INESSS
LE SAVOIR PREND FORME

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INTRAVENOUS IMMUNOGLOBULINS (IVIgs)

USE IN NEUROLOGY

This clinical guide is intended for neurologists, including pediatric neurologists, and other specialists who treat patients with autoimmune neurological diseases with IVIgs. It is provided as guidance and does not replace the practitioner's judgment. The recommendations were developed using a systematic approach, and they are supported by the scientific literature and the knowledge and experience of Québec clinicians and experts. For further details, visit inesss.qc.ca.

BACKGROUND

- The preparations of non specific human intravenous immunoglobulins (IVIgs) are stable products derived from human plasma.
- Their use in Québec has been steadily increasing in recent years, mostly for neurological indications. Because of their high cost and the risk of a shortage, it is important to ensure that they are used judiciously.
- The average cost of 1 gram of IVIgs is around $60 (2017). This figure can vary with the exchange rate for the Canadian dollar and the amount of fractionation plasma collected by Héma-Québec. The cost of IVIgs for a 70-kg adult at a dose of 2 g/kg is approximately $8400 per treatment.

INITIATING, MONITORING AND DISCONTINUING IVIgs TREATMENT

- Prior to initiating IVIgs treatment :
  - A diagnosis should be confirmed by a specialist ;
  - The patient's free and informed consent must be obtained and documented in his/her medical record.
- After treatment is initiated, for patients requiring maintenance IVIgs therapy :
  - A regular evaluation of the tolerance and effectiveness of the therapy should be performed by a specialist ;
  - The frequency of this evaluation should be determined on the basis of the patient's clinical status :
    - Initially, it should be performed at least every 3 months ;
    - Once the patient is stabilized, an evaluation is required every 6 to 12 months.
  - The patient's functional capacity and clinical response should be assessed to document the treatment's effectiveness. The use of validated disease-specific scales is encouraged, if they exist.
- If no benefit is observed in terms of the patient's clinical status after 3 to 6 months, the treatment should be discontinued and another treatment considered.

RECOMMENDATIONS FOR USING IVIgs BY INDICATION

A total of 25 neurological indications were examined (list not exhaustive)

IVIgs RECOMMENDED

INDICATION	CONDITIONS OF USE
Myasthenia gravis	▸ In cases of a severe exacerbation or a myasthenic crisis or in preparation for surgery in patients whose disease is poorly controlled
Multifocal motor neuropathy[1]	▸ As first-line treatment
Chronic inflammatory demyelinating polyneuropathy (CIDP)[1]	▸ As initial first-line treatment in patients with a moderate to severe disability ▸ As maintenance therapy : IVIgs can be considered for monotherapy or use in combination with immunosuppressive treatments in IVIgs responders
Guillain-Barré syndrome (or its variants, such as Miller-Fisher syndrome)[1]	▸ Preferably within the first 2 weeks after symptom onset in patients with a moderate to severe disability or whose disease is progressing ▸ A second treatment may be considered in the event of a relapse

1. Indication approved by Health Canada.

IVIgs NOT RECOMMENDED

INDICATION	
▸ Adrenoleukodystrophy	▸ Inclusion body myositis[1]
▸ Alzheimer's disease	▸ Critical illness polyneuropathy
▸ Amyotrophic lateral sclerosis	▸ Polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, skin changes (POEMS) syndrome
▸ Autism spectrum disorder	▸ Primary- or secondary-progressive multiple sclerosis
▸ IgM paraproteinemic neuropathy	

1. 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.

IVIgs A POSSIBLE TREATMENT OPTION

INDICATION	CONDITIONS OF USE
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
Acute disseminated encephalomyelitis (ADEM)	▸ Failure of or intolerance or contraindications to corticosteroids ▸ Failure of withdrawal from corticosteroids
Rasmussen's encephalitis	▸ Failure of antiepileptics or motor deficit progression when surgery is contraindicated
Myasthenia gravis	▸ As maintenance therapy : failure of or intolerance or contraindications to first-line treatments
Polymyositis (including immune-mediated necrotizing myopathies)[1]	▸ Always in combination with immunosuppressive treatments ▸ Failure of first-line treatments or to reduce chronic high doses of corticosteroids
Remitting multiple sclerosis	▸ Failure of or intolerance or contraindications to the recognized treatments or in special situations, such as pregnancy
Stiff person syndrome	▸ Failure of or contraindications to GABAergic drugs
Lambert-Eaton myasthenic syndrome	▸ Failure of or contraindications or intolerance to the other treatment options
Opsomyoclonus syndrome	▸ Failure of or contraindications or intolerance to the other treatment options

1. Based on the clinical experience of the expert committee's members, for patients with dermatomyositis or polymyositis, IVIgs can be considered on an exceptional basis as initial first-line treatment in combination with immunosuppressive treatments in cases of severe muscle weakness, including oropharyngeal dysphagia, or in special clinical situations (diagnosis of sclero-derma, gastrointestinal vasculitis and skin ulcers).

INSUFFICIENT DATA

INDICATION	
▸ Autoimmune encephalitis[1]	▸ PANDAS (pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections)
▸ Diabetic amyotrophy	▸ Paraneoplastic neuropathy[2]
▸ Neuromyelitis optica	

1. Based on the clinical experience of the expert committee's members, IVIgs may be considered for monotherapy or in combination with immunosuppressive treatments in cases of suspected autoimmune encephalitis or when the diagnosis is confirmed.

2. IVIgs can be considered an adjuvant to other therapeutic agents for certain forms of paraneoplastic neuropathy (especially subacute pure sensory neuropathies).

DOSE AND FREQUENCY OF ADMINISTRATION OF IVIgs

	ADULTS AND CHILDREN
Initial therapy	2 g/kg[1] over 2 to 5 days
Maintenance therapy	0.4 to 1 g/kg[1] every 2 to 6 weeks (or relapse time)
	Try to space out the treatments or to reduce the dose per treatment, based on the individual clinical response

1. kg of actual weight. Consideration may be given to using the adjusted weight in clinically obese patients.

IVIgs-RELATED TRANSFUSION REACTIONS

NON-SERIOUS TRANSFUSION REACTIONS (the most common ones)	SERIOUS TRANSFUSION REACTIONS (usually rare)
▸ Post-IVIgs headache, non-hemolytic febrile reaction, chills, rash, minor allergic reaction, asthenia, nausea, vomiting, flu-like symptoms and atypical pain (list not exhaustive)	▸ Major allergic reaction, thromboembolic reaction, delayed or immediate hemolytic reaction, transfusion-related hypertension or hypotension, 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 (especially those leading to a change in the dose, frequency or type of IVIgs administered) should be reported to the blood bank using Form AH-520

RELATIVE CONTRAINDICATIONS AND MAIN PRECAUTIONS CONCERNING IVIgs

RELATIVE CONTRAINDICATIONS

- A known allergy to one of the product's ingredients
- A history of severe immediate, anaphylactic-type, or severe delayed allergic reaction to Igs

PRECAUTIONS

Hemolysis	Thrombosis	Renal Function
▸ IVIgs-related hemolysis is more common in patients with A, B or AB type blood, patients who receive a high total dose of IVIgs (≥ 2g/kg) and those who have an underlying inflammatory condition ▸ Monitor the patient for signs and symptoms of hemolysis, such as fever, chills and dark urine. If any occur, the appropriate laboratory tests should be performed	▸ Thrombosis can occur with all types of Igs in patients with or without risk factors, regardless of the dose injected and the route of administration	▸ Check the patient's renal function if there appears to be an increased risk of acute renal failure ▸ Consider discontinuing the IVIgs if there is a deterioration in the patient's renal function

USE OF SUBCUTANEOUS Igs (SCIgs)

- SCIgs can be considered for replacing IVIgs in patients with CIDP or multifocal motor neuropathy if a clinical response was previously obtained with IVIgs
- The advisability of prescribing SCIgs to replace IVIgs depends on the patient's clinical situation and on practical considerations, such as the availability of a natural caregiver and nursing staff or the travel requirements due to IVIgs injections
- There are no Health Canada-approved neurological indications for SCIgs

This guide was prepared in collaboration with an expert committee. INESSS supports the recommendations made.

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