INESSS
LE SAVOIR PREND FORME

OCTOBER 2022

INTRAVENOUS OR SUBCUTANEOUS IMMUNOGLOBULINS

USE IN FERTILITY, CARDIOLOGY AND OTHER INDICATIONS

This optimal use guide is intended for gynecologists, cardiologists, immunologists and other medical specialists who treat patients with a disease or condition presented in this guide with IVIg. It is provided for information purposes only and should not replace the judgment 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

- Intravenous (IV) and subcutaneous (SC) non-specific human immunoglobulin (Ig) preparations are stable products derived from human plasma.
- Their use 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 one gram of IVIg is approximately $100 (2020). 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 $14,000 for short-term therapy (at a total dose of 2 g/kg divided over 2 to 5 days).

INITIATING, MONITORING AND DISCONTINUING IVIg OR SCIg THERAPY

- Before initiating IVIg or SCIg therapy:
  - The 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 IVIg therapy is initiated, for patients requiring maintenance IVIg or SCIg 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 according to the patient's clinical status:
    - For post-plasmapheresis hypogammaglobulinemia and systemic capillary leak syndrome, a first assessment should be carried out no later than 6 months after the start of treatment and then every 6 to 12 months;
    - For unexplained recurrent miscarriages, an assessment should be carried out at least every 3 months;
    - 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 adjusted or discontinued and another therapy considered.

RECOMMANDATIONS CONCERNING THE USE OF IVIg AND SCIg IN FERTILITY

A total of three fertility indications were evaluated – list not exhaustive

IVIg OR SCIg A POSSIBLE TREATMENT OPTION

INDICATION	CONDITIONS OF USE
Unexplained repeated miscarriages[1]	**After consultation with a specialist in reproductive immunology** ▸ On a case-by-case basis for women who have had at least 3 unexplained miscarriages[2,3] **and** • A 4th miscarriage with another therapeutic option or • Who have a contraindication or intolerance to the other therapeutic options
Échecs d'implantation répétés inexpliqués[1]	**After consultation with a specialist in reproductive immunology** ▸ On a case-by-case basis for women who have experienced at least 2 unexplained implantation failures[2] with good-quality day 5 embryos **and** • A 3rd implantation failure with another therapeutic option or • Who have a contraindication or intolerance to the other therapeutic options

1. There is little data available in the literature on the efficacy of Ig for these indications. This recommendation is based on the clinical experience of the experts consulted.
2. The main causes of miscarriage and implantation failure must have been ruled out, including age. Based on the available fertility data and the clinical experience of the experts consulted, this age is less than 41 years when women use their own eggs or less than 45 years when donated eggs are used.
3. In the presence of confirmed euploidy, Ig therapy may be considered after a 3rd miscarriage with another therapeutic option or after a 2nd miscarriage for women with a contraindication or intolerance to the other therapeutic options.

IVIg NOT RECOMMENDED

INDICATION
• Obstetrical antiphospholipid syndrome.

RECOMMENDATIONS CONCERNING THE USE OF IVIG IN CARDIOLOGY

A total of three cardiology indications were evaluated – list not exhaustive

IVIg A POSSIBLE TREATMENT OPTION

INDICATION	CONDITIONS OF USE
Pediatric myocarditis[4]	▸ For children with severe acute myocarditis and in the presence of a decreased ejection fraction or significant cardiac dysfunction
Adult myocarditis[5]	▸ For adults with fulminant myocarditis

4. There is little data available in the literature on the efficacy of Ig in treating myocarditis in children. This recommendation is therefore based on the clinical experience of the experts consulted. Consultation with a pediatric cardiologist is necessary in order to assess the relevance of prescribing IVIg therapy.
5. There is little data available in the literature on the efficacy of IVIg in the treatment of fulminant myocarditis in adults. This recommendation is therefore based on the clinical experience of the experts consulted. Consultation with a cardiologist is necessary in order to assess the relevance of prescribing IVIg therapy.

IVIg NOT RECOMMENDED

INDICATION
▸ Dilated cardiomyopathy ▸ Nonfulminant myocarditis in adults ▸ Peripartum cardiomyopathy

RECOMMANDATIONS CONCERNING THE USE OF IVIg AND SCIg – OTHER INDICATIONS

A total of three other indications were evaluated – list not exhaustive

IVIg AND SCIg RECOMMENDED

INDICATION	CONDITIONS OF USE
Neonatal hemochromatosis[6]	▸ For pregnant women who have previously had a pregnancy affected by neonatal hemochromatosis
Systemic capillary leak syndrome[6,7]	▸ To prevent the recurrence of life-threatening attacks in individuals with a confirmed diagnosis of systemic capillary leak syndrome

6. Little or no data is available in the literature on the efficacy of Ig for these indications. These recommendations are based on the clinical experience of the experts consulted.
7. Consultation with an immunologist is necessary in order to confirm the relevance of prescribing Ig.

IVIg OR SCIg A POSSIBLE TREATMENT OPTION

INDICATION	CONDITIONS OF USE
Post-plasmapheresis hypogammaglobulinemia[8]	**After consultation with an immunologist** ▸ For individuals with profound hypogammaglobulinemia, i.e., an IgG level below 2 g/L in adults associated with: • A severe, unusual or recurrent infection, or • Significant immunosuppression *Note: The subcutaneous route is preferable if administration is possible.*

8. Little or no data is available in the literature on the efficacy of Ig for this indication. This recommendation is based on the clinical experience of the experts consulted. For individuals with secondary hypogammaglobulinemia in the absence of plasmapheresis therapy, please refer to the optimal use guide on IVIg and SCIg in clinical immunology.

INSUFFICIENT DATA

INDICATION
• Treatment of an acute attack in an individual with systemic capillary leak syndrome.

DOSE AND FREQUENCY OF ADMINISTRATION OF IVIg OR SCIg

- The **dose calculator** should be used for calculating doses **in adults** who are taller than 1.52 m (5 feet) and who are not below the ideal weight. For women who are pregnant or planning to become pregnant, the calculator should **always** be used with the pre-pregnancy weight for the dose adjustment.

IVIg	UNEXPLAINED REPEATED MISCARRIAGES	
Treatment cycle	**Before pregnancy:** Adult: 0.4-0.6 g/kg[9] every 3 months for a maximum of 6 months **During pregnancy:** Adult: 0.4-0.6 g/kg[9] a month up to the 20th week of pregnancy	The dose can be adjusted or repeated according to the individual clinical response.
	REPEATED IMPLANTATION FAILURE	
	Adult: 0.4-0.6 g/kg once, 3 to 5 days before the embryo transfer[10]	
	FULMIMANT MYOCARDITIS	
	Adult: a total dose of 2 g/kg over 2 to 5 days Pediatric: a total dose of 2 g/kg over 2 days	
	NEONATAL HEMOCHROMATOSIS	
	Adult: 1 g/kg[9] during the 14th and 16th weeks of pregnancy, then every week from the 18th week to the end of pregnancy	
	POST-PLASMAPHERESIS HYPOGAMMAGLOBULINEMIA	
	Adult and pediatric: consult an immunologist in order to determine the dosage to be administered on a case-by-case basis.	

IVIg	SYSTEMIC CAPILLARY LEAK SYNDROME	
Starting dose	Adult: 1 to 2 g/kg over 2 to 5 days	The dose can be adjusted or repeated according to the individual clinical response.
Maintenance dose	Adult: 0.4 to 2 g/kg every 4 weeks	

SCIg	UNEXPLAINED REPEATED MISCARRIAGES	
Treatment cycle	**Before pregnancy:** Adult: 0.1-0.2 g/kg[11] a week for a maximum of 6 months **During pregnancy:** Adult: 0.1-0.2 g/kg[11] a week up to the 20th week of pregnancy	SCIg can be administered daily, weekly or every other week with an adjusted dose corresponding to a total dose of 0.1 to 0.2 g/kg a week. The dose can be adjusted or repeated according to the individual clinical response.
	POST-PLASMAPHERESIS HYPOGAMMAGLOBULINEMIA	
	Adult and pediatric: consult an immunologist in order to determine the dosage to be administered on a case-by-case basis	
	SYSTEMIC CAPILLARY LEAK SYNDROME[12]	
	Adult: 0.1 to 0.2 g/kg a week	

9. The dose is calculated using the pre-pregnancy weight and is then maintained throughout the treatment.
10. If implantation failure is combined with repeated miscarriages, therapy for repeated miscarriages during pregnancy may be considered.
11. Based on the clinical experience of the experts consulted, the SCIg dose should be adjusted to a dose approximately 10% higher than the equivalent dose of IVIg.
12. Little or no data is available in the literature regarding the use of SCIg for this indication. This recommendation is based on the clinical experience of the experts consulted.

TRANSFUSION REACTIONS ASSOCIATED WITH IVIg OR SCIg

NON-SERIOUS TRANSFUSION REACTIONS (the most common)	SERIOUS TRANSFUSION REACTIONS (usually rare)
▸ Post-IVIg headache, non-hemolytic febrile reaction, chills, urticaria, asthenia, nausea, vomiting, flu-like symptoms, atypical pain, and post-transfusion hypertension or hypotension (list not exhaustive)	▸ Immediate anaphylactic 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 or that warrant discontinuing the therapy) must be reported to the blood bank using Form AH-520	

RELATIVE CONTRAINDICATIONS AND MAIN PRECAUTIONS CONCERNING IVIg OR SCIg

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.	▸ Thrombus formation can occur with any type of Ig in patients with or without risk factors, regardless of the dose administered or 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.

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

Institut national d'excellence en santé et en services sociaux
Québec