INESSS
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ALTERNATIVE TREATMENT WITH IV OR SC IMMUNOGLOBULINS

USE IN CLINICAL IMMUNOLOGY

This optimal use guide is intended for immunologists and other medical specialists who treat patients with a primary or secondary immunodeficiency 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 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 treatment of the immunodéficiente listed and do not concern the infectious complications that may be associated with them.
- Intravenous (IV) and subcutaneous (SC) non-specific human immunoglobulin (Ig) preparations are stable products derived from human plasma.
- The efficacy of IVIg and SCIg is considered to be equivalent in preventing infections. At the start of treatment, IVIg or SCIg should be recommended according to the patient's preferences and on practical considerations.
- Their use continued to increase in Québec in the past several years. Because of their high cost and the risk of a shortages, it is important to ensure that they are used judiciously.
- The price of a gram of IVIg or SCIg is about $90 (2017). The cost of Ig for a 70-kg adult is approximately $32,760 per year for treatment at a dose of 0,4 g/kg repeated every 4 weeks.

INITIATING, MONITORING AND DISCONTINUING IVIg OR SCIg THERAPY

- Before initiating IVIg or SCIg 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.
- After IVIg or SCIg 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;
  - A first assessment should be carried out no later than 6 months after the start of treatment and then every 6 to 12 months or as needed.

RECOMMENDATIONS FOR USING IVIg OR SCIg BY INDICATION

IVIg or SCIg RECOMMENDED[1]

INDICATION	CONDITIONS OF USE
Severe combined immunodeficiencies	▸ In the presence of a confirmed or suspected diagnosis of severe combined immunodeficiency
Combined immunodeficiencies	▸ In the presence of a confirmed or suspected diagnosis of combined immunodeficiency
Combined immunodeficiencies with associated or syndromic features	▸ In the presence of a confirmed or suspected diagnosis of combined immunodeficiency with associated or syndromic features
Agammaglobulinemia	▸ In the presence of a confirmed or suspected diagnosis of agammaglobulinemia, whether genetically characterized or not
Common variable immunodeficiency	▸ In the presence of a confirmed or suspected diagnosis of common variable immunodeficiency, whether genetically characterized or not
Hyper IgM syndrome	▸ In the presence of a confirmed or suspected diagnosis of hyper IgM syndrome
Primary isolated IgG deficiency[2]	▸ In the presence of a confirmed or suspected diagnosis of primary isolated IgG deficiency
LRBA or CTLA4 deficiency	▸ In the presence of a confirmed or suspected diagnosis of LRBA or CTLA4 deficiency ▸ In the presence of a confirmed humoral deficiency
WHIM syndrome	▸ In the presence of a confirmed or suspected diagnosis of WHIM syndrome
Good syndrome	▸ In the presence of a thymoma with hypogammaglobulinemia
Hypogammaglobulinemia due to CAR-T cell therapies	▸ In the presence of hypogammaglobulinemia due to CAR-T cell therapy

1. Health Canada-approved indications (primary and secondary immunodeficiencies).
2. Before the prescription of Ig treatment, the patient must be investigated for a defect in the production of specific antibodies concurrent with the isolated IgG deficiency..

IVIg or SCIg NOT RECOMMENDED

INDICATIONS

- Selective IgA deficiency with a confirmed diagnosis
- Kappa chain deficiency
- Primary hemophagocytic lymphohistiocytosis
- Autoimmune lymphoproliferative syndromes
- Congenital defects in phagocyte number or function
- All defects in intrinsic or innate immunity (with the exception of WHIM syndrome)
- Auto-inflammatory disorders not associated with an antibody deficiency
- All complement deficiencies (except those associated with a syndrome similar to systemic lupus erythematosus)
- Phenocopies of primary immunodeficiencies associated with a somatic mutation[1]
- Selective IgM deficiency with a confirmed diagnosis[2]
- In preterm newborns in an infection prevention context

1. This group of indications includes autoimmune lymphoproliferative syndrome due to somatic FAS mutation, RAS-associated autoimmune leukoproliferative disease, cryopyrinopathy, and hypereosinophilic syndrome due to somatic mutations in STAT5b.
2. Another immunodeficiency concurrent with selective IgM deficiency may be present and need to be diagnosed before IVIg or SCIg administration. Following diagnosis, consult the recommendations concerning the identified immunodeficiency.

IVIg or SCIg POSSIBLE THERAPEUTIC OPTION[1]	
INDICATION	**CONDITIONS OF USE**
X-linked lymphoproliferative syndromes and other immunodeficiencies associated with susceptibility to Epstein-Barr virus	▸ In the presence of hypogammaglobulinemia
PLCg2 associated antibody deficiency and immune dysregulation or ADA2 deficiency	▸ In the presence of a severe, unusual or recurrent infection ▸ In the presence of hypogammaglobulinemia
Transient hypogammaglobulinemia in infancy[2]	▸ In case of failure of prophylactic antibiotic treatment against infection, in children under 4 years of age, at the time of diagnosis ▸ In the presence of a recurrent suppurative infection threatening the function of an organ ▸ In the presence of a severe, unusual or recurrent infection *After the Ig therapy is discontinued, the patient should be reevaluated at a later age to check whether the immunodeficiency has disappeared.*
IgG2 subclass deficiency associated or not with IgA deficiency[3]	▸ In case of failure of prophylactic antibiotic treatment against infection ▸ In the presence of advanced lung damage ▸ In the presence of a severe, unusual or recurrent infection
Specific antibody deficiencies with normal Ig levels	▸ In case of failure of prophylactic antibiotic treatment against infection[4]
CARD11 gain-of-function mutations	▸ In the presence of a severe, unusual or recurrent infection
STAT3 gain-of-function mutations	▸ In the presence of a severe, unusual or recurrent infection ▸ In the presence of hypogammaglobulinemia
Hypogammaglobulinemia due to treatment with B cell-targeted therapy, including rituximab[5], or with immunosuppressants, including high-dose corticosteroids[6], or with a drug, *(antineoplastic, antiepileptic, etc.)*	▸ In the presence of a severe, unusual or recurrent infection ▸ In the presence of severe hypogammaglobulinemia, i.e., an IgG level < 2 g/l in adults, that may be associated with a specific antibody deficiency ▸ In the presence of significant immunosuppression ▸ After a splenectomy
Hypogammaglobulinemia due to Steinert myotonic dystrophy	
Hypogammaglobulinemia due to chylothorax, or exudative enteropathy, or intestinal lymphangiectasia, or lymphedema, or nephrotic syndrome	▸ In the presence of a severe, unusual or recurrent infection ▸ In the presence of severe hypogammaglobulinemia, i.e., an IgG level < 2 g/l in adults ▸ In the presence of significant immunosuppression *The subcutaneous route is preferable, if administration is possible for hypogammaglobulinemia associated with protein loss.*
In preterm newborns in an infection treatment context	▸ In the presence of a severe, life-threatening infection despite optimal treatment in an intensive care unit[7]

1. Little or no data are available in the literature on the efficacy of Ig in these indications. Recommendations concerning these indications are therefore based on the opinion of the advisory committee's members.
2. In general, transient hypogammaglobulinemia in infancy does not require the use of Ig.
3. The IgG2 subclass deficiency should be documented concurrent with the prescription of Ig.
4. IVIg or SCIg therapy should be prescribed by an immunologist.
5. For the treatment of underlying diseases (multiple myeloma, lymphoproliferative syndromes, etc.) associated with secondary immunodeficiencies, please consult the optimal use guide - immunoglobulins in hematology.
6. The patient's immunological condition should be evaluated by an immunologist.
7. A consultation with a neonatologist or pediatric immunologist with experience treating infections in preterm newborns may be necessary to assess the appropriateness of prescribing IVIg therapy.

INSUFFICIENT DATA

INDICATIONS

- Regulatory T cell defects associated with immune dysregulation polyendocrinopathy enteropathy X-linked or CD25 deficiency or BACH2 deficiency
- Autoimmunity with or without lymphoproliferation
- Immune dysregulation with colitis
- Complement deficiencies associated with a syndrome similar to systemic lupus erythematosus
- Phenocopies of primary immunodeficiencies associated with auto-antibodies
- IgG subclass deficiencies associated or not with IgA deficiency (with the exception of IgG2 subclass deficiency)
- Hypogammaglobulinemia due to treatment with plasma cell targeting agents[1]
- Secondary hypogammaglobulinemia in a severe burn patient[2]
- Hypogammaglobulinemia associated with malnutrition[3]

1. For the treatment of underlying diseases (multiple myeloma, lymphoproliferative syndromes, etc.) associated with secondary immunodeficiencies, please consult the optimal use guide - immunoglobulins in hematology .
2. If IVIg or SCIg are used, this should be transient and reassessed regularly.
3. Correcting the malnutrition is sufficient for resolving the hypogammaglobulinemia.

DOSE AND FREQUENCY OF ADMINSTRATION OF IVIg OR SCIg

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

IVIg	ADULTS AND CHILDREN	
Starting dose[1]	0.4 – 0.6 g/kg	**Adjust the dose according to the situation and the individual clinical response**
Maintenance dose[2]	0.4 – 0.6 g/kg every 3 or 4 weeks	

IVIg	PRETERM NEWBORNS
Consult a neonatologist or pediatric immunologist with experience treating infections in preterm newborns to determine the dosage to be used.	

IgSC	ADULTES ET ENFANTS	
Starting dose[1]	0.1 – 0.2 g/kg	SCIg can be administered daily, weekly or every 2 weeks with an adjusted dose corresponding to a total dose of 0,1- 0,2 g/kg per week. **Adjust the dose according to the situation and the individual clinical response**
Maintenance dose[2]	0.1 – 0.2 g/kg per week	

1. In the case of a severe or life-threatening infection, the starting dose can be higher
2. The interval for the maintenance dose is provided as a guide only. A dosage outside this interval can be used, depending on the situation and the individual clinical response.

TRANSFUSION REACTIONS ASSOCIATED WITH IVIg OR SCIg

NON-SERIOUS TRANSFUSTION REACTIONS (the most common)	SERIOUS TRANSFUSION REACTIONS (usually rare)
▸ Post-IVIg headache, febrile non-hemolytic transfusion reaction, chills, urticaria, asthenia, nausea, vomiting, flu-like symptoms, atypical pain, post-transfusion hypertension or hypotension (list not exhaustive)	▸ Immediate anaphylactic-type 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 results in a change in the dose, frequency and type of Ig administered or that warrant discontinuing the treatment) 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)

PRÉCAUTIONS

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 administreted 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.

MAIN REFERENCES

The International Union of Immunological Societies (2018). The 2017 IUIS Phenotypic Classification for Primary Immunodeficiencies.

To consult all the references, see the report in support of the optimal use guide and the systematic review report.

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

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