation of treatment and at least annually thereafter. If clinical effectiveness has not been achieved, IVIG should be discontinued.
Evidence Source	CS (G8); EO (GDG-qSR)

See Appendix A for category definitions

LEGEND (see Appendix B for seed guideline references): CS – case series study; EO – expert opinion; G – guideline; GDG – guideline development group (IMEC); IVIG – intravenous immune globulin; NR – non-systematic/narrative review; qSR – quasi-systematic review; RCT – randomized controlled trial; SR: systematic review

? Sjogren syndrome

Do Not Know Recommendation	There is insufficient evidence to recommend for or against IVIG.
Dose	There is insufficient evidence to recommend a dose. Once the patient's condition has stabilized, consider titrating the dose and/or the treatment interval to the lowest dose necessary to maintain clinical effectiveness.
Review Criteria	Continued use of IVIG should be based on objective measures of effectiveness established at the outset of treatment. These measures should be assessed no later than 6 months after initiation of treatment and at least annually thereafter. If clinical effectiveness has not been achieved, IVIG should be discontinued.
Evidence Source	EO (GDG)

? Systemic juvenile idiopathic arthritis (JIA) (adult Still disease)

See separate entry for macrophage activation syndrome (MAS).

Do Not Know Recommendation	There is insufficient evidence to recommend for or against IVIG. IVIG may be considered in exceptional circumstances when patients do not respond to primary standard therapy.
Dose	There is insufficient evidence to recommend a dose. Once the patient's condition has stabilized, consider titrating the dose and/or the treatment interval to the lowest dose necessary to maintain clinical effectiveness.
Review Criteria	Continued use of IVIG should be based on objective measures of effectiveness established at the outset of treatment. These measures should be assessed no later than 6 months after initiation of treatment and at least annually thereafter. If clinical effectiveness has not been achieved, IVIG should be discontinued.
Evidence Source	EO (GDG-CS)

? Systemic lupus erythematosus (SLE)

Do Not Know Recommendation	There is insufficient evidence for or against IVIG. IVIG may be considered in exceptional circumstances for SLE when no other treatment options are effective or appropriate. *Care should be taken in the setting of connective tissue disease as the infusion of IVIG in patients with high titre rheumatoid factor (RF) has been associated with renal damage.*
Dose	2 g/kg adjusted body weight divided over 2 to 5 days. Long-term therapy can be recommended only in exceptional cases. Once the patient's condition has stabilized, consider titrating the dose and/or the treatment interval to the lowest dose necessary to maintain clinical effectiveness.
Review Criteria	Continued use of IVIG should be based on objective measures of effectiveness established at the outset of treatment. These measures should be assessed no later than 6 months after initiation of treatment and at least annually thereafter. If clinical effectiveness has not been achieved, IVIG should be discontinued.
Evidence Source	CS (G8)

See Appendix A for category definitions

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LEGEND (see Appendix B for seed guideline references): CS – case series study; EO – expert opinion; G – guideline; GDG – guideline development group (IMEC); IVIG – intravenous immune globulin; NR – non-systematic/narrative review; qSR – quasi-systematic review; RCT – randomized controlled trial; SR: systematic review

? Vasculitic syndromes

See separate entries for Behçet disease, eosinophilic granulomatosis with polyangiitis (EGPA) (Churg–Strauss disease), and Kawasaki disease.

Recommendation includes but is not limited to	o granulomatosis with polyangiitis (Wegener granulomatosis) o IgA-associated small vessel vasculitis (Henoch–Schonlein purpura) o microscopic polyangiitis
Do Not Know Recommendation	There is insufficient evidence to recommend for or against IVIG. IVIG may be considered as an option when primary standard therapy is ineffective or contraindicated.
Dose	2 g/kg adjusted body weight divided over 2 to 5 days. In rare circumstances, longer term therapy may be required.
Review Criteria	In rare circumstances when long-term treatment is required, continued use of IVIG should be based on objective measures of effectiveness established at the outset of treatment. These measures should be assessed no later than 6 months after initiation of treatment and at least annually thereafter. If clinical effectiveness has not been achieved, IVIG should be discontinued.
Evidence Source	CS (G8); EO (GDG)

See Appendix A for category definitions

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LEGEND (see Appendix B for seed guideline references): CS – case series study; EO – expert opinion; G – guideline; GDG – guideline development group (IMEC); IVIG – intravenous immune globulin; NR – non-systematic/narrative review; qSR – quasi-systematic review; RCT – randomized controlled trial; SR: systematic review

SECTION 9: Other Indications

? Graves disease	
Do Not Know Recommendation	IVIG is not recommended as first-line treatment because preferable alternative treatment is available. IVIG may be considered in exceptional circumstances when steroids are ineffective or contraindicated.
Dose	2 g/kg adjusted body weight divided over 2 to 5 days, every 3 to 4 weeks. Once the patient's condition has stabilized, consider titrating the dose and/or the treatment interval to the lowest dose necessary to maintain clinical effectiveness.
Review Criteria	Continued use of IVIG should be based on objective measures of effectiveness established at the outset of treatment. These measures should be assessed no later than 6 months after initiation of treatment and at least annually thereafter. If clinical effectiveness has not been achieved, IVIG should be discontinued.
Evidence Source	CS (G1); EO (GDG)

×/? Hemophagocytic lymphohistiocytosis (HLH) syndrome	
Without thrombocytopenia	
Do Not Do Recommendation	IVIG is not recommended.
Evidence Source	EO (GDG)
With thrombocytopenia	
Do Not Know Recommendation	There is insufficient evidence to recommend for or against IVIG. IVIG may be considered in exceptional circumstances with appropriate consultation.
Dose	2 g/kg adjusted body weight divided over 2 to 5 days.
Review Criteria	Patient response should be documented according to objective measures of effectiveness established at the outset of treatment.
Evidence Source	EO (GDG-CS)

✓ Systemic capillary leak syndrome (SCLS)	
Do Recommendation	IVIG may be considered for prophylaxis, in addition to other therapies.
Dose	1 to 2 g/kg adjusted body weight divided over 2 to 5 days, every 4 weeks. Once the patient's condition has stabilized, consider titrating the dose and/or the treatment interval to the lowest dose necessary to maintain clinical effectiveness.
Review Criteria	Continued use of IVIG should be based on objective measures of effectiveness established at the outset of treatment. These measures should be assessed no later than 6 months after initiation of treatment and at least annually thereafter. If clinical effectiveness has not been achieved, IVIG should be discontinued.
Evidence Source	CS (G1); EO (GDG-qSR)

See Appendix A for category definitions

LEGEND (see Appendix B for seed guideline references): CS – case series study; EO – expert opinion; G – guideline; GDG – guideline development group (IMEC); IVIg – intravenous immunoglobulin; qSR – quasi-systematic review

APPENDIX A: Categorization of Recommendations

Summary of Criteria to Determine the Categorization of Recommendations

Do ✓	• The Guideline Development Group (GDG) accepted the original recommendation (from the seed guideline), which provided a prescriptive direction to perform the action or used the term "effective" to describe it. • The GDG supplemented a recommendation or created a new one, based on their collective professional opinion (with or without additional research evidence), which supported the action.
Do Not Know ?	• The GDG accepted the original recommendation, which did not recommend for or against the action or stated that there was "no evidence," "insufficient or conflicting evidence," or "no good evidence" to support its use. • The GDG supplemented a recommendation or created a new one, based on their collective professional opinion (with or without additional research evidence), which was equivocal with respect to supporting the action. o "Inconclusive evidence to recommend for or against": the additional research evidence comprised at least one systematic review presenting conflicting or equivocal results or stating that the evidence in relation to the action was "limited," "inconclusive," "inconsistent," or "insufficient." o "Insufficient evidence to recommend for or against": the additional research evidence did not include a systematic review.
Do Not Do ✘	• The GDG accepted the original recommendation, which provided a prescriptive direction not to perform the action, used the term "ineffective" to describe it, or stated that the evidence does "not support" it. • The GDG supplemented a recommendation or created a new one, based on their collective professional opinion (with or without additional research evidence), which did not support the action.

APPENDIX B: Evidence Sources

This guideline was developed by a multidisciplinary Inter-Provincial Medical Expert Committee (IMEC), referred to as the Guideline Development Group (GDG) throughout this document. Recommendations are based on a review of 45 "seed" guidelines (referenced as G1 to G45; published between January 2012 and September 2017) and additional systematic review evidence, or were created by the GDG based on their collective professional opinion and an analysis of relevant evidence. Note that only some (n=18) of these guidelines were directly used by the GDG to formulate recommendations. The references for the "seed" guidelines are available at the end of this document. A full description of the methods used to develop this evidence-based guideline is available from: http://www.ihe.ca.

Each recommendation in the guideline came from one or more seed guidelines or was created by the GDG, based on their collective professional opinion and an analysis of additional evidence on immune globulin. The *Evidence Source* row of the recommendations provides information on the seed guideline(s) that were used to develop the guideline recommendations and the design of the studies referenced by the seed guideline(s) and the GDG in support of their recommendations. The following evidence sources were considered:

- Systematic review (SR), quasi-systematic review (qSR) (a review that does not include a critical appraisal of the included studies), randomized controlled trial (RCT), non-randomized comparative study (NRCS), case series study (CS), guideline (G), narrative review (NR), case report (CR).
- Expert opinion (EO) – as cited by the seed guideline(s) or when no evidence was provided by the seed guideline in support of the recommendation.
- EO (GDG) – the GDG examined the individual studies cited by the seed guideline(s) or additional evidence on immune globulin, as identified by a supplementary literature search, and drafted a new recommendation based on their collective EO.
    - When EO (GDG) recommendations were based on specific studies, the study design of the evidence was listed, e.g., EO (GDG-SR), EO (GDG-RCT). For a full listing of these studies, please see: http://www.ihe.ca.

For evidence cited by the seed guideline(s) or the GDG, only the highest level of evidence was listed for each indication. For example, when the evidence cited from SRs and studies of other design (i.e., qSR, RCT, NRCS, CS, G, NR, or CR), only SR is listed as the source. When no SR was referenced in the seed guideline or by the GDG, the evidence source is indicated in the following order: qSR, RCT, NRCS, CS, G, NR, CR, EO. For recommendations combining multiple indications, the level of evidence was listed for each indication according to the rules stated above.

The general statements were sourced from the seed guidelines or were created by the GDG, based on their collective professional opinion and an analysis of relevant evidence referenced by the members of the GDG or provided by the research team, such as recently published systematic reviews or studies/trials not captured by the literature searches.

Statements in italics relate to harm. These statements were sourced from the recommendations or elsewhere in the seed guidelines, or were created by the GDG.

APPENDIX C: Participants in the Guideline Development Process

A full listing of participant affiliations is available from: http://www.ihe.ca.

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References for reviewed seed guidelines

The guidelines are not presented in any specific order. G1, G2, etc., are randomly assigned and for the purpose of organization only.

Only those guidelines directly used by the GDG to formulate recommendations (n=18*) are cited as evidence sources in the document.

G1* **Australia**	Jurisdictional Blood Committee, for and on behalf of the Australian Health Ministers' Conference. *Criteria for the clinical use of intravenous immunoglobulin in Australia*. *Second Edition*. Canberra: Commonwealth of Australia; 2012.
G2* **Canada**	Ontario Regional Blood Coordinating Network. *Ontario intravenous immune globulin (IVIG) utilization management guidelines Version 2.0*. Toronto: Ontario Regional Blood Coordinating Network; 2012.
G3 **USA**	Ringold S, Weiss PF, Beukelman T, DeWitt EM, Ilowite NT, Kimura Y, et al. 2013 update of the 2011 American College of Rheumatology recommendations for the treatment of juvenile idiopathic arthritis: Recommendations for the medical therapy of children with systemic juvenile idiopathic arthritis and tuberculosis screening among children receiving biologic medications. *Arthritis and Rheumatism* 2013;65(10):2499-512.
G4 **Japan**	Research Committee of the Japanese Society of Pediatric Cardiology; Cardiac Surgery Committee for Development of Guidelines for Medical Treatment of Acute Kawasaki Disease. Guidelines for medical treatment of acute Kawasaki disease: Report of the Research Committee of the Japanese Society of Pediatric Cardiology and Cardiac Surgery (2012 revised version). *Pediatrics International* 2014;56(2):135-58.
G5 **Australia, New Zealand**	RHDAustralia (ARF/RHD writing group), National Heart Foundation of Australia, Cardiac Society of Australia and New Zealand. *Australian guideline for prevention, diagnosis and management of acute rheumatic fever and rheumatic heart disease (2nd edition)*. Casuarina, Australia: RHDAustralia; 2012.
G6* **USA**	Sidbury R, Davis DM, Cohen DE, Cordoro KM, Berger TG, Bergman JN, et al. Guidelines of care for the management of atopic dermatitis. Section 3. Management and treatment with phototherapy and systemic agents. *Journal of the American Academy of Dermatology* 2014;71(2):327-49.
G7* **United Kingdom**	Venning VA, Taghipour K, Mohd Mustapa MF, Highet AS, Kirtschig G. British Association of Dermatologists' guidelines for the management of bullous pemphigoid 2012. *British Journal of Dermatology* 2012;167(6):1200-14.
G8* **Europe**	Enk AH, Hadaschik EN, Eming R, Fierlbeck G, French LE, Girolomoni G, et al. European Guidelines (S1) on the use of high-dose intravenous immunoglobulin in dermatology. *Journal of the European Academy of Dermatology and Venereology* 2016: doi:10.1111/jdv.13725.
G9 **United Kingdom**	Oscier D, Dearden C, Erem E, Fegan C, Follows G, Hillmen P, et al. *Guidelines on the diagnosis, investigation and management of chronic lymphocytic leukaemia*. London, United Kingdom: British Society for Haematology; 2012.

G10 United Kingdom	National Collaborating Centre for Cancer. *Myeloma: diagnosis and management*. London (UK): National Institute for Health and Care Excellence (NICE); 2016.
G11 USA	Monagle P, Chan AK, Goldenberg NA, Ichord RN, Journeycake JM, Nowak-Göttl U, et al. Antithrombotic therapy in neonates and children: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest* 2012;141(2 Suppl):e737S-801S.
G12 Australia	Queensland Maternity and Neonatal Clinical Guidelines Program. *Neonatal jaundice*. Brisbane: Queensland Health; 2012.
G13 Canada	Barrington KJ, Sankaran K; Canadian Paediatric Society, Fetus and Newborn Committee. Guidelines for detection, management and prevention of hyperbilirubinemia in term and late preterm newborn infants. *Paediatrics & Child Health* 2007;12(Suppl B):1B-12B. Reaffirmed 2016.
G14 Italy	Romagnoli C, Barone G, Pratesi S, Raimondi F, Capasso L, Zecca E, et al. Italian guidelines for management and treatment of hyperbilirubinaemia of newborn infants ≥ 35 weeks' gestational age. *Italian Journal of Pediatrics* 2014;31;40(1):11.
G15 United Kingdom	NHS Blood and Transplant (NHSBT) Services. *Neonatal alloimmune thrombocytopenia*. London: NHSBT; 2014.
G16 USA	Rajasekhar A, Gernsheimer T, Stasi R, James AH. *2013 Clinical practice guide on thrombocytopenia in pregnancy*. Washington, DC: American Society of Hematology; 2013.
G17* USA	Surawicz CM, Brandt LJ, Binion DG, Ananthakrishnan AN, Curry SR, Gilligan PH, et al. Guidelines for diagnosis, treatment, and prevention of Clostridium difficile infections. *American Journal of Gastroenterology* 2013;108(4):478-98.
G18 Spain	Working Group of the Clinical Practice Guideline on the Management of Invasive Meningococcal Disease. *Clinical practice guideline on the management of invasive meningococcal disease*. Madrid (Spain): Ministry of Health, Social Services and Equality; Aragon Institute for Health Sciences; 2013.
G19 United Kingdom	Royal College of Obstetricians and Gynaecologists (RCOG). *Bacterial sepsis in pregnancy*. London, United Kingdom: RCOG; 2012.
G20 United Kingdom	Royal College of Obstetricians and Gynaecologists (RCOG). *Bacterial sepsis following pregnancy*. London, United Kingdom: RCOG; 2012.
G21 Belgium	Kidney Disease: Improving Global Outcomes (KDIGO) Glomerulonephritis Work Group. KDIGO clinical practice guideline for glomerulonephritis. *Kidney International Supplements* 2012;2(2):139-274.
G22 Canada	Kantor PF, Lougheed J, Dancea A, McGillion M, Barbosa N, Chan C, et al. Presentation, diagnosis, and medical management of heart failure in children: Canadian Cardiovascular Society guidelines. *Canadian Journal of Cardiology* 2013;29(12):1535-52.

G23 **USA**	Go CY, Mackay MT, Weiss SK, Stephens D, Adams-Webber T, Ashwal S, et al. Evidence-based guideline update: medical treatment of infantile spasms: report of the Guideline Development Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. *Neurology* 2012;78(24):1974-80.
G24* **Europe**	EFNS Task Force on Diagnosis and Management of Amyotrophic Lateral Sclerosis, Andersen PM, Abrahams S, Borasio GD, de Carvalho M, Chio A, et al. EFNS guidelines on the clinical management of amyotrophic lateral sclerosis (MALS) – revised report of an EFNS task force. *European Journal of Neurology* 2012;19(3):360-75.
G25* **USA**	Patwa HS, Chaudhry V, Katzberg H, Rae-Grant AD, So YT. Evidence-based guideline: intravenous immunoglobulin in the treatment of neuromuscular disorders. Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology* 2012;78(13):1009-15.
G26 **United Kingdom**	Dignan FL, Scarisbrick JJ, Cornish J, Clark A, Amrolia P, Jackson G, et al. Organ-specific management and supportive care in chronic graft-versus-host disease. *British Journal of Haematology* 2012;158(1):62-78.
G27 **USA**	Cincinnati Children's Hospital Medical Center. *Evidence based clinical practice guideline for management of EBV-associated post-transplant lymphoproliferative disease (PTLD) in solid organ transplant*. Cincinnati (OH): Cincinnati Children's Hospital Medical Center; 2012.
G28* **United Kingdom**	Emery V, Zuckerman M, Jackson G, Aitken C, Osman H, Pagliuca A, et al. Management of cytomegalovirus infection in haemopoietic stem cell transplantation. *British Journal of Haematology* 2013;162(1):25-39.
G29* **United Kingdom**	Nottingham Neonatal Service. *Neonatal thrombocytopenia*. Nottingham, United Kingdom: Nottingham University Hospitals NHS Trust; 2016.
G30 **USA**	Alexander EK, Pearce EN, Brent GA, Brown RS, Chen H, Dosiou C, et al. 2017 Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and the postpartum. *Thyroid* 2017;27(3):315-89.
G31* **Japan**	Ichinose M, Sugiura H, Nagase H, Yamaguchi M, Inoue H, Sagara H, et al. Japanese guidelines for adult asthma 2017. *Allergology International* 66(2017):163-89.
G32 **Europe**	Straube A, Bronstein A, Straumann D. Nystagmus and oscillopsia. *European Journal of Neurology* 2012;19(1):6-14.
G33* **Europe**	Styczynski J, van der Velden W, Fox CP, Engelhard D, de la Camara R, Cordonnier C, et al. Management of Epstein-Barr Virus infections and post-transplant lymphoproliferative disorders in patients after allogeneic hematopoietic stem cell transplantation: Sixth European Conference on Infections in Leukemia (ECIL-6) guidelines. *Haematologica* 2016;101(7):803-11.
G34* **USA**	Bonilla FA, Khan DA, Ballas ZK, Chinen J, Frank MM, Hsu JT, et al.; Joint Task Force on Practice Parameters, representing the American Academy of Allergy, Asthma & Immunology; the American College of Allergy, Asthma & Immunology; and the Joint Council of Allergy, Asthma & Immunology. Practice parameter for the diagnosis and management of primary immunodeficiency. *Journal of Allergy and Clinical Immunology* 2015;136(5):e1-78.

G35 Europe	Hirsch HH, Martino R, Ward KN, Boeckh M, Einsele H, Ljungman P. Fourth European Conference on Infections in Leukaemia (ECIL-4): Guidelines for diagnosis and treatment of human respiratory syncytial virus, parainfluenza virus, metapneumovirus, rhinovirus, and coronavirus. *Clinical Infectious Diseases* 2013;56(2):258-66.
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G37* USA	McCrindle BW, Rowley AH, Newburger JW, Burns JC, Bolger AF, Gewitz M, et al. Diagnosis, treatment, and long-term management of Kawasaki disease: A scientific statement for health professionals from the American Heart Association. *Circulation* 2017;135:e927-99.
G38* Japan	Murai H. Japanese clinical guidelines for myasthenia gravis: putting into practice. *Clinical and Experimental Neuroimmunology* 2015;6:21-31.
G39 United Kingdom	Creamer D, Walsh SA, Dziewulski P, Exton LS, Lee HY, Dart JKG, et al. UK guidelines for the management of Stevens–Johnson syndrome/toxic epidermal necrolysis in adults 2016. *Journal of Plastic, Reconstructive & Aesthetic Surgery* 2016:69(6):e119-53.
G40* USA	Panel on Opportunistic Infections in HIV-Exposed and HIV-Infected Children. *Guidelines for the prevention and treatment of opportunistic infections among HIV-exposed and HIV-infected children*. New York, NY: National Institutes of Health; 2017.
G41* United Kingdom	Baker RJ, Mark PB, Patel RK, Stevens KK, Palmer N. Renal association clinical practice guideline in post-operative care in the kidney transplant recipient. *BMC Nephrology* 2017;18(1):174.
G42 USA	National Comprehensive Cancer Network®. *The NCCN Clinical Practice Guidelines in Oncology. Chronic lymphocytic leukemia/small lymphocytic lymphoma (Version 2.2018)*. Fort Washington, PA: National Comprehensive Cancer Network; 2017.
G43 United Kingdom	Sussman J, Farrugia ME, Maddison P, Hill M, Leite MI, Hilton-Jones D. Myasthenia gravis: Association of British Neurologists' management guidelines. *Practical Neurology* 2015; 15:199-206.
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