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Criteria for the Clinical Use of Immune Globulin

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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 behaviour 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 arrangement 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 regarding 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 – List of New and Revised Recommendations
- Appendix D – 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 should occur before 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. Round dose to nearest vial size to minimize product wastage.
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):[1] Dosing weight = ideal body weight (IBW) + [0.4 x (Actual - IBW)] Note: If actual body weight is less than IBW, then dosing weight = actual body weight. **Ideal Body Weight (IBW)**,[2] Devine formula is: IBW (male) = 50.0 kg + (2.3 kg x each inch over 5 feet) IBW (female) = 45.5 kg + (2.3 kg x 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. Grindeland JW, et al. *Annals of Pharmacotherapy* 2020;54(3):205-12. 2. 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 remit or resolve completely and permit discontinuation of treatment.
Dosing in Pregnancy	Patients with immunodeficiency should be monitored monthly to ensure that doses are increased appropriately to maintain proper trough levels. Other patients should continue to be treated based on their adjusted body weight, unless otherwise stipulated. For additional advice on dosing in pregnancy consult with the transfusion medicine physician on call.
Subcutaneous administration	
General	Subcutaneous administration of immune globulin (SCIG) is encouraged as an alternative to IVIG for maintenance treatment for an expanding group of indications in patients who have demonstrated response to IVIG and need long-term therapy. This is particularly pertinent for primary and secondary immune deficiencies. Each patient should be assessed regularly regarding the need for ongoing IG therapy and the effectiveness of SCIG as a substitute for IVIG.
Frequency of follow up and assessment of effectiveness	
General	Patients receiving IG products require regular review. For most long-term indications, an assessment of IVIG effectiveness should be considered between 3 and 4 months, but no later than 6 months after initiation of IG therapy, and then at least annually thereafter. This should include a clinical assessment and, for certain indications, laboratory assessment of IgG levels. Some provincial IG stewardship programs may require more frequent follow up of patients for inventory management and planning purposes.
Weaning patients off IG	

General	If treatment with IG does not achieve the desired clinical outcome, it should be discontinued.
	For long-term immunomodulatory therapy, once the desired clinical outcome is achieved the dose should be titrated downward to establish the minimum dose necessary to sustain that clinical outcome. Experienced clinicians accomplish this in many ways. For example:
	• *Reduce the monthly dose* by about 20 to 30%, rounded down to the nearest 5 grams; continue for 4 to 6 months and reassess
	  ○ If the patient is clinically stable, proceed with a further 20 to 30% dosage reduction; repeat as clinical circumstances permit. If the patient is clinically stable at a dose of <0.5 g/kg/month, consider discontinuing IG.
	  ○ If clinical problems recur, return to the previous effective dose.
	• *Increase the dosing interval* to 6 weeks; continue for 6 months and reassess
	  ○ If the patient is clinically stable, increase the dosing interval to 8 weeks; repeat with intervals of 10 and 12 weeks, as clinical circumstances permit. If the patient is clinically stable through two consecutive 12-week intervals, consider discontinuing IG.
	  ○ If clinical problems recur, return to the previous effective dosing interval.

	In some patients, IG may be put on hold without tapering provided there is close clinical follow up and the ability to reinstitute IG as needed.
Off-label use, including very rare diseases	
General	If 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 and may decline the provision of IG altogether if there is insufficient evidence for its use. Information regarding access to IG may be obtained from your local transfusion medicine service.
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. High-dose IVIG may limit the efficacy of concomitantly administered monoclonal antibodies, such as rituximab, by increasing antibody clearance[1,2]. Therefore, avoid using IVIG and monoclonal antibodies at the same time. To prevent rapid clearance, it is preferable to use these therapies separately, with time between infusions. 1. Jordan SC, et al. *American Journal of Transplantation* 2020;20(9):2581-8. 2. Moreso F, et al. *American Journal of Transplantation* 2018;18(4):927-35.
Vaccination in patients receiving IG	
General	Vaccination against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)/COVID-19 and seasonal influenza should be provided to all patients regardless of the timing of their IG treatment. For measles-mumps-rubella (MMR) and measles-mumps-rubella-varicella (MMRV) vaccinations, consult the Canadian Immunization Guide.
Adverse effects	
General	There are risks associated with IVIG that include, but are not limited to, hemolysis in patients who have non-group O blood[1, 2], nephrotoxicity with some sucrose-stabilized formulations of IVIG in patients with pre-existing kidney impairment[3], and thromboembolism in patients with hypertension, diabetes, smoking, and hypercoagulable states[4]. Currently licensed products are considered safe with respect to transmission of HIV and the hepatitis viruses[5]. Discussion of risks with patients should be tailored to their specific circumstances. ***Statements in italics in the recommendations relate to harm.*** Although some advice is provided about 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. 4. National Health Service England. 2019. Available from: *https://igd.mdsas.com/wp-content/uploads/NHSE_Commissioning_Criteria_for_the_use_of_Ig_V1.4_November_2019.pdf* (G7 seed guideline). 5. Rutledge Harding S, Lazarus A. 2018. Available from: https://professionaleducation.blood.ca/en/transfusion/clinical-guide/immune-globulin-products.

SECTION 2: Dermatology Indications

See separate entries for vasculitic syndromes, dermatomyositis, Kawasaki disease, scleroderma, and systemic lupus erythematosus in the Rheumatology Indications section; and for graft-versus-host disease in the Transplant Medicine Indications section.

? Atopic dermatitis

Do Not Know Recommendation	There is insufficient evidence to recommend for or against using IVIG. IVIG may be considered in patients with atopic dermatitis who have: • the most severe forms of atopic 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 contraindicated. Once the patient's condition has stabilized, the interval between infusions should be gradually increased to determine whether ongoing treatment is required. 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.
Evidence Source	RCT (G8); EO (GDG)

See Appendix A for category definitions

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LEGEND (see References for the list of "seed" guidelines): CR – case report; CS – case series study; EO – expert opinion; G – guideline; GDG – guideline development group (IMEC); IgA – immunoglobuin A; IVIG – intravenous immune globulin; NR – non-systematic/narrative review; qSR – quasi-systematic review; RCT – randomized controlled trial; SR – systematic review

✓ Autoimmune blistering diseases

Recommendation includes but is not limited to	○ bullous pemphigoid ○ epidermolysis bullosa acquisita ○ IgA pemphigus ○ linear IgA disease and chronic bullous disease of childhood ○ mucous membrane pemphigoid/cicatricial pemphigoid ○ paraneoplastic autoimmune multiorgan syndrome ○ pemphigoid/herpes gestationis ○ pemphigus foliaceus ○ pemphigus herpetiformis ○ pemphigus vulgaris
Do Recommendation	IVIG is recommended for all severe forms of autoimmune blistering diseases when other therapies are ineffective or contraindicated. 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, IgA pemphigus, pemphigus herpetiformis, pemphigoid/herpes gestationis, linear IgA disease and chronic bullous disease of childhood, and paraneoplastic autoimmune multiorgan syndrome.
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. Once the patient's condition has stabilized, the interval between infusions should be gradually increased to determine whether ongoing treatment is required. 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.
Qualifying Criteria	Diagnosis should be made by an appropriate specialist, such as a dermatologist, immunologist, ophthalmologist, otolaryngologist, or oral pathologist. Diagnosis should be confirmed by both routine pathology and appropriate direct or indirect immunofluorescence studies, whenever possible.
Review Criteria	If clinical effectiveness has not been achieved after 6 treatment cycles, IVIG should be discontinued.
Evidence Source	SR (G1, G8)

? Chronic idiopathic urticaria

Do Not Know Recommendation	There is insufficient evidence for or against using IVIG. IVIG may be considered as a last resort in patients with severe disease when conventional therapies are ineffective or contraindicated.

See Appendix A for category definitions

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LEGEND (see References for the list of "seed" guidelines): CR – case report; CS – case series study; EO – expert opinion; G – guideline; GDG – guideline development group (IMEC); IgA – immunoglobuin A; IVIG – intravenous immune globulin; NR – non-systematic/narrative review; qSR – quasi-systematic review; RCT – randomized controlled trial; SR – systematic review

? Chronic idiopathic urticaria

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.
Qualifying Criteria	Patients must meet both of the following criteria: • Contraindications or no response to high dose antihistamines; AND • Contraindications or no response to omalizumab (if covered).
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)

? Drug reaction with eosinophilia and systemic symptoms (DRESS)

Do Not Know Recommendation	There is insufficient evidence for or against using IVIG. IVIG may be considered for severe cases when corticosteroids and steroid-sparing agents are ineffective or contraindicated.
Dose	2 g/kg adjusted body weight divided over 2 to 5 days. A single treatment is usually sufficient. One additional dose may be given after an initial response if symptoms recur.
Evidence Source	SR (G5); EO (GDG)

? Eosinophilic fasciitis

Do Not Know Recommendation	There is insufficient evidence for or against using IVIG. IVIG may be considered for severe cases when systemic steroids and steroid-sparing agents are ineffective or contraindicated.
Dose	2 g/kg adjusted body weight divided over 2 to 5 days. A single treatment is usually sufficient. One additional dose may be given after an initial response if symptoms recur.
Evidence Source	EO (GDG-CR)

See Appendix A for category definitions

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LEGEND (see References for the list of "seed" guidelines): CR – case report; CS – case series study; EO – expert opinion; G – guideline; GDG – guideline development group (IMEC); IgA – immunoglobuin A; IVIG – intravenous immune globulin; NR – non-systematic/narrative review; qSR – quasi-systematic review; RCT – randomized controlled trial; SR – systematic review

? Livedoid vasculopathy

Do Not Know Recommendation	There is insufficient evidence for or against using IVIG. IVIG may be considered in exceptional circumstances when standard therapy is 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	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); EO (GDG)

? Mast cell activation syndrome (MCAS)

Do Not Know Recommendation	There is insufficient evidence to recommend the use of IVIG. IVIG should only be considered for severe cases when antihistamines, mast cell stabilizers, leukotriene inhibitors, corticosteroids, or other therapies are ineffective or contraindicated.
Dose	1.5 g/kg adjusted body weight divided over 2 to 5 days, every 4 weeks.
Review Criteria	If clinical effectiveness has not been achieved after 6 treatment cycles, IVIG should be discontinued. Once the patient's condition has stabilized, the interval between infusions should be gradually increased to determine whether ongoing treatment is required.
Evidence Source	EO (GDG-CR)

? Morphea

Do Not Know Recommendation	There is insufficient evidence for or against using IVIG. IVIG may be considered for severe cases when corticosteroids or other therapies are ineffective or contraindicated.
Dose	2 g/kg adjusted body weight divided over 2 to 5 days, every 4 weeks.
Review Criteria	If clinical effectiveness has not been achieved after 6 treatment cycles, IVIG should be discontinued. Once the patient's condition has stabilized, the interval between infusions should be gradually increased to determine whether ongoing treatment is required.
Evidence Source	CS (G4); EO (GDG)

See Appendix A for category definitions

LEGEND (see References for the list of "seed" guidelines): CR – case report; CS – case series study; EO – expert opinion; G – guideline; GDG – guideline development group (IMEC); IgA – immunoglobuin A; IVIG – intravenous immune globulin; NR – non-systematic/narrative review; qSR – quasi-systematic review; RCT – randomized controlled trial; SR – systematic review

? Mycoplasma induced rash and mucositis (MIRM)

Do Not Know Recommendation	There is insufficient evidence for or against using IVIG. IVIG may be considered for severe cases when systemic steroids, cyclosporine, and TNF-alpha inhibitors are ineffective or contraindicated.
Dose	2 g/kg adjusted body weight divided over 2 to 5 days. A single treatment is usually sufficient. One additional dose may be given after an initial response if symptoms recur.
Evidence Source	EO (GDG-qSR)

? Necrobiotic xanthogranuloma

Do Not Know Recommendation	There is insufficient evidence to recommend the use of IVIG. IVIG should only be considered for severe cases when corticosteroids or other therapies are ineffective or contraindicated.
Dose	2 g/kg adjusted body weight divided over 2 to 5 days, every 4 weeks.
Review Criteria	If clinical effectiveness has not been achieved after 6 treatment cycles, IVIG should be discontinued. Once the patient's condition has stabilized, the interval between infusions should be gradually increased to determine whether ongoing treatment is required.
Evidence Source	CR (G3); EO (GDG)

? Netherton syndrome

Do Not Know Recommendation	There is insufficient evidence for or against using IVIG. IVIG may be considered for immunodeficient patients who present with severe allergies, atopic dermatitis, or other skin disease when standard therapies are ineffective or contraindicated.
Dose	Typical immunoglobulin replacement dose ranges from 0.2 to 0.5 g/kg per month (see separate entry for secondary hypogammaglobulinemia). Occasionally, high immunomodulatory doses of 1 to 2 g/kg per month may be considered for immune-mediated disease.
Review Criteria	If clinical effectiveness has not been achieved after 6 treatment cycles, IVIG should be discontinued. Once the patient's condition has stabilized, the interval between infusions should be gradually increased to determine whether ongoing treatment is required.
Evidence Source	EO (GDG-CS)

? Pretibial myxedema

Do Not Know Recommendation	There is insufficient evidence for or against using IVIG. IVIG may be considered for severe cases when intralesional or oral corticosteroids and steroid-sparing agents are ineffective or contraindicated.
Dose	1.5 to 2 g/kg adjusted body weight divided over 2 to 5 days, every 4 weeks.

See Appendix A for category definitions

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LEGEND (see References for the list of "seed" guidelines): CR – case report; CS – case series study; EO – expert opinion; G – guideline; GDG – guideline development group (IMEC); IgA – immunoglobuin A; IVIG – intravenous immune globulin; NR – non-systematic/narrative review; qSR – quasi-systematic review; RCT – randomized controlled trial; SR – systematic review

? Pretibial myxedema	
Review Criteria	If clinical effectiveness has not been achieved after 6 treatment cycles, IVIG should be discontinued. Once the patient's condition has stabilized, the interval between infusions should be gradually increased to determine whether ongoing treatment is required.
Evidence Source	EO (G3, GDG)

? Psoriasis	
Do Not Know Recommendation	There is insufficient evidence to recommend the use of IVIG. IVIG should only be considered when all other therapies, including phototherapy, methotrexate, cyclosporine, retinoids, small molecule inhibitors, and biologics are ineffective or contraindicated.
Dose	2 g/kg adjusted body weight divided over 2 to 5 days, every 4 weeks.
Review Criteria	If clinical effectiveness has not been achieved after 6 treatment cycles, IVIG should be discontinued. Once the patient's condition has stabilized, the interval between infusions should be gradually increased to determine whether ongoing treatment is required.
Evidence Source	EO (GDG-CR)

See Appendix A for category definitions

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✓ Pyoderma gangrenosum	
Do Recommendation	IVIG may be considered in patients with significant pyoderma gangrenosum, as diagnosed by a dermatologist, when other therapies are ineffective or contraindicated. The diagnostic criteria for pyoderma gangrenosum should be met, and the relevant differential diagnoses (i.e., infections) must be excluded.
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. 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 (G1); EO (GDG)

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

LEGEND (see References for the list of "seed" guidelines): CR – case report; CS – case series study; EO – expert opinion; G – guideline; GDG – guideline development group (IMEC); IgA – immunoglobuin A; IVIG – intravenous immune globulin; NR – non-systematic/narrative review; qSR – quasi-systematic review; RCT – randomized controlled trial; SR – systematic review

✓ 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.
Qualifying Criteria	Diagnosis should be made by an appropriate specialist such as a dermatologist.
Review Criteria	Patient response should be documented according to objective measures of effectiveness established at the outset of treatment. 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	CS (G1, G8)

See Appendix A for category definitions

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✓ Toxic epidermal necrolysis (TEN)/Stevens–Johnson syndrome (SJS)	
Do Recommendation	IVIG may be considered in severe scleromyxedema when other therapies are ineffective or contraindicated.
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: • Consultation with a dermatologist or an allergist; AND • Characteristic cutaneous and mucous membrane involvement; AND • 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, G8); EO (GDG-SR)

LEGEND (see References for the list of "seed" guidelines): CR – case report; CS – case series study; EO – expert opinion; G – guideline; GDG – guideline development group (IMEC); IgA – immunoglobuin A; IVIG – intravenous immune globulin; NR – non-systematic/narrative review; qSR – quasi-systematic review; RCT – randomized controlled trial; SR – systematic review

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 for or against using IVIG. IVIG is not recommended for routine use but may be considered as one of several options in urgent situations. IVIG is less likely to be helpful in cold AIHA.
Dose	1 g/kg adjusted body weight divided over 1 to 5 days. A single treatment is usually sufficient. One additional dose may be given if response to the first dose is suboptimal. *Note: IVIG interferes with the direct antiglobulin test and may exacerbate hemolysis in patients who have non-group O blood.* *High-dose IVIG may limit the efficacy of concomitantly administered monoclonal antibodies.*[1] 1. Jordan SC, et al. *American Journal of Transplantation* 2020;20(9):2581-8.
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-NRCS)

? Autoimmune neutropenia

Do Not Know Recommendation	There is insufficient evidence for or against using IVIG. IVIG may be considered as one of several options in rare circumstances when standard therapy fails for severe symptomatic neutropenia.
Dose	1 g/kg adjusted body weight divided over 1 to 5 days. A single treatment is usually sufficient. One additional dose may be given if response to the first dose is suboptimal.
Review Criteria	Patient response should be documented according to objective measures of effectiveness established at the outset of treatment.
Evidence Source	CS (G1); G (G2); EO (GDG).

× Coagulation factor inhibitors

Recommendation includes but is not limited to	○ acquired hemophilia ○ acquired von Willebrand disease ○ inhibitors to factor VIII in hemophilia A ○ inhibitors to factor IX in hemophilia B
Do Not Do Recommendation	IVIG is not recommended.

See Appendix A for category definitions

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LEGEND (see References for the list of "seed" guidelines): 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

× Coagulation factor inhibitors

Evidence Source	EO (GDG)

✓ Feto-maternal/neonatal alloimmune thrombocytopenia (FMAIT/NAIT)

Do Recommendation	IVIG is recommended for preventing or treating fetal or neonatal thrombocytopenia or hemorrhage. Management should be under the direction of specialists with expertise in high-risk obstetrics, neonatology, and/or pediatric hematology.
Dose	Maternal: 1 g/kg adjusted body weight (up to a maximum dose of 100 g) 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 one of the following: • Thrombocytopenia or spontaneous hemorrhage in the fetus; • Thrombocytopenia with or without hemorrhage in the neonate; or • 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).
Evidence Source	SR (G1); G (G2); EO (GDG)

✓ Gestational alloimmune liver disease (GALD)/alloimmune neonatal hemochromatosis

Do Recommendation	IVIG is recommended for women with a previously affected pregnancy.
Dose	1 g/kg (capped at 60 g per week) for at-risk mothers at 14 weeks, 16 weeks, and then weekly from 18 weeks' gestation until delivery between 37 and 38 weeks. The dose is based on the mother's adjusted body weight at initial presentation and is continued unchanged throughout pregnancy.
Evidence Source	EO (G7, GDG-CS)

✓ Hemolytic disease of the fetus (HDF), prevention

Do Recommendation	IVIG may be considered in severe disease when there are maternal antibodies against fetal antigens and a high risk of early fetal hydrops or death. Management should be under the direction of a high-risk obstetrician or maternal-fetal medicine specialist, with assistance from hematology as appropriate.
Dose	1 g/kg adjusted body weight (up to a maximum dose of 100 g) weekly throughout pregnancy.
Evidence Source	SR (G1); EO (GDG)

See Appendix A for category definitions

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LEGEND (see References for the list of "seed" guidelines): 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

✓ Hemolytic disease of the newborn (HDN)

Do Recommendation	IVIG may be considered in selected cases in consultation with experts in neonatology, pediatric hematology, and transfusion medicine.
Dose	Single dose of 1 g/kg. Dose may be repeated if clinically indicated.
Evidence Source	G (G2); EO (GDG-G)

× Hemolytic uremic syndrome (HUS)

Do Not Do Recommendation	IVIG is not recommended because there is insufficient evidence of benefit and preferable alternative therapies are available.
Evidence Source	EO (G1)

×/? Hemophagocytic lymphohistiocytosis (HLH) syndrome

Primary HLH	
Do Not Do Recommendation	Immunomodulatory doses of IVIG are not recommended for the treatment of HLH. (See below for management of HLH treatment-related hypogammaglobulinemia with infection.)
Evidence Source	EO (GDG)
Secondary (acquired) HLH	
Do Not Know Recommendation	There is insufficient evidence for or against using IVIG. Immunomodulatory doses of IVIG may be considered in exceptional circumstances with appropriate consultation. (See below for management of underlying primary hypogammaglobulinemia with infection.)
Dose	Single dose of 1.6 to 2 g/kg adjusted body weight divided over 2 to 5 days.
Qualifying criteria	Genetic, clinical, and/or laboratory evidence supporting a diagnosis of secondary HLH per diagnostic criteria.[1,2] 1. Jordan MB, et al. *Blood* 2011;118(15):4041-52. 2. McClain KL, Eckstein O [Internet]. 2017. Available from: *https://www.uptodate.com/contents/clinical-features-and-diagnosis-of-hemophagocytic-lymphohistiocytosis*.
Exclusion criteria	The presence of a gene known to cause primary HLH.
Review criteria	Patient response should be documented according to objective measures of effectiveness established at the outset of treatment.
Evidence Source	G (G11); EO (GDG-NRCS)
HLH-associated hypogammaglobulinemia with infection	
Do Not Know Recommendation	There is insufficient evidence for or against using IVIG. Replacement doses of IVIG may be used to reduce the risk of infection due to the hypogammaglobulinemia that is often associated with HLH and/or its treatment.

See Appendix A for category definitions

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LEGEND (see References for the list of "seed" guidelines): 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

×/? Hemophagocytic lymphohistiocytosis (HLH) syndrome

Dose	See separate entries for primary immunodeficiency disorders and secondary hypogammaglobulinemia in the Immunology Indications section as appropriate.
Evidence Source	EO (GDG)

✓ Heparin-induced thrombocytopenia (HIT)

Do Recommendation	IVIG may be considered as an option for severe HIT refractory to standard interventions.
Dose	Single dose of 1 g/kg **actual** body weight. Dose may be repeated if clinically indicated.
Evidence Source	EO (GDG-SR)

Hypogammaglobulinemia, acquired secondary to hematological malignancies

Includes but is not limited to	○ chronic lymphocytic leukemia ○ lymphoma ○ myeloma ○ 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: • Refractory ITP on the recommendation of an appropriate clinical specialist Patients with severe thrombocytopenia (platelets less than 20 x 10^9/L) in whom other therapies are ineffective or contraindicated. • 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. • ITP in pregnancy Pregnant patients with ITP and impending delivery. • Specific circumstances ○ Planned surgery; ○ Other concurrent risk factors for bleeding (e.g., concurrent anticoagulant therapy); ○ Severe ITP (platelets less than 20 x 10^9/L) where corticosteroids and other immunosuppressives are contraindicated; and/or ○ Chronic ITP under the guidance of a clinical hematologist, in addition to other therapies or where other therapies are ineffective or contraindicated. • HIV–associated ITP Patients unresponsive to antiviral therapy and:

See Appendix A for category definitions

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LEGEND (see References for the list of "seed" guidelines): 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

✓ Immune thrombocytopenic purpura (ITP) – adult	
	○ have a platelet count less than 20 x 10^9/L; or ○ have a platelet count less than 50 x 10^9/L with bleeding. • Lupus–associated ITP See separate entry for systemic lupus erythematosus. For each of these indications, consultation with a clinical hematologist is strongly recommended.
Dose	Induction: Single dose of 1 g/kg adjusted body weight divided over 1 to 5 days. Ongoing therapy: When indicated, 1 g/kg adjusted body weight divided over 1 to 5 days every 4 to 6 weeks, titrated as needed to achieve a clinical effect.
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	SR (G1); G (G2)

✓ 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 in rare situations (e.g., to increase platelet count before surgery or for severe bleeding) but should not be used for regular maintenance to maintain a particular platelet count over time in the absence of bleeding.
Dose	Acute or chronic ITP: Single dose of 0.8 to 1 g/kg adjusted body weight, with a second dose as needed to control bleeding.
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	SR (G1); G (G2); CS (G6)

See Appendix A for category definitions

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LEGEND (see References for the list of "seed" guidelines): 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

✓ Neonatal hemochromatosis, prevention	
Do Recommendation	IVIG is recommended for: • neonates with hemochromatosis confirmed by findings of high iron on biopsy or by MRI demonstration of iron overload; and • pregnant women who have had a previous pregnancy affected by neonatal hemochromatosis.
Dose	Neonatal: Maintenance dose of 1 to 2 g/kg following exchange transfusion in the first 7 days and then up to 1 g/kg weekly, as required. Maternal: Maintenance dose of 1 g/kg adjusted body weight (to a maximum dose of 100 g) weekly from 18 weeks' gestation until delivery.
Evidence Source	SR (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 and/or a pediatric hematologist.
Dose	Single dose of 1 g/kg. Dose may be repeated if clinically indicated.
Evidence Source	CS (G9)

✓ Post-transfusion purpura (PTP)	
Do Recommendation	IVIG is recommended as standard first-line therapy for suspected or confirmed PTP with life-threatening bleeding.
Dose	1 g/kg/day adjusted body weight over 1 to 5 days.
Evidence Source	CS (G1); G (G2); EO (GDG-NR)

✓ Pure red cell aplasia (PRCA)	
Do Recommendation	IVIG is recommended for viral PRCA associated with proven parvovirus B19 in immunocompromised patients. When there is high clinical suspicion of parvovirus B19 infection, it may be reasonable to start IVIG while awaiting final serology results. IVIG may be considered for other patients with PRCA who have not responded to other therapies.
Dose	Up to 2 g/kg adjusted body weight divided over 2 to 5 days. Dose may be repeated if clinically indicated.
Evidence Source	CS (G1); G (G2)

? Sickle cell disease, hyperhemolysis syndrome	
Do Not Know Recommendation	There is insufficient evidence for or against using IVIG. IVIG may be considered as one of several options in urgent situations.

See Appendix A for category definitions

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LEGEND (see References for the list of "seed" guidelines): 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

? Sickle cell disease, hyperhemolysis syndrome	
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	CS (G1); G (G2)

? Thrombotic thrombocytopenic purpura (TTP)	
Do Not Know Recommendation	There is insufficient evidence to recommend the use of 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)

✓ Vaccine induced immune thrombotic thrombocytopenia (VITT)/vaccine induced prothrombotic immune thrombocytopenia (VIPIT)	
Do Recommendation	IVIG is recommended for suspected or confirmed VITT. Diagnosis must be made by a hematologist.
Dose	2 g/kg actual body weight divided over 2 to 5 days. Dose may be repeated if clinically indicated.
Evidence Source	G (G1); EO (GDG)

See Appendix A for category definitions

LEGEND (see References for the list of "seed" guidelines): 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

SECTION 4: Immunology Indications

See separate entry for hemophagocytic lymphohistiocytosis (HLH) syndrome in the Hematology Indications section.

✓ 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 secondary prevention of recurrent, severe infection due to hypogammaglobulinemia (excluding paraprotein) related to other diseases or medical therapy in patients who have a history of infections. It is not recommended for routine replacement of Ig as primary prophylaxis against infections in the setting of an isolated low IgG level without infection. Note: This includes bacterial infections as well as select viral, protozoal, and fungal infections, as directed by a physician with recognized expertise in immunodeficiency disorders.
Dose	Aim to use the dose that achieves a significant reduction in the number of infections. SCIG and IVIG are equally effective. Maintenance: 0.4 to 0.6 g/kg adjusted body weight IVIG every 4 weeks, or SCIG 0.1 to 0.15 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. Disseminated enterovirus infection: One dose of 2 g/kg adjusted body weight (IVIG or SCIG) divided over 2 to 5 days at any stage is permitted (in addition to the maintenance dose).

See Appendix A for category definitions

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LEGEND (see References for the list of "seed" guidelines): EO – expert opinion; G – guideline; GDG – guideline development group (IMEC); HSCT: hematopoietic stem cell transplant; IG – immune globulin; IgA – immunoglobulin A; IgG – immunoglobulin G; IgM – immunoglobulin M; IVIG – intravenous immune globulin; SCIG – subcutaneous immune globulin; SR – systematic review

✓ Hypogammaglobulinemia, secondary

Qualifying Criteria	The decision to use IVIG should be made in consultation with a physician with recognized expertise in immunodeficiency disorders.
	Hypogammaglobulinemia secondary to underlying disease or medical therapy (including HSCT) with all of the following:
	• Serum IgG less than the lower limit of the reference range on two separate occasions
	AND
	• At least one of the following:
	  ○ One invasive or life-threatening infection (e.g., pneumonia, meningitis, sepsis) in the previous year;
	  ○ Recurrent, severe infections;
	  ○ Clinically active bronchiectasis confirmed by radiology; or
	  ○ Assessment by a physician specializing in immunodeficiency indicating a significant antibody defect that would benefit from immunoglobulin replacement.
	See the Transplant Medicine Indications section for further guidance.

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 with recognized expertise in immunodeficiency disorders. The following outcome measures should be recorded: • IgG level every 3 to 6 months; and • number of infections and hospital admissions for infection. 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); EO (G7, G10, GDG-G)

See Appendix A for category definitions

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✓ Primary immunodeficiency (PID) disorders

Do Recommendation	Immunoglobulin replacement is recommended for preventing infection. Note: This includes bacterial infections as well as select viral, protozoal, and fungal infections, as directed by a physician with recognized expertise in immunodeficiency disorders.

LEGEND (see References for the list of "seed" guidelines): EO – expert opinion; G – guideline; GDG – guideline development group (IMEC); HSCT: hematopoietic stem cell transplant; IG – immune globulin; IgA – immunoglobulin A; IgG – immunoglobulin G; IgM – immunoglobulin M; IVIG – intravenous immune globulin; SCIG – subcutaneous immune globulin; SR – systematic review

✓ Primary immunodeficiency (PID) disorders	
Dose	Aim to use the dose that achieves a significant reduction in the number of infections. SCIG and IVIG are equally effective. Maintenance: 0.4 to 0.6 g/kg adjusted body weight IVIG every 4 weeks or SCIG 0.1 to 0.15 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 with recognized expertise in immunodeficiency disorders. Functional criteria are required to establish diagnosis for the following-specific disorders: • common variable immunodeficiency (CVID) and associated disorders • specific antibody deficiency • IgG subclass deficiency • combined immunodeficiency Functional criteria at a minimum should include total IgG, IgA, IgM, protein vaccine titres (tetanus, diphtheria, measles, and rubella), and polysaccharide (pneumococcal) titres.
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 with recognized expertise in immunodeficiency disorders. The following outcome measures should be recorded: • IgG level every 3 to 6 months; and • number of infections and hospital admissions for infection. If clinical effectiveness has not been achieved, IG treatment should be reassessed.
Evidence Source	SR (G1); G (G7, G10); EO (GDG-SR)

See Appendix A for category definitions

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LEGEND (see References for the list of "seed" guidelines): EO – expert opinion; G – guideline; GDG – guideline development group (IMEC); HSCT: hematopoietic stem cell transplant; IG – immune globulin; IgA – immunoglobulin A; IgG – immunoglobulin G; IgM – immunoglobulin M; IVIG – intravenous immune globulin; SCIG – subcutaneous immune globulin; SR – systematic review

SECTION 5: Infectious Disease Indications

See separate entry for mycoplasma induced rash and mucositis in the Dermatology Indications section.

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× *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	EO (GDG-SR)

✓ Hepatitis A, post-exposure prophylaxis (PEP)

Do Recommendation	Intramuscular IG should be administered within 2 weeks of exposure for select patients. Individuals receiving replacement IG are considered protected and do not require IG if the last dose was received in the 3 weeks before hepatitis A exposure.
Dose	Usually 0.1 mL/kg of actual body weight intramuscular IG (e.g., GamaSTAN®), given as soon as possible after an exposure. The efficacy of IG is unknown if more than 14 days have elapsed since the last exposure.
Qualifying Criteria	• Hepatitis A vaccine is unavailable. OR • Infants less than 6 months of age. OR • Individuals with a history of anaphylaxis after previous administration of hepatitis A vaccine and those with proven immediate or anaphylactic hypersensitivity to any component of the hepatitis A vaccine or its container. OR • Immunocompromised individuals*. OR • Individuals with chronic liver disease*. OR • Susceptible adults aged 60 years or older*. *Note: These individuals should receive hepatitis A vaccine in addition to intramuscular IG.
Evidence Source	EO (G7, GDG-G)

× 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)

See Appendix A for category definitions

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LEGEND (see References for the list of "seed" guidelines): AIDS – acquired immune deficiency syndrome; CS – case series study; EO – expert opinion; G – guideline; GDG – guideline development group (IMEC); HIV – human immunodeficiency virus; IG – immune globulin; IVIG – intravenous immune globulin; RCT – randomized controlled trial; SR – systematic review

✓/× Measles, post-exposure prophylaxis (PEP)

Do Recommendation	IG is recommended for those with contraindications to active measles immunization, including: • susceptible pregnant women; • infants aged <6 months; and • immunocompromised patients. Susceptible infants aged 6 to 12 months presenting more than 72 hours after measles exposure can also receive IG PEP.
Dose	Single dose of intramuscular IG 0.5 mL/kg actual body weight. For patients weighing more than 30 kg or who cannot tolerate the intramuscular volume, IVIG should be provided at a single dose of 0.4 g/kg adjusted body weight (use actual body weight in pregnancy).
Evidence Source	CS (G13)

Immunocompetent individuals older than 12 months	
Do Not Do Recommendation	IVIG is not recommended.
Evidence Source	CS (G13)

? Necrotizing fasciitis

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

Do Not Know Recommendation	There is insufficient evidence for or against using IVIG in patients without concomitant toxic shock syndrome.
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, prophylaxis

See separate entry for secondary hypogammaglobulinemia.

Do Not Do Recommendation	IVIG is not recommended for patients of any age in the absence of hypogammaglobulinemia.
Evidence Source	RCT (G1)

See Appendix A for category definitions

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LEGEND (see References for the list of "seed" guidelines): AIDS – acquired immune deficiency syndrome; CS – case series study; EO – expert opinion; G – guideline; GDG – guideline development group (IMEC); HIV – human immunodeficiency virus; IG – immune globulin; IVIG – intravenous immune globulin; RCT – randomized controlled trial; SR – systematic review

× Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)/ COVID-19

See separate entry for multisystem inflammatory syndrome in children (MIS-C) in the Rheumatology Indications section.

Do Not Do Recommendation	IVIG is not recommended.
Evidence Source	SR (G14)

✓ Toxic shock syndrome (TSS)

Do Recommendation	IVIG is recommended in addition to surgical intervention, antibiotic therapy, and other supportive measures for suspected or confirmed TSS. Consultation with an infectious disease specialist is strongly recommended.
Dose	Single dose of 2 g/kg adjusted body weight or 1 g/kg on day 1 and 0.5 g/kg on days 2 and 3.
Evidence Source	RCT (G1, G2); EO (GDG-RCT)

×/✓ Varicella-zoster virus (VZV), prophylaxis

See Appendix A for category definitions

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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 (G12)

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 are protected.
Evidence Source	EO (G12)

LEGEND (see References for the list of "seed" guidelines): AIDS – acquired immune deficiency syndrome; CS – case series study; EO – expert opinion; G – guideline; GDG – guideline development group (IMEC); HIV – human immunodeficiency virus; IG – immune globulin; IVIG – intravenous immune globulin; RCT – randomized controlled trial; SR – systematic review

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

? Adenovirus in solid organ transplant recipients

Do Not Know Recommendation	There is insufficient evidence for or against using IVIG in addition to antivirals for disseminated adenovirus infection without hypogammaglobulinemia. IVIG may be considered in addition to antiviral medications in solid organ transplant recipients with established disseminated adenovirus infection and hypogammaglobulinemia. See separate entry for secondary hypogammaglobulinemia.
Dose	There is insufficient evidence to recommend a dose.
Evidence Source	EO (GDG-CR)

? BK polyomavirus nephropathy in solid organ transplant recipients

Do Not Know Recommendation	There is insufficient evidence for or against using IVIG. IVIG may be considered in patients with established BK polyoma virus-associated nephropathy who do not respond to a reduction in immunosuppression.
Dose	There is insufficient evidence to recommend a dose.
Evidence Source	NRCS (G19)

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

Proven respiratory syncytial virus (RSV) in high-risk patients*	
Do Recommendation	IVIG may be used to prevent progression to lower respiratory tract infection.
Dose	Single dose of 1 g/kg adjusted body weight, with IgG level reassessed weekly. Consider retreatment if IgG level remains below the lower limit of normal.
Evidence Source	G (G15); EO (GDG-G)

Non-RSV in high-risk patients*	
Do Not Know Recommendation	There is insufficient evidence for or against using IVIG. Certain viruses may portend a greater risk for progression to a more severe lower respiratory tract infection, including parainfluenza, adenovirus, and human metapneumovirus. IVIG may be considered to prevent progression to a lower respiratory tract infection or worsening of an established lower respiratory tract infection in these high-risk situations.
Dose	Single dose of 1 g/kg adjusted body weight, with IgG level reassessed weekly. Consider retreatment if IgG level remains below the lower limit of normal.
Evidence Source	G (G15); EO (GDG-G)

See Appendix A for category definitions

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LEGEND (see References for the list of "seed" guidelines): CR – case report; CS – case series study; EO – expert opinion; G – guideline; GDG – guideline development group (IMEC); HSCT: hematopoietic stem cell transplant; IG – immune globulin; IgG – immunoglobulin G; IVIG – intravenous immune globulin; NRCS – non-randomized comparative study; RCT – randomized controlled trial; SCIG – subcutaneous immune globulin; SR – systematic review

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

All other patient groups, including solid organ transplant recipients (other than lung)	
Do Not Do Recommendation	IVIG is not recommended.
Evidence Source	G (G15); EO (GDG-G)

***Note**	The term "high-risk patient"[1] signifies:
	• Lung transplant recipients.
	• Allogeneic HSCT recipients with at least one of the following:
	  ○ hypogammaglobulinemia, defined as an IgG level less than the lower limit of normal or <4 g/L;
	  ○ absolute lymphocyte count <0.5 x 10^9/L;
	  ○ CD4 T-cell count <0.2 x 10^9/L;
	  ○ 6 months post alemtuzumab, anti-thymocyte globulin, rituximab therapy, or other B-cell depleting therapy (e.g., blinatumomab);
	  ○ steroid refractory or steroid dependent acute graft-versus-host disease;
	  ○ moderate to severe chronic graft-versus-host disease; or
	  ○ Prolonged use of systemic corticosteroids at a dose of at least 0.5 mg prednisone equivalents/kg/day for at least 1 week.
	• Recipients of chimeric antigen receptor T-cells (CAR-T) for relapsed or refractory acute leukemia, multiple myeloma, chronic lymphocytic leukemia, or non-Hodgkin lymphoma (or other indication) with ongoing evidence of B-cell lymphopenia who are not receiving regular immunoglobulin replacement.
	1. von Lilienfeld-Toal, Berger A, et al. *European Journal of Cancer* 2016;67:200-12. (G16 seed guideline)

See Appendix A for category definitions

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

High-risk patients*	
Do Not Know Recommendation	There is insufficient evidence for or against using IVIG. In some circumstances, IVIG may be considered in addition to antiviral therapy on a case-by-case basis.
Dose	Single dose of 1 g/kg adjusted body weight, with IgG level reassessed weekly. Consider retreatment if IgG level remains below the lower limit of normal.
Evidence Source	CS (G16, G17)
All other patient groups, including solid organ transplant recipients (other than lung)	
Do Not Do Recommendation	IVIG is not recommended.

LEGEND (see References for the list of "seed" guidelines): CR – case report; CS – case series study; EO – expert opinion; G – guideline; GDG – guideline development group (IMEC); HSCT: hematopoietic stem cell transplant; IG – immune globulin; IgG – immunoglobulin G; IVIG – intravenous immune globulin; 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)

Evidence Source	CS (G16)
***Note**	The term "high-risk patient"[1] signifies: • Lung transplant recipients. • Allogeneic HSCT recipients with at least one of the following: ○ hypogammaglobulinemia, defined as an IgG level less than the lower limit of normal or <4 g/L; ○ absolute lymphocyte count <0.5 x 10^9/L; ○ CD4 T-cell count <0.2 x 10^9/L; ○ 6 months post alemtuzumab, anti-thymocyte globulin, rituximab therapy, or other B-cell depleting therapy (e.g., blinatumomab); ○ steroid refractory or steroid dependent acute graft-versus-host disease; ○ moderate to severe chronic graft-versus-host disease; or ○ Prolonged use of systemic corticosteroids at a dose of at least 0.5 mg prednisone equivalents/kg/day for at least 1 week. • Recipients of chimeric antigen receptor T-cells (CAR-T) for relapsed or refractory acute leukemia, multiple myeloma, chronic lymphocytic leukemia, or non-Hodgkin lymphoma (or other indication) with ongoing evidence of B-cell lymphopenia who are not receiving regular immunoglobulin replacement. 1. von Lilienfeld-Toal, Berger A, et al. *European Journal of Cancer* 2016;67:200-12. (G16 seed guideline)

× *Cytomegalovirus* (CMV) infection, prevention

Recommendation includes	○ hematopoietic stem cell transplant (HSCT) ○ solid organ transplant
Do Not Do Recommendation	IVIG is not recommended for prophylaxis or pre-emptive treatment.
Evidence Source	EO (G15, GDG-NR)

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

Recommendation includes	○ hematopoietic stem cell transplant (HSCT) ○ solid organ transplant
Do Not Do Recommendation	IVIG is not recommended for prophylaxis or treatment.
Evidence Source	EO (G18, GDG)

See Appendix A for category definitions

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LEGEND (see References for the list of "seed" guidelines): CR – case report; CS – case series study; EO – expert opinion; G – guideline; GDG – guideline development group (IMEC); HSCT: hematopoietic stem cell transplant; IG – immune globulin; IgG – immunoglobulin G; IVIG – intravenous immune globulin; 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 for or against using 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-CS)

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	1 g/kg adjusted body weight once daily for 2 days, with weekly reassessment of IgG level. Consider retreatment with IVIG if needed for hypogammaglobulinemia and ongoing evidence of CMV pneumonitis.
Evidence Source	G (G2, G15); EO (GDG-NRCS)

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

Do Not Do Recommendation	IVIG is not recommended for the specific prevention or treatment of graft-versus-host disease in allogeneic HSCT (see separate entry for secondary hypogammaglobulinemia).
Evidence Source	EO (GDG-SR)

× Hematopoietic stem cell transplant (HSCT), autologous

Do Not Do Recommendation	IVIG is not recommended for routine post-transplant care in autologous HSCT (see separate entry for secondary hypogammaglobulinemia).
Evidence Source	SR (G1)

See Appendix A for category definitions

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LEGEND (see References for the list of "seed" guidelines): CR – case report; CS – case series study; EO – expert opinion; G – guideline; GDG – guideline development group (IMEC); HSCT: hematopoietic stem cell transplant; IG – immune globulin; IgG – immunoglobulin G; IVIG – intravenous immune globulin; 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.
Review Criteria	See separate entry for secondary hypogammaglobulinemia.
Evidence Source	SR (G1)

? Kidney transplant, isolated acute/active T-cell mediated rejection (TCMR) management

Do Not Know Recommendation	There is insufficient evidence 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	EO (GDG-G)

✓/× Parvovirus B19 in solid organ transplant recipients

Do Recommendation	IVIG may be used in patients with established parvovirus B19 infection. Retreatment may be considered for non-response or symptomatic relapse.
Dose	2 g/kg adjusted body weight divided over 5 days. *Note: Shorter courses may be considered, but daily doses of more than 1 g/kg are associated with nephrotoxicity.*
Evidence Source	CS (G20)
Do Not Do Recommendation	IVIG is not recommended to prevent recurrence of parvovirus B19 infection.
Evidence Source	CS (G20)

See Appendix A for category definitions

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LEGEND (see References for the list of "seed" guidelines): CR – case report; CS – case series study; EO – expert opinion; G – guideline; GDG – guideline development group (IMEC); HSCT: hematopoietic stem cell transplant; IG – immune globulin; IgG – immunoglobulin G; IVIG – intravenous immune globulin; NRCS – non-randomized comparative study; RCT – randomized controlled trial; SCIG – subcutaneous immune globulin; SR – systematic review

✕ Pulmonary graft-versus-host disease	
Do Not Do Recommendation	IVIG is not recommended for the specific treatment of pulmonary graft-versus-host disease (see separate entry for secondary hypogammaglobulinemia).
Evidence Source	EO (GDG)

✓ Solid organ transplant, 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 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, G2)

See Appendix A for category definitions

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LEGEND (see References for the list of "seed" guidelines): CR – case report; CS – case series study; EO – expert opinion; G – guideline; GDG – guideline development group (IMEC); HSCT: hematopoietic stem cell transplant; IG – immune globulin; IgG – immunoglobulin G; IVIG – intravenous immune globulin; NRCS – non-randomized comparative study; RCT – randomized controlled trial; SCIG – subcutaneous immune globulin; SR – systematic review

✓ Solid organ transplant, ongoing desensitization, prevention or treatment of graft rejection	
Do Recommendation	IVIG may be used in: • highly sensitized patients awaiting transplantation; • transplant recipients to prevent or treat graft rejection when conventional immunosuppressive therapy is contraindicated; or • ABO incompatible transplant.
Dose	0.1 to 0.5 g/kg adjusted body weight, which may be given in divided doses up to a total maximum dose of 2 g/kg adjusted body weight in a 4-week period.
Review Criteria	Patient response should be documented according to objective measures of effectiveness established at the outset of treatment. Therapy should be reviewed and cessation considered if an improvement has not been achieved after two consecutive treatment cycles.
Evidence Source	RCT (G1, G2); EO (GDG)

See Appendix A for category definitions

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LEGEND (see References for the list of "seed" guidelines): CR – case report; CS – case series study; EO – expert opinion; G – guideline; GDG – guideline development group (IMEC); HSCT: hematopoietic stem cell transplant; IG – immune globulin; IgG – immunoglobulin G; IVIG – intravenous immune globulin; NRCS – non-randomized comparative study; RCT – randomized controlled trial; SCIG – subcutaneous immune globulin; SR – systematic review

SECTION 7: Neurology and Neuromuscular Indications

? Acute flaccid myelitis

Do Not Know Recommendation	There is insufficient evidence to recommend the use of 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-G)

✓ Acute disseminated encephalomyelitis (ADEM)

Do Recommendation	IVIG is recommended for: • ADEM unresponsive to steroid therapy or where steroids are contraindicated. • Recurrent or multiphasic ADEM unresponsive to steroid therapy or where steroid therapy is contraindicated or has become intolerable. For patients with relapsing ADEM, alternative diagnoses should be considered, including multiple sclerosis (MS), myelin oligodendrocyte glycoprotein antibody disorder (MOGAD), or neuromyelitis optica spectrum disorder (NMOSD), and other therapies may be offered as applicable.
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 optic neuritis

See separate entry for neuromyelitis optica spectrum disorders.	
Do Not Do Recommendation	IVIG is not recommended.
Evidence Source	RCT (G1)

See Appendix A for category definitions

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LEGEND (see References for the list of "seed" guidelines): CS – case series study; EO – expert opinion; G – guideline; GDG – guideline development group (IMEC); IgA – immunoglobulin A; IgG – immunoglobulin G; IgM – immunoglobulin M; IVIG – intravenous immune globulin; NR – non-systematic/narrative review; NRCS – non-randomized comparative study; qSR – quasi-systematic review; RCT – randomized controlled trial; SCIG – subcutaneous immune globulin; SR – systematic review

× Adrenoleukodystrophy

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

? Aicardi-Goutières syndrome

Do Not Know Recommendation	There is insufficient evidence to recommend the use of 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-NR)

× Alzheimer disease

Do Not Do Recommendation	IVIG is not recommended.
Evidence Source	RCT (G10); EO (GDG-RCT)

× Autism

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

✓ Autoimmune encephalitis mediated by antibodies (AMAE) targeting cell-surface antigens

See separate entry for Rasmussen syndrome.

Recommendation includes	○ Encephalitis associated with antibodies to: NMDA receptor, VGKC, LGI1, CASPR2, DPPX, AMPA receptor, glycine receptor, or GABA (A or B) receptor ○ Highly suspected autoimmune encephalitis ○ Paraneoplastic encephalitis ○ Seronegative autoimmune encephalitis ○ Seronegative limbic encephalitis ○ Suspected autoimmune limbic encephalitis

See Appendix A for category definitions

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LEGEND (see References for the list of "seed" guidelines): CS – case series study; EO – expert opinion; G – guideline; GDG – guideline development group (IMEC); IgA – immunoglobulin A; IgG – immunoglobulin G; IgM – immunoglobulin M; IVIG – intravenous immune globulin; NR – non-systematic/narrative review; NRCS – non-randomized comparative study; qSR – quasi-systematic review; RCT – randomized controlled trial; SCIG – subcutaneous immune globulin; SR – systematic review

✓ Autoimmune encephalitis mediated by antibodies (AMAE) targeting cell-surface antigens

Do Recommendation	IVIG may be used as an option with expert consultation.
Dose	Induction: 2 g/kg adjusted body weight divided over 2 to 5 days. Maintenance: 0.5 to 2 g/kg adjusted body weight monthly, if necessary.
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); EO (GDG-qSR)

? Childhood epilepsy, drug resistant

Recommendation includes but is not limited to	○ Infantile spasms ○ Landau–Kleffner syndrome ○ Lennox–Gastaut syndrome
Do Not Know Recommendation	There is insufficient evidence for or against using IVIG. IVIG should be considered only when conventional therapies including steroids, if appropriate, 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 as follows: • 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 1 to 5 days (maximum 1 g/kg/day), 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	SR (G1); EO (GDG-RCT)

× Chronic fatigue syndrome (myalgic encephalomyelitis)

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

See Appendix A for category definitions

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LEGEND (see References for the list of "seed" guidelines): CS – case series study; EO – expert opinion; G – guideline; GDG – guideline development group (IMEC); IgA – immunoglobulin A; IgG – immunoglobulin G; IgM – immunoglobulin M; IVIG – intravenous immune globulin; NR – non-systematic/narrative review; NRCS – non-randomized comparative study; qSR – quasi-systematic review; RCT – randomized controlled trial; SCIG – subcutaneous immune globulin; SR – systematic review

✓ Chronic inflammatory demyelinating polyneuropathy (CIDP)

Recommendation includes but is not limited to	○ 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	Induction: 2 g/kg adjusted body weight divided over 2 to 5 days. Maintenance: 1 g/kg adjusted body weight divided over 1 to 5 days (maximum 1 g/kg/day), every 3 to 4 weeks. SCIG should be considered as an alternative to IVIG following stabilization with IVIG. 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. Some patients may require a higher maintenance 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, 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)

? Diabetic amyotrophy

Do Not Know Recommendation	There is insufficient evidence for or against using IVIG. IVIG may be considered in exceptional circumstances with expert consultation.
Dose	There is insufficient evidence to recommend a dose.

See Appendix A for category definitions

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LEGEND (see References for the list of "seed" guidelines): CS – case series study; EO – expert opinion; G – guideline; GDG – guideline development group (IMEC); IgA – immunoglobulin A; IgG – immunoglobulin G; IgM – immunoglobulin M; IVIG – intravenous immune globulin; NR – non-systematic/narrative review; NRCS – non-randomized comparative study; qSR – quasi-systematic review; RCT – randomized controlled trial; SCIG – subcutaneous immune globulin; SR – systematic review

? Diabetic amyotrophy

Review Criteria	In rare instances when longer-term treatment is required, continued use of IVIG should be based on objective measures of effectiveness as detailed below. These measures should be assessed no later than 6 months after initiation of treatment and at least annually thereafter. Diabetic amyotrophy is a monophasic illness with worsening function while the disease is active followed by slow improvement in function as the peripheral nervous system regenerates. This may take as long as 2 years. If IVIG has been used it should be discontinued once the disease is no longer active. This may be indicated by lack of progression of motor and sensory deficits.
Evidence Source	EO (G21, 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 should not be given unless the patient has improved or plateaued and then subsequently worsened. See general statement on immune globulin in combination with other therapies, if treatment includes plasma exchange.
Evidence Source	SR (G1); EO (GDG-RCT)

? 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.
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. The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.
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)

✓ Lambert–Eaton myasthenic syndrome (LEMS)

Do Recommendation	IVIG is recommended as an option for treatment. Maintenance therapy with IVIG may be used in patients who show objective evidence of clinical improvement with IVIG therapy but have incomplete response to oral maintenance therapies.

See Appendix A for category definitions

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LEGEND (see References for the list of "seed" guidelines): CS – case series study; EO – expert opinion; G – guideline; GDG – guideline development group (IMEC); IgA – immunoglobulin A; IgG – immunoglobulin G; IgM – immunoglobulin M; IVIG – intravenous immune globulin; NR – non-systematic/narrative review; NRCS – non-randomized comparative study; qSR – quasi-systematic review; RCT – randomized controlled trial; SCIG – subcutaneous immune globulin; SR – systematic review

✓ Lambert–Eaton myasthenic syndrome (LEMS)

Dose	Induction: 2 g/kg adjusted body weight divided over 2 to 5 days. Maintenance: 0.4 to 1 g/kg adjusted body weight, every 2 to 6 weeks. A maximum dose of 2 g/kg may be given in any 4-week period. 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. It is preferable to discontinue IVIG in favour of oral immunosuppressants, where possible.
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); EO (GDG)

× Motor neuron disease

See separate entry for multifocal motor neuropathy.

Recommendation includes but is not limited to	○ amyotrophic lateral sclerosis (ALS)
Do Not Do Recommendation	IVIG is not recommended.
Evidence Source	EO (G1)

✓ 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: Maximum 2 g/kg adjusted body weight in a 4-week period. Some patients may require a higher maintenance 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	IVIG should be used for no longer than 6 months before determining whether the patient has responded. If there is no benefit after this treatment, IVIG therapy should be abandoned. Review by a neurologist is required no later than 6 months of treatment and annually thereafter. Documentation of clinical efficacy is necessary for continuation of IVIG therapy. For patients in remission on maintenance therapy, a trial of weaning leading to cessation should be considered.

See Appendix A for category definitions

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LEGEND (see References for the list of "seed" guidelines): CS – case series study; EO – expert opinion; G – guideline; GDG – guideline development group (IMEC); IgA – immunoglobulin A; IgG – immunoglobulin G; IgM – immunoglobulin M; IVIG – intravenous immune globulin; NR – non-systematic/narrative review; NRCS – non-randomized comparative study; qSR – quasi-systematic review; RCT – randomized controlled trial; SCIG – subcutaneous immune globulin; SR – systematic review

✓ Multifocal motor neuropathy (MMN)	
Evidence Source	SR (G1); CS (G2); EO (GDG)

✓/× Multiple sclerosis (MS)	
Relapsing remitting multiple sclerosis (RRMS), short-term therapy	
Do Recommendation	IVIG is recommended for short-term therapy in patients with clinically definite relapsing remitting MS, confirmed by a neurologist, and one of the following indications: • Severe relapse of clinically definite RRMS with no response to high-dose methylprednisolone or where methylprednisolone is contraindicated. • Prevention of relapse of clinically definite RRMS where alternative therapies are inappropriate, unavailable, or contraindicated.
Dose	Induction: 1 to 2 g/kg adjusted body weight divided over 1 to 5 days (maximum 1 g/kg/day). Maintenance (for indication 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. If clinical effectiveness has not been achieved, IVIG should be discontinued. After a maximum of 12 months of treatment, patients should be reassessed as to whether a more appropriate treatment is available.
Evidence Source	SR (G1)
RRMS, long-term therapy	
Do Not Do Recommendation	IVIG is not recommended.
Evidence Source	EO (GDG)
Primary progressive MS; progressive phase of MS without relapse	
Do Not Do Recommendation	IVIG is not recommended.
Evidence Source	EO (G1, GDG)

See Appendix A for category definitions

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LEGEND (see References for the list of "seed" guidelines): CS – case series study; EO – expert opinion; G – guideline; GDG – guideline development group (IMEC); IgA – immunoglobulin A; IgG – immunoglobulin G; IgM – immunoglobulin M; IVIG – intravenous immune globulin; NR – non-systematic/narrative review; NRCS – non-randomized comparative study; qSR – quasi-systematic review; RCT – randomized controlled trial; SCIG – subcutaneous immune globulin; SR – systematic review

✓/?/× Myasthenia gravis (MG)

MG, moderate to severe generalized	
Do Recommendation	IVIG is recommended as: • An alternative to plasma exchange in an acute exacerbation (myasthenic crisis) or before surgery, including thymectomy. • Maintenance therapy for moderate to severe generalized MG when other treatments are ineffective or have caused intolerable side effects.
Dose	Induction (before surgery or during myasthenic crisis): 1 to 2 g/kg adjusted body weight divided over 1 to 5 days (maximum 1 g/kg/day). 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)

MG, mild generalized - adult	
Do Not Do Recommendation	IVIG is not recommended.
Evidence Source	EO (GDG)

MG - juvenile	
Do Not Know Recommendation	There is insufficient evidence to recommend for or against using IVIG.
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	EO (G22)

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

See Appendix A for category definitions

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✓ Myelin oligodendrocyte glycoprotein antibody-associated disorders (MOGAD) – pediatric	
Do Recommendation	IVIG is recommended as second-line therapy when there is insufficient response to steroids or other standard immunosuppressant therapies.
Dose	Induction: 1 to 2 g/kg adjusted body weight divided over 1 to 5 days (maximum 1 g/kg/day). Maintenance: 1 g/kg adjusted body weight divided over 1 to 3 days (maximum 1 g/kg/day), every 4 weeks.
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 (G23)

× Narcolepsy/cataplexy	
Do Not Do Recommendation	IVIG is not recommended because there is insufficient evidence of benefit and preferable alternative therapies are available.
Evidence Source	EO (G1, GDG)

? Neuromyelitis optica spectrum disorders (NMOSD)	
Do Not Know Recommendation	There is insufficient evidence for or against using IVIG. IVIG is not first-line therapy for NMOSD. IVIG may be a reasonable therapeutic option for patients with active NMOSD, despite treatment with corticosteroids and/or plasma exchange. In general, IVIG alone should not be used for maintenance therapy.
Dose	Induction: 2 g/kg adjusted body weight divided over 2 to 5 days. Maintenance: 1 to 2 g/kg adjusted body weight over 1 to 5 days. The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome.
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	NRCS (G1); G (G3); EO (GDG)

× Neuropathic pain	
Do Not Do Recommendation	IVIG is not recommended.

See Appendix A for category definitions

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× Neuropathic pain	
Evidence Source	EO (GDG-RCT)

✓/?/× Neuropathy associated with IgM paraproteinemia	
Demyelinating neuropathy associated with IgM paraproteinemia, without anti-MAG antibodies	
Do Recommendation	IVIG is recommended for neuropathy associated with IgM, with clinical and electrophysiological features consistent with CIDP, in the absence of anti-MAG antibodies.
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.
Review Criteria	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	EO (GDG-SR)
Demyelinating neuropathy with anti-MAG antibodies	
Do Not Know Recommendation	There is insufficient evidence for or against using IVIG. However, since other therapies are ineffective, a trial of IVIG may be considered in patients with disabling symptoms.
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	EO (GDG-SR)
Axonal neuropathy associated with IgM paraproteinemia	
Do Not Do Recommendation	IVIG is not recommended.
Evidence Source	EO (G21, GDG)

See Appendix A for category definitions

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? Opsoclonus-myoclonus ataxia (OMA) – adult onset	
Do Not Know Recommendation	There is insufficient evidence for or against using IVIG. IVIG may be considered when steroids are contraindicated or ineffective.
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-NR)

✓ Opsoclonus-myoclonus ataxia (OMA) – pediatric onset	
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 1 to 5 days (maximum 1 g/kg/day). Maintenance: 0.4 to 1 g/kg adjusted body weight divided over 1 to 5 days (maximum 1 g/kg/day), 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 for or against using IVIG for paraneoplastic neurological syndromes that are not otherwise specified.
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)

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 for or against using IVIG. The utility of IVIG appears to be limited to patients with a confirmed diagnosis and: • significant impairment requiring further intervention; or • relapse of symptoms within three months of commencing a trial off IVIG. Diagnosis of PANDAS requires expert consultation.
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 1 to 5 days (maximum 1 g/kg/day), every 4 to 6 weeks. If there is a need to continue use of IVIG, reassess no later than 3 months. IVIG should be discontinued as soon as possible.
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-SR)

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

Do Not Do Recommendation	IVIG is not recommended. Treatment should target the underlying hematologic malignancy.
Evidence Source	EO (G21, GDG)

× Post-polio syndrome

Do Not Do Recommendation	IVIG is not recommended.
Evidence Source	EO (GDG-SR)

? Postural orthostatic tachycardia syndrome (POTS)

Do Not Know Recommendation	There is insufficient evidence for or against using IVIG. IVIG may be considered when other therapies are ineffective.
Dose	2 g/kg adjusted body weight divided over 2 to 5 days, every 4 weeks.
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)

See Appendix A for category definitions

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? Rasmussen syndrome

Do Not Know Recommendation	There is insufficient evidence for or against using IVIG. Diagnosis must be made by a neurologist. IVIG may be an option to ameliorate the burden of seizures associated with this disorder.
Dose	Induction: 2 g/kg adjusted body weight divided over 2 to 5 days. Maintenance: 1 g/kg adjusted body weight divided over 1 to 5 days (maximum 1 g/kg/day), every 3 to 6 weeks, titrated to clinical response.
Review Criteria	Treatment should be reassessed every 6 months and would rarely be continued past 18 months. 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 (G1); G (G2); EO (GDG)

? Sensory ganglionopathy

Do Not Know Recommendation	There is insufficient evidence for or against using IVIG. A trial of IVIG may be considered for cases with a clear or suspected immune-mediated mechanism.
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 focusing on functional status, 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 (G21, GDG)

✓ Sjögren syndrome associated neuropathy

Do Recommendation	IVIG may be considered in severe, functionally disabling peripheral neuropathies associated with Sjögren syndrome or when other immunosuppressive therapies are contraindicated or ineffective.
Dose	Induction: 1 to 2 g/kg adjusted body weight divided over 1 to 5 days (maximum 1 g/kg/day). Maintenance: 0.4 to 1 g/kg adjusted body weight divided over 1 to 5 days (maximum 1 g/kg/day), 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.

See Appendix A for category definitions

LEGEND (see References for the list of "seed" guidelines): CS – case series study; EO – expert opinion; G – guideline; GDG – guideline development group (IMEC); IgA – immunoglobulin A; IgG – immunoglobulin G; IgM – immunoglobulin M; IVIG – intravenous immune globulin; NR – non-systematic/narrative review; NRCS – non-randomized comparative study; qSR – quasi-systematic review; RCT – randomized controlled trial; SCIG – subcutaneous immune globulin; SR – systematic review

✓ Sjögren syndrome associated neuropathy	
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	NRCS (G1); EO (GDG)

✓ Stiff person syndrome (Moersch–Woltman syndrome)	
Do Recommendation	IVIG is recommended for treatment of patients with significant functional impairment, in consultation with a neurologist.
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 1 to 5 days (maximum 1 g/kg/day), every 3 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)

? Susac syndrome	
Do Not Know Recommendation	While there is insufficient evidence for or against using IVIG, clinical experts support its use.
Dose	Induction: Up to 2 g/kg adjusted body weight divided over 2 to 5 days. Maintenance: 0.5 to 1 g/kg adjusted body weight divided over 1 to 5 days (maximum 1g/kg/day), 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.
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 the disease.
Evidence Source	NRCS (G1); EO (GDG)

See Appendix A for category definitions

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✓/? Sydenham chorea

Short-term therapy	
Do Recommendation	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 divided over 2 to 5 days.
Evidence Source	EO (GDG-qSR)

Long-term therapy	
Do Not Know Recommendation	There is insufficient evidence for or against using 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)

? Transverse myelitis

Do Not Know Recommendation	There is insufficient evidence for or against using IVIG. See general statement on immune globulin in combination with other therapies.
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-qSR)

✓ Vasculitic neuropathy as part of a systemic disorder (systemic vasculitis affecting the peripheral nervous system)

Do Recommendation	IVIG may be used as an option if indicated for the systemic disorder. Systemic vasculitis can affect multiple organ systems and treatment should be guided with input from appropriate specialists. See Rheumatology Indications section for further details.
Evidence Source	EO (GDG)

See Appendix A for category definitions

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LEGEND (see References for the list of "seed" guidelines): CS – case series study; EO – expert opinion; G – guideline; GDG – guideline development group (IMEC); IgA – immunoglobulin A; IgG – immunoglobulin G; IgM – immunoglobulin M; IVIG – intravenous immune globulin; NR – non-systematic/narrative review; NRCS – non-randomized comparative study; qSR – quasi-systematic review; RCT – randomized controlled trial; SCIG – subcutaneous immune globulin; SR – systematic review

? Vasculitic neuropathy, non-systemic (vasculitis solely affecting the peripheral nervous system; isolated vasculitic neuropathy)

See separate entry for vasculitic neuropathy as part of a systemic disorder (systemic vasculitis affecting the peripheral nervous system).

Do Not Know Recommendation	There is insufficient evidence for or against using IVIG. IVIG may be considered among other therapies when steroids are contraindicated or ineffective.
Dose	2 g/kg adjusted body weight divided over 2 to 5 days, every 4 weeks.
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 (G21, GDG-SR)

See Appendix A for category definitions

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SECTION 8: Rheumatology Indications

See separate entries for eosinophilic fasciitis, livedoid vasculopathy, and morphea in the Dermatology Indications section; and for hemophagocytic lymphohistiocytosis (HLH) syndrome in the Hematology Indications section.

× 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 prothrombotic effect of IVIG should be considered in this indication*.
Qualifying Criteria	All of the following criteria must be met: • Evidence of rapidly evolving thrombosis involving two or more organs. • Unequivocal laboratory evidence of antiphospholipid antibodies (lupus anticoagulant and/or anticardiolipin antibodies and/or beta 2 glycoprotein I antibodies). • Other causes of thrombotic microangiopathy are considered less likely.
Evidence Source	NRCS (G1)

✓ Autoimmune retinopathy (AIR)

See separate entry for immune-mediated uveitis.

Do Recommendation	Early administration of IVIG is recommended in autoimmune retinopathy for treatment of severe disease threatening eyesight.
Dose	Induction: 1.5 g/kg adjusted body weight divided over 3 days. Maintenance: 0.4 to 1.5 g/kg adjusted body weight in single or divided dose (maximum 1 g/kg/day), monthly. 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 References for the list of "seed" guidelines): CS – case series study; EO – expert opinion; G – guideline; GDG – guideline development group (IMEC); IVIG – intravenous immune globulin; NR – non-systematic/narrative review; NRCS – non-randomized comparative study; qSR – quasi-systematic review; RCT – randomized controlled trial; SR – systematic review

✓ Autoimmune retinopathy (AIR)

Review Criteria	Continued use of IVIG should be based on objective measures of effectiveness established at the outset of treatment. Patient response (improvement in visual function or an arrest in the decline of visual function as determined by an ophthalmologist) should be assessed within 3 months of 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)

× 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 for or against using 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 (G24, GDG-CS)

✓ Dermatomyositis – pediatric

See separate entries for inclusion body myositis, myopathies, inflammatory – adult: dermatomyositis, polymyositis, necrotizing autoimmune myopathy, and polymyositis – pediatric.

Do Recommendation	IVIG may be used:
	• in addition to corticosteroids and/or immunosuppressives:
	  ○ at the outset of treatment; or
	  ○ 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 1 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.

See Appendix A for category definitions

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LEGEND (see References for the list of "seed" guidelines): CS – case series study; EO – expert opinion; G – guideline; GDG – guideline development group (IMEC); IVIG – intravenous immune globulin; NR – non-systematic/narrative review; NRCS – non-randomized comparative study; qSR – quasi-systematic review; RCT – randomized controlled trial; SR – systematic review

✓ Dermatomyositis – pediatric

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); EO (GDG-G)

✓ Eosinophilic granulomatosis with polyangiitis (EGPA) (Churg–Strauss disease)

Do Recommendation	IVIG may be used for patients with nervous system or cardiac disorders who do not respond to 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.
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, G25, GDG-NR)

? Immune-mediated uveitis

See separate entry for autoimmune retinopathy.	
Do Not Know Recommendation	There is insufficient evidence for or against using 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 (maximum 1 g/kg/day), in single or divided dose, every 4 weeks for 3 months. 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	EO (GDG-G)

× Inclusion body myositis (IBM)

See separate entries for dermatomyositis – pediatric, myopathies, inflammatory – adult: dermatomyositis, polymyositis, necrotizing autoimmune myopathy, and polymyositis – pediatric.	
Do Not Do Recommendation	IVIG is not recommended.

See Appendix A for category definitions

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LEGEND (see References for the list of "seed" guidelines): CS – case series study; EO – expert opinion; G – guideline; GDG – guideline development group (IMEC); IVIG – intravenous immune globulin; NR – non-systematic/narrative review; NRCS – non-randomized comparative study; qSR – quasi-systematic review; RCT – randomized controlled trial; SR – systematic review

× Inclusion body myositis (IBM)

Evidence Source	EO (G21)

? Kawasaki disease – adult

Do Not Know Recommendation	There is insufficient evidence for or against using 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)

✓ Kawasaki disease – pediatric

Do Recommendation	IVIG is recommended early to prevent coronary artery involvement.
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 treatment may be given if there is ongoing inflammation. A third treatment is not recommended.
Qualifying Criteria	Clinical diagnosis of Kawasaki disease by a pediatrician, rheumatologist, or immunologist.
Evidence Source	SR (G1, G26)

✓ 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.
Evidence Source	EO (GDG-qSR)

✓ Multisystem inflammatory syndrome in children (MIS-C) associated with SARS-CoV-2/COVID-19 infection

See separate entry for: multisystem inflammatory syndrome in adults (MIS-A) associated with SARS-CoV-2/COVID-19 infection.

Do Recommendation	IVIG is recommended for all patients who require hospitalization.

See Appendix A for category definitions

LEGEND (see References for the list of "seed" guidelines): CS – case series study; EO – expert opinion; G – guideline; GDG – guideline development group (IMEC); IVIG – intravenous immune globulin; NR – non-systematic/narrative review; NRCS – non-randomized comparative study; qSR – quasi-systematic review; RCT – randomized controlled trial; SR – systematic review

✓ Multisystem inflammatory syndrome in children (MIS-C) associated with SARS-CoV-2/COVID-19 infection

Dose	2 g/kg adjusted body weight over 12 hours unless cardiac function and/or fluid status necessitates dividing the dose over 2 days. A single treatment is usually sufficient. One additional treatment may be given in exceptional circumstances in refractory MIS-C with appropriate expert consultation.
Evidence Source	SR (G27); NRCS (G28)

? Multisystem inflammatory syndrome in adults (MIS-A) associated with SARS-CoV-2/COVID-19 infection

Do Not Know Recommendation	There is insufficient evidence for or against using 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-qSR)

See Appendix A for category definitions

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✓ Myopathies, inflammatory – adult: dermatomyositis, polymyositis, necrotizing autoimmune myopathy

See separate entries for dermatomyositis – pediatric, inclusion body myositis, and polymyositis – pediatric.

Do Recommendation	IVIG may be used for patients with severe forms of disease when first-line therapies are ineffective or contraindicated. In severe or life-threatening situations, e.g., dysphagia or severe weakness, IVIG 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	SR (G1); EO (GDG-RCT)

? Polymyositis – pediatric

See separate entries for dermatomyositis – pediatric, inclusion body myositis, and myopathies, inflammatory – adult: dermatomyositis, polymyositis, necrotizing autoimmune myopathy.

Do Not Know Recommendation	There is insufficient evidence for or against using IVIG.

LEGEND (see References for the list of "seed" guidelines): CS – case series study; EO – expert opinion; G – guideline; GDG – guideline development group (IMEC); IVIG – intravenous immune globulin; NR – non-systematic/narrative review; NRCS – non-randomized comparative study; qSR – quasi-systematic review; RCT – randomized controlled trial; SR – systematic review

? Polymyositis – pediatric	
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	
For vasculitis associated with rheumatoid arthritis (rheumatoid vasculitis) see vasculitic syndromes.	
Do Not Do Recommendation	IVIG is not recommended.
Evidence Source	EO (G1)

? Scleroderma	
Do Not Know Recommendation	There is insufficient evidence for or against using 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	CS (G8); EO (GDG-qSR)

? Sjögren syndrome	
See separate entry for Sjögren syndrome associated neuropathy in the Neurology and Neuromuscular Indications section.	
Do Not Know Recommendation	There is insufficient evidence for or against using 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

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LEGEND (see References for the list of "seed" guidelines): CS – case series study; EO – expert opinion; G – guideline; GDG – guideline development group (IMEC); IVIG – intravenous immune globulin; NR – non-systematic/narrative review; NRCS – non-randomized comparative study; qSR – quasi-systematic review; RCT – randomized controlled trial; SR – systematic review

? Sjögren 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.
Evidence Source	NR (G3); EO (GDG)

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

See separate entry for macrophage activation syndrome.

Do Not Know Recommendation	There is insufficient evidence for or against using IVIG. IVIG may be considered in exceptional circumstances when patients do not respond to 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 using IVIG. IVIG may be considered in exceptional circumstances, e.g., presence of refractory skin disease or severe myositis, 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 may be considered 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	qSR (G29); CS (G8)

See Appendix A for category definitions

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LEGEND (see References for the list of "seed" guidelines): CS – case series study; EO – expert opinion; G – guideline; GDG – guideline development group (IMEC); IVIG – intravenous immune globulin; NR – non-systematic/narrative review; NRCS – non-randomized comparative study; 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	○ granulomatosis with polyangiitis (Wegener granulomatosis) ○ IgA-associated small vessel vasculitis (Henoch–Schönlein purpura) ○ microscopic polyangiitis
Do Not Know Recommendation	There is insufficient evidence for or against using IVIG. IVIG may be considered as an option when 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 (G1, GDG)

See Appendix A for category definitions

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LEGEND (see References for the list of "seed" guidelines): CS – case series study; EO – expert opinion; G – guideline; GDG – guideline development group (IMEC); IVIG – intravenous immune globulin; NR – non-systematic/narrative review; NRCS – non-randomized comparative study; 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)

✓ Systemic capillary leak syndrome (SCLS)	
Do Recommendation	IVIG may be used for prevention of recurrent, life-threatening episodes, in addition to other therapies.
Dose	1 to 2 g/kg adjusted body weight divided over 2 to 5 days (maximum 1 g/kg/day), 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 References for the list of "seed" guidelines): CS – case series study; EO – expert opinion; G – guideline; GDG – guideline development group (IMEC); IVIG – intravenous immune globulin; qSR – quasi-systematic review

APPENDIX A: Recommendation Categories

Summary of Criteria to Determine the Recommendation Categories

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.
	  ○ "Insufficient evidence for or against using IVIG. IVIG may be considered…" indicates that IVIG could be trialled.
	  ○ "Insufficient evidence to recommend the use of IVIG. IVIG should only be used…" indicates that IVIG use is generally discouraged.

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 64 "seed" guidelines (referenced as G1 to G59; published between January 2016 and March 2021) 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=29) 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 SRs 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: List of New and Revised Recommendations

New or revised recommendation(s)	Nature of revision	Final category*	Page #
General statements			
Dosing in pregnancy	New statement	NA	4
Subcutaneous administration	Revised wording	NA	4
Frequency of follow up and assessment of effectiveness	New statement	NA	4
Weaning patients off IG	New statement	NA	4
Vaccination in patients receiving IG	New statement	NA	5
Adverse effects	Revised wording	NA	5
Dermatology indications			
Drug reaction with eosinophilia and systemic symptoms (DRESS)	New recommendation	**?**	9
Eosinophilic fasciitis	New recommendation	**?**	9
Mast cell activation syndrome (MCAS)	New recommendation	**?**	10
Morphea	New recommendation	**?**	10
Mycoplasma induced rash and mucositis (MIRM)	New recommendation	**?**	10
Necrobiotic xanthogranuloma	New recommendation	**?**	11
Netherton syndrome	New recommendation	**?**	11
Pretibial myxedema	New recommendation	**?**	11
Psoriasis	New recommendation	**?**	12
Hematology indications			
Coagulation factor inhibitors	Category change from **?** to ✗	✗	14
Gestational alloimmune liver disease (GALD)/alloimmune neonatal hemochromatosis	New recommendation	✓	15
Hemolytic disease of the fetus, prevention	New recommendation	✓	15
Hemolytic uremic syndrome	Category change from **?** to ✗	✗	16
Hemophagocytic lymphohistiocytosis (HLH) syndrome	Revised indication	✗/?	16
Neonatal hemochromatosis, prevention	Category change from **?** to ✓	✓	19
Vaccine induced immune thrombotic thrombocytopenia (VITT)/Vaccine induced prothrombotic immune thrombocytopenia (VIPIT)	New recommendation	✓	20

New or revised recommendation(s)	Nature of revision	Final category*	Page #
Infectious Disease Indications			
Hepatitis A, post-exposure prophylaxis (PEP)	New recommendation	✓	24
Measles, post-exposure prophylaxis (PEP)	New recommendation	✓/×	25
Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)/COVID-19	New recommendation	×	26
Transplant Medicine Indications			
Adenovirus in solid organ transplant recipients	New recommendation	?	27
BK polyomavirus nephropathy in solid organ transplant recipients	New recommendation	?	27
Kidney, non-active rejection management	Removed	NA	NA
Parvovirus B19 in solid organ transplant recipients	New recommendation	✓/×	31
Kidney, active antibody-mediated rejection (ABMR) prevention and management Solid organ (other than kidney), antibody-mediated rejection (ABMR)	Combined into single recommendation for all solid organ transplantation	✓	32
Solid organ (other than kidney)	New title: *Solid organ transplantation, ongoing desensitization, prevention or treatment of graft rejection* Category change from **?** to ✓	✓	33
Neurology and Neuromuscular Indications			
Anti-NMDA receptor encephalitis Paraneoplastic or sporadic autoimmune encephalitis	Combined into single recommendation: *Autoimmune encephalitis mediated by antibodies (AMAE) targeting cell-surface antigens*	✓	35
Primary progressive multiple sclerosis (MS); Progressive phase of MS without relapse	New recommendation	×	40
Myasthenia gravis, ocular and/or mild generalized	Spit into two recommendations: *Myasthenia gravis (MG), mild generalized – adults* *MG – ocular* Category change from **?** to ×	×	41
Myasthenia gravis - juvenile	New recommendation	?	41
Myelin oligodendrocyte glycoprotein antibody-associated disorders (MOGAD) – pediatric	New recommendation	✓	42

New or revised recommendation(s)	Nature of revision	Final category*	Page #
Narcolepsy/ cataplexy	Category change from **?** to ✗	✗	42
Post-polio syndrome	Category change from **?** to ✗	✗	45
Postural orthostatic tachycardia syndrome (POTS)	New recommendation	**?**	45
Rasmussen syndrome (short- and long-term therapy)	Combined into one recommendation: Rasmussen syndrome	**?**	46
Sensory ganglionopathy	New recommendation	**?**	46
Sjögren syndrome associated neuropathy	New recommendation	✓	46
Vasculitic neuropathy as part of systemic disorder (systemic vasculitis affecting the peripheral nervous system)	New recommendation	✓	48
Vasculitic neuropathy, non-systemic (vasculitis solely affecting the peripheral nervous system; isolated vasculitic neuropathy)	New recommendation	**?**	49
Rheumatology Indications			
Autoimmune retinopathy	New recommendation	✓	50
Inclusion body myositis (IBM) without dysphagia IBM with dysphagia	Combined into a single recommendation: *Inclusion body myositis (IBM)*	✗	52
Multisystem inflammatory syndrome in children (MIS-C) associated with SARS-CoV-2/COVID-19 infection	New recommendation	✓	53
Multisystem inflammatory syndrome in adults (MIS-A) associated with SARS-CoV-2/COVID-19 infection	New recommendation	**?**	54
Dermatomyositis – adult Polymyositis – adult	Combined into a single recommendation: *Myopathies, inflammatory – adult: dermatomyositis, polymyositis, necrotizing autoimmune myopathy*	✓	54

NA: not applicable.

*✓ ("Do" category) - indicates that the action should be undertaken; **x** ("Do Not Do" category) - indicates that the action should not be undertaken; **?** ("Do Not Know" category) - indicates that there was insufficient evidence to make a definitive decision regarding the action. See Appendix A for further information on recommendation categories.

APPENDIX D: Participants in the Guideline Development Process

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

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REFERENCES

References for reviewed seed guidelines

The guidelines are not presented in any specific order. G1, G2, etc., are randomly assigned and for organizational purposes only.

Only those guidelines directly used by the GDG to formulate recommendations (n=29) are cited as evidence sources in the document.

G1 Australia	National Blood Authority. *Criteria for the clinical use of immunoglobulin in Australia (the Criteria).* BloodSTAR Production v.3.5.0. Available from: *www.blood.gov.au/igcriteria-version3* (accessed 22 May 2021).
G2 Canada	Ontario Regional Blood Coordinating Network. *Ontario immune globulin (IG) utilization management guidelines Version 4.0*. Toronto (ON): Ontario Regional Blood Coordinating Network; 2018. Available from: *https://transfusionontario.org/wp-content/uploads/2020/06/ontario-ig-utilization-management-guidelines-v4.0.pdf*.
G3 Canada	The Atlantic IVIG Utilization Working Group. *Atlantic Clinical indications and criteria for intravenous and subcutaneous immunoglobulin (IVIG/SCIG) Version 1.0*. Halifax (NS): The Atlantic IVIG Utilization Working Group; 2018. Available from: *www.gov.nl.ca/hcs/files/bloodservices-resources-pdf-atlantic-clinical-indications-and-criteria-for-intravenous-and-subcutaneous-immunoglobulin-ivig-scig-may-1-2018.pdf*.
G4 Europe	Knobler R, Moinzadeh P, Hunzelmann N, Kreuter A, Cozzio A, Mouthon L, et al. European Dermatology Forum S1-guideline on the diagnosis and treatment of sclerosing diseases of the skin, part 1: Localized scleroderma, systemic sclerosis and overlap syndromes. *Journal of the European Academy of Dermatology and Venereology* 2017;31(9):1401-24.
G5 Spain	Cabañas R, Ramirez E, Sendagorta E, Alamar R, Barranco R, Blanca-Lopez N, et al. Spanish guidelines for diagnosis, management, treatment, and prevention of DRESS syndrome. *Journal of Investigational Allergology and Clinical Immunology* 2020;30(4):229-53.
G6 Canada	Canadian Pediatric Society. *Diagnosis and management of typical, newly diagnosed primary immune thrombocytopenia (ITP) of childhood*. 2020. Available from: *https://cps.ca/documents/position/immune-thrombocytopenia (*accessed 9 January 2022). Friedman JN, Beck CE. Diagnosis and management of typical, newly diagnosed primary immune thrombocytopenia (ITP) of childhood. *Paediatric & Child Health* 2019;24(1):54-5.
G7 United Kingdom	National Health Service England. *Updated Commissioning Criteria for the use of therapeutic immunoglobulin (Ig) in immunology, haematology, neurology and infectious diseases in England, November 2019*. 2019. Available from: *http://igd.mdsas.com/wp-content/uploads/NHSE_Commissioning_Criteria_for_the_use_of_Ig_V1.4_November_2019.pdf*.
G8 Europe	Hadaschik E, Eming R, French LE, Girolomomi G, Hertl M, Jolles S, et al. *European Guidelines (S1) on the use of high-dose intravenous immunoglobulin in dermatology*. 2019. Available from: *https://www.edf.one/dam/jcr:818f3581-1097-46ef-a0b3-3c464aa2d014/IVIG_2019_GL.pdf.*
G9 United Kingdom	Nottingham Neonatal Service. *Neonatal thrombocytopenia*. Nottingham (United Kingdom): Nottingham University Hospitals NHS Trust; 2016.

G10 **USA**	University of Wisconsin Hospitals and Clinics Authority. *Intravenous immune globulin – adult/pediatric – inpatient/ambulatory clinical practice guideline*. 2020. Available from: *www.uwhealth.org/cckm/cpg/medications/Intravenous-Immune-Globulin---Adult-Pediatric---Inpatient-Ambulatory-Guideline-210126.pdf*.
G11 **International**	La Rosée P, Horne A, Hines M, von Bahr Greenwood T, Machowicz R, Berliner N, et al. Recommendations for the management of hemophagocytic lymphohistiocytosis in adults. *Blood* 2019;133(23):2465-77.
G12 **US**	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.
G13 **Canada**	Tunis MC, Salvadori MI, Dubey V, Baclic O, on behalf of the National Advisory Committee on Immunization (NACI). Updated NACI recommendations for measles post-exposure prophylaxis. *Canada Communicable Disease Report* 2018;44(9):226-30.
G14 **International**	Liu E, Smyth RI, Luo Z, Qaseem A, Mathew JL, Lu Q, et al. Rapid advice guidelines for management of children with COVID-19. *Annals of Translational Medicine* 2020;8(10):617.
G15 **USA**	National Comprehensive Cancer Network®. *The NCCN Clinical Practice Guidelines in Oncology. Prevention and treatment of cancer-related infections (Version 2.2020)*. Fort Washington (PA): National Comprehensive Cancer Network; 2020.
G16 **Germany**	von Lilienfeld-Toal, Berger A, Christopeit M, Hentrich M, Heussel CP, Kalkreuth J, et al. Community acquired respiratory virus infections in cancer patients-Guideline on diagnosis and management by the Infectious Diseases Working Party of the German Society for Haematology and Medical Oncology. *European Journal of Cancer* 2016;67:200-12.
G17 **USA**	Manuel O, Estabrook M, American Society of Transplantation Infectious Diseases Community of Practice. RNA respiratory viral infections in solid organ transplant recipients: Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. *Clinical Transplantation* 2019;33(9):e13511.
G18 **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.
G19 **USA**	Hirsch HH, Randhawa PS, American Society of Transplantation Infectious Diseases Community of Practice. BK polyomavirus in solid organ transplantation—Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. *Clinical Transplantation* 2019;33:e13528.
G20 **USA**	Eid AJ, Ardura MI, American Society of Transplantation Infectious Diseases Community of Practice. Human parvovirus B19 in solid organ transplantation: Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. *Clinical Transplantation* 2019;33(9):e13535.
G21 **Canada**	BC Provincial Blood Coordinating Office. *Intravenous immune globulin (IVIG) utilization management guideline.* 2019. Available from: *https://www.pbco.ca/images/Programs/IVIG_Provincial_Program/UMIVIG0007_IVIG_Utilization_Management_Program_Guidelines_V42.pdf*.

G22 International	Narayanaswami P, Sanders DB, Wolfe G, Benatar M, Cea G, Evoli A, et al. International consensus guidance for management of myasthenia gravis 2020 update. *Neurology* 2021;96(3):114-22.
G23 International	Bruijstens AL, Wendel EM, Lechner C, Bartels F, Finke C, Breu M, et al. E.U. paediatric MOG consortium consensus: Part 5 - Treatment of paediatric myelin oligodendrocyte glycoprotein antibody-associated disorders. *European Journal of Paediatric Neurology* 2020;29:41-53.
G24 United Kingdom	Wiles K, Chappell L, Clark K, Elman L, Hall M, Lightstone L, et al. *Clinical practice guideline pregnancy and renal disease*. The Renal Association; 2019. Available from: *https://renal.org/sites/renal.org/files/FINAL-Pregnancy-Guideline-September-2019.pdf*.
G25 Japan	Nakamura Y, Tamaoki J, Nagase H. Japanese guidelines for adult asthma 2020. *Allergology International* 2020;69(4):519-48.
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