ORBCoN
Ontario Regional Blood Coordinating Network

Ontario

Immune Globulin Toolkit for Ontario

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Acknowledgements version 3.0 January 31, 2018

Copies of these documents can be downloaded from http://transfusionontario.org/en/documents/?cat=ivig

The Ontario Regional Blood Coordinating Network acknowledges with sincere appreciation the funding support of the Ministry of Health and Long-Term Care (MOHLTC).

Introduction

Intravenous immune globulin (IVIG) and subcutaneous immune globulin (SCIG) are products prepared by several commercial manufacturers who use plasma derived from donors to extract immunoglobulin subclass gamma (IgG). Immune Globulin (IG) is commonly used to treat patients for a number of labeled and unlabeled indications through either replacement of IG or immune modulation.

In 2006, the Blood Programs Coordinating Office (now known as the Provincial Agencies Trillium Gift of Life Network/ Blood and Specialized Programs or PATB) in Ontario launched a new blood programs initiative, the Ontario Regional Blood Coordinating Network (ORBCoN). This network was mandated to engage Ontario hospitals with transfusion services by setting up educational and communication opportunities, and to support hospitals with utilization improvement and inventory management tools. One of the many projects undertaken by ORBCoN was an IVIG utilization management initiative.

The first IG toolkit was launched in September 2010 with the purpose to:
- Provide guidelines for appropriate use of Intravenous Immune Globulin
- Provide health care practitioners involved in the infusion of IVIG with best practice information

The second iteration of the toolkit was released in 2012 and this version included a MOHLTC request form, dose calculator, new IG utilization management and infusion guidelines and a subsequent IG audit.

IG use has risen dramatically across Canada over the past 15 years and continues to do so, exceeding a 10% increase in some years. After the introduction of the MOHLTC strategy and new version of the toolkit in 2012, the IG use in Ontario actually decreased by 1.4% in 2012/13. However, since that time, the number of grams issued to hospitals in Ontario increased from approximately 1.78 M in 2012/13 to over 2.28 M in 2016/17. At a cost per gram of between $55 and $65 this translates to over $143 M annually. There are concerns that continued growth in IG utilization may become unsustainable. Seeking ways to ensure use of this product is appropriate the MOHLTC introduced a process to determine the feasibility of implementing an external screening and review mechanism for IG neurology requests. The Immune Globulin Screening Program (IGSP) pilot for neurology was launched on May 30, 2016. Data gathered from this pilot has been analyzed to determine if it is feasible to apply this process in the future to improve monitoring and understanding of IG use in the province of Ontario. See full report here: http://transfusionontario.org/en/documents/?cat=ivig.

This third version of the IG toolkit contains the following changes:
- Ontario IG Utilization Management Guidelines version 4.0 January 31, 2018
- MOHLTC IG Request Forms.
  - Non-Neurology version 5.0 January 2018 and
  - Neurology version 3.0 January 2018
- Implementation of a new Dose Calculator platform with an accompanying tool to calculate the BMI
- New version of the Ontario Intravenous Immune Globulin Infusion Guide and Adverse Reaction Chart version 2.0 October 31, 2015
- IVIG Facts for Outpatients version 2 0 October 31, 2015
- Travelling with IVIG; documents to support patients travelling with IG version1.0 January 31, 2018.

For more information relating to specific brands of IVIG available please refer to the following Canadian Blood Services document "Immune Globulin Comparison table". The current version can be found on the CBS website at www.blood.ca.

Abbreviations and Definitions

Abbreviations

ADEM	Acute Disseminated Encephalomyelitis
AIHA	Auto Immune Hemolytic Anemia
AvWD	Acquired von Willebrand disease
BMI	Body Mass Index
CBC	Complete blood count
CIDP	Chronic Inflammatory Demyelinating Polyneuropathy
F/NAIT	Fetal Neonatal Alloimmune Thrombocytopenia
GBS	Guillain–Barré Syndrome
GVHD	Graft vs Host disease
HDFN	Hemolytic Disease of the Fetus and Newborn
HIT	Heparin Induced Thrombocytopenia
HIV	Human Immunodeficiency Virus
HSCT	Hematopoietic Stem Cell Transplant
HTR	Hemolytic Transfusion Reaction
HTRSC	Hemolytic Transfusion Reaction in Sickle Cell disease
IBM	Inclusion Body Myositis
IgG	Immunoglobulin G
IGSP	Immune Globulin Screening Pilot
IIM	Idiopathic Inflammatory Myopathy
ITP	Immune Thrombocytopenia
IVIG	Intravenous Immune Globulin
J-IM	Juvenile Idiopathic Myopathy
LEMS	Lambert Eaton Myasthenic Syndrome
MG	Myasthenia Gravis
MMN	Multifocal Motor Neuropathy
NMDA	N-methyl-D aspartate encephalitis
MOHLTC	Ministry of Health and Long-Term Care
ORBCoN	Ontario Regional Blood Coordinating Network
PANDAS	Pediatric Autoimmune Neuropsychiatric Disorders with Streptococcal Infections
PID	Primary Immune Deficiency
PTP	Post Transfusion Purpura
PV	Pemphigus Vulgaris
SCD	Sickle Cell Disease
SCIG	Subcutaneous Immune Globulin
SID	Secondary Immune Deficiency
SJS	Stevens-Johnson Syndrome
TACO	Transfusion Associated Circulatory Overload
TEN	Toxic Epidermal Necrolysis
TML	Transfusion Medicine Laboratory
TTISS	Transfusion Transmitted Injuries Surveillance System
VAHS	Virus Associated Hemophagocytic Syndrome

Abbreviations and Definitions

Definitions

Adverse events	An undesirable and unintended occurrence during or after the administration of whole blood, blood components, or blood products, whether or not considered to be related to the administration of the blood, blood component, or blood product
Dyspnea	Difficult or labored respiration
Pharyngitis	Sore throat caused by inflammation of the back of the throat
Photophobia	An abnormal sensitivity to, and discomfort from, light
Urticaria	Hives; skin that erupts into red welts, often with severe itching

IVIG Utilization Management Guidelines and IVIG Strategy

On November 11, 2009, physicians in charge of Blood Transfusion Services and contact personnel in Transfusion Medicine Laboratories (TML) received Version 1.0 of the Ontario Intravenous Immune Globulin Utilization Management Guidelines. The Ministry of Health and Long-term Care acknowledged that work and on April 1, 2012 launched an IVIG strategy. Part of the strategy was to formally endorse the Ontario IVIG Utilization Management Guidelines. Version 4.0 of these guidelines accompany this document.

A document titled "Ontario Intravenous Immune Globulin Strategy Update" is also included to describe the update to the overall strategy and the place the guidelines hold within that strategy. This summary of guidelines and information on IVIG utilization has been prepared specifically for use in Ontario. The guidelines document provides clinicians with updated information about the common and clinically appropriate uses of Immune Globulin. In 2015 working groups from each medical specialty updated the guidelines which were subsequently endorsed by their associations before approval by the Ontario IG Advisory Panel. It is critically important that physicians in each hospital are aware of this information.

Recommendations on Maximum Dose of IVIG

Recommendations on Maximum Dose of IVIG
For the following clinical indications that appear on the Ontario IVIG Utilization Management Guidelines under 'IVIG is recommended', ***the maximum dose is 2 g/kg per treatment course***, as quoted in the Feasby et al article listed below:

- Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)
- Idiopathic Inflammatory Myopathy (IIM)

For the following clinical indications that appear on the Ontario IVIG Utilization Management Guidelines under "IVIG is recommended as an Option for treatment", ***the maximum dose is 2 g/kg per treatment course****, as quoted in the Feasby et al article listed below:

- Lambert-Eaton Myasthenic Syndrome
- Stiff Person Syndrome

*except in rare circumstances like some cases of TENS (Dermatology)

Source of Maximum Dose Recommendations:
Feasby T et al. Guidelines on the use of intravenous immune globulin for neurologic conditions Transfusion Medicine Reviews 2007(April); 21(1, Suppl 1):S57-S107.

Communication of the guidelines documents:

Electronic copies can be downloaded from:
http://transfusionontario.org/en/download/ontario-ig-utilization-management-guidelines/

Ministry of Health and Long-Term Care

Ontario IG Utilization Management Strategy Update

Provincial Agencies Trillium Gift of Life Network, Blood and Specialized Programs
Ministry of Health and Long -Term Care

January 31, 2018

Ontario

IG Utilization Management Strategy Update

Background

The Ontario Ministry of Health and Long-Term Care (MOHLTC) developed its first Ontario IG Utilization Management Strategy in 2012 and it was updated in 2015. The following items reflect the core requirements from these strategies that are still valid in mitigating unsustainable increases in IG utilization.

Scope

The IG Utilization Management Strategy applies to all hospitals where IG is dispensed by either a transfusion service or pharmacy. Physicians and practitioners who order IG must be made aware of and adhere to these directives.

Strategy

1. Adherence to Ontario IG Utilization Management Guidelines. The clinical indication, dose, frequency and duration of therapy must be in accordance with the Ontario IG Utilization Management Guidelines. The Guidelines are located in the IG Toolkit available at http://transfusionontario.org/en/download/immune-globulin-toolkit-for-ontario/
2. Implementation of the MOHLTC IG Request Form. All new requests for IG must be submitted using the MOHLTC Form. A record of the completed forms must be retained for five (5) years to permit spot audits. The record can be either paper, microfilm or electronic.
3. Review/Approval for Indications NOT Listed on Request Form. IG ordered for clinical indications not approved in the guidelines will be subject to screening at the hospital level. A physician appointed to serve as the approving physician, or their designate, must sign the form. NOTE: in the case of a life-threatening situation, the request for IG will be filled immediately.
4. Dosing Through “Adjusted Body Weight” Calculation. Ideal dosing reduces both the demand for IG and adverse events like hemolysis. Hospitals may elect to use the dose calculator for all patients to confirm the accuracy of the requested dose, but it must be used for all obese patients. The dose calculator and BMI tool can be found on : http://transfusionontario.org/en/download/bmi-dose-calculator/
5. Evaluating Clinical Outcomes and Need for Reassessment. For patients being treated regularly over a period of time, a mechanism to evaluate clinical impact must be established. A patient must be evaluated 6 months after the initial

prescription and every 12 months after that. A new MOHLTC request form must be completed initially and for each reassessment, especially for patients on long term therapy. The target shall be to prescribe the minimum effective dose.

6. No Outdating of Product. There must be no expiry of IG. Canadian Blood Services does not accept returns, but the Ontario Regional Blood Coordinating Network (ORBCoN) will assist you in the redistribution of this expensive product to another hospital that will use it before it expires.
7. Use for both IVIG and SCIG. The MOHLTC request form is to be used for both IVIG and SCIG requests.

In the Future

The MOHLTC is currently exploring alternate funding models with an expert working group. A letter was sent to patient groups and LHIN CEOs on September 29, 2017 informing them of this initiative. Depending on the solutions developed by this group, there may be upcoming changes to the IG ordering process at Ontario hospitals. The MOHLTC in conjunction with ORBCoN will keep hospitals apprised of any changes.


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Ontario Immune Globulin (IG) Utilization Management Guidelines

Version 4.0

January 31, 2018

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Disclaimer:

The Ontario IG Utilization Management Guidelines are not intended to replace sound clinical judgment concerning a patient's unique situation.

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 version 4.0 of the Ontario Immune Globulin Management Guidelines Version 1.0 was first circulated November 5, 2009 with subsequent versions in March, 2012 and May 2016. The guidelines were also included in the Intravenous Immune Globulin Toolkit, published by the Ontario Regional Blood Coordinating Network in September 2010 and October 2015.

The information in this document is intended as a guideline document for clinicians seeking clarification on the common and clinically appropriate uses of Immune Globulin.

This summary of guidelines and information on IG Utilization has been prepared specifically for use in Ontario, based on the input from the Ontario IG Advisory Panel. In 2015, the Ontario IVIG guidelines were reviewed by physicians within each of the specialties with indications for IVIG following a literature review of current evidence. The guidelines for Rheumatology, Neurology, Hematology, and Solid Organ Transplantation were published in May 2016. No revisions were deemed necessary at that time for Infectious Disease conditions and review of Dermatology and Immunology were completed in July 2017.

Recommended Hematology Indications

	Medical Condition	Recommendations	Dose/Frequency of Administration
Specialty: Hematology	Fetal/ Neonatal alloimmune thrombocytopenia (F/NAIT) [1,2,38]	**Antenatal treatment**: IVIG (with or without corticosteroids) is recommended as first line treatment for women with a previously affected infant.	**Maternal dose** based on the following risk stratification: • Previous fetus with intracranial hemorrhage: Up to a total of 2 g/kg weekly starting as early as 12-16 weeks gestation. • No previous fetus with intracranial hemorrhage: Up to 1g/kg weekly, starting as early as 20-26 weeks current gestation.
		Newborn with F/NAIT: IVIG is recommended as adjunct to provision of platelets for infants with F/NAIT who have severe thrombocytopenia. Treatment should be administered in consultation with obstetrical medicine and transfusion medicine with expertise in F/NAIT.	**Infant dose:** initial dose of 1 g/kg, reassess following initial dose.
	Hemolytic Disease of the Fetus and Newborn (HDFN) [1,2,3]	IVIG is recommended in infants with HDFN and severe hyperbilirubinemia if total serum bilirubin (TSB) is rising despite intensive phototherapy/hydration, in consultation with experts in fetomaternal medicine and transfusion medicine.	0.5 g/kg over 4 hours.
	Immune thrombocytopenia (ITP) Adult [1,2,3,4]	**Acute ITP with or at risk for severe bleeding:** IVIG is recommended as part of multimodality therapy for patients with ITP, severe thrombocytopenia (platelets less than 30 x 10^9/L) and severe bleeding. **IVIG may be considered in the following situations:** • ITP in pregnancy: when platelets are less than 30 x 10^9/L, or in preparation for delivery. • Planned surgery: safe platelet threshold will vary with the nature of the surgery. • Treatment of ITP in patients with other concurrent risk factors for bleeding (e.g. concurrent anticoagulant therapy). **Chronic ITP:** IVIG may be considered as a possible adjunctive therapy as a steroid-sparing measure.	**Acute:** 1 g/kg as a single dose. Repeat if platelet count does not respond. I.e. still less than 30 x 10^9/L. **Chronic:** In consultation with a hematologist, as adjunctive therapy or where other therapies have failed or are not appropriate. Consider 1-2 g/kg. The use of regular IVIG as a treatment for chronic ITP should be considered as exceptional and alternative approaches (e.g. splenectomy, rituximab, thrombopoietin receptor agonists) should be considered.
	Immune Thrombocytopenia (ITP) Pediatric [1,2,3,4]	Acute: Children with no bleeding or mild bleeding only (mild bruising or petechiae) should be managed with observation alone regardless of platelet count. For children with moderate to severe mucosal and/or cutaneous bleeding and platelet count less than 30 x 10^9/L, IVIG can be used. Chronic: IVIG can be used in chronic ITP for previous responders.	For patients who require treatment, a single dose of IVIG may be considered a front-line treatment (0.8 to 1 g/kg). A second dose can be repeated if there is no clinical response. IVIG will result in a faster increment in platelet count compared with steroids. In emergent management, IVIG is recommended as part of multimodal therapy.
	Post-transfusion purpura (PTP) [1]	IVIG is recommended as standard first-line therapy for PTP.	Up to 2 g/kg divided over 2 to 5 consecutive days, repeat if necessary; for short term use.

For the following conditions, IVIG treatment is not recommended for routine use.
When screening requests for approval the following information may be taken into account as there is some evidence for IVIG to be considered as an option.

Specialty: Hematology	Medical Condition	Recommendations	Dose/Frequency of Administration
	Acquired hemophilia [1]	IVIG may be considered one option among adjunctive therapies, such as steroids, in urgent situations. Not recommended for routine use. Prescribed only in consultation with specialized hemophilia care centre.	Up to a total of 2 g/kg divided over 2 to 5 consecutive days, for short term use.
	Acquired red cell aplasia[1,3]	IVIG is an 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.	Up to 2 g/kg divided over 2 to 5 consecutive days; for short term use. Repeated on relapse.
	Acquired von Willebrand's disease (AvWD) [1,3]	IVIG should be considered part of multimodal therapy in emergent situations (together with desmopressin and FVIII/VWF concentrates) in patients who have not responded to other treatments. Prescribed only in consultation with specialized hemophilia care centre.	Initial therapy: Up to 2 g/kg divided over 2 to 5 consecutive days.
	Allogeneic bone marrow or stem cell transplantation[2,3,38]	IVIG is not recommended for routine use after HSCT. IVIG may be considered in exceptional cases: 1) Active CMV-induced pneumonitis following transplantation. 2) High risk allogeneic stem cell transplantation (e.g. If hypogammaglobulinemia) for prevention of GVHD.	1) No recommended dose or duration listed; use in conjunction with appropriate antiviral medication. 2) 0.4 g/kg weekly, starting one day before transplantation and continuing to day 100 post-transplant.
	Autoimmune hemolytic anemia[1,3] (AIHA)	May be considered one option among adjunctive therapies in urgent situations. Not recommended as routine.	No recommended dose or duration listed; however, expert panel recommends up to 2 g/kg divided over 2 to 5 consecutive days.
	Autoimmune neutropenia[1,3]	May be considered one option among adjunctive therapies in urgent situations.Not recommended as routine.	
	Hemolytic transfusion reaction in sickle cell disease[1] (HTRSCD)	IVIG may be considered among the options for treatment of serious, life-threatening, delayed hemolytic transfusion reactions in SCD patients.	
	Virus associated hemophagocytic syndrome[1] (VAHS)	IVIG is not recommended for routine use in the treatment of VAHS. IVIG may be considered among the options for treatment of severe life threatening VAHS.	
	Hemolytic transfusion reaction [1](HTR)	IVIG may be considered as an option among supportive therapies for urgent situations in this disorder.	Up to 2 g/kg divided over 2 to 5 consecutive days, short term up to 3 months.

Recommended Neurology Indications

Specialty: Neurology	Medical Condition	Recommendations	Dose/Frequency of Administration
	Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)[2,5,6,7]	IVIG is recommended as first-line therapy in CIDP. Immunosuppressive therapy in combination with IVIG can be considered in refractory cases. All patients receiving IVIG for chronic treatment of CIDP should be followed by a neuromuscular specialist.	Initial dose: 2 g/kg divided over 2 to 5 days Maintenance dose: 1g/kg every 3 weeks. Continued use should be based on objective measures of sustained effectiveness. Aim for minimum dose to maintain optimal functional status.
	Guillain-Barré Syndrome (GBS) including Miller-Fisher syndrome and other variants[2,5,8]	IVIG is recommended for symptoms of grade 3 severity (able to walk with aid) or greater; or symptoms less than grade 3 severity that are progressing. Treatment should be given within 2 weeks of symptom onset. Re-treatment for patients who do not respond may be considered.	Adult: Total dose of 2 g/kg divided over 2 to 5 days. Pediatric: Total dose of 2 g/kg divided over 2 days. Repeat treatment with IVIG at 2 g/kg divided over 2 to 5 days.
	Multifocal motor neuropathy (MMN)[2,5,9]	IVIG is recommended as first-line treatment for MMN.	Initial dose: 2 g/kg divided over 2 to 5 days. Maintenance dose: tailor to the lowest dose that maintains clinical efficacy, usually 1g/kg or less per treatment course. Some patients may require higher doses for efficacy, up to 2 g/kg every 4 weeks.
	Myasthenia gravis (MG)[2,5,10,11,12,13]	IVIG is recommended as first-line treatment in moderate-severe MG or in myasthenic crisis. IVIG in combinations with immunosuppressive therapy can be considered in refractory cases.	Initial dose: 2 g/kg divided 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.

For the following conditions, IVIG treatment is not recommended for routine use.
When screening requests for approval the following information may be taken into account as there is some evidence for IVIG to be considered as an option.

	Medical Condition	Recommendations	Dose/Frequency of Administration
Specialty: Neurology	Acute disseminated encephalomyelitis[3,5] (ADEM)	IVIG is an option for monophasic ADEM when first-line therapy with high-dose corticosteroids fails or when there are contraindications to steroid use, and for 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 divided over 2 to 5 days. Pediatric: Total dose of 2 g/kg divided over 2 days.
	Lambert-Eaton Myasthenic Syndrome[3,5] (LEMS)	IVIG is an option for treatment of LEMS. Objective evidence of clinical improvement is needed for sustained use of IVIG.	Initial dose: Total dose of 2 g/kg divided over 2 to 5 days. Maintenance dose: 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.
	Pediatric Autoimmune Neuropsychiatric Disorders Associated With Streptococcal Infections[3,5] (PANDAS)	IVIG is an option for treatment of patients with PANDAS. Diagnosis of PANDAS requires expert consultation.	Total dose of 2 g/kg divided over 2 days is recommended as a reasonable option.
	Rasmussen's encephalitis[3,5]	IVIG is an option as a short-term, temporizing measure for patients with Rasmussen's encephalitis. Not recommended for long-term therapy.	Adults: Total dose of 2 g/kg divided over 2 to 5 days. Pediatric: Total dose of 2 g/kg divided over 2 days.
	Stiff Person's syndrome[3,5]	IVIG is an option for treatment of Stiff Person syndrome if GABAergic medications fail or for patients who have contraindications to GABAergic medications.	Initial dose: Adults: Total dose of 2 g/kg divided over 2 to 5 days. Pediatric: Total dose of 2 g/kg divided over 2 days. Maintenance dose: 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.
	N-methyl-D-aspartate (NMDA) encephalitis[14]	IVIG is an option for treatment of patients with NMDA. Diagnosis of NMDA requires expert consultation. IVIG is used in conjunction with immunosuppressive medications and/or plasmapheresis.	Initial dose: Total dose of 2 g/kg divided over 2 to 5 days in adults and children. Maintenance dose may be considered depending on response to treatment.

Recommended Dermatology Indications

Specialty: Dermatology	Medical Condition	Recommendations	Dose/Frequency of Administration
	Pemphigus Vulgaris (PV) and Variants [2,3,39,40]	Consider IVIG when there is no response or a contraindication to corticosteroids, immunosuppressive agents or biologics (e.g. rituximab) in conjunction with one of the above. First line therapy: corticosteroids Second line: immunosuppressive agents Third line: IVIG	Total dose 2 g/kg divided over 2 to 5 days every 4 weeks. Dose every 6 weeks after 6 months of therapy.

For the following conditions, IVIG treatment is not recommended for routine use.
When screening requests for approval the following information may be taken into account as there is some evidence for IVIG to be considered as an option.

Specialty: Dermatology	Medical Condition	Recommendations	Dose/Frequency of Administration
	Toxic epidermal necrolysis (TEN)/ Stevens-Johnson Syndrome (SJS)[3,38,40]	IVIG is an option when other treatments are contraindicated, or when the condition is life-threatening. Early intervention is strongly recommended.	3 g/kg divided over 3-5 days.

Recommended Rheumatology Indications

	Medical Condition	Recommendations	Dose/Frequency of Administration
Specialty: Pediatric Rheumatolog	Juvenile Idiopathic Inflammatory Myopathy (J-IIM)[2,5,15,16,17] (Previously Juvenile Dermatomyositis)	IVIG is recommended when there is a lack of response or contraindication to corticosteroids, Methotrexate and/or Azathioprine therapy. 1st line: Corticosteroids and Methotrexate 2nd line: IVIG 3rd line: Cyclosporine	Initial dose: Total dose of 2 g/kg divided over 2 days. Maintenance dose: A systematic approach should be taken to determine minimum effective dose. Continued use should be based on objective measures of sustained effectiveness. Maximum dose should not exceed 2 g/kg.
	Kawasaki Disease [2,18,19,20,21,22]	IVIG is recommended when Kawasaki diagnosis confirmed.	2 g/kg for 1 day (second dose can be given for patients who fail to respond to initial dose).
Specialty: Adult Rheumatology	Idiopathic Inflammatory myopathy (IIM) [2,5,15,23,24,26,25] Includes Dermatomyositis and Polymyositis *does not include Inclusion Body Myositis (IBM)	IVIG is indicated in patients with IIM as adjunctive therapy to corticosteroids and/or a steroid sparing agent in patients with IIM who have failed 1st line therapy or as clinically indicated in the management of severe disease. *IVIG benefit has not been established in IBM. 1st line: Corticosteroids and Methotrexate and/or Azathioprine 2nd line: IVIG 3rd line: Cyclosporine or cellcept	Maximum dose is 2 g/kg to be given over 2 days initially monthly for 3-6 months and if effective to be continued at decreasing frequency (determine minimum effective dose) over approximately 2 years. Survival of patients with IIM has been shown to be substantially improved in patients given IVIG.

Recommended Infectious Disease Indications

	Medical Condition	Recommendations	Dose/Frequency of Administration
Specialty: Infectious Diseases	Staphylococcal toxic shock[2,3,15]	IVIG is 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 for 5 days.
	Invasive Group A streptococcal fasciitis with associated toxic shock[2,3,15,29,30]		

Recommended Immunology Indications

	Medical Condition	Recommendations	Dose/Frequency of Administration
Specialty: Immunology	Primary Immune Deficiency (PID)[2,31] Secondary Immune Deficiency (SID)[2,31]	IVIG is recommended in hypogammaglobulinemia (total IgG reduced or inadequate antibody production) with recurrent bacterial infections. Children and adults with a suspected immunodeficiency should be referred to an immunologist with expertise in the field of primary immunodeficiency ('expert' in PID). Ideally, this should be carried out in an academic centre with the capability of performing specialized diagnostic tests for immunodeficiency. Management should be performed by a specialized team including physicians, nurses and allied health care providers.	Adult: 0.4-0 .6 g/kg every 3-4 weeks Pediatric: 0.3-0 .6 g/kg every 3-4 weeks Doses or frequency to be adjusted by experts according to desired trough level (more than 500 mg/dL and ideally 700 mg/dL) and according to individual patient clinical needs.
	Hematopoietic Stem Cell Transplant in primary immunodeficiencies[3]	IVIG is recommended in PID patients undergoing stem cell transplant.	0.4 to 0.6 g/kg every 3-4 weeks; requirements may increase and should be based on clinical outcome.

Recommended Solid Organ Transplant Indications

	Medical Condition	Recommendations	Dose/Frequency of Administration
Specialty: Solid Organ Transplantation	Kidney transplant from living donor to whom the patient is sensitized[15,32]	IVIG is recommended to decrease donor-specific sensitization.	2 g/kg/month for 4 months.
	Pre-Transplant (heart)[32,33,34,35,36]	For desensitization in selected heart transplant recipients who are highly sensitized, medically urgent and unlikely to receive a transplant otherwise – this should be preceded by discussion at the transplant program level.	Suggested dose is up to 1 g/kg/month until transplant.
	Peri- Transplant (heart, lung, kidney, pancreas[31,33,34,35,36]	Solid-organ transplant recipient with donor-specific antibodies identified at time of transplant surgery (heart, lung, kidney, pancreas) on virtual crossmatch – first-line agent.	Suggested dose 1 g/kg, can give as divided doses if in association with a course of plasmapheresis.
	Post-Transplant [32,33,34,35,36,37]	Acute antibody-mediated rejection in a solid-organ transplant recipient – first-line agent. Chronic antibody-mediated rejection in a solid-organ transplant recipient.	1 g/kg/dose, can give as divided doses if in association with a course of plasmapheresis. 1 g/kg/month.

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Use of the MOHLTC IG Request Form

ALL requests for IG must be submitted using the appropriate MOHLTC IG Request Form:
Use the Neurology form for IG requests for neurology requests only.
Use the Non–neurology form for all non-neurology requests for IG.
*This includes initial or renewal requests for all patients whether for induction or maintenance therapy with either IVIG or SCIG.

Duration of Approval. When a request for an Approved medical condition includes multiple infusions of IG (e.g. a course of treatment rather than a single infusion), completing the form once is sufficient until:
a. Dose is modified, or
b. Six months have elapsed since the initial treatment, or
c. Twelve months have elapsed for renewal requests.

Duration of Approval for Unapproved Medical Conditions. If a request for an Unapproved medical condition is approved, IG will be provided for up to a maximum trial period of three months. A reassessment should be done to confirm IG treatment continues to be effective and that minimum effective dose is being applied.

URGENT Requests. IG will always be provided in life-threatening situations, the appropriate request form to be completed when time allows.

Completing the Form (Complete all requested information and print clearly to avoid delays in access to IG)

Ordering Physician (or Designate) is responsible for completing the MOHLTC IG Request Form and submitting it to their TML.
1. Complete all requested physician, patient and hospital information.
2. Complete to indicate if request is for SCIG or IVIG.
3. Complete to indicate the medical condition for which IG is being requested. Check 'Other' if the medical condition does not appear on the list of approved conditions. **Please refer to the Ontario IG Guidelines for additional conditions for which IG may be appropriate.** If applicable, include information to confirm diagnosis and describe treatment to date to explain/ support the need for IG.
4. Complete to indicate dose and duration of IG treatment. Dose must be adjusted for obese patients (i.e., BMI ≥ 30). Hospitals that do not adopt the Dose Calculator tool are required to use an alternative strategy for adjusting dose for obese patients. Consider adjusting dose for overweight patients to ensure minimum effective dose is being applied. For other patients, the Dose Calculator maybe used to verify dose calculations. Use actual body weight to calculate dose for both adult and pediatric patients less than 5 feet in height. Requests for dose/duration greater than what is recommended in the Ontario Guidelines will be sent for review by the approving physician (or designate).

HealthCare Professional receiving the request (e.g. Laboratory technologist, pharmacy personnel)
1. Verify that the clinical indication coincides with one of the clinical indications listed. If not refer to 4 below.
2. Verify the dose requested using the dose calculator if appropriate.
3. Doses that require adjustment must be confirmed with the treating physician and documented on the bottom of the form.
4. Requests listing 'Other' as the clinical indication or requesting a dose that is greater than what is recommended in the Ontario Guidelines should be referred to an approving physician for screening.

Approving Physician or Designate
1. Screening of all IG requests for clinical indications listed under 'Other' or those with a dose greater than recommended in the Ontario Guidelines is required.
2. Document whether the request is approved or denied using the shaded area at the bottom of the request form including a signature, date and checking the appropriate box.

Hemolytic reactions due to anti-A and/or anti-B in IVIG have been noted.
Patients should be monitored for signs of hemolysis. CBC, blood group and antibody screen should be ordered prior to initial infusion. In Group A, B or AB patients, within 1 week of initial infusion the following tests are recommended: CBC, direct antiglobulin test (DAT), total and direct bilirubin, reticulocyte count, LDH, and haptoglobin.
Refer to the Adverse Reaction Chart for IVIG Infusion for more information.

MOHLTC IVIG Request Form

The forms on the following pages of this toolkit are intended to be used by hospitals where IVIG/SCIG is infused.

MOHLTC IG Request form for Non-neurology indications:
This form is to be used for all IG requests for indications other than neurology.

This type of ordering form can be built into a Laboratory Ordering System or Intranet, or used in paper format. The form is available at http://transfusionontario.org/en/download/ontario-mohltc-ig-request-form-non-neurology/.
All new non-neurology requests for IVIG must be ordered using the MOHLTC IG Request Form, whether the product is handled through the Transfusion Service or through the Pharmacy. This will ensure that the request is in accordance with provincial guidelines and that any specific prerequisites have been addressed. Hospitals that have already implemented an IG Request Form will need to adopt the MOHLTC January 31, 2018 version. Modification of the Request Form is not permitted. This will prevent the addition of indications not on the Guidelines and allow for standardized data collection. A record of completed Request Forms must be kept for five (5) years to allow for spot audits to measure compliance with the IG Strategy. The record can be paper based, electronic, or microfilm.

MOHLTC IG Request form for Neurology indications:

In May 2016, the MOHLTC implemented a pilot to provide an external screening process for immune globulin (IG) requests for neurological indications. Named the immune globulin screening program (IGSP) pilot*, a request form was developed for all requests for IVIG or SCIG for any neurology requests. Following the pilot, a revised IG request form for neurology indications is to be used. http://transfusionontario.org/en/download/ontario-mohltc-ig-request-form-neurology/.

*IGSP report is under review by the MOHLTC, final version will be posted here http://transfusionontario.org/en/download/.

Ontario

MOHLTC IVIG Request Form

For non-neurology use only

Patient Name
Patient Hospital/Medical Record#
D.O.B.
Gender
Location
Ontario Health Insurance#

ALL FIELDS BELOW ARE MANDATORY

Date Requested: (YYYY/MM/DD)	Treating Physician:
Date Required: (YYYY/MM/DD)	Physician Specialty:
Hospital where patient will receive IG.	Physician Phone #:

Dosage Information: (Verification of dose using Dose Calculator tool is recommended)

☐ Intravenous IG (IVIG) ☐ Subcutaneous IG (SCIG)						
Patient Weight: kg	Patient Height: cm	BMI:	**Dose must be adjusted for BMI greater than or equal to 30**			
☐ Induction/One-time dose	g/kg = Total dose of	g; divided over	days			
☐ Maintenance dose	g/kg = Total dose of	g; divided over	days; every	weeks; Duration:	months	
Dose Calculator Used? ☐ Yes ☐ No If No, why was it not used						
IgG level/Platelet count/other test results relevant to patient condition: Result: Date:						

Clinical indication for use: **Refer to Ontario IG Management Utilization Guidelines for additional indications where IG may be appropriate.**

Specialty	
Hematology	☐ Fetal/Neonatal Alloimmune Thrombocytopenia (F/NAIT)
	☐ Hemolytic Disease of the Fetus and Newborn (HDFN)
	☐ Immune Thrombocytopenia (ITP) ☐ Adult ☐ Pediatric
	☐ Post-transfusion Purpura
Dermatology	☐ Pemphigus Vulgaris (PV) and Variants
Rheumatology: Pediatric	☐ Juvenile Idiopathic Inflammatory Myopathy (J-IIM) (previously Juvenile Dermatomyositis)
	☐ Kawasaki Disease (KD)
Rheumatology: Adult	☐ Idiopathic Inflammatory Myopathy (IIM) Includes Dermatomyositis and Polymyositis
Immunology	☐ Primary Immune Deficiency (PID)
	☐ Secondary Immune Deficiency (SID)
	☐ Hematopoietic Stem Cell Transplant in primary immunodeficiencies
Solid Organ Transplant	☐ Kidney transplant from living donor to whom the patient is sensitized
	☐ Pre-transplant (Heart)
	☐ Peri-transplant (heart, lung, kidney, pancreas)
	☐ Post-transplant
Infectious Disease	☐ Invasive Group A streptococcal fasciitis with associated toxic shock
	☐ Staphylococcal Toxic Shock
***OTHER (requires approval)**	

For Transfusion Medicine Use Only

☐ **Dose verified** ☐ **Dose adjusted to:**	**By (signature req'd):**
☐ **Confirmed with ordering physician**	**Date:**
☐ **Approved** ☐ **Denied**	**Date:**
Signature of Approving Physician:	

Please fax/send to:

Medical Condition	Suggested initial dose and duration
Fetal/Neonatal Alloimmune Thrombocytopenia (F/NAIT)	*Maternal*: Previous fetus with intracranial hemorrhage: Up to 2 g/kg/week starting as early as 12-16 weeks gestation. No previous fetus with intracranial hemorrhage: Up to 1 g/kg/week. Starting as early as 20 -26 weeks current gestation. *Infant*: Initial dose of 1 g/kg reassess following initial dose.
Hemolytic Disease of the Fetus and Newborn (HDFN)	0.5 g/kg over 4 hours
Immune Thrombocytopenia (ITP) Adult	*Acute*: 1 g/kg as a single dose. Repeat if PLT count does not respond I.e. still less than 30 x 10^9 /L. *Chronic*: In consultation with a hematologist, as adjunctive therapy or where other therapies have failed or are not appropriate. Consider 1-2 g/kg. The use of regular IVIG as a treatment for chronic ITP should be considered as exceptional and alternative approaches (e .g. splenectomy, rituximab, thrombopoietin receptor agonists) should be considered.
Immune Thrombocytopenia (ITP) Pediatric	For patients who require treatment, a single dose of IVIG may be considered a front-line treatment (0 .8 to 1 g/kg). A second dose can be repeated if there is no clinical response. IVIG will result in a faster increment in platelet count compared with steroids. In emergent management, IVIG is recommended as part of multimodal therapy
Post-transfusion Purpura	Up to 2 g/kg divided over 2 to 5 consecutive days. Repeat if necessary; for short term use.
Pemphigus Vulgaris (PV) and variants	Total dose of 2 g/kg divided over 2 to 5 days every 4 weeks. Dose every 6 weeks after 6 months of therapy.
Juvenile Idiopathic Inflammatory Myopathy (J-IIM) (previously Juvenile Dermatomyositis)	*Initial dose*: Total dose of 2 g/kg divided over 2 days. *Maintenance dose*: A systematic approach should be taken to determine minimum effective dose.Continued use should be based on objective measures of sustained effectiveness. Maximum dose should not exceed 2 g/kg.
Kawasaki Disease (KD)	2 g/kg for 1 day (second dose can be given for patients that fail to respond to initial dose).
Idiopathic Inflammatory Myopathy (IIM) Includes Dermatomyositis and Polymyositis * does not include Inclusion Body Myositis	Maximum dose is 2 g/kg to be given over 2 days initially monthly for 3-6 months and if effective to be continued at decreasing frequency (determine minimum effective dose) over approximately 2 years.Survival of patients with IIM has been shown to be substantially improved in patients given IVIG.
Primary Immune Deficiency (PID) Secondary Immune Deficiency (SID)	*Adult*: 0.4-0.6 g/kg every 3-4 weeks *Pediatric*: 0.3-0.6 g/kg every 3-4 weeks Doses or frequency to be adjusted by experts according to desired trough level (more than 500 mg/dL and ideally 700 mg/dL) and according to individual patient clinical needs.
Hematopoietic Stem Cell Transplant in primary immunodeficiency	0.4-0.6 g/kg every 3-4 weeks; requirements may increase and should be based on clinical outcome.
Kidney transplant from living donor to whom the patient is sensitized	2 g/kg/month for 4 months.
Pre-transplant (Heart)	Suggested dose up to 1 g/kg/month until transplant.
Peri-transplant (heart, lung, kidney, pancreas)	Suggested dose 1 g/kg can give as divided doses if in association with a course of plasmapheresis.
Post-transplant	*Acute*: 1 g/kg/dose. Can be given as divided doses if in association with a course of plasmapheresis. *Chronic:* 1 g/kg/month.
Invasive Group A streptococcal fasciitis with associated toxic shock	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 for 5 days .
Staphylococcal Toxic Shock	

*** Refer to Ontario IVIG Management Utilization Guidelines for additional indications where IG may be appropriate.**
If you are unsure of the process for IG requests please refer to Ordering IG in Ontario

Ontario

MOHLTC IG Request Form

For Neurology Use Only

Patient Name:
Patient Hospital/Medical Record#:
Patient DOB (YYYY/MM/DD):
Gender M/F:
Location:
Ontario Health Insurance#:

ALL FIELDS BELOW ARE MANDATORY

SECTION A: Physician & Hospital Information

Date of Request (YYYY/MM/DD)	Date Required (YYYY/MM/DD)	Hospital Transfusion Service (HTS) Fax Number
Name of Ordering Physician	Physician's Contact Phone Number	Physician's Email
Is the patient being seen by a Neurologist/ Neuromuscular Specialist? ☐ Yes ☐ No	Is the request for a hospital inpatient? ☐ Yes ☐ No	Hospital where patient will receive IG

SECTION B: Request Type

☐ Initial Request: Maximum 6 month approval	☐ Renewal Request: A reassessment should be done to confirm IG treatment continues to be effective and that minimum effective dose is being applied. Maximum 12 month approval.

SECTION C: Clinical Indication

Refer to Ontario IG Management Utilization Guidelines for additional indications where IG may be appropriate

Approved Condition	Guidelines for INITIAL Request	Guidelines for RENEWAL Request
☐ Guillain–Barré Syndrome (GBS) including Miller Fisher Syndrome and other variants	▪ IG recommended for Grade 3 severity (able to walk with aid) or greater; or less than Grade 3 severity that are progressing. ▪ IG should be given within 2 weeks of symptom onset. ▪ Adult: Total Dose of 2 g/kg divided over 2 to 5 days. ▪ Pediatric: Total Dose of 2 g/kg divided over 2 days.	▪ IG treatment for GBS is typically one-time/in the acute setting. ▪ Re-treatment for patients who do not respond may be considered. Repeat treatment with IVIG at 2g/kg divided over 2-5 days.
☐ Myasthenia Gravis (MG)	▪ IG is recommended as first-line treatment in moderate-severe MG or in myasthenic crisis. ▪ Induction Dose: 2g/kg divided over 2-5 days. ▪ Initial requests may be made for induction plus two maintenance doses; fill out Section D accordingly.	▪ IG in combinations with immunosuppressive therapy can be considered in refractory cases. If additional IG is required, dose should be adjusted depending upon response and titrated to the minimum effective dose. ▪ Maintenance Dose: 1g/kg
☐ Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)	▪ IG is recommended as first-line therapy in CIDP. ▪ Induction Dose: 2 g/kg divided over 2 to 5 days. ▪ All patients receiving IG for chronic treatment of CIDP should be followed by a neuromuscular specialist.	▪ Immunosuppressive therapy in combination with IG can be considered in refractory cases. Continued use should be based on objective measures of sustained effectiveness. Aim for minimum effective dose. ▪ Maintenance Dose: 1g/kg every 3 weeks.
☐ Multifocal Motor Neuropathy (MMN)	▪ IG is recommended as first-line treatment for MMN. ▪ Induction Dose: 2g/kg divided over 2-5 days.	▪ Maintenance Dose: Tailor to the lowest dose that maintains clinical efficacy, usually 1g/kg or less per treatment course. Some patients may require higher doses for efficacy, up to 2g/kg every 4 weeks.

Other (please specify the diagnosis): _____

These requests will require screening by Transfusion Service. Please include information regarding treatment to date and documentation to support IG treatment for an unapproved indication.

Has the patient used other therapies to treat this condition? ☐ Yes, specify other treatments below ☐ No

Treatment	Dose (if applicable)	Duration of treatment	What was the outcome?
			☐ No response ☐ Contraindications ☐ Intolerance
			☐ No response ☐ Contraindications ☐ Intolerance

Other Comments: (include notes regarding response to IG therapy)

SECTION D: Dosage Information (Verification of dose using Dose Calculator tool is recommended. Refer to http://ivig.transfusionontario.org/dose/)

☐ Intravenous IG (IVIG) ☐ Subcutaneous IG (SCIG)

Patient Weight: kg Patient Height: cm BMI: **Dose must be adjusted for BMI greater than or equal to 30**

Induction/One-time dose	g/kg = Total dose of	g; divided over	days			
Maintenance dose	g/kg = Total dose of	g; divided over	days; every	weeks; Duration:	months	

Dose Calculator Used? ☐ Yes ☐ No If No, why was it not used?

SECTION E: For Transfusion Medicine Use Only

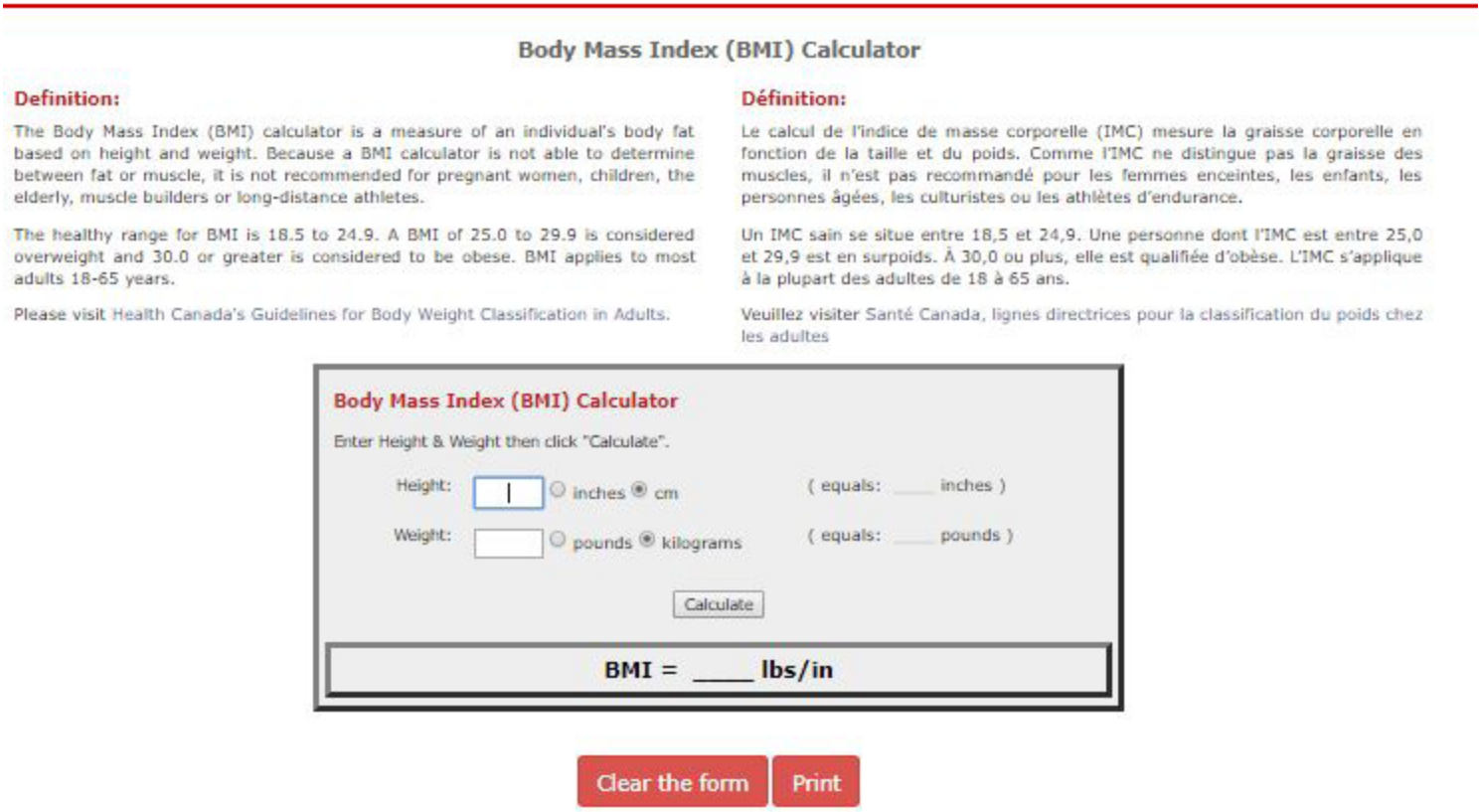
☐ Dose verified ☐ Dose adjusted to:	By (signature req'd):
☐ Confirmed with ordering physician	Date:
☐ Approved ☐ Denied	
Signature of Approving Physician or designate:	Date:

Please fax/send to :

Dosing Using Adjusted Body Weight

IG therapy has been used for many years to treat both primary immune deficiency patients and patients with several autoimmune disorders. While its usefulness in treatment cannot be denied, caregivers need to remember IG must be used with caution. One issue of particular concern is the proper dosage of product, especially in the obese patient.

According to Statistics Canada's published data for 2005, the rate of Canadians in the obese category (body mass index BMI higher than 30 kg/m^2) has almost doubled between 1978 and 2005, rising from 13.8% to 24.3% of the adult population, almost 1 in 4 individuals. In 2005, the number of obese Canadians 18 or older was 5.5 million; 36% of the adult population was considered overweight. We have provided a BMI calculator http://transfusionontario.org/en/download/bmi-dose-calculator/ to help determine your patients BMI.



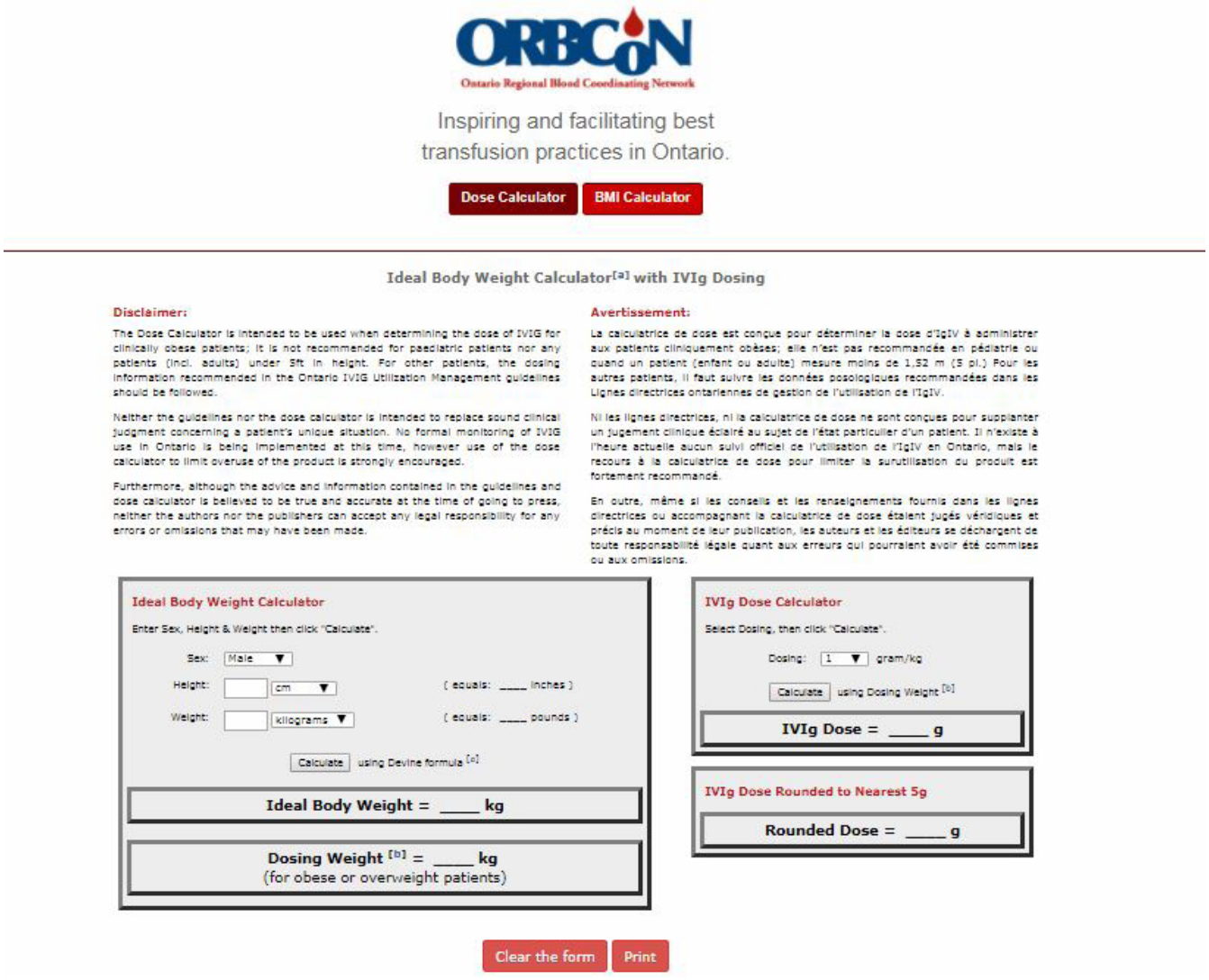
Dosing Using Adjusted Body Weight

The dose of IVIG administered varies depending on the clinical indication In the case of obese patients. The appropriate dosing regimen is unclear. There is some agreement in the literature that IVIG should be dosed using actual body weight in patients weighing up to 100 kg, with a BMI less than 30 kg/m 2. In contrast, obese patients should have IVIG dosing calculated using an adjusted body weight to account for the increase in volume of distribution (Vd) without accounting for the increase in fat.

Adverse reactions due to IVIG are substantially more likely to happen when a high dose of the product is infused Adverse reactions are summarized in the Adverse Reactions Chart for IVIG Infusion. http://transfusionontario.org/en/download/ontario-ivig-infusion-guide-adverse-reaction-chart/.

There are jurisdictions in Canada, the United States and abroad where the use of a dose calculator is either in place and recommended, or is in the works for future implementation.

See "Ontario IVIG Strategy Update Nov 2015" for the policy statement on use of a mechanism to adjust doses for obese patients. A link to a Dose Calculator tool is available on the Transfusion Ontario website: http://transfusionontario.org/en/download/bmi-dose-calculator/.



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Relevant Sources of Information

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IVIG (Intravenous Immune Globulin) Infusion Guide and Adverse Reaction Chart for Ontario

Purpose

- This document provides health care practitioners involved in the infusion of IVIG with evidence informed, best practice guidance.
- The information can be incorporated into hospital specific policies and procedures.
- The material is limited to IVIG infusion and *is not applicable to infusion of subcutaneous immune globulin*.

Possible IVIG Shortage

- The growing demand for IG leaves the global supply limited. Canadian Blood Services communicated with all manufacturers to obtain additional IVIG. The global situation is ever changing; an IVIG shortage may occur.
- In Canada at least until spring 2022, some vial sizes and some IVIG brands will be in short supply.
- Patient Care Implications:
    - To administer the ordered dose, vial sizes may be substituted (e.g., for a 40 g dose, two 20 g or four 10 g vials may be issued).
    - Some patients will need to change to another IVIG brand.
    - The first infusion of each brand of IVIG must be given at a slower rate.
      For patients receiving chronic IVIG treatment, if changed to a different brand, infusion time and thus their clinic appointment will be longer.

General Principles

- Refer to hospital specific policies/procedures.
- Documented IVIG clinical indication and dose (g/kg) must align with Ontario IG Utilization Management Guidelines or be approved by your hospital's Transfusion Medicine Medical Director.
- As appropriate, the Dose Calculator is used to calculate the patient's dosing weight and IVIG dose.
  Dose Calculator:
    - Is referenced from the Pharmacy perspective, for prescribing when actual body weight should be adjusted in the dose calculation
    - Is NOT recommended for pediatric patients
    - Is NOT recommended for patients less than 5 feet (152.4 cm) in height
    - Is recommended for clinically obese or overweight adult patients
    - Requires the patient's height and weight to be entered
    - Calculates the patient's *ideal body weight (IBW)* based on the Devine formula
      males = 50.0 kg + 2.3 kg (each inch > 5 feet)
      females = 45.5 kg + 2.3 kg (each inch > 5 feet)
    - Calculates the dosing weight based on the patient's actual weight and *IBW*
      dosing weight = *IBW* + [0.4 x (actual weight - *IBW*)]
      Exception - if patient's actual weight is less than *IBW*,
      then dosing weight = actual weight

  - Uses dosing weight to calculate IVIG dose
  - Rounds the calculated IVIG dose to the nearest 5 g dose
  - Is used in some hospitals for calculating IVIG dose for all adult patients with height of 5 feet (152.4 cm) or greater (high dose IVIG is associated with adverse effects)
- If patient reports significant weight change, re-assess IVIG dose.
- For chronic disease IVIG indications, objective measures of the effectiveness of IVIG should be determined at the onset of treatment. Assess these measures 6 months after initiation of treatment. Subsequently, re-assessment should be annually at minimum. IVIG should be discontinued if clinical effectiveness is not demonstrated.
- For chronic disease IVIG indications when the patient has stabilized, titrating dose and/or treatment interval to the lowest dose and/or greatest interval needed to provide clinical effectiveness should be considered.
- Caution (also refer to Appendix B IVIG Adverse Reaction Chart):
  - IVIG has been associated with renal dysfunction, osmotic nephrosis, and acute renal failure. For patients with renal insufficiency or at risk of developing renal dysfunction (i.e., pre-existing renal insufficiency, diabetes mellitus, hypertension, age greater than 64 years, volume depletion, sepsis, paraproteinemia, or receiving known nephrotoxic drugs), administer IVIG at a slow rate of infusion, the patient should be well hydrated (additional PO fluids several hours prior to and following IVIG or IV pre-hydration) and monitored closely.
  - IVIG has been associated with thromboembolic events (i.e., deep vein thrombosis, myocardial infarction, pulmonary embolism, stroke, transient ischemic attack). Assess patients for risk factors for thrombotic events. IVIG should be administered at a slow rate of infusion, the patient should be well hydrated (additional PO fluids several hours prior to and following IVIG or IV pre-hydration) and monitored closely.
  - Administer IVIG at the slowest infusion rate feasible.
  - Hemolysis/hemolytic anemia have been reported post IVIG administration. Monitor patients for clinical signs and symptoms of hemolysis.
  - Patients with severe immunoglobulin A (IgA) deficiency (serum IgA less then 0.05 g/L), with known anti-IgA antibodies [assess if IVIG benefits outweigh risks; Gammagard S/D - lowest IgA (2.2 micrograms/mL) content].
  - For diabetic patients, some IVIG brands contain sugars that may interfere with test results of some glucose monitoring devices (refer to product monograph and manufacturer of the glucose monitoring device).
  - IVIG administration may temporarily impact the efficacy of live attenuated virus vaccines (i.e., measles, mumps, rubella, and varicella/chickenpox) for 6 weeks to 3 months. Notify prescriber if vaccination is planned within this timeframe post IVIG administration.
  - IVIG is manufactured from human plasma (plasma is pooled from thousands of healthy donors). The manufacturing procedures and donor screening steps reduce the risk of transmission of infectious pathogens, however potential risk of transmission cannot be entirely excluded.
- All IVIG brands are equivalent in terms of clinical effectiveness (even though there are slight differences in licensed indications/medical conditions).
- Adverse reactions occur with all IVIG brands. Canadian data has not found a difference in rates of adverse reactions between brands.
- An adverse reaction may be more likely when receiving IVIG for the first time, when changing to another IVIG brand, when there is a prolonged time (more than 8 weeks) since the previous infusion, with high doses of IVIG, with rapid infusion rates and if the patient is not well hydrated.
- Suggestions to mitigate recurrent adverse reactions (refer to Appendix B: IVIG Adverse Reaction Chart):
  - Divide the infusion of high doses (greater than 1g/kg) over more than 1 day

  - Slow infusion rate
  - Pre-hydration
  - Premedication
- Some patients may have an adverse reaction to a certain IVIG lot number or brand but will tolerate a different IVIG lot number or IVIG brand.

Pre-Infusion

- Validate IVIG clinical indication and dose (confirm details of prescriber's order).
- Verify informed consent for transfusion has been obtained and is valid based on hospital specific policy.
- Prior to first IVIG infusion
  - Record allergies, medications, and baseline height and weight.
  - Review history for previous IVIG treatment; if previously received IVIG, any history of adverse reactions to IVIG or to other blood components (history of anaphylaxis, anti-IgA antibodies).
  - As per prescriber, baseline blood work:
    - ABO blood group
    - Hemoglobin (IVIG contains anti-A and anti-B antibodies; non-O blood group patients treated with IVIG may develop hemolysis, especially if given high dose IVIG)
    - Kidney function tests.
    - Additionally, as patient's clinical status and IG indication infer (e.g., liver function tests, platelet count, serum IgG level).
- Assess patient for TACO (Transfusion Associated Circulatory Overload) risk factors (advanced age, history of heart failure or myocardial infarction, left ventricular dysfunction, renal dysfunction, positive fluid balance). If risk identified, review with prescriber for prevention strategies (slow infusion rate, pre-infusion diuretic, divide infusion of high doses/high volumes over more than 1 day).
- As per prescriber, interval bloodwork to monitor IG treatment (e.g., hemoglobin, kidney and liver function tests, platelet count, serum IgG level).
- All patients should be well hydrated before and after IVIG treatments, especially patients with or at risk for renal dysfunction (pre-hydration reduces possible nephrotoxic effects of IVIG protein molecules and stabilizers).
- Anaphylaxis precautions, ensure readily available:
  - Rescue IV line [5% dextrose in water (D5W) or 0.9 % sodium chloride (NaCl)].
  - Epinephrine (as well as IV steroid and antihistamine).
- As per the manufacturers' direction, IVIG should be allowed to reach room temperature prior to infusion.

IVIG (Intravenous Immune Globulin) Infusion Guide and Adverse Reaction Chart for Ontario

Infusion

- Prescriber or their delegate must be readily available (on pager or as per hospital policy) during IVIG treatment.
- Follow hospital specific policy for checking blood products [patient identification (must be wearing armband; check surname, first name and unique identification number), lot number, visual inspection, and expiry time].
- Visual inspection: bottle seal intact, product appears as clear or slightly opalescent solution that is colourless to pale yellow in colour.
  If seal is broken or if solution appears turbid, cloudy, or having deposits, do not infuse and follow up with Transfusion Medicine Laboratory (TML).
- Expiry time: Manufacturer's expiry date is noted on packaging.
  Infusion of each bottle must be completed within 4 hours from time the bottle's seal was punctured; otherwise discard any remainder.
- DO NOT infuse different IVIG brands during a single infusion (Exception: Gamunex and IGIVnex).
- Begin infusion with smallest bottle size and end with largest bottle size of the bottles issued for the dose ordered (to minimize wastage in the event of a reaction).
- Requires dedicated IV line (IV site or lumen of a mulit-lumen catheter).
- Can be flushed with 5% dextrose in water (D5W) or 0.9 % sodium chloride (NaCl) for injection (exception: Gammagard S/D – only D5W).
- Do not mix with any other medications.
- Do not dilute IVIG.
- Use aseptic technique when handling IVIG.
- Administer with standard vented IV tubing (to allow filtered air to enter the bottle). An in-line filter is not required (exception: Gammagard S/D – filter for the reconstituted product included in packaging).
- One standard vented IV tubing set can be used for each IVIG treatment (maximum time 24 hours) or as specified by the tubing manufacturer.
- To minimize bubbling of IVIG:
  - Allow the IVIG to come to room temperature.
  - Do not shake the IVIG.
  - Place IVIG bottle on a flat surface, insert the spike of the vented IV tubing set at a 90° angle through the centre circle of the stopper. Invert and hang the bottle on the IV pole, squeeze the drip chamber to ½ full, then open the drip chamber vent and roller clamp.
  - Prior to spiking each bottle, close the roller clamp and ensure the drip chamber vent of the vented IV tubing set is also closed.
- For added patient safety, administration using a Health Canada approved infusion pump is suggested to set the infusion rate precisely and allow for greater patient mobility.
- <u>Infusion Rate:</u> Refer to Appendix A: IVIG Brands Infusion Rate Tables
  - Confirm per prescriber's order and hospital specific policies.
  - Review General Guidance information.
  - Select the Infusion Rate Table specific to the IVIG brand being infused and then select the patient's weight column (round down).
  - Select the corresponding suggested infusion rates and the maximum rate remainder of infusion appropriate for the incidence of this IVIG infusion and the patient's clinical status as detailed.

  - For patient safety, comply with each brand's suggested guidance for infusion rate.
- Subsequent bottles, with same or different lot numbers do not require returning to the starting infusion rate.
- Patient assessment and vital signs, at minimum:
  - Within 30 minutes prior to the start of the infusion
  - 15 minutes after of start of the infusion
  - After each rate increase, then hourly until the infusion is completed
  - On completion of the infusion
  - For inpatients, 1 hour following completion of the infusion
  - For outpatients, prior to discharge
  - If clinically indicated, or when a reaction is suspected
- Patient Education (side-effects are not uncommon, some symptoms may occur up to 72 hours post infusion; hemolysis signs/symptoms may occur up to ten days after infusion)

  Advise patient to report:
  - Chills/rigors
  - Diarrhea
  - Eye pain
  - Facial or tongue swelling
  - Fatigue
  - Fever
  - Flushing
  - Headache (often mild, rarely severe)
  - Heart racing/palpitations
  - Hives, rash, itching
  - Myalgias (muscle aches and pains)
  - Nausea
  - Neck stiffness
  - Pain – back, chest, abdomen (cramping)
  - Photophobia (light sensitivity)
  - Shortness of breath
  - Urine colour change to red/brown or tea coloured
  - Vomiting
  - Yellow skin or eye colour
- If an infusion reaction is suspected, refer to Appendix B: IVIG Adverse Reaction Chart

Post-Infusion

- Document as per TML/hospital policy:
  - Complete infusion chart label/tag (includes IVIG brand, dose, and lot numbers; add date and infusion start time and stop time)
  - Record volume infused
  - Patient assessments and vital signs
- Return any IVIG (intact bottles) not infused to TML. Discard empty IVIG bottles and tubing in biohazardous waste.
- For IVIG infused in an outpatient setting
  - Monitor patient for 30 minutes post infusion for potential side effects.
  - At discharge, provide instructions (e.g., IVIG Facts for Outpatients).
  - Specify contact information for follow up if any patient concerns or symptoms arise post discharge.

Appendix A: IVIG Brands Infusion Rate Tables

General Guidance IVIG Brands Infusion Rate Tables (Patients weighing 30 to 125 kg)

- Refer to hospital specific policies/procedures.
- For each IVIG brand, based on patient's weight, the table includes suggested starting rate, suggested subsequent rate increase intervals, and considerations for maximum rate remainder of infusion.
  NOTE:
  All IVIG brand monographs designate infusion starting rate, maximum rate for specific patient clinical factors, and a recommended maximum rate. As well, all IVIG brand monographs specify that if well tolerated, the rate of infusion may gradually be increased to the recommended maximum. The following tables reflect suggested gradual increases for the rate of infusion (specific hospital policies/procedures may include alternative gradual increases for the rate of infusion).
- If patient's weight is between 2 increments, round down and administer at the hourly rates for the rounded down category.
- For patients weighing less than 30 kg (pediatric and neonates), suggest calculating hourly infusion rates with patient specific weight.
  Formula: Rate (mL/kg/hr) x Weight (kg) = Hourly infusion rate (mL/hr). Perform double check of all calculations as per hospital specific policy.
- For each IVIG infusion, select maximum rate remainder of infusion as appropriate for the incidence of this IVIG infusion and the patient's clinical status.
- Patients at risk of renal dysfunction or thrombotic events: for maximum rate remainder of infusion, administer at the minimum infusion rate feasible.
- Infusion rate can be ordered at a decreased rate at the discretion of the prescriber.
- Some hospitals may specify a maximum mL/hr infusion rate regardless of patient weight (e.g., maximum infusion rate of 250 mL/hr).
- For patients tolerating chronic IVIG treatment, prescriber may order a patient specific treatment plan, excluding some interval infusion rates and increased infusion rates (absolute maximum infusion rate as per manufacturer's recommendations).
- Assess the patient (document vital signs) at each rate change.
- Slower infusion rates will ease rate related adverse reactions (symptoms: headache, flushing, chills).
- As per hospital specific policy, it may be appropriate for nursing staff to notify the prescriber and resume the infusion at a previously tolerated rate if the patient's rate related symptoms resolve with stopping the IVIG infusion.
- All IVIG adverse reactions must be documented and reported to TML.
- Refer to Appendix B IVIG Adverse Reactions Chart for additional strategies to mitigate rate related symptoms.

IVIG (Intravenous Immune Globulin) Infusion Guide and Adverse Reaction Chart for Ontario

*Gammagard Liquid® Infusion Rate Table (mL/hr)																				
Infusion Rate Increments		**Patient Weight in kg.**																		
		30	**35**	**40**	**45**	**50**	**55**	**60**	**65**	**70**	**75**	**80**	**85**	**90**	**95**	**100**	**105**	**110**	**115**	**120**	**125**
Starting Rate for first 30 minutes	**0.5 mL/kg/hr**	15	18	20	23	25	28	30	33	35	38	40	43	45	48	50	53	55	58	60	63
Rate next 15 - 30 minutes	**1.2 mL/kg/hr**	36	42	48	54	60	66	72	78	84	90	96	102	108	114	120	126	132	138	144	150
Rate next 15 - 30 minutes	**2.4 mL/kg/hr**	72	84	96	108	120	132	144	156	168	180	192	204	216	228	240	252	264	276	288	300
Maximum Rate Remainder of Infusion Receiving IgG for the first time; or Had been receiving another IgG brand; or Have not received IgG in more than 8 weeks	**4.8 mL/kg/hr**	144	168	192	216	240	264	288	312	336	360	384	408	432	456	480	504	528	552	576	600
Maximum Rate Remainder of Infusion For patients judged to be at increased risk for developing renal dysfunction	**2.0 mL/kg/hr**	60	70	80	90	100	110	120	130	140	150	160	170	180	190	200	210	220	230	240	250
Maximum Rate Remainder of Infusion Indication: Multifocal Motor Neuropathy (MMN)	**5.4 mL/kg/hr**	162	189	216	243	270	297	324	351	378	405	432	459	486	513	540	567	594	621	648	675
Maximum Rate Remainder of Infusion Following first infusion of this brand, next 3 consecutive infusions	**7.2 mL/kg/hr**	216	252	288	324	360	396	432	468	504	540	576	612	648	684	720	756	792	828	864	900
Maximum Rate Remainder of Infusion Per manufacturer's recommended maximum	**8.0 mL/kg/hr**	240	280	320	360	400	440	480	520	560	600	640	680	720	760	800	840	880	920	960	1000
Gammagard Liquid® monograph		* Requires dedicated IV line; can be flushed with 5% dextrose in water (D5W) or 0.9 % sodium chloride (NaCl) Contains glycine (an amino acid) as stabilizer (does not contain sucrose)																		

IVIG (Intravenous Immune Globulin) Infusion Guide and Adverse Reaction Chart for Ontario

*Gammagard S/D® 5 % solution Infusion Rate Table (mL/hr)

Infusion Rate Increments		Patient Weight in kg.																			
		30	**35**	**40**	**45**	**50**	**55**	**60**	**65**	**70**	**75**	**80**	**85**	**90**	**95**	**100**	**105**	**110**	**115**	**120**	**125**
Starting Rate for first 30 minutes	**0.5 mL/kg/hr**	15	18	20	23	25	28	30	33	35	38	40	43	45	48	50	53	55	58	60	63
Rate next 15 - 30 minutes	**1.0 mL/kg/hr**	30	35	40	45	50	55	60	65	70	75	80	85	90	95	100	105	110	115	120	125
Rate next 15 - 30 minutes	**2.0 mL/kg/hr**	60	70	80	90	100	110	120	130	140	150	160	170	180	190	200	210	220	230	240	250
Maximum Rate Remainder of Infusion **Receiving IgG for the first time; or Had been receiving another IgG brand; or Have not received IgG in more than 8 weeks**	**3.0 mL/kg/hr**	90	105	120	135	150	165	180	195	210	225	240	255	270	285	300	315	330	345	360	375
Maximum Rate Remainder of Infusion **For patients judged to be at increased risk for developing renal dysfunction**	**3.0 mL/kg/hr**	90	105	120	135	150	165	180	195	210	225	240	255	270	285	300	315	330	345	360	375
Maximum Rate Remainder of Infusion Following first infusion of this brand, next 3 consecutive infusions	**3.0 mL/kg/hr**	90	105	120	135	150	165	180	195	210	225	240	255	270	285	300	315	330	345	360	375
Maximum Rate Remainder of Infusion **Per manufacturer's recommended maximum**	**4.0 mL/kg/hr**	120	140	160	180	200	220	240	260	280	300	320	340	360	380	400	420	440	460	480	500
Gammagard S/D® monograph		* Requires dedicated IV line; can be flushed with 5% dextrose in water (D5W). * **Infuse with the administration set provided in the packaging** (the required filter is included) Gammagard S/D® (S/D = solvent detergent treated) is a freeze-dried concentrate form of IVIG. It is reconstituted (diluent, sterile water for injection is included in the packaging), usually as a 5% solution. Refer to the product monograph for detailed information (can also be reconstituted to a 10 % solution). Gammagard S/D contains only trace amounts of IgA (≤ 2.2 micrograms/mL in a 5% solution). Contains albumin, glycine (an amino acid) and glucose as stabilizers (does not contain sucrose)																			

IVIG (Intravenous Immune Globulin) Infusion Guide and Adverse Reaction Chart for Ontario

*Gamunex® / *IGIVnex® Infusion Rate Table (mL/hr)																				
Infusion Rate Increments		**Patient weight in kg.**																		
		30	**35**	**40**	**45**	**50**	**55**	**60**	**65**	**70**	**75**	**80**	**85**	**90**	**95**	**100**	**105**	**110**	**115**	**120**	**125**
Starting Rate for first 30 minutes	**0.6 mL/kg/hr**	18	21	24	27	30	33	36	39	42	45	48	51	54	57	60	63	66	69	72	75
Rate next 15 - 30 minutes	**1.2 mL/kg/hr**	36	42	48	54	60	66	72	78	84	90	96	102	108	114	120	126	132	138	144	150
Rate next 15 - 30 minutes	**2.4 mL/kg/hr**	72	84	96	108	120	132	144	156	168	180	192	204	216	228	240	252	264	276	288	300
Maximum Rate Remainder of Infusion **Receiving IgG for the first time; or Had been receiving another IgG brand; or Have not received IgG in more than 8 weeks**	**4.8 mL/kg/hr**	144	168	192	216	240	264	288	312	336	360	384	408	432	456	480	504	528	552	576	600
Maximum Rate Remainder of Infusion **For patients judged to be at increased risk for developing renal dysfunction**	**4.8 mL/kg/hr**	144	168	192	216	240	264	288	312	336	360	384	408	432	456	480	504	528	552	576	600
Maximum Rate Remainder of Infusion **Following first infusion of this brand, next 3 consecutive infusions**	**7.2 mL/kg/hr**	216	252	288	324	360	396	432	468	504	540	576	612	648	684	720	756	792	828	864	900
Maximum Rate Remainder of Infusion **Per manufacturer's recommended maximum**	**8.4 mL/kg/hr**	252	294	336	378	420	462	504	546	588	630	672	714	756	798	840	882	924	966	1008	1050
Gamunex® monograph IGIVnex® monograph		* Requires dedicated IV line; can be flushed with 5% dextrose in water (D5W) or 0.9 % sodium chloride (NaCl) Contains glycine (an amino acid) as stabilizer (does not contain sucrose)																		

IVIG (Intravenous Immune Globulin) Infusion Guide and Adverse Reaction Chart for Ontario

*Octagam® Infusion Rate Table (mL/hr)																				
Infusion Rate Increments		**Patient Weight in kg.**																		
		30	**35**	**40**	**45**	**50**	**55**	**60**	**65**	**70**	**75**	**80**	**85**	**90**	**95**	**100**	**105**	**110**	**115**	**120**	**125**
Starting Rate for first 30 minutes	**0.6 mL/kg/hr**	18	21	24	27	30	33	36	39	42	45	48	51	54	57	60	63	66	69	72	75
Rate next 15 - 30 minutes	**1.2 mL/kg/hr**	36	42	48	54	60	66	72	78	84	90	96	102	108	114	120	126	132	138	144	150
Rate next 15 - 30 minutes	**2.4 mL/kg/hr**	72	84	96	108	120	132	144	156	168	180	192	204	216	228	240	252	264	276	288	300
Maximum Rate Remainder of Infusion **Receiving IgG for the first time; or Had been receiving another IgG brand; or Have not received IgG in more than 8 weeks**	**4.8 mL/kg/hr**	144	168	192	216	240	264	288	312	336	360	384	408	432	456	480	504	528	552	576	600
Maximum Rate Remainder of Infusion Following first infusion of this brand, next 3 consecutive infusions	**6.0 mL/kg/hr**	180	210	240	270	300	330	360	390	420	450	480	510	540	570	600	630	660	690	720	750
Maximum Rate Remainder of Infusion **Per manufacturer's recommended maximum**	**7.2 mL/kg/hr**	216	252	288	324	360	396	432	468	504	540	576	612	648	684	720	756	792	828	864	900
Octagam® monograph		* Requires dedicated IV line; can be flushed with 5% dextrose in water (D5W) or 0.9 % sodium chloride (NaCl) Contains maltose as a stabilizer (does not contain sucrose)																		

IVIG (Intravenous Immune Globulin) Infusion Guide and Adverse Reaction Chart for Ontario

*Panzyga® Infusion Rate Table (mL/hr)																				
Infusion Rate Increments		**Patient Weight in kg.**																		
		30	**35**	**40**	**45**	**50**	**55**	**60**	**65**	**70**	**75**	**80**	**85**	**90**	**95**	**100**	**105**	**110**	**115**	**120**	**125**
Starting Rate for first 30 minutes	**0.6 mL/kg/hr**	18	21	24	27	30	33	36	39	42	45	48	51	54	57	60	63	66	69	72	75
Rate next 15 - 30 minutes	**1.2 mL/kg/hr**	36	42	48	54	60	66	72	78	84	90	96	102	108	114	120	126	132	138	144	150
Rate next 15 - 30 minutes	**2.4 mL/kg/hr**	72	84	96	108	120	132	144	156	168	180	192	204	216	228	240	252	264	276	288	300
Maximum Rate Remainder of Infusion **Receiving IgG for the first time; or Had been receiving another IgG brand; or Have not received IgG in more than 8 weeks**	**4.8 mL/kg/hr**	144	168	192	216	240	264	288	312	336	360	384	408	432	456	480	504	528	552	576	600
Maximum Rate Remainder of Infusion **Indication: Chronic Immune Thrombocytopenic Purpura (ITP)**	**4.8 mL/kg/hr**	144	168	192	216	240	264	288	312	336	360	384	408	432	456	480	504	528	552	576	600
Maximum Rate Remainder of Infusion **Following first infusion of this brand, next 3 consecutive infusions**	**6.0 mL/kg/hr**	180	210	240	270	300	330	360	390	420	450	480	510	540	570	600	630	660	690	720	750
Maximum Rate Remainder of Infusion **Per manufacturer's recommended maximum**	**8.4 mL/kg/hr**	252	294	336	378	420	462	504	546	588	630	672	714	756	798	840	882	924	966	1008	1050
Panzyga® monograph		* Requires dedicated IV line; can be flushed with 5% dextrose in water (D5W) or 0.9 % sodium chloride (NaCl) Contains glycine (an amino acid) as stabilizer (does not contain sucrose)																		

IVIG (Intravenous Immune Globulin) Infusion Guide and Adverse Reaction Chart for Ontario

*Privigen® Infusion Rate Table (mL/hr)																				
Infusion Rate Increments		**Patient Weight in kg.**																		
		30	**35**	**40**	**45**	**50**	**55**	**60**	**65**	**70**	**75**	**80**	**85**	**90**	**95**	**100**	**105**	**110**	**115**	**120**	**125**
Starting Rate for first 30 minutes	**0.3 mL/kg/hr**	9	11	12	14	15	17	18	20	21	23	24	26	27	29	30	32	33	35	36	38
Rate next 15 - 30 minutes	**1.0 mL/kg/hr**	30	35	40	45	50	55	60	65	70	75	80	85	90	95	100	105	110	115	120	125
Rate next 15 - 30 minutes	**2.0 mL/kg/hr**	60	70	80	90	100	110	120	130	140	150	160	170	180	190	200	210	220	230	240	250
Maximum Rate Remainder of Infusion Receiving IgG for the first time; or Had been receiving another IgG brand; or Have not received IgG in more than 8 weeks	**2.4 mL/kg/hr**	72	84	96	108	120	132	144	156	168	180	192	204	216	228	240	252	264	276	288	300
Maximum Rate Remainder of Infusion If high dose i.e., ≥ 1g/kg	**4.8 mL/kg/hr**	144	168	192	216	240	264	288	312	336	360	384	408	432	456	480	504	528	552	576	600
Maximum Rate Remainder of Infusion Following first infusion of this brand, next 3 consecutive infusions	**6.0 mL/kg/hr**	180	210	240	270	300	330	360	390	420	450	480	510	540	570	600	630	660	690	720	750
Maximum Rate Remainder of Infusion Per manufacturer's recommended maximum	**7.2 mL/kg/hr**	216	252	288	324	360	396	432	468	504	540	576	612	648	684	720	756	792	828	864	900
Privigen® monograph		* Requires dedicated IV line; can be flushed with 5% dextrose in water (D5W) or 0.9 % sodium chloride (NaCl) Contains L- proline as stabilizer (does not contain sucrose)																		

IVIG (Intravenous Immune Globulin) Infusion Guide and Adverse Reaction Chart for Ontario

Appendix B: IVIG Adverse Reaction Chart (refer to hospital specific policies/procedures)

Immediate Actions if an adverse reaction is suspected:

1. **STOP** the transfusion
2. Maintain **IV access**
3. Check **vital signs**
4. Verify **patient identification** matches transfusion label/tag
5. Notify **prescriber**
6. **Patient care** as ordered; for every reaction **report to TML; document**

Signs & Symptoms	Possible Etiology	Suggested Treatment & Actions; Strategies to Mitigate
Mild Reactions		
Chills/rigors, fever*, flushing, malaise, myalgia, nausea (during or up to 24 hours post-IVIG)	**Febrile non-hemolytic reaction**	○ Hold the infusion ○ As per prescriber administer antipyretic, analgesic, antihistamine, or non-steroid anti-inflammatory medication (if appropriate for patient [caution elderly, decreased renal function]) ○ As ordered, resume infusion at slow infusion rate ○ If recurrent, consider: - Divide high dose (> 1g/kg) infusions over 2 to 5 days - Longer rate increase intervals and slow maximum rate remainder of infusion - Pre-hydration (as per patient clinical status, additional PO fluids several hours prior to and following IVIG or 500 to 1000 mL 0.9 % sodium chloride IV prior to IVIG infusion) - Premedication with anti-pyretic, analgesic, or non-steroid anti-inflammatory medication - If history of migraines, premedicate with anti-migraine medication - If persistently recurrent, change brand of IVIG
Headache Migraine headache can be triggered in patients with history of migraines (during or up to 72 hours post-IVIG)	**IVIG headache** Most common IVIG reaction	
Itchiness, rash, urticaria (less than 2/3 of body surface), nausea/vomiting, pain - abdominal (during or up to 4 hours post-IVIG)	**Minor allergic reaction**	○ Hold the infusion ○ As per prescriber administer antihistamine, may require steroid if symptoms slow to resolve ○ If symptoms resolve and product viable, as ordered cautiously resume infusion ○ If recurrent, consider - Premedication with antihistamine or steroid - If persistently recurrent, change brand of IVIG

IVIG (Intravenous Immune Globulin) Infusion Guide and Adverse Reaction Chart for Ontario

Signs & Symptoms	Possible Etiology	Suggested Treatment & Actions; Strategies to Mitigate
Moderate to Severe Reactions		
Airway edema, dyspnea, decreased oxygen saturation, facial and/or tongue swelling, hypotension, itching, nausea/vomiting, rash, tachycardia, urticaria (during or up to 4 hours post-IVIG)	**Anaphylaxis/ Anaphylactoid**	○ DO NOT resume infusion ○ Epinephrine ○ Also consider steroid, antihistamine as per prescriber ○ Supportive care per prescriber's discretion: oxygen, respiratory support, vasopressors ○ Suggest consult Transfusion Medicine physician: explore if indication for - TML: Group & Screen, DAT - Haptoglobin - IgA level (ideally pre-transfusion sample available) - Anti-IgA testing (performed via Canadian Blood Services, TML will assist in sending samples) ○ Re-assess indication for IVIG; consider change brand of IVIG to Gammagard S/D, premedication with steroid
Severe persistent headache with eye pain, fever*, lethargy/decreased level of consciousness, nausea/vomiting, neck rigidity/stiffness, photophobia (up to 72 hours post-IVIG)	**Aseptic meningitis**	○ DO NOT resume infusion ○ Patients with history of migraines at greater risk ○ Supportive care per prescriber's discretion: analgesics, anti-emetics, IV fluids, anti-migraine medication ○ Frequently resolves spontaneously within 24 to 48 hours ○ To prevent or decrease incidence: - Longer rate increase intervals and slow maximum rate remainder of infusion - Pre-hydration (as per patient clinical status, additional PO fluids several hours prior to and following IVIG or 500 to 1000 mL 0.9 % sodium chloride IV prior to IVIG infusion) - Premedication with analgesic (acetaminophen) or antihistamine - If history of migraines, premedicate with anti-migraine medication
Fever* with dyspnea, hypotension, tachycardia or High-risk fever alone (greater than 38.9 ° C) (during or up to 4 hours post-IVIG)	**Bacterial contamination** Occurs extremely rarely	○ DO NOT resume infusion ○ Patient blood culture (from a different peripheral site) ○ Broad spectrum IV antibiotics; DO NOT wait for culture results ○ Return IVIG to TML for product culture ○ Supportive care per physician's discretion: vasopressors, oxygen, respiratory support ○ Serious reaction, call TML immediately

IVIG (Intravenous Immune Globulin) Infusion Guide and Adverse Reaction Chart for Ontario

Acute: fever*, dyspnea, hypotension, pain (back, IV site), tachycardia, urine - red/ brown or tea coloured (during or up to 24 hours post-IVIG) Delayed: back pain, decreased hemoglobin, fever*, fatigue - extreme/unexpected/unexplained, jaundice, tachycardia, urine - red/brown or tea coloured (24 hours to 10 days post-IVIG)	**Hemolysis: acute or delayed** Defined as: 10 g/L or greater decrease in hemoglobin, positive direct antiglobulin test (DAT) AND at least two of the following: increased reticulocyte count, increased lactate dehydrogenase, low haptoglobin, hyperbilirubinemia, hemoglobinemia, hemoglobinuria	○ DO NOT resume infusion ○ Supportive care per physician's discretion: IV fluid (aggressive hydration; maintain good urine output), vasopressors, oxygen, respiratory support ○ TML: Group & Screen, DAT ○ Urinalysis (first void post-reaction) ○ Hemolysis work-up: CBC, bilirubin, LDH, AST, haptoglobin, reticulocyte count, blood film ○ If indicated, assess for - AKI (Acute Kidney Injury): electrolytes, creatinine - DIC (Disseminated Intravascular Coagulation): INR, PTT, fibrinogen, D-dimer - Thrombosis ○ Severity is variable (self-limiting to requiring RBC transfusion support); steroid treatment has been utilized ○ Consider: pause IVIG treatment, avoid implicated lot number of IVIG, change brand of IVIG ○ Educate patient regarding signs and symptoms; if noted, notify prescriber promptly ○ Most often occurs with first treatment, blood group AB, A, B patients receiving high dose IVIG; mechanism of hemolysis not clearly differentiated (IVIG contains anti-A and anti-B antibodies
Edema (periorbital, peripheral), hematuria, hypertension, pain (back, flank), serum creatinine – increased, urination - decreased (oliguria) (1 to 10 days post-IVIG)	**Renal Failure**	○ IVIG-related renal impairment has been related to IVIG stabilized with sucrose (at this time, these brands are not licenced in Canada) ○ Renal impairment has also been reported in patients receiving sucrose-free IVIG ○ All patients receiving IVIG - should be screened for renal disease risk factors (pre-existing renal insufficiency, diabetes mellitus, hypertension, age greater than 64 years, volume depletion, sepsis, paraproteinemia, or receiving known nephrotoxic drugs) - serum creatinine should be monitored at baseline ○ For patients with renal insufficiency or with risk factors: - Longer rate increase intervals and slow maximum rate remainder of infusion - Pre-hydration (as per patient clinical status, additional PO fluids several hours prior to and following IVIG or 500 to 1000 mL 0.9 % sodium chloride IV prior to IVIG infusion) - Close monitoring (interval serum creatinine testing) ○ If renal function declines, discontinuation of IVIG should be considered; SCIG might be an alternative (dose administered per infusion is lower)

IVIG (Intravenous Immune Globulin) Infusion Guide and Adverse Reaction Chart for Ontario

Dyspnea, hypertension, increased jugular venous pressure, orthopnea, tachycardia, (during or up to 12 hours post-IVIG)	**Transfusion Associated Circulatory Overload (TACO)**	○ DO NOT resume infusion ○ Oxygen, high fowler's position, diuretics (document fluid balance) ○ Consider chest x-ray; Findings - pulmonary edema, Kerley B lines, peri bronchial cuffing, may be pleural fluid ○ Future infusion/prevention strategies: - Slow maximum rate remainder of infusion - Pre-infusion diuretic ** - Divide infusion of high doses/high volumes over more than 1 day ○ Prevention: - Assess all patients for TACO risk factors (advanced age, history of heart failure or myocardial infarction, left ventricular dysfunction, renal dysfunction, positive fluid balance) - If risk identified, review with prescriber for prevention strategies (infuse slowly over longer time period; administer pre-transfusion diuretic**)
Acute dyspnea with decreased oxygen saturation, hypotension, tachycardia, +/- *fever (during or up to 6 hours post-IVIG)	**Transfusion Related Acute Lung Injury (TRALI)** Occurs extremely rarely	○ DO NOT resume infusion ○ Supportive care per physician's discretion: oxygen, respiratory support, vasopressors (benefit uncertain for diuretics [document fluid balance], steroids, and bronchodilators) ○ Chest x-ray: Findings – bilateral interstitial/alveolar infiltrates without elevated pulmonary pressures ○ If also hypoxia: blood gases ○ Canadian Blood Services requires follow up information & patient blood tests, contact TML, will assist in sending samples ○ Serious reaction, call TML immediately
Symptoms related to deep vein thrombosis, myocardial infarction, pulmonary embolism, stroke, transient ischemic attack (within 24 hours to days to weeks post-IVIG)	**Thromboembolic events**	○ Proposed possible mechanisms of IVIG-related thrombotic events include - Increase in plasma viscosity due to IVIG's high protein load and protein polymerization - Pro-coagulant potential (presence of contaminants in IVIG i.e., activated coagulation factor XI, factor XII, pre-kallikrein, antiphospholipid antibodies) - Increased platelet count and aggregation activity ○ All patients receiving IVIG should be screened for thromboembolic event risk factors (including but not limited to) - Advanced age - Pre-existing atherosclerotic disease (hypertension, diabetes mellitus, hypercholesterolemia, smoking, previous history of stroke, carotid artery stenosis, myocardial infarction/coronary disease, obesity) - Previous/current venous thrombosis or pulmonary embolism

		- Immobilization - Hereditary hypercoagulable state (antithrombin III, protein C or S deficiency, factor V Leiden or prothrombin mutation) - Increased serum viscosity (monoclonal gammopathy, polycythemia, thrombocythemia) - Permanent indwelling venous catheter - Medications (estrogen, steroids, antineoplastics, diuretics) o IVIG-related thromboembolic events have been reported in the absence of patient risk factors o For patients with risk factors: - Slow maximum rate remainder of infusion - Pre-hydration (as per patient clinical status, additional PO fluids several hours prior to and following IVIG or 500 to 1000 mL 0.9 % sodium chloride IV prior to IVIG infusion) - Divide infusion of high doses (> 1g/kg) over 2 to 5 days (viscous effect is dose dependant) - Close monitoring and educate patient regarding signs and symptoms; if evident, patient should notify prescriber promptly o IVIG should be administered via infusion pumps to promote mobility and minimize period restricted to bed/chair o If thromboembolic event occurs, IVIG should be discontinued; SCIG might be an alternative (dose administered per infusion is lower)
* Fever: Temperature of at least 38° C and an increase of at least 1° C from pre-transfusion		
** Pre-infusion diuretic: Furosemide PO: onset 30 to 60 minutes, maximal effect 1-2 hours, effect persists about 6-8 hours Furosemide IV: onset 5 minutes, maximal effect 20-60 minutes, effect persists about 2 hours		

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Disclaimer

IVIG *Facts* FOR OUTPATIENTS

What is IVIG?

Intravenous Immune Globulin (IVIG) is a blood product that contains antibodies in a concentrated form. It is made from plasma collected from human blood donors. There are several different brands of IVIG in Canada and they are all similar.

Why am I getting it? What does it do?

IVIG is used to replace antibodies in patients that have lower than normal levels (e.g. Primary Immunodeficiency). These antibodies help to fight infections.

It can also be used to treat other conditions, some in which the body attacks its own tissues or organs (e.g. autoimmune disease).

Ask your doctor to explain your individual treatment with IVIG.

You will be asked to sign a consent for blood transfusion as IVIG is made from blood plasma.

Risks

IVIG is considered to be a safe blood product with a low risk of transmitting disease.

Blood donors are carefully tested before they donate, and during manufacturing IVIG is treated to destroy the viruses that cause HIV, Hepatitis B and Hepatitis C.

How is it given?

Your nurse will start an intravenous (IV) line.

IVIG is given through a vein in your arm or hand. It is a clear liquid that usually comes in glass bottles and is given slowly over several hours.

Your nurse will check your vital signs (blood pressure, temperature and pulse) before and during the infusion.

Side effects

Side effects from IVIG usually occur during or up to 24 hours following infusion and tend to be mild and short lived.

Patients who are well hydrated before infusion seem to have fewer side effects.

5-10% of patients experience minor side effects related to the rate of transfusion, these can often be reduced by slowing the rate of infusion and giving medications such as acetaminophen (e.g. Tylenol®) or an antihistamine (e.g. Benadryl®).

Seek immediate, emergency medical attention if you experience:

- Severe headache, eye pain, extreme drowsiness
- Facial and/or tongue swelling
- Difficulty breathing, chest tightness
- Changes in urine colour (red urine, dark coloured urine)
- Intense back pain that is new
- Feeling faint or severe fatigue

It is important to report any of these symptoms to your doctor or nurse.

If symptoms happen after you have returned home your records need to be updated, therefore at your earliest convenience please notify the clinic of any side effects you might experience at home.

Please contact:

Out of Ontario Administration of IVIG

In rare circumstances, it may be necessary for patients to take IVIG dispensed in Ontario to be infused outside of the province, and in many cases outside of Canada. Patients working outside of Ontario for periods of time, attending school or vacationing may all require this service.

If Ontario patients are eligible for provincial health insurance benefits during their travel period, then Ontario hospitals may provide IVIG for this time period when requested by the treating physician or health care provider.

Instructions and examples of helpful documents are provided in this section of the IG Toolkit for patients and physicians involved with the administration of IVIG outside of Ontario.

Instructions for Requests for Intravenous Immune Globulin (IVIG) for Infusion out of Province or out of Country

Occasionally, requests are received from patients currently receiving IVIG therapy to obtain sufficient product to take with them if they are traveling out of province or out of the country for extended periods of time. These requests are rare according to an ORBCoN survey done in 2016 (5 of 53 hospitals responded they had received a request in the past 5 years). In order to provide a consistent approach to these requests across Ontario, information is provided within this toolkit.

In general, the following should be suggested/considered:

1. Encourage the patient's physician to consider transitioning the patient to SCIG if feasible.
2. If the patient is traveling outside of the province but within Canada, request that the patient's physician to arrange for a treating physician in the other province so that the patient can receive their infusion treatment at a hospital. There are agreements in place between the Ministries of Health in each province to cover such requests to ensure patient care is not interrupted.
3. If the patient is traveling outside of the country and their medical insurance will not cover this treatment during this time, it is possible to issue IVIG for up to six months as long as the patient is still eligible to be covered by Ontario Health Insurance.
4. It is important that the processes for travel and infusion of this product follow the same elements of a home infusion program for safe issue/storage/transport of the product, documentation of the disposition of the product, reporting of any adverse reaction to the product. Instructions for home infusion can be found on ORBCoN's website at: http://transfusionontario.org/en/documents/?cat=home-infusion-toolkit.

Policy and Procedure Considerations for Patients Traveling with IVIG Outside of Ontario

The Ontario Regional Blood Coordinating Network (ORBCoN) conducted a survey to determine the frequency of these types of requests in Canada and they are rare. Therefore, a hospital may want to seek the authority of the transfusion medical director or manager for each request, but this should be defined in each individual hospital's policies and procedures.

When developing these documents, some points to consider are:

1. Preparation of an IG inventory list: itemize the IG products eligible for transportation outside of Ontario and the maximum amount permitted per out of Ontario infusion occurrence. While constructing this list, hospital transfusion services may also want to consider what other blood and blood products may need to be included. For example: RhIG, SCIG and C1 esterase inhibitor (see Home Infusion Toolkit also).
2. Patients: How will the patient be trained on transporting and storing the product? What record keeping needs to be done by the patient? What records, if any, are submitted to the provider hospital in Ontario? How will the patient handle broken, outdated or inappropriately stored product? What are the disposal requirements should this occur? Does the patient know what to do if an adverse event occurs during or after infusion? Which health care provider(s) will receive the adverse event information?
3. Issuing and disposition: How does the Ontario hospital issue the product? Are there any special comments to be included? Is the default entry "presumed transfused"? How are the infusion records the patient returns reconciled? Are these infusion records returned to the Ontario physician caring for this patient?
4. Physician communication: Arrangements between the treating and external physicians are the responsibility of the physicians, although some tools are provided in this toolkit to facilitate this communication.
5. Additional costs: Patients are responsible for extra costs incurred including ancillary supplies and any costs for infusion procedures not covered by Ontario or private health insurance.

Patient Participation Agreement Form

Physician Information

Patient Information

PARTICIPATION AGREEMENT - I will -

- ☐ Obtain, transport and store IVIG according to instructions
- ☐ Arrange to carry out the infusions as instructed
- ☐ Keep accurate infusion notes to provide to my Ontario physician
- ☐ Report to the appropriate health care provider any possible adverse reactions to IVIG and seek treatment if necessary
- ☐ Be responsible for any expenses incurred by out of Ontario infusion of IVIG
- ☐ Ensure these parameters are met, or I will not receive any further IVIG

I acknowledge that IVIG for out of Ontario infusion can be withdrawn at any time if I fail to adhere to the above or to any other requirements, or if unmanageable complications of IVIG infusion therapy occur.

X _____
Signature of patient

_____
Date & time of signature

If applicable:

_____
Signature of Caregiver

_____
Date

_____
Print Caregiver's Name

Caregiver: Retain a copy for your records and give one to the patient

Letter from treating (home) physician to travel (remote) physician/health care provider for IVIG administration outside of Ontario

[insert address or letterhead if desired]

Date:

Dear Health Care Provider:

Re: Patient's name, DOB, etc.

This patient has a medical condition requiring regular IV infusions of immunoglobulins (IG) which are manufactured from human blood. He/she will be outside of Ontario for an extended period of time and requires medical assistance in accessing this necessary medical treatment.

To maintain sufficient levels of immunoglobulins, this patient requires ___g of IVIG to be infused every ___ weeks. The patient will be given a sufficient supply of this product for ___ weeks and he/she will maintain it at a controlled temperature. Coordination and assistance will be required in infusing this product either in his/her home environment or in a medical facility or clinic. Ancillary supplies will be needed for each infusion.

This patient will need to be monitored for any adverse events from these infusions and will require an emergency contact (e.g. the local emergency department of a hospital) in the event of any severe reactions.

Please feel free to contact me at _____ with any questions. Thank you for your assistance in caring for this patient.

Sincerely,

IVIG Travel Letter

Re: Required medical supplies for _____

Date of birth: _____

To whom it may concern:

_____ has a chronic medical condition which is treated by injections of replacement immunoglobulins in the form of a medication called intravenous immune globulin (IVIG) which is manufactured from human blood.

To maintain sufficient levels of immunoglobulins and avoid significant impacts to their health, patients need to take this medication and the equipment required to administer it with them when traveling. This product must be kept at a controlled temperature and the following items will need to be carried onto the airplane (or other mode of travel) by the above named individual:

- IVIG vials
- Possibly administrative supplies like needles, administration sets, alcohol swabs, gauze and tape
- Medication to manage side-effects (non-drowsy antihistamine and over the counter pain medication)
- A container and possible gel packs (required to keep IVIG and other medications at the correct temperature during travel)

Yours sincerely,

Treating physician

If additional information is required, please contact Dr. _____ at (_____) _ _ _ - _ _ _ _.

Acknowledgements

Members of Ontario IG Advisory Panel (as of April 01, 2016)

- Dr Lois Shepherd, Chair, Kingston General Hospital
- Dr Yulia Lin, Vice-chair, Sunnybrook Health Sciences
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- Dr Michelle Zeller, McMaster University
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- Ms Jennifer T Davis, Canadian Blood Services
- Mr Peter Saunders, Canadian Blood Services
- Ms Ramona Muneswar, Blood Programs Coordinating Office
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