Ontario Regional Blood Coordinating Network

Inspiring and facilitating best transfusion practices in Ontario.

INTRAVENOUS IMMUNE GLOBULIN (IVIG): WHAT'S SO UNIQUE?

Donna Berta RN, BScN
Clinical Project Coordinator – Nursing
Ontario Regional Blood Coordinating Network (ORBCoN)

March 22, 2023

ORBCoN
Ontario Regional Blood Coordinating Network

Inspiring and facilitating best transfusion practices in Ontario.

We do our work in support of our vision of appropriate and safe transfusion practices for every Ontarian, every time.

Patient Safety

Accountability

Leading Practice

Collaboration

Quality

ORBCoN Values

Strategic Goals

1. Utilization of Blood Components and Products
2. Educational Resources
3. Inventory Management
4. Communication
5. Quality and Safety

Speaker Disclosure

- No commercial product conflicts of interest to declare
- Transfusion Transmitted Injuries Surveillance System, member Education Committee
- Using Blood Wisely initiative, member nursing education development
- Canadian Society of Transfusion Medicine, member Standards Committee

IVIG: What's So Unique

Objectives:

- To understand the nature of the indications for IVIG treatment.
- To define nursing actions to safely administer IVIG (dose, infusion rate, cautions & side effects).

Outline:

- IVIG Mechanisms of Action
- Patient Case
- Indications & Dose Calculator
- Infusing IVIG
- Cautions & Side Effects

Pre Transfusion Knowledge Question 1

For adult and paediatric patients, IVIG is indicated:

a) Only if the patient is immune globulin G (IgG) deficient, serum IgG is less than 6 g/L.

b) If the patient's diagnosis is supported as per the Ontario Immune Globulin (IG) Utilization Management Guidelines.

c) Only if the patient is diagnosed with an inflammatory/ autoimmune disorder, such as chronic inflammatory demyelinating polyneuropathy or Guillain-Barré syndrome.

d) If all the above criteria are met.

Pre Transfusion Knowledge Question 2

The initial IVIG dose ordered is based on:

a) The molecular weight of IVIG.
b) The brand of IVIG being administered.
c) The patient's weight and height.
d) The patient's ABO blood group.

IVIG Mechanisms of Action

- IVIG is a manufactured from plasma (pooled from several thousand donors). Thorough viral inactivation steps are followed (e.g., low pH, chromatography, solvent detergent treatment).
- Contains antibodies (immunoglobulin proteins), greater than 90% IgG.

- In diagnoses of IG deficiency, IVIG provides additional antibodies the body is not producing or that are not functioning, to fight infection.
- Proposed anti-inflammatory & immunomodulatory effects, more than 1 mechanism may predominate in different diagnoses.
  Some of these mechanisms include inhibiting certain cellular maturation steps, blocking certain receptors, supressing cytokine production, effecting the complement system, supplying antibodies that neutralize microbial toxins, altering regulatory T cells.
- Unclear if all or only a small subset of the IgG molecules present in IVIG are responsible for clinical benefits.

Patient Case

- Johnny, 46 year old otherwise healthy male admitted to your medical-surgical unit from ED 2 hours ago, diagnosis is presumed toxic shock syndrome.
- Yesterday, Johnny fell while hiking and cut his leg on some rocks. He is experiencing significant leg pain, nausea, fever (temperature 38.6 C) and borderline hypotension (BP 96/52 mmHg). Analgesia and IV antibiotics were initiated. His 15 cm wound was swabbed, and surgical consultation is pending.
- ORDER:
  IVIG 100 g IV now (day 1) and 50 g days 2 and 3, infusion rate as per protocol.

Patient Case: Indications

- Your hospital's Transfusion Medicine Lab (TML, aka Blood Bank) approved IVIG indication list may be based on Ontario IG Utilization Management Guidelines

Specialty: Infectious Diseases	Medical Condition	Recommendations	Dose/Frequency of Administration
	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]		

- Updated 2022: Prairie Collaborative Immune Globulin Utilization Management Criteria for the Clinical Use of Immune Globulin

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

Patient Case: Question 1

Johnny's weight is 100 kg and height is 175 cm.
Per your hospital and Ontario IG guidelines, the appropriate IVIG now (day 1) dose is 1g/kg.

Select the correct number of grams of IVIG to be administered to Johnny now:

a) 80 g, as per dosing using adjusted body weight
b) 100 g
c) 50 g
d) 175 g

Patient Case: Dose Calculator (1)

- Indications include dose & frequency (dose ranges: 0.3 g/kg to 2 g/kg [exception 3g/kg for Toxic epidermal necrolysis/Stevens-Johnson syndrome]).

- Adult patients: height 152.4 cm or greater, BMI of 30 kg/m^2 or greater; use ideal body weight calculation & IVIG dose calculator (to minimize potential adverse effects of high dose IVIG & limit overuse of IVIG).

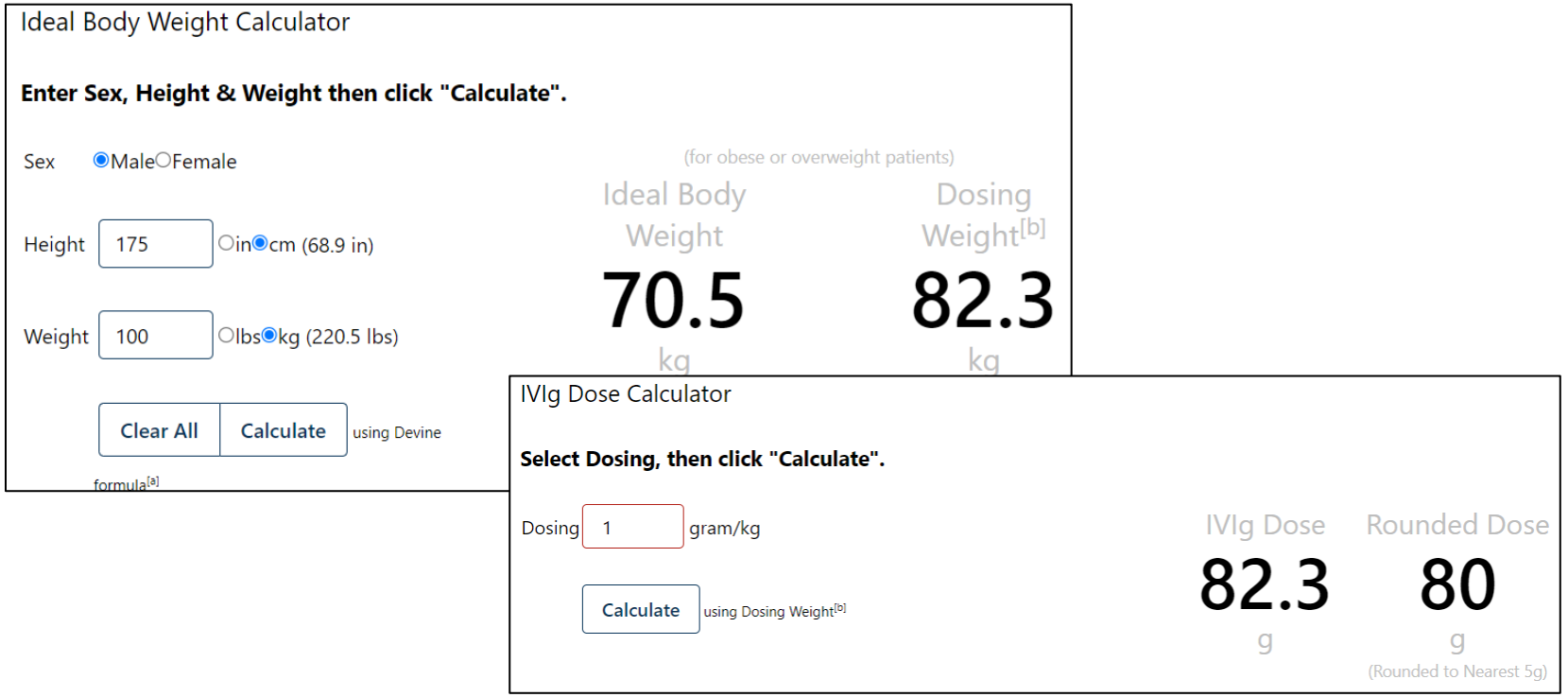
- Some hospital TML's policy: for all adult patients, use adjusted body weight computation for IVIG dose calculation (dosing weight is based on the patient's actual weight and ideal body weight).

- Note: chronic disease IVIG indications when the patient has stabilized, consider titrating dose and/or treatment interval to the lowest dose and/or greatest interval needed to provide clinical effectiveness.

Patient Case: Dose Calculator (2)

- ORDER: IVIG 100 g IV now (day 1) and 50 g days 2 and 3, infusion rate as per protocol.

- Ontario IG Dose Calculator



Patient Case: Question 2

ORDER: IVIG 1 g/kg IV now (day 1) and 0.5 g/kg days 2 and 3, infusion rate as per protocol.
TML issues Gammagard liquid 80 g.
Johnny's weight is 100 kg and height is 175 cm.

Select the correct rate for Johnny's IVIG infusion:

a) Initial rate 40 mL/hr., increase to maximum 250 mL/hr.
b) As per the brand specific manufacturer's monograph recommendations.
c) Initial rate 40 mL/hr., increase to maximum 1000 mL/hr.
d) Initial rate 40 mL/hr., increase to maximum 500 mL/hr.

Patient Case: Infusing IVIG (1)

- ORDER: IVIG 1 g/kg IV now (day 1) and 0.5 g/kg days 2 and 3, infusion rate as per protocol. TML issues Gammagard liquid 80 g.

- All brands are equivalent in terms of clinical effectiveness.
- Each brand's monograph defines specific infusion starting rate, maximum rate for certain patient clinical factors, & recommended maximum rate. If well tolerated, the rate of infusion may gradually be increased to the recommended maximum.
- Rate calculation formula (individual calculations are necessary for neonatal and paediatric patients, weight less than 30 kg.):
  Rate (mL/kg/hr) x Weight (kg) = Hourly infusion rate (mL/hr).
- Alternative to using formula for adults & weight 30 kg or greater:
  ORBCoN's Infusion Guide and Adverse Events
  Refer to Appendix A: IVIG Brands Infusion Rate Tables

Patient Case: Infusing IVIG (2)

ORBCoN's Infusion Guide and Adverse Events Appendix A

*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)																			

Patient Case: Infusing IVIG (3)

ORBCoN's Infusion Guide and Adverse Events

- Blood usuals: informed consent, prescriber/delegate on pager, aseptic technique, dedicated IV line (peripheral or central), do not mix with other other medications, checks per policy, anaphylaxis precautions.
- Visual inspection: bottle seal intact, product appears as clear or slightly opalescent solution that is colourless to pale yellow in colour.
  If concerns, do not infuse and follow up with 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 in a single infusion
  (Exception: Gamunex & IGIVnex).
- To minimize bubbling of IVIG: Allow the IVIG to come to room temperature; do not shake the IVIG.
- Flush with 5% dextrose in water (D5W) or 0.9 % sodium chloride (NaCl) for injection (exception: Gammagard S/D – only D5W).

Patient Case: Infusing IVIG (4)

ORBCoN's Infusion Guide and Adverse Events

- Begin infusion with smallest bottle size, end with largest bottle size of those issued (to minimize wastage in the event of a reaction).
- Subsequent bottles, with the same or different lot numbers do not require returning to the starting infusion rate.
- 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 per tubing manufacturer.
- For patient safety, administer using an approved infusion pump to set infusion rate precisely and allow for greater patient mobility.
- Patient assessment and vital signs: 30 minutes prior; 15 minutes after start; after each rate increase, then hourly until completed; for inpatients 1-hour post, for outpatients prior to discharge; if clinically indicated, or when a reaction is suspected.

Patient Case: Question 3

ORDER: IVIG 1 g/kg IV now (day 1) and 0.5 g/kg days 2 and 3, infusion rate as per protocol.
TML issues Gammagard liquid® 80 g.

To minimize possible side effects:

a) Divide the infusion of high doses (greater than 1g/kg) over more than 1 day.
b) Administer with slow infusion rate, as feasible.
c) Pre-hydration (PO fluids several hours prior to & following or IV fluid).
d) All the above measures minimize possible side effects.

Patient Case: Cautions & Side Effects

- Always administer at the slowest infusion rate feasible.
- IVIG has been associated with:
  - renal dysfunction, osmotic nephrosis, and acute renal failure.
  - thromboembolic events.

  Assess the patient for history and risk factors. If evident, use slow rate of infusion, ensure well hydrated & monitor closely.
- Review for TACO (Transfusion Associated Circulatory Overload) risk.
- Hemolysis/hemolytic anemia have been reported. Perform baseline lab tests. Monitor patients for clinical signs & symptoms of hemolysis.
- IVIG may affect the efficacy of live attenuated virus vaccines (i.e., measles, mumps, rubella, varicella/chickenpox) for 6 -12 weeks.
- IVIG is manufactured from human plasma. Measures to decrease the risk of transmission of infectious pathogens are followed, however potential risk of transmission remains.

Patient Case: Cautions & Side Effects (1)

- If side effects/adverse reactions are suspected, follow the usual blood steps (stop infusion, maintain IV access, check vital signs, notify prescriber, provide care as ordered, report all to TML, even if minor)

- Minor Side effects/adverse reactions may be more likely
  - if receiving IVIG for the first time
  - when changing to another IVIG brand
  - if prolonged time (more than 8 weeks) since the previous infusion
  - with high doses
  - with rapid infusion rates
  - if the patient is not well hydrated.

- Canadian data – No difference in side effects rates between brands.
- Patients may have side effects/adverse reactions to a certain IVIG lot number or brand but will tolerate a different lot number or brand.

Patient Case: Cautions & Side Effects (2)

- Not uncommon, some symptoms may occur up to 72 hours post infusion (hemolysis signs/symptoms may occur up to 10 days post).

- Advise patients to report:
  - Chills/rigors
  - Eye pain
  - Facial or tongue swelling, Fatigue, Fever, Flushing
  - Gastrointestinal symptoms: diarrhea, vomiting
  - 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
  - Yellow skin or eye colour

Patient Case: Cautions & Side Effects (3)

Etiology of side effects/adverse reactions

- Minor
  - Febrile non-hemolytic reaction
  - IVIG headache (most common IVIG reaction)
  - Minor allergic reaction
- Moderate to severe
  - Anaphylaxis/ Anaphylactoid
  - Aseptic meningitis
  - Bacterial contamination (extremely rarely)
  - Hemolysis (acute or delayed)
  - Renal Failure
  - Transfusion Associated Circulatory Overload (TACO)
  - Transfusion Related Acute Lung Injury (TRALI) (extremely rarely)
  - Thrombotic events
- See Appendix B: Suggested treatment & actions, strategies to mitigate

ORBCoN Website – Resources Tab

Website: https://transfusionontario.org/en/

Bloody Easy E-Tools & Publications

- Bloody Easy Blood Administration (BEBA)
- Bloody Easy for Healthcare Professionals
- Bloody Easy Lite
- ORBCoN Tech Assess

Blood Utilization & Audits

- Audits Tools
- Blood Utilization Graphs
- COPTN Reports
- O Negative RBC Utilization
- Provincial Audit Reports
- RBC Benchmarking
- STAT and ASAP Delivery Study

COVID-19

IVIG/SCIG

- Dosing Using Adjusted Body Weight
- Facts for Patients
- Immune Globulin Toolkit
- Infusion Guide and Adverse Events
- IVIG App
- Ordering IG in Ontario
- Travelling with IG
- Utilization Management Guidelines

Massive Hemorrhage Protocol

- eLearning
- Provincial MHP Toolkit
- Supplementary Resources
- Recommendation Statements
- Simulation Videos

ORBCoN Resources

- Helpful Apps
- Interesting Podcasts
- Newsletter
- Order Resources
- Presentation Library

Toolkits

- Bedside Audit
- Dispensary and Administration
- Emergency Blood Management
- Home Infusion Toolkit
- Implementing an Evaluation Process for your Transfusion CAP
- Inventory Management
- IVIG
- New Product
- OTTRM
- Resources for Midwives
- Special Blood Requirements
- Transporting Blood Internally
- Transfusion Committee
- Transfusion Safety Officer Resource Manual
- Quality Improvement Plan

TM Guidelines, Standards, & Recommendations

- Guidelines
- NAC Guidelines and Recommendations
- Recommendations
- Resource Manual for Medical Directors of Transfusion Medicine
- Standards

Quality Improvement

Post Transfusion Knowledge Question 1

For adult and paediatric patients, IVIG is indicated:

a) Only if the patient is immune globulin G (IgG) deficient, serum IgG is less than 6 g/L.

b) If the patient's diagnosis is supported as per the Ontario Immune Globulin (IG) Utilization Management Guidelines.

c) Only if the patient is diagnosed with an inflammatory/ autoimmune disorder, such as chronic inflammatory demyelinating polyneuropathy or Guillain-Barré syndrome.

d) If all the above criteria are met.

Post Transfusion Knowledge Question 2

The initial IVIG dose ordered is based on:

a) The molecular weight of IVIG.
b) The brand of IVIG being administered.
c) The patient's weight and height.
d) The patient's ABO blood group.

Acknowledgements

- The Ontario Regional Blood Coordinating Network (ORBCoN) gratefully acknowledges funding support provided by the Ontario Ministry of Health. The views expressed in this presentation are those of the authors and of ORBCoN and do not necessarily reflect those of the Ontario Ministry of Health or the Government of Ontario.

- Many thanks to my ORBCoN and Transfusion Medicine family for their ongoing mentorship and support.

References

Ballow M, Shehata N. Overview of intravenous immune globulin therapy. Post TW, ed. UpToDate. Waltham, MA: UpToDate Inc.; 2023 [cited 2023 Mar 15]. Available from: https://www.uptodate.com

Callum JL, Pinkerton PH, Lin Y, Cope S, Karkouti K, Lieberman L, Pendergrast JM, Robitaille N, Tinmouth AT, Webert KE. Bloody easy 5 blood transfusions, blood alternatives and transfusion reactions a guide to transfusion medicine. 5th ed. Toronto: Ontario Regional Blood Coordinating Network; 2022 [cited 2023 Mar 15]. 145p.
Available from: https://transfusionontario.org/en/category/bloody-easy-e-tools-publications/bloody-easy-for-healthcare-professionals/

Ontario Regional Blood Coordinating Network. Bloody easy blood administration. version 3. Toronto: Ontario Regional Blood Coordinating Network; 2020 [cited 2023 Mar 15]. 146p.
Available from: https://transfusionontario.org/en/category/bloody-easy-e-tools-publications/bloody-easy-blood-administration/

Ontario Regional Blood Coordinating Network. Infusion Guide and Adverse Events. version 3. Toronto: Ontario Regional Blood Coordinating Network; 2022 [cited 2023 Mar 15]. 25p.
Available from: https://transfusionontario.org/wp-content/uploads/2020/06/Ontario-Intravenous-Immune-Globulin-Infusion-Guide-and-Adverse-Reaction-Chart-v3.0.pdf

Ontario Regional Blood Coordinating Network. Ontario immune globulin (IG) utilization management guidelines. version 4. Toronto: Ontario Regional Blood Coordinating Network; 2018 [cited 2023 Mar 15]. 12p.
Available from: https://transfusionontario.org/wp-content/uploads/2020/06/ontario-ig-utilization-management-guidelines-v4.0.pdf

Prairie Collaborative Immune Globulin Utilization Management Framework Project. Criteria for the clinical use of immune globulin. second edition. Alberta Ministry of Health, Shared Health Manitoba, and Saskatchewan Ministry of Health. Edmonton: Institute of Health Economics; 2022 [cited 2023 Mar 15]. 77p.
Available from: https://saskblood.ca/download/criteria-for-the-clinical-use-of-immune-globulin-first-edition/

IVIG: What's So Unique

Email: bertad@mcmaster.ca