INESSS
LE SAVOIR PREND FORME

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INTRAVEINOUS IMMUNOGLOBULIN (IVIg)

USE IN HEMATOLOGY

This optimal use guide is intended for hematologists and other medical specialists who treat patients with a hematological disease with IVIg. It is provided for information purposes only and should not replace the judgement of the clinician who performs activities reserved under an act or a regulation. The recommendations were developed using a systematic process and are supported by the scientific literature and by the knowledge and experience of Québec clinicians and experts. For further details, go to inesss.qc.ca.

GENERAL INFORMATION

- The recommendations presented in this optimal use guide apply only to the primary diagnosis of the hematological indications listed and do not concern the infectious complications that may be associated with them.
- Intravenous nonspecific human immunoglobulin (IVIg) preparations are stable products derived from human plasma.
- Their use has continued to increase in Québec in the past several years. Because of their high cost and the risk of a shortage, it is important to ensure that they are used judiciously.
- The price of a gram of IVIg is about $90 (2017). This price may vary, depending on the exchange rate for the Canadian dollar and the volume of fractionation plasma collected by Héma-Québec. The cost of IVIg for a 70-kg adult is approximately $12,600 for short-term treatment (at a total dose of 2 g/kg divided over 2 to 5 days) and approximately $32,760 per year for long-term treatment (at a dose of 0.4 g/kg every 4 weeks).

INITIATING, MONITORING AND DISCONTINUING IVIg THERAPY

- Before initiating IVIg therapy:
  - A diagnosis should be confirmed by a medical specialist;
  - The patient's free and informed consent must have been obtained and recorded in his or her medical record;
  - The patient's ideal weight should be calculated;
  - The patient's blood type should be determined, if it is not already indicated in his or her record.
- After the therapy is initiated, for patients requiring maintenance IVIg therapy:
  - The tolerance and effectiveness of the therapy should be assessed on a regular basis by a medical specialist;
  - The frequency of this assessment should be determined by the patient's clinical status:
    - Immunomodulatory therapy[1]: an assessment should be carried out at least every 3 months;
    - Replacement therapy[2]: a first assessment should be carried out no later than 6 months after the start of treatment, with an assessment every 6 to 12 months thereafter;
    - In pregnant women: an assessment should be carried out during the usual pregnancy follow-ups.
  - If no benefit is observed in terms of the patient's clinical status during the medical reassessment, the therapy should be discontinued and another therapy considered.

1. IVIg therapy administered in cases of an auto- or alloimmune disease.
2. IVIg therapy administered for infection prevention in cases of an allogeneic transplant or hypogammaglobulinemia secondary to a hematologic cancer.

RECOMMENDATIONS FOR USING IVIg BY INDICATION

A total of 25 hematological indications were evaluated – list not exhaustive

IVIg RECOMMENDED

INDICATIONS	CONDITIONS OF USE
Allogeneic hematopoietic stem cell transplant[1] (for infection prevention)	▸ In patients on steroid therapy for chronic graft-versus-host disease (or acute GvHD that is becoming chronic) ▸ In cases of a haploidentical transplant or a transplant from cord blood ▸ In patients with severe recurrent infections
Hypogammaglobulinemia secondary to a hematologic cancer[1, 2]	▸ In the presence of an IgG level less than 4 g/l and a history of severe infection or of recurrent infections since the disease was diagnosed[3]
Acute immune thrombocytopenia[1]	▸ In the presence of life-threatening bleeding ▸ In the presence of moderate to severe bleeding, if the platelet count is less than 30 x 10^9/l ▸ In the presence of a platelet count less than 10 x 10^9/l, in case of failure, contraindication or intolerance to steroids ▸ Prior to surgery, if necessary ▸ In case of failure, contraindication or intolerance to steroids
Immune thrombocytopenia during pregnancy[1]	▸ In the presence of life-threatening bleeding ▸ In the presence of a platelet count less than 30 x 10^9/l ▸ In preparation for childbirth to achieve a platelet count of at least 50 x 10^9/l
Fetal or neonatal alloimmune thrombocytopenia	▸ From the 12th to the 16th week of pregnancy, in cases of fetal-maternal incompatibility, in the presence of a history of fetal or neonatal intracranial bleeding associated with alloimmune thrombocytopenia[4] ▸ From the 20th to the 22nd week of pregnancy, in cases of fetal-maternal incompatibility, in the presence of a history of fetal or neonatal alloimmune thrombocytopenia[4] without intracranial bleeding ▸ In newborns, in the presence of life-threatening bleeding or a platelet count less than 30 x 10^9/l, when a platelet transfusion (selected or not for the human platelet antigen [HPA]) is not possible

1. A Health Canada-approved indication.
2. Including chronic lymphocytic leukemia, multiple myeloma and non-Hodgkin's lymphoma.
3. Based on the clinical experience of the advisory committee's members, IVIg may be considered as a treatment option for a patient with a secondary humoral immunodeficiency confirmed by a vaccine non-response.
4. Presence of maternal antiplatelet alloantibodies known or suspected to cause fetal or neonatal alloimmune thrombocytopenia (generally anti-HPA-1a or anti-HPA-5b).

IVIg NOT RECOMMENDED

INDICATIONS	
▸ Aplastic anemia	▸ Hemolytic-uremic syndrome[1]
▸ Pure red blood cell aplasia	▸ Secondary hemophagocytic syndrome[2]
▸ Thrombotic thrombocytopenic purpura	▸ Heparin-induced thrombocytopenia
▸ Hemolytic transfusion reaction (without hyperhemolysis)	

1. However, based on the clinical experience of the advisory committee's members, IVIg may be considered in the presence of anti-factor H antibodies in case of failure, contraindication or intolerance to the other therapeutic options.
2. However, based on the clinical experience of the advisory committee's members, IVIg may be considered in the presence of a precipitating factor.

IVIg A POSSIBLE THERAPEUTIC OPTION

INDICATIONS	CONDITIONS OF USE
Autoimmune hemolytic anemia[1]	▸ In case of failure, contraindication or intolerance to the other therapeutic options
Hemolytic disease of the newborn or fetus	▸ In combination with phototherapy when the disease is caused by an Rh[2] incompatibility and the serum bilirubin level is increasing at a rate greater than 8.5 µmol/l/hr ▸ In severe cases of fetal hemolytic disease when maternal antibodies against the fetus are detected, if there is a high risk of hydrops fetalis or premature death
Autoimmune neutropenia[1]	▸ In case of failure, contraindication or intolerance to the other therapeutic options
Post-transfusion purpura[1]	▸ In the presence of moderate to severe bleeding
Hyperhemolytic syndrome[1]	▸ In combination with steroids in the presence of a severe hemolytic reaction (a drop in hemoglobin to a level below the pre-transfusion level)
Catastrophic antiphospholipid syndrome[1]	▸ When rapid thrombosis affects at least 2 organs and the diagnosis of catastrophic antiphospholipid syndrome is based on laboratory results, in case of failure, contraindication or intolerance to the other therapeutic options
Evans syndrome[1]	▸ The conditions of use are the same as those for immune thrombocytopenia or autoimmune hemolytic anemia, depending on the patient's clinical picture.
Chronic immune thrombocytopenia[3]	▸ If the platelet count is less than 10 x 10^9/l ▸ To control moderate to severe bleeding or in the presence of a risk of bleeding when the platelet count is less than 30 x 10^9/l, in case of failure, contraindication or intolerance to the other therapeutic options ▸ Before surgery, if necessary ❗ Not recommended in a patient who experienced failures with prior IVIg therapy
Infection-induced immune thrombocytopenia (HIV, HCV)	▸ The conditions of use are the same as those for acute or chronic immune thrombocytopenia, as the case may be.

1. Little or no data are available in the literature on the efficacy of IVIg in this indication. Recommendations concerning this indication are therefore based on the opinion of the advisory committee's members.
2. There is insufficient data in the case of hemolytic disease of the newborn or fetus caused by an ABO incompatibility. It should be noted, however, that there is an increased risk of hemolysis because all IVIg preparations contain anti-A and anti-B.
3. A Health Canada-approved indication

INSUFFICIENT DATA

INDICATIONS	
▸ Parvovirus B19-induced red blood cell aplasia[1]	▸ Acquired hemophilia[2]

1. Based on the clinical experience of the advisory committee's members, IVIg may be considered in case of failure, contraindication or intolerance to the other therapeutic options.
2. Contact an inhibitor centre.

DOSE AND FREQUENCY OF ADMINISTRATION OF IVIg

▸ The use of the ideal weight should be considered when calculating the doses to be administered to a **clinically obese adult.**

	ADULTS AND CHILDREN	
Immunomodulatory therapy	Adult: 1 to 2 g/kg (total dose) divided over 2 to 5 days Pediatric: 1 g/kg as a single dose Pregnant women: 1 g/kg as a single dose (maximum dose : 60 g), once or twice a week	The dose can be adjusted downward, depending on the situation and the individual clinical response.
Replacement therapy	0.4-0.6 g/kg, once a month	

TRANSFUSION REACTIONS ASSOCIATED WITH IVIg

NON-SERIOUS TRANSFUSION REACTIONS (the most common)	SERIOUS TRANSFUSION REACTIONS (usually rare)
▸ Post-IVIg headache, non-hemolytic febrile reaction, chills, rash, minor allergic reaction, asthenia, nausea, vomiting, flu-like symptoms, atypical pain, and post-transfusion hypertension or hypotension (list not exhaustive)	▸ Major allergic reaction, thromboembolic event, immediate or delayed hemolytic reaction, aseptic meningitis, transfusion-related acute lung injury (TRALI), transfusion-associated circulatory overload (TACO), and acute renal failure (list not exhaustive)
▸ Serious and non-serious transfusion reactions (particularly those that result in a change in the dose, frequency or type of IVIg administered) must be reported to the blood bank using Form AH-520	

RELATIVE CONTRAINDICATIONS AND MAIN PRECAUTIONS CONCERNING IVIg

RELATIVE CONTRAINDICATIONS		
▸ A known allergy to any of the product's ingredients ▸ A history of severe allergic reaction to Ig (immediate anaphylactic or delayed)		
PRECAUTIONS		
Hemolysis	**Thrombosis**	**Renal function**
▸ IVIg-related hemolysis is more common in patients with type A, B or AB blood who receive a high total IVIg dose (≥ 2 g/kg). ▸ Monitor the patient for signs and symptoms of hemolysis. If any appear, order the appropriate laboratory tests.	▸ Thrombosis formation can occur with any type of Ig in patients with or without risk factors, regardless of the dose administered and the route of administration.	▸ Check renal function if there is an increased risk of acute renal failure. ▸ If renal function deteriorates, consider discontinuing the IVIg.

SUBCUTANEOUS Ig (SCIg) USE

- For the hematological indications, only the use of SCIg to treat secondary immunodeficiency is approved by Health Canada.
- SCIg may be considered as a substitute for IVIg in patients with hypogammaglobulinemia secondary to a hematologic cancer or who have had an allogeneic hematopoietic stem cell transplant. In such case, the monthly dose of Ig administered subcutaneously should be divided more frequently than if it had been administered intravenously, i.e., every 1 to 2 weeks, depending on the product used.
- When assessing the appropriateness of prescribing SCIg to replace IVIg, one should take into account the clinical situation of the patient being treated and certain practical considerations, such as the availability of a caregiver and nursing staff or the travel demands associated with IVIg injections.

This guide was developed in collaboration with an expert committee, and INESSS supports the recommendations made.

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