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Validation of the management framework for a nonspecific human immunoglobulin shortage

English summary

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SUMMARY

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Introduction

During the public health crisis caused by coronavirus disease (COVID-19), production and supply problems might lead to a reduction in immunoglobulin reserves or an immunoglobulin shortage in Québec. In order to manage such a situation, the Ministère de la Santé et des Services sociaux (MSSS) asked the Institut national d'excellence en santé et en services sociaux 1) to validate the rules proposed by the nonspecific human immunoglobulin (Ig) shortage management framework of the emergency measures plan developed by MSSS's *Direction de la biovigilance et de la biologie médicale* and 2) to determine whether an additional level of reserve availability should be created between the yellow and red levels in the current management framework to better meet the needs associated with the COVID-19 pandemic.

Methodology

The validation of the rules proposed by the nonspecific human immunoglobulin shortage management framework was based on the clinical recommendations in the five immunoglobulin optimal use guides developed outside of the context of the COVID-19 pandemic by INESSS, as well as on contextual information and stakeholders' perspectives regarding the current public health crisis. The guides contain clinical recommendations on the optimal use of immunoglobulins for indications in neurology, hematology, clinical immunology, dermatology and rheumatology. The validation of the information and rules in the immunoglobulin shortage management framework was enhanced by gathering the perspectives of various experts, including clinicians and an ethicist, and took the legislative, regulatory, organizational and economic context specific to Québec into account. The advisability of creating an additional phase between the yellow and red levels was assessed in light of the perspectives of the various stakeholders and on the basis of the contextual data. In addition, as part of this work, a narrative review of the ethical issues surrounding immunoglobulin shortages was conducted.

Results

The rules in the immunoglobulin shortage management framework of the emergency measures plan are optimal for 12 of the 30 indications. However, changes to the conditions of use of immunoglobulins are proposed for the following 18 indications: primary immune deficiencies, including severe immunodeficiency, combined immunodeficiency, combined immunodeficiency with associated or syndromic features, genetically or non-genetically characterized agammaglobulinemia, common variable immune deficiency, hyper-IgM syndrome, isolated primary IgG deficiency, LRBA or

CTL4A deficiency, WHIM syndrome and Good syndrome, hypogammaglobulinemia secondary to hematologic cancer, Kawasaki disease, acute immune thrombocytopenia, chronic immune thrombocytopenia, fetal or neonatal alloimmune thrombocytopenia, immune thrombocytopenia during pregnancy, autoimmune hemolytic anemia, hemolytic disease of the newborn or fetus, autoimmune neutropenia, allogeneic hematopoietic stem cell transplant, parvovirus B19-induced red cell aplasia, Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy, Rasmussen's encephalitis, bullous dermatoses and Stevens-Johnson syndrome/toxic epidermal necrolysis. As well, the addition of an indication – multisystem inflammatory syndrome in children temporally associated with COVID-19 – is recommended under the same conditions of use as for Kawasaki disease.

The creation of an additional level of reserve availability between the yellow and red levels does not appear necessary. However, the lime green and yellow levels should be adjusted according to different situations and in light of the many factors that can set the Ig shortage management plan in motion.

Conclusion

The purpose of this report was to provide the MSSS with guidance regarding the rules to be included in the Ig shortage management framework of the emergency measures plan. An examination of the entirety of the data led to the development of recommendations on the indications to be included in the management framework, the conditions of use for each indication, and the reserve availability levels. In addition, several ethical considerations to be taken into account when allocating limited resources were identified. In the event of a decrease in Ig reserve availability or of an Ig shortage, the recommendations in this report will promote fair and equitable use of these products in order to maximize the health and well-being of those who need them in Québec.

Recommendations regarding the content of the Ig shortage management framework of the emergency measures plan in the case of an Ig supply shortage in Québec
The rules proposed by the Ig shortage management framework of the emergency measures plan should remain unchanged for the following 12 indications: post-transfusion purpura, hyperhemolytic syndrome, catastrophic antiphospholipid syndrome, acquired hemophilia, myasthenia gravis, dermatomyositis (including the juvenile form), polymyositis, acute disseminated encephalomyelitis, relapsing-remitting multiple sclerosis, Lambert-Eaton myasthenic syndrome, stiff man syndrome, and opsoclonus myoclonus syndrome.
The rules proposed by the Ig shortage management framework of the emergency measures plan should be modified for 18 indications. The recommendations for each of these indications are as follows: **IMMUNOLOGY** • Primary immunodeficiency disorders[2], which includes severe immunodeficiency, combined immunodeficiency, combined immunodeficiency with associated or syndromic features, genetically or non-genetically characterized agammaglobulinemia, common

variable immunodeficiency, hyper-IgM syndrome, isolated primary IgG deficiency, LRBA or CTL4A deficiency, WHIM syndrome and Good syndrome. Conditions of use:

  - Yellow level: Priority use. Refer the patient to an immunologist.
  - Red level: Priority use. Lower the IgG target level to be achieved to the minimum as tolerated on a case-by-case basis and refer the patient to an immunologist.

- Secondary hypogammaglobulinemia[2]. Conditions of use:
  - Yellow and red levels: To be considered only in the presence of confirmed secondary hypogammaglobulinemia and in the presence or absence of an infection. Consult an immunologist experienced in the treatment of secondary hypogammaglobulinemias. Lower the IgG target level to be achieved to the minimum as tolerated on a case-by-case basis and with iterative monitoring of serum IgG levels.

RHEUMATOLOGY

- Kawasaki disease. Conditions of use:
  - Yellow level: Priority use.
  - Red level: Priority use. Consult a rheumatologist to confirm the diagnosis. If the initial IVIg treatment fails, do not repeat the treatment.

HEMATOLOGY

- Acute immune thrombocytopenia. Conditions of use:
  - Yellow level: Failure, contraindication or intolerance to steroids and anti-D Ig (e.g., Rh-) AND in the presence of a platelet count < 10 x 10^9/l or < 30 x 10^9/l if moderate to severe bleeding OR before emergency surgery OR in the presence of life-threatening bleeding.
  - Red level: Failure, contraindication or intolerance to steroids, anti-D Ig (e.g., Rh-), rituximab and TPO receptor agonists AND in the presence of moderate to severe bleeding AND in the presence of a platelet count < 30 x 10^9/l OR before emergency surgery OR in the presence of life-threatening bleeding.
- Chronic immune thrombocytopenia. Conditions of use:
  - Yellow level: Failure, contraindication or intolerance to steroids, anti-D Ig (e.g., Rh-), rituximab and TPO receptor agonists AND in the presence of a platelet count < 10 x 10^9/l OR failure, contraindication or intolerance to steroids and anti-D Ig (e.g., Rh-) AND in the presence of moderate to severe bleeding AND in the presence of a platelet count < 30 x 10^9/l OR before emergency surgery OR in the presence of life-threatening bleeding.
  - Red level: Failure, contraindication or intolerance to steroids, anti-D Ig (e.g., Rh-), rituximab and TPO receptor agonists AND in the presence of moderate to severe

bleeding AND in the presence of a platelet count < 30 x 10^9/l OR before emergency surgery.

- Fetal or neonatal alloimmune thrombocytopenia. Conditions of use:
  - Yellow level:
    - Treatment of the mother during pregnancy:
      - Use permitted. Do not exceed 1 g/kg/week.
      - In women with fetal-maternal incompatibility and a history of fetal or neonatal intracranial hemorrhage due to alloimmune thrombocytopenia, a dose of 2 g/kg/week may be considered.
    - Treatment of the newborn:
      - In the presence of life-threatening bleeding or a platelet count < 25 x 10^9/l, when a transfusion of platelets (selected or not selected for the human platelet antigen [HPA]) is not an option;
      - Refer the newborn to a pediatric hematologist, an obstetrician or a neonatologist who specializes in this clinical area.
  - Red level:
    - Treatment of the mother during pregnancy:
      - Use permitted. Do not exceed 1 g/kg/week;
      - In women with fetal-maternal incompatibility and a history of fetal or neonatal intracranial hemorrhage due to alloimmune thrombocytopenia, a dose of 2 g/kg/week can be considered only in the case of contraindication to steroids.
    - Treatment of the newborn:
      - In the presence of life-threatening bleeding or a platelet count < 25 x 10^9/l, when a transfusion of platelets (selected or not selected for the human platelet antigen [HPA]) is not an option.
      - Refer the newborn to a pediatric hematologist, an obstetrician or a neonatologist who specializes in this clinical area.
- Immune thrombocytopenia during pregnancy. Conditions of use:
  - Yellow and red levels: Failure, contraindication or intolerance to steroids AND in the presence of a platelet count < 30 x 10^9/l AND/OR moderate to severe bleeding, OR in preparation for delivery to achieve a platelet count ≥ 50 x 10^9/l if failure, contraindication or intolerance to steroids OR in the presence of life-threatening bleeding. Re-evaluate the minimum IVIg dose and frequency that achieve a satisfactory clinical response.

- Autoimmune hemolytic anemia. Conditions of use:
  - Yellow level: In the case of failure, contraindication or intolerance to the other therapeutic options and transfusion dependency.
  - Red level: Do not use.
- Hemolytic disease of the newborn or fetus. Conditions of use:
  - Yellow level:
    - Treatment of the mother during pregnancy: Use permitted in the presence of a high risk AND contraindication to intrauterine transfusion.
    - Treatment of the newborn: Use permitted in the case of hyperbilirubinemia due to Rh incompatibility if phototherapy fails. Re-evaluate the minimum IVIg dose and frequency that achieve a satisfactory clinical response.
  - Red level:
    - Treatment of the mother during pregnancy: Use permitted in the presence of a high risk AND contraindication to intrauterine transfusion.
    - Treatment of the newborn: Use permitted in the case of hyperbilirubinemia due to Rh incompatibility if phototherapy fails and if an exchange transfusion is not possible within a reasonable delay. Re-evaluate the minimum IVIg dose and frequency that achieve a satisfactory clinical response.
- Autoimmune neutropenia. Conditions of use:
  - Yellow level: in the case of failure, contraindication or intolerance to the other treatment options.
  - Red level: in the case of failure, contraindication or intolerance to the other treatment options AND in the presence of a severe active infection.
- Allogeneic hematopoietic stem cell transplant[1 and 2]. Conditions of use:
  - Yellow level: Use permitted in any of the following four circumstances:
    - For a patient being treated with steroids for chronic graft-versus-host disease, GVHD (or acute GVHD that is becoming chronic);
    - In the case of a haploidentical or cord blood transplant;
    - For a patient with severe recurring infections;
    - For a patient with profound hypogammaglobulinemia.
  - Red level: Use permitted for patients with profound hypogammaglobulinemia.
- Parvovirus B19-induced red cell aplasia. Conditions of use:
  - Yellow level: Permitted in the case of failure, contraindication or intolerance to the other treatment options.

- Red level: Permitted in the case of failure, contraindication or intolerance to the other treatment options and in the case of transfusion dependency.

NEUROLOGY

- Guillain-Barré syndrome and its variants, including Miller-Fischer syndrome. Conditions of use:
  - Yellow level: Priority use.
  - Red level: In the case of contraindication, non-availability or intolerance to plasma exchanges.
- Chronic inflammatory demyelinating polyneuropathy. Conditions of use:
  - Yellow and red levels:
    - Initial treatment: First line for patients with a moderate or severe disability.
    - Maintenance treatment[2]: Re-evaluate the minimum IVIg dose that achieves a satisfactory clinical response or reduce the frequency of the treatments. Consult a neurologist.
- Multifocal motor neuropathy. Conditions of use:
  - Yellow and red levels: Priority use[3].
- Rasmussen's encephalitis. Conditions of use:
  - Yellow and red levels: In the case of failure, contraindication or intolerance to the other treatment options[3]. IVIg therapy must be continued if the patient shows disease stability with immunoglobulin.

DERMATOLOGY

- Pemphigus and the group of pemphigoid (mucous membrane pemphigoid, bullous pemphigoid and pemphigoid gestationis). Conditions of use:
  - Yellow and red levels: For patients with a severe form of the disease to achieve rapid remissio. In the case of failure, contraindication or intolerance to the other treatment options.
- Stevens-Johnson syndrome/toxic epidermal necrolysis:
  - Yellow and red levels: The use of IVIg is not recommended.

Footnotes

1. In the red phase, an adjudication committee will be used to evaluate requests that do not meet the criteria and may approve these on a case-by-case basis.
2. Preference should be given to using SCIg for approved indications during an IVIg shortage.
3. For chronic conditions, when immunoglobulin is administered as maintenance therapy, attempt to lower the dose to the minimum that achieves a satisfactory clinical response or reduce the frequency of treatments during the yellow and red phases.

INESSS recommends adding an indication, namely, multisystem inflammatory syndrome in children temporally associated with COVID-19, with the following conditions of use:

- Yellow level: Priority us.
- Red level: Priority use. Consult a rheumatologist to confirm the diagnosis. If the initial IVIg treatment fails, do not repeat the treatment.

Recommendations regarding the creation of an additional level of reserve availability between the yellow and red levels

For the purpose of managing Ig shortages, Ig reserve levels are defined as follows:

- *Green level: The Ig reserves meet the demand.*
- *Lime green level: The Ig reserves have decreased or are still sufficient, but there are signs that the demand could exceed capacity in the short term.*
- *Yellow level: The Ig reserves are low for a brief or prolonged period.*
- *Red level: There is a severe and prolonged Ig shortage.*

A reserve availability level between the yellow level and the red level should not be created.

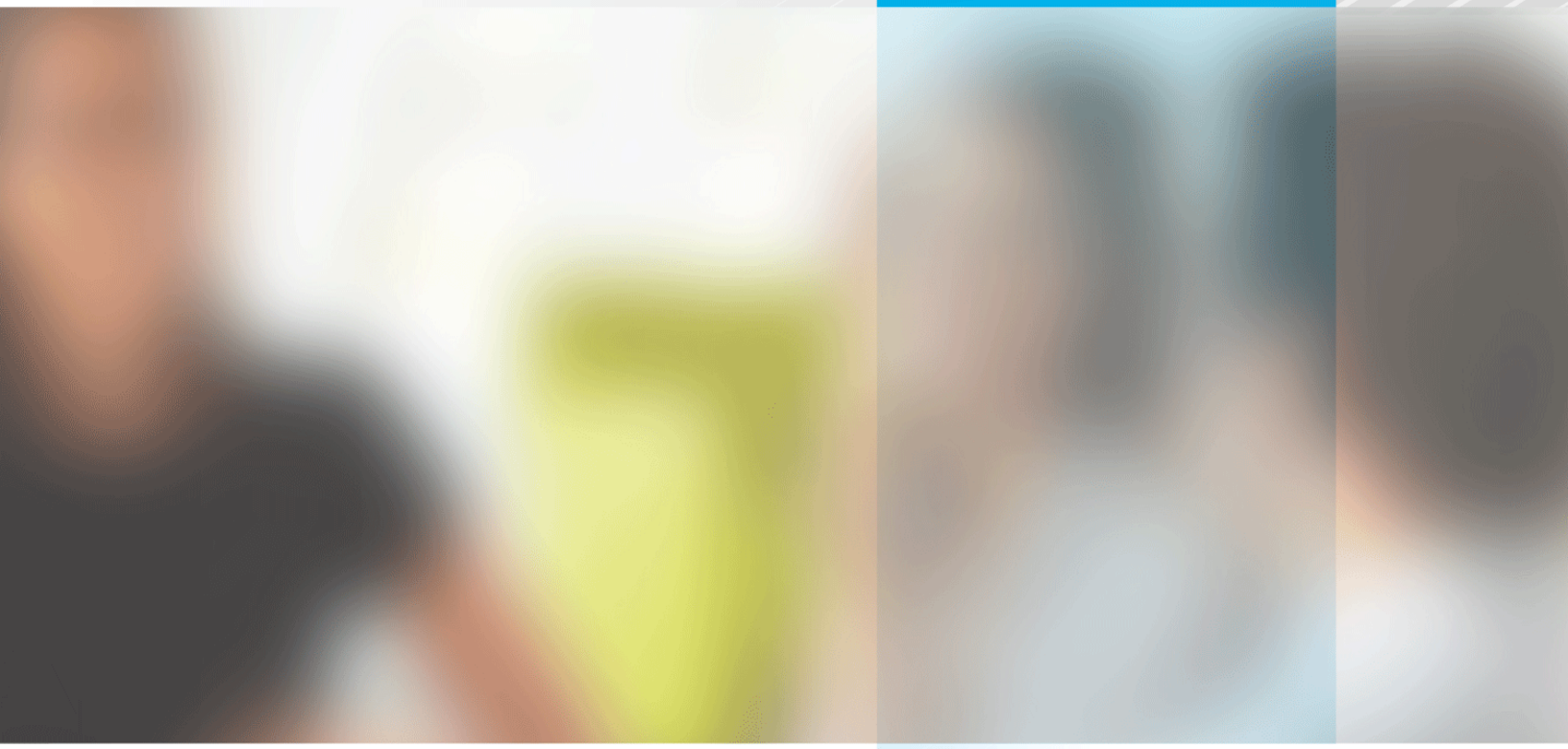
However, the definitions of the lime green and yellow levels could be modified according to the particular situation that requires launching the Ig shortage management framework. In the current context of the COVID-19 pandemic, for which the issue is an Ig supply problem, a reduction in Ig use of 20 to 50% instead of 15 to 50% is recommended for the yellow level. The lime green level should also be redefined to specify a reduction in Ig use of 5 to 20% instead of 5 to 15%.

These availability levels are arbitrary, and the Ig reserve availability thresholds could be adjusted depending on the situation and the numerous factors that can set the Ig shortage management plan in motion.

Implementation recommendations

To limit the impact of a reduction in Ig reserves or of an Ig shortage on patients who use these products, MSSS should put conditions in place that favour the dissemination and implementation of the Ig shortage management framework of the emergency measures plan within Québec's system of health and social services. MSSS should also ensure institutional compliance with the rules proposed therein in order to standardize prescribing practices among prescribers and institutions, to promote optimal Ig use, and to ensure fair and equitable access for those most in need of this treatment.

To promote optimal Ig use, the standardized AH-240 and AH-241 forms should be used for all IVIg prescriptions.



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