CHAPTER 4

IMMUNOGLOBULIN PRODUCTS

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BACKGROUND

Immunoglobulin (Ig) products are manufactured from plasma collected from a large number of carefully screened donors. Ig products may be used as replacement therapy for immunodeficient patients or as immunomodulatory therapy for autoimmune and alloimmune disorders. Ig products include intravenous Ig (IVIg), subcutaneous Ig (SCIg), and hyperimmune globulins such as RhD Ig (RhIg).

Patients receiving Ig products may have reduced response to immunization with parenteral live virus vaccines but IVIg has minimal interference or interaction with inactivated viruses, live oral vaccines, live intranasal vaccines and the Bacillus Calmette–Guérin (BCG) vaccine. For guidance, please refer to the Canadian Immunization Guide from the Public Health Agency of Canada.[1]

IMMUNOGLOBULIN PRODUCTS

Immunoglobulin products are sterile solutions or lyophilized concentrates of human immunoglobulin G (IgG) that have been processed to remove multimers and aggregates of IgG, allowing intravenous infusion. The distribution of IgG subclasses in Ig products is similar to the human plasma. Depending on the method of preparation, some commercial products may contain trace amounts of other immunoglobulin classes: IgA, IgM, IgE and IgD.

The various products differ in their manufacturing processes, in terms of plasma pool sizes, steps to improve Ig yields, removal of contaminants, pathogen inactivation technology, and use of stabilizing or preservative agents. The relevance of such modifications has not been established and different products may be used interchangeably in clinical practice.[2,3]

After infusion of Ig, the various passively transferred antibodies in the patient's blood may yield positive serological testing results, with the potential for misleading interpretation. Passive transmission of antibodies to red cell antigens (e.g., A, B, and D) may cause a positive direct or indirect antiglobulin (Coombs) test. For this

reason, serological testing results for other antibody-mediated tests (e.g., hepatitis B core antibody [anti-HBc], hepatitis A, varicella) may also be misleading. Because of this, consideration should be given to performing hepatitis B testing with hepatitis B surface antigen (HBsAg) in patients before Ig therapy is initiated to inform the risk of hepatitis B reactivation.[4,5]

For the names and product-specific details of the Ig products carried by Canadian Blood Services, see Canadian Blood Services' national e-formulary for plasma protein and related products. Please refer to the manufacturer's product monograph for the most up-to-date information on indications, dosing, administration and potential side effects.

INTRAVENOUS IMMUNOGLOBULIN

MECHANISM OF ACTION

Although the mechanism of action for IVIg has not yet been clearly elucidated, the proposed mechanisms are described in Table 1.

Table 1: Proven and hypothesized mechanisms of action of IVIg with some evidence[6-8]

Use	Mechanism of action	References
Protection against infection and supplementation for congenital/primary and acquired/secondary immune deficiency	• Mechanism proven • Supplementing array of IgG antibodies to facilitate destruction and neutralization of pathogens	9, 10
Immune modulation in autoimmune or modulatory conditions	• Mechanism not yet proven • Suspected anti-inflammatory activity by dendritic cells and/or blockade of Fc receptors in the reticuloendothelial system	6, 8, 11, 12
Prevention of alloimmunization against RhD with RhIg	• Mechanism not yet proven • Accelerated clearance of RhIg coated cells • Suppression of B-cell mediated response to Rh exposure and mitigation of Rh alloimmunization	13-15

INDICATIONS

The licensed indications for IVIg in Canada vary slightly by product but currently include:

- Primary immune deficiency (PID)
- Immune thrombocytopenic purpura (ITP)
- Secondary immune deficiency (SID) states
- Chronic inflammatory demyelinating polyneuropathy (CIDP)
- Guillain-Barré syndrome (GBS)
- Multifocal motor neuropathy (MMN)

IVIg is often used as an off-label therapy for diseases that may have an immune-mediated or unknown etiology. This off-label use accounts for a significant proportion of IVIg use in most Canadian provinces.[16]

In the attempt to ensure appropriate utilization of IVIg, many jurisdictions across Canada have developed policies and practices that may dictate specific prerequisites and an authorization process prior to the release of products. Regional guidance on IVIg utilization management is provided by the BC Provincial Blood Coordinating Office, the Ontario Regional Blood Coordinating Network and the Atlantic Blood Utilization Strategy Working Group. The Prairie Collaborative Immune Globulin Utilization Management Framework Project developed criteria for the clinical use of immunoglobulin as part of an evidence-based framework to aid transfusion services and clinicians. The second edition was published in February 2022; Appendix C provides a list of new and revised recommendations.[17]

The COVID-19 pandemic heightened concerns about possible future shortages of IVIg. The National Advisory Committee on Blood and Blood Products (NAC) provides interim guidance on managing Ig shortages and a project is underway to build on this guidance to develop a national plan for managing Ig shortages[18,19] Deliverables are expected for submission to the provincial and territorial ministries of health by March 31, 2024.

CONTRAINDICATIONS

Most manufacturers state that IVIg is contraindicated for individuals with IgA deficiency who have anti-IgA antibodies, but these individuals may be successfully treated with SCIg therapy.[20] There is no requirement to routinely test for IgA deficiency prior to IVIg therapy. There are also reports of patients with demonstrated anti-IgA IgG antibodies tolerating IVIg infusions.[21] For patients who have had anaphylactic or multiple severe allergic reactions to IVIg previously, consideration may be given to the use of solvent-detergent treated products. In addition, one product, Privigen, recommends against use in patients with hyperprolinemia.

DOSING AND ADMINISTRATION

Dosing for IVIg infusion is dependent on the clinical indication. Generally, the immune replacement dose is 0.4–0.6 g/kg every 3–4 weeks. One additional dose of 0.4 g/kg may be given in the first month of therapy if the serum IgG level is markedly reduced. The immunosuppressive dose is 1–2 g/kg over 1–5 days, and some conditions may require ongoing maintenance therapy, usually given monthly, with efforts made to reduce the dose or extend the treatment interval based on the patient's clinical response. Local practice guidelines, consensus documents and manufacturers' product monographs provide more specific information on dose, frequency and duration of therapy for specific indications.

The NAC and several provincial health authorities and blood offices recommend IVIg dosing based on adjusted body weight calculators (e.g., Ontario,[22] Alberta,[23] Nova Scotia,[24] British Columbia[25]) and/or absolute dose caps. For additional details, refer to the online dose calculators provided and local policies. Figure 1 provides an example of an adjusted body weight dosing calculation.

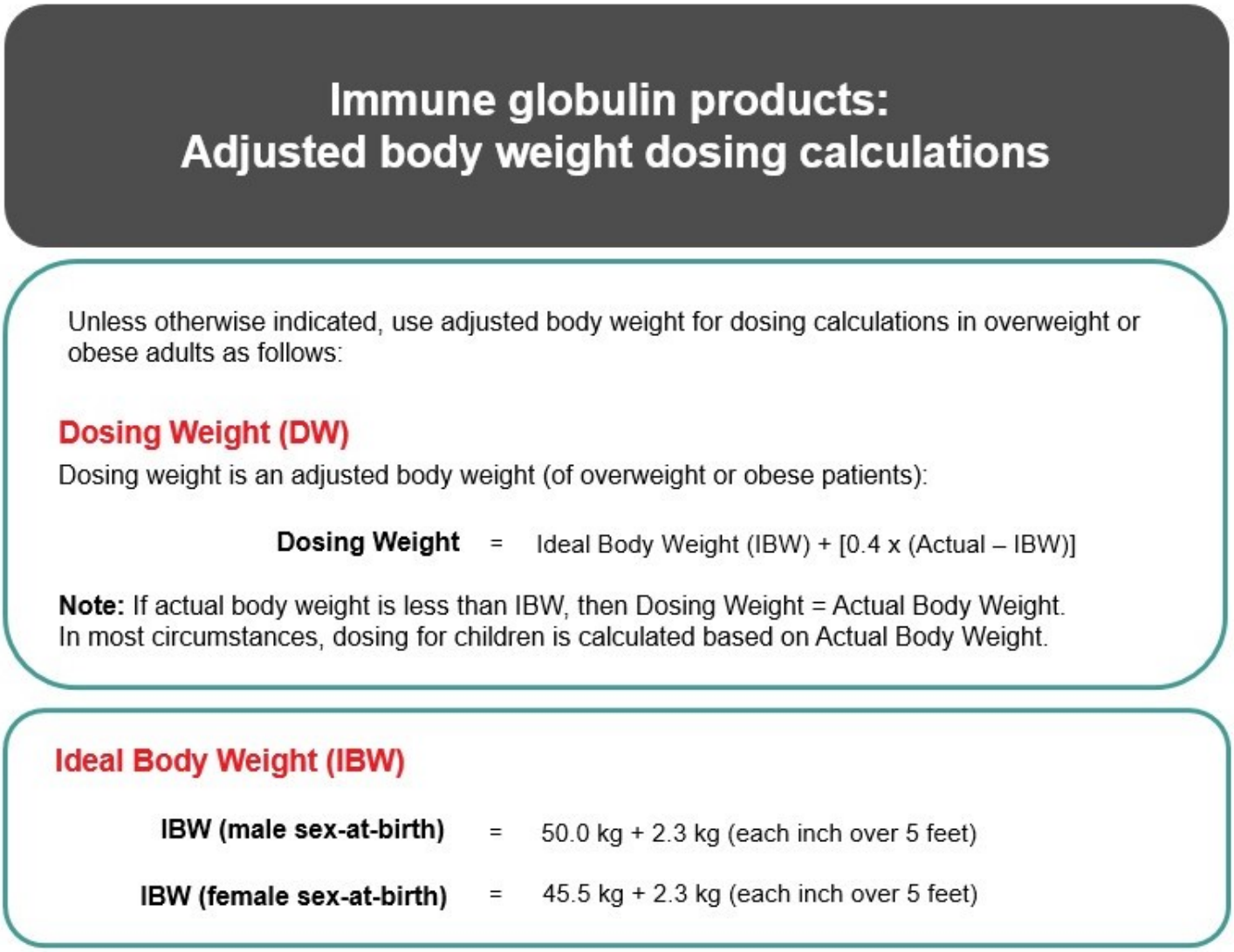

Figure 1. Example of an adjusted body weight dosing calculations.[17] Ideal body weight is calculated using the Devine formula.[26] In most circumstances, dosing for children is calculated based on Actual Body Weight.

IVIg must be administered intravenously at an infusion rate appropriate for the indication and specified by the ordering physician. Some reactions can be prevented or controlled in many cases by slowing the infusion rate.

Protocols for IVIg infusion vary by institution but are based on the following principles:

- Start with a slow infusion rate (e.g., 0.01 mL/kg/minute) and monitor vital signs frequently.
- As tolerated, increase the infusion rate at regular intervals with progressively less frequent monitoring of vital signs.

A patient's response to the infusion will dictate an individualized maximum tolerable rate of infusion that may be lower than the manufacturer's recommended infusion rate.

STORAGE

Storage temperatures range from 2–25°C but the product shelf life may differ with some products if stored at room temperature. Please consult each product monograph for the maximal allowable time at each temperature range.

ADVERSE EVENTS

The prevalence of IVIg-associated adverse events reported in the literature varies widely.[27,30] Patients receiving immunoglobulin as supplementation for primary or secondary hypoglobulinemia appear to have a much lower frequency of side effects than do patients who are receiving higher IVIg doses as a treatment for immune-mediated or systemic inflammatory disorders.[31]

Minor side effects are quite common with IVIg infusion and are often related to infusion rate. These reactions include headache, chills, fever, malaise, anxiety, chest pain, nausea, pruritus, and rash. Most of these side effects will resolve by slowing or stopping the IVIg infusion. If recurrent, they can typically be managed by providing premedication or switching to an alternate product. The more serious and potentially fatal adverse events—including severe hemolysis, aseptic meningitis, anaphylaxis, viral transmission, transfusion-related acute lung injury (TRALI) and thromboembolic events—are rare. Since the implementation of donor testing and routine viral inactivation processes, the currently licensed products are considered safe with respect to transmission of human immunodeficiency virus (HIV) and the hepatitis viruses.[32] Cases of IVIg-associated TRALI reactions have been reported and may be increasing as a result of TRALI mitigation strategies that divert plasma from donors with previous history of pregnancy (and potential for HLA sensitization) to fractionation processing.[33,34]

HEMOLYSIS

IVIg administration commonly results in a positive direct antiglobulin test (DAT) and, in up to 32% of cases, contributes to clinically significant hemolytic events.[35] IVIg-associated hemolysis has been defined by the IVIg Hemolysis Pharmacovigilance Group of Canada as:

- A drop in hemoglobin of at least 10 g/L and a positive DAT within 10 days following IVIg infusion with supporting evidence of hemolysis as indicated by at least two of:
  - increased reticulocyte count
  - increased lactate dehydrogenase level
  - low haptoglobin level
  - increased unconjugated bilirubin level
  - hemoglobinemia (visibly red serum)
  - hemoglobinuria
- or the presence of significant spherocytosis and no alternate etiology for the anemia.[36]

Many case series have described IVIg-associated hemolysis as having a higher occurrence rate in patients receiving high doses, especially at doses of 2 g/kg.[35,37,39] The higher prevalence of IVIg-associated hemolysis in those with non-O blood groups occurs as a function of both the quantity of passively transferred anti-A and anti-B isohemagglutinins as well as the density of A and B antigens on the red cell surface of the recipient.[35,40] Some manufacturers are now providing IVIg products that are isohemagglutinin-depleted to minimize risk. The risk of hemolysis appears highest when a product with a high isohemagglutinin titre is administered at doses of 2 g/kg or

higher to a blood group A or AB recipient[41] some Canadian jurisdictions have implemented prospective hemolysis monitoring processes for these patients.

ASEPTIC MENINGITIS

Aseptic meningitis secondary to IVIg appears to be dose-related; the majority of reported cases received immunomodulatory doses of 2 g/kg/cycle.[42] Meningeal signs and symptoms typically present within 6 to 48 hours of the infusion. On examination, the cerebrospinal fluid demonstrates elevated protein levels, normal to low glucose levels, and a leukocyte pleocytosis with negative cultures.[43] The majority of patients recover within five days of symptom onset and tolerate subsequent infusions, but some patients report the recurrence of symptoms with subsequent infusions.[44]

ANAPHYLAXIS

Severe anaphylactic and allergic reactions have been reported in association with IVIg. Some of these reactions have occurred in patients with IgA deficiency and anti-IgA antibodies but there is debate regarding the significance of IgG versus IgE anti-IgA, the role of complement activation, and the persistence of the reactivity.[21,45,46] The use of SCIg may be one effective substitute in patients with a history of anaphylactic or severe allergic reactions who require future Ig therapy.[20] Others recommend the use of IgA-depleted products in those with confirmed anti-IgA antibodies and prior confirmed reactions.[47]

THROMBOEMBOLIC EVENTS

Health Canada and the US Food and Drug Administration (FDA) have both issued safety warnings regarding the potential of thromboembolic complications with Ig products.[48,49] Reported thromboembolic complications include stroke, transient ischemic attacks, deep vein thromboses, pulmonary emboli, retinal vein occlusion, and retinal artery infarcts.[50] These thrombotic complications can occur during the IVIg infusion or up to eight days following. Patients with cardiovascular risk factors, advanced age, prolonged immobilization and those with a history of thromboembolic events are considered at a higher risk, although thrombosis may occur in the absence of any identifiable risk factors. High-risk patients should be carefully monitored and adequately hydrated prior to the IVIg administration. The Ig products should also be administered at the lowest feasible dose and an infusion rate appropriate for the indication and patient condition.

SUBCUTANEOUS IMMUNOGLOBULIN

In Canada, subcutaneous immunoglobulin (SCIg) is predominantly used as replacement therapy for primary and secondary immunodeficiency patients. Since these patients require lifelong therapy with Ig replacement, many may have better quality of life parameters with SCIg use instead of IVIg. These benefits includes improved side effect profile given no need for vascular access, increased convenience due to self-administered home infusions and fewer restrictions in travel.[51] As it pertains to decreasing the frequency and duration of infection in patients with primary immune deficiency, SCIg and IVIg are considered equally effective.[52] As with any blood product managed at home, the use of SCIg should be overseen by a comprehensive care clinic that provides training for patients and caregivers in administration, proper handling, storage and monitoring for adverse effects.

INDICATIONS

The licensed indication for SCIg includes both replacement therapy for primary and secondary immunodeficiency as well as for immunomodulation in patients with the neurologic condition chronic inflammatory demyelination polyneuropathy (CIDP). Home/self-administration of SCIg is a safe, effective and preferred approach for many people offering increased quality of life and reduced risk of adverse reactions.[53] [54]

CONTRAINDICATIONS

The main contraindication for SCIg is a history of anaphylactic or severe allergic reactions to Ig preparations. However, this is often a reason for switching a patient from intravenous to subcutaneous products. Some, but not all, products advise against use in those with a history anti-IgA antibodies. One product, Hizentra, recommends against use in patients with hyperprolinemia.

DOSE AND ADMINISTRATION

For initiation of replacement therapy in patients with primary immunodeficiency, SCIg starting dose depends on the specific brand being used. Generally, the doses vary between 100–200 mg/kg per week depending on the product used. The recommended rate of infusion varies by brand.[55] [57] One additional dose of 0.4 g/kg may be given in the first month of therapy if the serum IgG level is markedly reduced.

If transitioning from IVIg, the easiest calculation is to take the monthly total IVIg dose and divide by 4 to obtain the weekly SCIg dose followed by titration to achieve an IgG trough level of at least the lower limit of the age-specific serum IgG reference range, or as needed to achieve clinical effectiveness.[58]

One SCIg product, HyQvia, approved for primary and secondary immunodeficiency, may be administered once monthly. It is administered along with hyaluronidase, which allows a larger volume of Ig to be injected. The usual dose is 100-125 mg/kg per week, which may begin as weekly doses then be given cumulatively every 3 to 4 weeks.

For immunomodulation therapy in CIDP, the only licensed SCIg is Hizentra and the monograph recommends dosing between 200 to 400 mg/kg per week.[56]

STORAGE

Storage temperatures range from 2–25°C but product shelf life may differ with some products if stored at room temperature. For products that should be stored in the fridge until administered to the patient, the date the product was removed from the fridge should be noted. Depending on the product specifications, some products may be stored at room temperature in the patient's home. Please consult each product monograph for maximal time at each temperature range.

ADVERSE EVENTS

The minor adverse event profile with SCIg is similar to that of IVIg, with the additional side effect of discomfort from subcutaneous injection. Please refer to the above section on adverse events for IVIg.

The BC Provincial Blood Coordinating Office (PBCO), in collaboration with immunologists and transfusion medicine physicians, and with support from Canadian Blood Services' BloodTechNet program, developed a Primary Immunodeficiency Disease (PIDD) toolkit to support the diagnosis, treatment and monitoring of patients with primary immunodeficiency disease (PIDD). The toolkit contains diagnostic and treatment algorithms, a dose calculator to determine IVIg or SCIg dose, a dose adjustment calculator and links to references of interest.

HYPERIMMUNE GLOBULINS

Hyperimmune globulin fractionation products are created from pools of human plasma specifically chosen for high titres of antibodies with selected specificities. Each product undergoes viral inactivation procedures but the process used is dependent on the individual manufacturer.

CONTRAINDICATIONS

- IgA deficiency
- Previous severe or allergic reaction to the product
- Any condition that would contraindicate intramuscular injections

RH IMMUNOGLOBULIN

Rh immunoglobulin (RhIg) is a freeze-dried preparation of human immunoglobulin of the IgG class with antibody specificity directed against the RhD antigen. This product is prepared from pooled human plasma collected from paid donors who selectively produce anti-D.[59,60] RhIg is not antigen affinity-purified and can be expected to contain background levels of some other IgG antibodies. Although most RhIg products have high purity without high levels of complement activity, some products will contain residual antibodies against other Rh antigens.

PRODUCT DESCRIPTION

The available vial sizes include: 600 IU (120 µg), 1,500 IU (300 µg) and 5,000 IU (1,000 µg) anti-D. See the package insert for additional product-specific details. See Chapter 12, Hemolytic disease of the fetus and newborn and perinatal immune thrombocytopenia, for more information on RhIg.

CLINICAL USE[61-63]

There are two broad categories for clinical use of RhIg: prevention of alloimmunization to the RhD antigen (see Table 2) and for treatment of immune thrombocytopenic purpura (see Table 3).

Table 2: RhIg for prevention of alloimmunization to the RhD antigen: indications, contraindications and dose and administration

Category 1: Prevention of alloimmunization to the RhD antigen	
Indications	1. Prophylaxis for RhD hemolytic disease of the newborn during pregnancy. See Chapter 12, Hemolytic disease of the fetus and newborn and perinatal immune thrombocytopenia, for more information. 2. Prophylaxis against anti-D formation following transfusion. RhIg administration should be considered whenever Rh-positive platelets or red blood cells are transfused to an Rh-negative recipient. Most jurisdictions recommend RhIg administration for female patients of child-bearing potential (less than 45 years of age) receiving Rh-positive blood components. However, additional risk-benefit determinations may be required prior to RhIg administration. Some of these factors would include the volume of Rh-mismatched red blood cells transfused, availability of Rh-negative red blood cell support in the event of hemolysis, renal function and clinical status of the patient.
Contraindications	• RhD-positive individuals • RhD-negative women who are RhD alloimmunized as evidenced by a positive antibody screening test and a demonstrated allogeneic anti-D • Individuals with a history of anaphylactic or other severe reactions to immunoglobulin or plasma products • The manufacturer also recommends avoidance in patients with IgA deficiency. However, no IgA-depleted RhIg products are currently available in Canada. Reports of successful intramuscular administration in patients with anti-IgA antibodies exist. In these rare situations, a risk benefit discussion with each patient is recommended. If RhIg administration is undertaken in this setting, it should be under monitored conditions with available treatment for anaphylaxis.
Dose and administration	• RhIg (usually supplied in Canada as WinRho SDF) can be administered by either an intravenous or intramuscular route for prevention of RhD alloimmunization. • It should be administered within 72 hours of a potentially sensitizing event. However, even if delayed, it should be given as soon as the need is recognized, up to 28 days. • For obstetrical indications, see Chapter 12, Hemolytic disease of the fetus and newborn and perinatal immune thrombocytopenia. • For transfusion-associated red blood cell exposure, the dose may vary depending on the route of administration and may range between 90 to 120 IU per mL of RhD-positive red blood cells (whole blood dosing 45-60 IU) with the intramuscular dosing at the higher end of the scale. A common rule of thumb is 1,500 IU (300 µg) for each 15 mL of red cells or 30 mL of whole blood. ◦ For larger volume exposures, intravenous administration may require multiple doses of 3,000 IU (600 µg) every 8 hours until the total dose can be administered. In this setting monitoring for hemolysis and consideration of repeat RhD-negative red blood cell transfusion in symptomatic patients may be required.

Table 3: RhIg for the treatment of immune thrombocytopenic purpura: indications, contraindications and dose and administration

Category 2: Immune thrombocytopenic purpura	
Indications	Administration of RhIg for ITP differs from its other uses in that the patient must be RhD-positive and must have an intact and functional spleen.
Contraindications	• RhD-negative patients • Patients with prior splenectomy • Individuals with a history of anaphylactic or other severe reactions to immunoglobulin or plasma products • The manufacturer also recommends that it should not be used in patients with secondary ITP, patients with evidence of autoimmune hemolytic anemia (Evan's syndrome), patients with systemic lupus erythematosus (SLE), patients with anti-phospholipid antibody syndrome and patients with underlying cardiac, renal or hepatic co-morbidities that would be predisposed to complications of acute hemolysis induced by RhIg.
Dose and administration	• RhIg is most commonly administered by an intravenous route but some jurisdictions and published evidence support subcutaneous administration.[64] Intramuscular administration is not recommended for this indication due to the risk of bleeding. • Dosing will vary between 25–60 µg/kg depending on the patient's baseline hemoglobin and local practice. • Monitoring of hemoglobin concentration post administration should be undertaken to detect significant hemolysis.

HEPATITIS B IMMUNOGLOBULIN

Hepatitis B Immune Globulin is a sterile solution of the purified IgG fraction of human plasma containing antibodies to hepatitis B surface antigen (anti-HBs). Hepatitis B Immune Globulin is manufactured from plasma collected from healthy, screened donors with high titres of anti-HBs.

Table 4: Hepatitis B immunoglobulin for providing passive immunization [65]

Indications	To provide passive immunization to hepatitis B in the following situations: • Acute exposure to blood containing HBsAg • Perinatal exposure of infants born to HBSAg-positive mothers • Sexual exposure to an HBsAg-positive person • Household exposure to persons with acute HBV infection • Prevention of recurrence of Hepatitis B post-liver transplantation (a conditional indication for one product HepaGam B)
Contraindications	0.06 mL/kg given IM or 0.5 mL for infants as soon as possible, preferably < 24 hours

OTHER HYPERIMMUNOGLOBULINS

Indications and dose and administration for other hyperimmune globulin fractionation products carried on the Canadian Blood Services product formulary are provided in Table 5. Please refer to the product monograph for specific dosing recommendations for each specific disease exposure.

Table 5: Other hyperimmunoglobulin fractionation products on the Canadian Blood Services product formulary.

Product name	Indication	Dose and administration
Varicella-Zoster Immune Globulin (VariZIG)	Prevention or reduction in severity of maternal infections in pregnant women that have had a significant exposure to the varicella zoster virus (VZV) providing that the exposed individual does NOT have known immunity to the varicella zoster virus (secondary to either vaccination or previous infection).[66]	The recommended adult dose is 125 IU/10 kg body weight up to a maximum dose of 625 IU. Each vial contains approximately 125 IU of anti-VZV. VariZIG can be given by intravenous (IV) or intramuscular (IM) administration. VariZIG should be administered as soon as possible but at least within 96 hours of exposure. However, the efficacy after this time frame has not been established.
Intramuscular Immune Globulin (GamaSTAN S/D)	Passive immunization using IMIg may be considered for immediate post exposure prophylaxis when vaccines for active immunization are not available or are contraindicated due to the exposed individual's age or underlying medical condition.	GamaSTAN S/D is administered intramuscularly preferably in the anterolateral aspects of the upper thigh and the deltoid muscle of the upper arm. The gluteal region should not be used routinely as an injection site because of the risk of injury to the sciatic nerve. Dosing recommendations differ for different indications. Please refer to product monograph or Canadian Immunization Guide. Doses over 10 mL should be divided and injected into several muscle sites to reduce local pain and discomfort.

Product name	Indication	Dose and administration
Cytomegalovirus Immunoglobulin (Cytogam)	Cytomegalovirus (CMV) Immunoglobulin Intravenous (Human) is primarily indicated for solid organ transplant recipients who are seronegative for CMV but are receiving an organ from a CMV seropositive donor to mitigate the development of primary (1°) CMV disease. In transplants of organs other than kidneys, concomitant therapy with ganciclovir may be administered. Of note, in Canada, Cytogam is only approved for use in Kidney transplant.	The maximum recommended total dosage per infusion is 150 mg/kg. The product should be administered intravenously according to the following schedule but should not exceed a rate of: • Within 72 hours of transplant: 150 mg/kg • 2 weeks post transplant: 100 mg/kg • 4 weeks post transplant: 100 mg/kg • 6 weeks post transplant: 100 mg/kg • 8 weeks post transplant: 100 mg/kg • 12 weeks post transplant: 50 mg/kg • 16 weeks post transplant: 50 mg/kg

STORAGE

The storage temperature ranges from 2–8ºC. The product must be used within four hours of reconstitution.

ADVERSE EVENTS

WinRho SDF (Anti-D IG) RhIg has a serious warning and precautions label regarding the risk of severe hemolysis when used for immune thrombocytopenic purpura – see contraindications above. Otherwise, the adverse event profile is similar to that of other immunoglobulins.

CONTINUING PROFESSIONAL DEVELOPMENT CREDITS

Fellows and health-care professionals who participate in the Canadian Royal College's Maintenance of Certification (MOC) program can claim the reading of theClinical Guide to Transfusion as a continuing professional development (CPD) activity underSection 2: Self-learning credit. The reading of one chapter is equivalent to two credits.

Medical laboratory technologists who participate in the Canadian Society for Medical Laboratory Science's Professional Enhancement Program (PEP) can claim the reading of theClinical Guide to Transfusion as a non-verified activity.

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