INESSS
LE SAVOIR PREND FORME

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INTRAVEINOUS IMMUNOGLOBULIN (IVIg)

USE IN RHEUMATOLOGY

This optimal use guide is intended for rheumatologists and other medical specialists who treat patients with rheumatological disease 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 non-specific human immunoglobulin (IVIg) preparations are stable products derived from human plasma.
- Their us 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 THERAPY

- Before initiating IVIg 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:
  - 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.
- 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.

RECOMMENDATIONS FOR USING IVIg BY INDICATION

A total of 34 rheumatological indications were evaluated (list not exhaustive).

IVIg RECOMMENDED	
INDICATIONS	**CONDITIONS OF USED**
Kawasaki disease	▸ In patients with Kawasaki disease ▸ IVIg therapy can be repeated once if necessary in the event that it fails the first time.

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IVIg A POSSIBLE TREATMENT OPTION	
INDICATIONS	**CONDITIONS OF USE**
Juvenile idiopathic arthritis	▸ In patients with a severe, systemic form of the disease, with or without an associated hemophagocytic syndrome
Adult Still's disease	
Dermatomyositis (including the juvenile form)[1]	▸ Always in combination with immunosuppressive treatments ▸ Failure of first-line treatments or to reduce chronic high doses of corticosteroids
Polymyositis (including immune-mediated necrotizing myopathies)[1]	
Diffuse or localized systemic sclerosis	▸ In patients with a severe form of systemic sclerosis with concurrent myositis ▸ In the event of failure, contraindication or intolerance to the other therapeutic options
Sjögren's syndrome	▸ In patients with a severe form of the disease
Systemic lupus erythematosus	▸ In patients with a severe form of the disease ▸ In the event of failure, contraindication or intolerance to the other therapeutic options
Eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome)	
Granulomatosis with polyangiitis (Wegener's syndrome)	
Microscopic polyangiitis	
Catastrophic antiphospholipid syndrome[2]	▸ 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
Neonatal lupus[3, 4]	▸ In pregnant women with anti-Ro/SSA or anti-La/SSB antibodies when the fetus has 2nd-degree atrioventricular block or shows signs of myocarditis or endocardial fibroelastosis ▸ In newborns of mothers with anti-Ro/SSA or anti-La/SSB antibodies, with in utero 3rd-degree atrioventricular block that has resolved or regressed after maternal treatment OR with 2nd-degree atrioventricular block OR who have shown signs of myocarditis or endocardial fibroelastosis OR with severe thrombocytopenia or thrombocytopenia associated with significant bleeding due to neonatal lupus OR with fulminant hepatitis or severe neonatal lupus-related liver damage that threatens the liver's integrity

1. Based on the clinical experience of the expert committee's members, for patients with dermatomyositis or polymyositis, IVIg can be considered on an exceptional basis as initial first-line therapy in combination with immunosuppressive treatments in cases of severe muscle weakness, including oropharyngeal dysphagia and diaphragmatic muscle damage and myocarditis or in special clinical situations (diagnosis of systemic sclerosis, gastrointestinal vasculitis or skin ulcers).
2. Little or no data 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.
3. Based on the experts' clinical experience, IVIg can be considered in certain cases when the fetus or newborn has 1st-degree atrioventricular block, especially if the mother previously gave birth to a child with neonatal lupus.
4. A consultation with neonatologist or obstetrician with expertise in monitoring this indication may be necessary in order to assess the relevance of prescribing treatment with IVIg.

IVIg NOT RECOMMENDED

INDICATIONS

- Rheumatoid arthritis
- Cryopyrinopathies[5]
- Inclusion body myositis[6]
- Cutaneous lupus[7]
- Localized scleroderma (morphea)[8]
- Antiphospholipid syndrome[9](non-catastrophic)
- Temporal arteritis
- Behçet's disease
- IgA vasculitis
- Leukocytoclastic vasculitis
- Lymphocytic vasculitis

5. The group of cryopyrinopathies include familial cold autoinflammatory syndrome, Muckle-Wells syndrome and neonatal-onset multisystem inflammatory disease.
6. Based on the clinical experience of the expert committee's members, IVIgs can, however, be considered in patients with inclusion body myositis who have severe dysphagia.
7. IVIg may be considered in the event of failure, contraindication or intolerance to the other therapeutic options.
8. IVIg may be considered in the event of failure, contraindication or intolerance to the other therapeutic options in cases of generalized or pansclerotic morphea.
9. For fertility or pregnancy problems in women with antiphospholipid syndrome, please refer to the immunoglobulin optimal use guide concerning fertility problems .

INSUFFICIENT DATA

INDICATIONS

- Overlap syndromes[10]
- Takayasu's arteritis
- Cogan syndrome
- Susac syndrome[12]
- Primary central nervous system vasculitis
- Levamisole vasculopathy
- Eosinophilic fasciitis
- Sneddon syndrome
- Polyarteritis nodosa[11]
- Hypocomplementemic urticarial vasculitis syndrome

10. For the treatment of the predominant overlap syndrome picture, please refer to the other indications in the optimal use guide in rheumatology .
11. Based on the clinical experience of the expert committee's members, IVIg may be considered for the treatment of the juvenile form of polyarteritis nodosa, when the patient has a severe form of the disease or in the event of failure, contraindication or intolerance to the other therapeutic options.
12. Based on the limited data available in the literature and the clinical experience of the expert committee's members, IVIg may be considered for the treatment of this disorder.

DOSE AND FREQUENCY OF ADMINISTRATION OF IVIg

- The dose calculator should be used for calculating doses in adults who are overweight or clinically obese, but it can also be used safely in people over 1.52 m (5 feet) and whose weight is not less than the ideal weight. The calculator should not be used for pregnant women.

IVIg	ADULTS AND CHILDREN	
Treatment cycle	Adult: 2 g/kg (total dose) divided over 2 to 5 days [13] Child: 1 to 2 g/kg (total dose)[14] divided over 1 to 5 days Newborn: 2 g/kg as a single dose[15]	The dose can be adjusted or repeated based on the individual clinical response[16].
	Pregnant woman with anti-Ro/SSA or anti-La/SSB antibodies[17]: 1 g/kg (maximum: 70 g)	The dose is repeated every 2 to 3 weeks up to delivery.

13. The minimum dose of IVIg that requires clinical efficacy should be, as required.
14. Based on the clinical experience of the advisory committee's members, IVIg prescribed at a dose greater than 1 g/kg in children with a rheumatological disorder, except Kawasaki disease, should be administered over several days at a dose not exceeding 1 g/kg/day. When the initial dose has been well tolerated, IVIg may be administered at a dose of 2 g/kg/day, as appropriate for the patient.
15. If hemodynamic non-tolerance is anticipated, the single IVIg dose can be divided in two, i.e., 1 g/kg for 2 days.
16. Maintenance treatment for dermatomyositis and polymyositis is 0.4-1 g/kg every 2 to 6 weeks (or relapse time). Please refer to clinical guide : immunoglobulins use in neurology.
17. Based on the experts' clinical experience, the dose of 1 g/kg (maximum: 70 g) should be administered to pregnant women with systemic lupus erythematosus who have anti-Ro/SSA or anti-La/SSB antibodies if the fetus has atrioventricular block.

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, 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 formulaire 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 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.

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