



**Ontario Intravenous Immune Globulin (IVIG)
Utilization Management Guidelines**

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Disclaimer:

The Ontario IVIG Utilization Management Guidelines are not intended to replace sound clinical judgment concerning a patient’s unique situation. No formal monitoring of IVIG use in Ontario is being implemented at this time.

Furthermore, although the advice and information contained in these guidelines is believed to be true and accurate at the time of going to press, neither the authors nor the publishers can accept any legal responsibility for any errors or omissions that may have been made.

Introduction

The information in this document is intended as a guideline document for clinicians seeking clarification on the common and clinically appropriate uses of Intravenous Immune Globulin, as of October, 2009. Accompanying this detailed document is a concise two page document called "Ontario IVIG Utilization Management Guidelines Brief Version 1.0" which contains the same list of medical conditions and recommended treatments.

This summary of guidelines and information on IVIG utilization has been prepared specifically for use in Ontario. The group of individuals who prepared this document simply reviewed existing, recently published Canadian guidelines for IVIG utilization. For a few medical conditions in specialties for which Canadian guidelines were not available, recently published Australian and United Kingdom IVIG utilization guidelines were considered. It should be noted that these Ontario guidelines were not prepared in the rigorous manner, including consensus and literature review, in which the Canadian, Australian and United Kingdom guidelines were compiled.

A toolkit for IVIG Utilization Management in Ontario, including suggested policies, procedures, forms and safe administration of the IVIG products will be completed to accompany this introduction and all documents will be available at www.transfusionontario.ca.

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General Recommendations for IVIG Orders

The Ontario IVIG Planning Group, consisting of medical and technical specialist members from across Ontario, agreed that the following best practice information should be included in a utilization guideline for IVIG:

- i. Medical conditions where IVIG should be used, and where it should not be used. Doses appropriate for those indications and recommended duration of use should be listed in a concise document of recommended uses in Ontario

Other recommendations:

- ii. A definitive diagnosis should be confirmed prior to issuing IVIG
- iii. Product should not be provided without a documented clinical indication, except in life-threatening situations and product should not be provided when 'unknown' is the listed clinical indication
- iv. Best practices for infusion of IVIG should be available at each institution using IVIG*
- v. New orders for IVIG should be checked prospectively at the site where the order is made, preferably through an SOP applied through the blood transfusion service or pharmacy, where the IVIG orders are received and product is dispensed*
- vi. Conduct and document regular monitoring of patient's weight for patients who use IVIG over a period of time
- vii. Monitor platelet counts in ITP patients using IVIG
- viii. Conduct regular testing of patients to detect hemolysis arising from use of IVIG*
- ix. Clear direction on the practice of 'rounding up' and 'rounding down' of IVIG doses*
- x. Hospitals should monitor, collect and report specific information on wastage of IVIG to ORBCoN
- xi. Specific direction on maximum doses of IVIG for patients >100 kg*
- xii. Perform and document pre infusion serum immunoglobulin levels for Primary and Secondary Immune Deficiency patients (baseline and trough)

*Examples of procedures and forms that relate to recommended practices will be available in an IVIG Utilization Management Toolkit scheduled for completion March 2010.

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The charts that follow present the Clinical Recommendations by:

- **Specialty**
 - **Medical Condition**
 - **Recommendations**
 - **Dose and Frequency of Administration where applicable**
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Hematology Indications

Specialty	Medical Condition	Recommendations	Dose/Frequency of Administration
Hematology	Acquired hemophilia ^{1,4}	May be considered one option among adjunctive therapies, such as steroids, in urgent situations in this disorder. Life threatening or limb threatening situations only. Not recommended for routine use.	No recommended dose or duration listed.
Hematology	Acquired hypogammaglobulinemia secondary to malignancy ¹	<ol style="list-style-type: none"> Adult: Recommended treatment for infection prophylaxis with malignant hematologic disorders associated with hypogammaglobulinemia or dysfunctional gammaglobulinemia and either of the following: <ol style="list-style-type: none"> A recent episode of a life-threatening infection that is reasonably thought to be caused by low levels of polyclonal immunoglobulins; or Recurrent episodes of clinically significant infections (e.g., pneumonia) that are reasonably thought to be caused by low levels of polyclonal immunoglobulins. Pediatric: Not recommended for routine use in children with hematologic malignancies (with or without hypogammaglobulinemia). Possible exceptions; <ol style="list-style-type: none"> Children with hematologic malignancies with acquired hypogammaglobulinemia and either a history of severe invasive infection or recurrent sinopulmonary infections, IVIG may be considered a treatment option according to the above recommendations for adult patients. Some multinational protocols for the treatment of hematologic malignancies (and/or hematopoietic stem cell [HSC] transplantation) in childhood recommend routine use of IVIG for hypogammaglobulinemia, even in the absence of severe or recurrent infections. These recommendations are protocol-specific and not necessarily consistent across protocols of similar intensity. 	Adult Dose: 0.4 g/kg every 3 weeks with re-evaluation every 4 to 6 months.

Hematology Indications

Specialty	Medical Condition	Recommendations	Dose/Frequency of Administration
Hematology	Acquired red cell aplasia ¹	Option for patients with immunologic pure red cell aplasia (PRCA) who have failed other therapies (e.g., prednisone or cyclosporin). IVIG should be considered first-line therapy for viral PRCA associated with parvovirus B19 in immunocompromised patients. Not recommended as a first line therapy.	0.5 g/kg weekly for 4 weeks.
Hematology	Acquired von Willebrand's disease ^{1,4} (AvWD)	May be considered one option among adjunctive therapies in the treatment of AvWD in urgent situations (e.g., active bleeding or preoperatively). Not recommended for routine use.	No recommended dose or duration listed.
Hematology	Allogeneic bone marrow or stem cell transplantation ^{4,5}	Options for treatment in: 1) CMV-induced pneumonitis following transplantation: Use IVIg in conjunction with ganciclovir. 2) High risk allogeneic stem cell transplantation, prevention of GVHD.	1) No recommended dose or duration listed. 2) 0.4 g/kg weekly, starting one day before transplantation and continuing to day 100 post-transplant.
Hematology	Autoimmune hemolytic anemia ^{1,4} (AIHA)	May be considered one option among adjunctive therapies in urgent situations. Not recommended as routine.	No recommended dose or duration listed.
Hematology	Autoimmune neutropenia ^{1,4}	May be considered one option among adjunctive therapies in urgent situations. Not recommended as routine.	No recommended dose or duration listed.

Hematology Indications

Specialty	Medical Condition	Recommendations	Dose/Frequency of Administration
Hematology	Fetal Neonatal alloimmune thrombocytopenia ^{1,3,4} (F/NAIT)	<p>Treatment of Pregnant Women with F/NAIT Before Delivery: Recommended first line treatment for:</p> <ol style="list-style-type: none"> 1. Pregnant women with a previously affected pregnancy. Intravenous immune globulin should be initiated at a time in the pregnancy that corresponds to a gestational age in the present fetus that precedes by some weeks the time at which bleeding was thought or known to occur in the first pregnancy. 2. Pregnant women with a familial history of F/NAIT or those found on screening to have platelet alloantibodies. Timing of IVIG treatment should be based on the severity of fetal thrombocytopenia determined by cordocentesis. Expert opinion suggests treatment should be initiated around 20 weeks and no later than 30 weeks. <p>Treatment of a Newborn with F/NAIT Recommended as standard first line treatment.</p>	<p>Maternal Dose: weekly 1 g/kg.</p> <p>Infant: an initial dose of 1g/kg might provide benefit when platelets are not available.</p>
Hematology	Hemolytic Disease of the Fetus and Newborn ^{1,3} (HDFN)	Recommended only for infants with HDN as treatment for severe hyperbilirubinemia if total serum bilirubin (TSB) rising despite intensive phototherapy or TSB level within 34-51 micromol/L of the exchange level.	0.5 g/kg over 2 hours. If necessary dose can be repeated in 12 hours.
Hematology	Hemolytic transfusion reaction ¹ (HTR)	May be considered as an option among supportive therapies for urgent situations in this disorder. Not recommended for either the prophylaxis or routine treatment of hemolytic transfusion reactions.	No recommended dose or duration listed.
Hematology	Hemolytic transfusion reaction in sickle cell disease ¹ (HTRSCD)	May be considered among the options for treatment of serious, life-threatening, delayed hemolytic transfusion reactions in patients with SCD.	No recommended dose or duration listed.
Hematology	Hemolytic Uremic Syndrome (HUS) and Thrombotic Thrombocytopenic Purpura ¹ (TTP)	One option among adjunctive therapies when first-line therapy has failed. Not recommended as first-line therapy in either the pediatric or adult population.	No recommended dose or duration listed.

Hematology Indications

Specialty	Medical Condition	Recommendations	Dose/Frequency of Administration
Hematology	Heparin induced thrombocytopenia ^{1,3} (HIT)	Contraindicated.	Not applicable.
Hematology	Idiopathic Thrombocytopenic Purpura (ITP) Adult ^{1,3}	<p>IVIG is strongly recommended as part of multimodality therapy for:</p> <ol style="list-style-type: none"> Adults with acute ITP and major or life-threatening bleeding complications and/or clinically important mucocutaneous bleeding. Adult Acute ITP with Severe Thrombocytopenia but No Bleeding, Not recommended as firstline therapy alone for acute ITP with severe thrombocytopenia but with no major bleeding or wet purpura, except for patients with contraindications to steroids. Adult ITP with No or Slow Response to Adequate Dose Steroids: IVIG may be considered as a possible adjunctive therapy for patients not responding or slowly responding to steroids. Adult Chronic ITP Postsplenectomy: IVIG may be considered as a possible adjunctive therapy as a steroid-sparing measure. Re-evaluate every 3-6 months. Consider alternative therapies for patients not achieving a durable response for a minimum of 2-3 weeks. Adult ITP – Pregnancy associated. Patients with Platelet counts > 50 x 10⁹/L do not routinely require treatment. Platelet counts between 30 x 10⁹/L and 50 x 10⁹/L in first or second trimester also should not receive treatment. 	<p>Acute ITP: 1 g/kg daily for 2 days.</p> <p>ITP with No or Slow Response to Adequate Dose Steroids: 1 g/kg daily for 2 days.</p> <p>Chronic ITP Postsplenectomy: 0.5 g/kg every 4 weeks; gradually decrease to the minimum effective dose at maximum intervals to maintain safe platelet levels.</p>

Hematology Indications

Specialty	Medical Condition	Recommendations	Dose/Frequency of Administration
Hematology	Idiopathic Thrombocytopenic Purpura (ITP) Pediatric ^{1,3}	<ol style="list-style-type: none"> 1. Acute ITP: Initial therapy IVIG if platelet count < 20 x 10⁹/L. 2. NOTE: ITP refractory to standard treatment, platelet count < 20 x 10⁹/L and ITP with persistent or life-threatening bleeding and platelet count < 50 x 10⁹/L = 1 g/kg. 3. Chronic ITP: IVIG may be considered. 	<p>One dose of 0.8 to 1 g/kg, with a second dose given within 48 hours if the platelet count has not increased to > 20 x 10⁹/L.</p> <p>Pediatric ITP with Life-Threatening Bleeding: 1 g/kg daily for 2 days.</p> <p>Chronic Pediatric ITP: One dose of 0.8 to 1 g/kg, with a second dose given within 48 hours if the platelet count has not increased to > 20 x 10⁹/L.</p> <p>Neonate of Mother with ITP: 1 g/kg daily for 2 days with the second 1 g/kg dose to be given only if the platelet count is < 30 x 10⁹/L.</p>
Hematology	Post transfusion purpura ¹ (PTP)	Recommended as the standard first-line therapy for PTP.	1 g/kg for 2 days.
Hematology	Virus associated Hemaphagocytic Syndrome ¹ (VAHS)	May be considered among options for treatment of severe life-threatening VAHS. Not recommended for routine use.	No recommended dose or duration listed.

Neurology Indications

Specialty	Medical Condition	Recommendations	Dose/Frequency of Administration
Neurology	Acute disseminated encephalomyelitis ² (ADEM)	Options: 1. Monophasic ADEM when first-line therapy with high-dose corticosteroids fails or when there are contraindications to steroid use. 2. Treatment of relapsing ADEM to eliminate steroid dependency or for those patients who fail to respond, or have contraindications, to steroids.	Adults: Total dose of 2 g/kg given over 2 to 5 days. Children: Total dose of 2 g/kg given over 2 days.
Neurology	Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) ^{2,3}	1. Acute Recommended for the short-term management of new-onset CIDP or CIDP relapses. 2. Chronic May be considered in combination with other immunosuppressive therapy for the long-term management of CIDP.	Total dose of 2 g/kg given over 2 to 5 days. Maintenance therapy: a systematic approach should be taken to determine the minimum effective dose, and continued use of IVIG should be based on objective measures of its sustained effectiveness. Maximum dose per treatment course should be 2 g/kg.
Neurology	Guillain-Barré Syndrome (GBS) (including Miller-Fisher syndrome and other variants) ^{2,3}	Options: Within 2 weeks of symptom onset for: 1. Patients with symptoms of grade 3 severity (able to walk with aid) or greater; or 2. Patients with symptoms less than grade 3 severity whose symptoms are progressing. 3. Patients who initially responded to IVIG and who are experiencing a relapse of symptoms.	Adults: Total dose of 2 g/kg given over 2 to 5 days. Children: Total dose of 2 g/kg given over 2 days.

Neurology Indications

Specialty	Medical Condition	Recommendations	Dose/Frequency of Administration
Neurology	Lambert-Eaton Myasthenic Syndrome ² (LEMS)	Option for treatment of LEMS. Objective evidence of clinical improvement is needed for sustained use of IVIG.	Initial treatment: Total dose of 2 g/kg given over 2 to 5 days. Maintenance therapy: a systematic approach should be taken to determine the minimum effective dose, and continued use of IVIG should be based on objective measures of its sustained effectiveness. The maximum dose of IVIG per treatment course should be 2 g/kg.
Neurology	Multifocal motor neuropathy ^{2,3} (MMN)	Recommended as first-line treatment of for MMN. Diagnosis of MMN should be made by a neuromuscular specialist, as the diagnosis requires very specific electrodiagnostic expertise.	Initial Treatment: total dose of 2 g/kg given over 2 to 5 days. Maintenance therapy: should be tailored to the lowest dose that maintains clinical efficacy, usually 1 g/kg or less per treatment course. The frequency of IVIG treatment will vary and may shorten over time.
Neurology	Multiple sclerosis ^{2,3} (MS)	Option for treatment of patients with relapsing-remitting MS who fail, decline, or are not able to take standard immunomodulatory drug therapies.	Starting option for treatment for patients with relapsing-remitting MS: 1 g/kg monthly with or without a 5 day induction of 0.4 g/kg daily.
Neurology	Myasthenia gravis ^{2,3} (MG)	1. Adult and Juvenile Myasthenia Gravis: Recommended as a treatment option for patients with severe exacerbations of myasthenia gravis or myasthenic crises. 2. Neonatal Myasthenia Gravis: Based on consensus by the expert panel, IVIG may be considered among the treatment options for neonates severely affected with myasthenia gravis.	Total dose of 2 g/kg given over 2 to 5 days. If additional therapy is required, the dose should be adjusted depending upon response and titrated to the minimum effective dose.

Neurology Indications

Specialty	Medical Condition	Recommendations	Dose/Frequency of Administration
Neurology	Opsoclonus-Myoclonus ²	Option for treatment of opsoclonus-myoclonus.	Initial treatment: Total dose of 2 g/kg given over 2 to 5 days for adults and over 2 days for children. Maintenance therapy: A systematic approach should be taken to determine the minimum effective dose, and continued use of IVIG should be based on objective measures of its sustained effectiveness. Maximum dose of IVIG per treatment course should be 2 g/kg.
Neurology	Pediatric Autoimmune Neuropsychiatric Disorders Associated With Streptococcal Infections (PANDAS) ²	Option for treatment of patients with PANDAS. Diagnosis of PANDAS requires expert consultation.	Total dose of 2 g/kg given over 2 days is recommended as a reasonable option.
Neurology	Polymyositis ²	May be considered among the treatment options for patients with polymyositis who fail to respond to first-line therapies (e.g., steroids).	Initial treatment: Total dose of 2 g/kg given over 2 to 5 days. Maintenance therapy: A systematic approach should be taken to determine the minimum effective dose, and continued use of IVIG should be based on objective measures of its sustained effectiveness. Maximum dose of IVIG per treatment course should be 2 g/kg.
Neurology	Rasmussen's encephalitis ²	Option as a short-term, temporizing measure for patients with Rasmussen's encephalitis. Not recommended for long-term therapy for Rasmussen's encephalitis as surgical treatment is the current standard of care.	Adults: Total dose of 2 g/kg given over 2 to 5 days for adults. Children: Total dose of 2 g/kg given and over 2 days.
Neurology	Stiff Person's syndrome ²	Option for treatment of Stiff Person syndrome if gabaergic medications fail or for patients who have contraindications to gabaergic medications.	Initial treatment: Adults: Total dose of 2 g/kg given over 2 to 5 days. Children: Total dose of 2 g/kg given over 2 days. Maintenance therapy: A systematic approach should be taken to determine the minimum effective dose, and continued use of IVIG should be based on objective measures of its sustained effectiveness. Maximum dose of IVIG per treatment course should be 2 g/kg.

Dermatology

Specialty	Medical Condition	Recommendations	Dose/Frequency of Administration
Dermatology	Dermatomyositis ^{2,3}	Not recommended as monotherapy. Option: use combined with other agents for patients not responding adequately to other immunosuppressive therapies or as a “steroidsparing” option.	Adults: 2 g/kg over 2 to 5 days. Children: 2 g/kg over 2 days.
Dermatology	Pemphigus Vulgaris and Variants ^{3,4}	Recommended to use IVIG as an effective treatment in severely affected patients when combined conventional corticosteroid treatment with adjuvant agents has failed or is inappropriate (grade C, level III evidence). (UK) (Note: UK Guidelines use term “Immunobullous diseases” includes bullous pemphigoid, pemphigus foliaceus, pemphigus vulgaris, epidermolysis bullosa acquisita and linear IgA disease).	2 g/kg over 5 days (BC) (ONT discussion changes this to 2 to 5 days).
Dermatology	Toxic epidermal necrolysis/Stephen-Johnson syndrome ⁴	IVIG is recommended when other treatments are contraindicated, or when the condition is life-threatening.	1 g/kg/day for 3 days.

Rheumatology

Specialty	Medical Condition	Recommendations	Dose/Frequency of Administration
Rheumatology	Juvenile Dermatomyositis ^{2,3} (JD)	Recommended when there is a lack of response or contraindication to corticosteroids, Methotrexate and/or Azathioprine therapy.	Initial treatment: 2 g/kg over 2 days. Maintenance therapy: A systematic approach should be taken to determine minimum effective dose. Continued use should be based on objective measures of sustained effectiveness.
Rheumatology	Kawasaki disease ³ (KD)	Recommended when Kawasaki diagnosis confirmed.	2 g/kg x 1 day (second dose can be given for patients who fail to respond the first time).

Infectious Diseases

Specialty	Medical Condition	Recommendations	Dose/Frequency of Administration
Infectious Diseases	Staphylococcal toxic shock ^{3,4}	Recommended when evidence of systemic inflammation and end organ hypoperfusion with fever, tachycardia, tachypnea and hypotension.	1 g/kg on day one and 0.5 g/kg per day on days 2 and 3 OR 0.15 g/kg per day over 5 days.
	Invasive Group A streptococcal fasciitis with associated toxic shock ^{3,4}	IVIG is only recommended for severe invasive group A streptococcal disease if other approaches have failed. IVIG is recommended for staphylococcal toxic shock syndrome when other therapies have failed.	1 g/kg on day one and 0.5 g/kg per day on days 2 and 3 OR 0.15 g/kg per day over 5 days (BC).

Immunology

Specialty	Medical Condition	Recommendations	Dose/Frequency of Administration
Immunology	Primary Immune Deficiency ^{3,6} (PID) Secondary Immune Deficiency ^{3,6} (SID)	Recommended in hypogammaglobulinemia (IgG or IgG subclasses reduced) with recurrent bacterial infections.	<ol style="list-style-type: none"> 0.4-0.6 g/kg/every 4 weeks or SCIG 0.1-0.5 g/kg/week. Minimum trough level 5 g/L, aim for 7 g/L for most patients. Monitor trough level every 3-6 months. Pediatric: 0.3-0.6 g/kg/once every 4 weeks. Monitor IgG trough level to maintain low range.

Solid Organ Transplant

Specialty	Medical Condition	Recommendations	Dose/Frequency of Administration
Solid Organ Transplantation	Kidney transplant from living donor ⁷	Recommended to decrease donor specific sensitization.	2 g/kg/month for 4 months.
	Kidney transplantation with donor-specific antibodies in recipient ⁷	Recommended.	Insufficient evidence for recommending a dose.
	Acute antibody mediated rejection ⁷	Recommended after plasmapheresis.	0.1 g/kg/treatment day, or as a set dose of 2 g/kg total.
	Kidney transplant with steroid resistant rejection ⁷	IVIG should be considered to improve graft survival when other therapies are deemed unacceptable or ineffective.	2-3.5 g/kg up to 10 consecutive days.
	Other forms of rejection kidney transplant ⁷	Insufficient evidence.	No recommended dose or duration listed.
	ABO incompatible kidney transplantation ⁷	Insufficient evidence.	No recommended dose or duration listed.
	Desensitization heart/lung/liver transplant ⁷	Insufficient evidence.	No recommended dose or duration listed.