The National Plan for Management of Shortages of Immunoglobulin Products (Ig) – Interim Guidance

2020-07-27

Canadian Blood Services
BLOOD PLASMA STEM CELLS ORGANS & TISSUES

National Advisory Committee on Blood and Blood Products | Comité consultatif national sur le sang et les produits sanguins

Table of Contents

Abbreviations

CBS	Canadian Blood Services
CBS-P/TBLC	Canadian Blood Services Provincial/Territorial Blood Liaison Committee
H/REBMC	Hospital/Regional Emergency Blood Management Committee
HQ	Héma-Québec
HTC	Hospital Transfusion Committee
Ig	Immunoglobulin
IVIg	Intravenous immunoglobulin
NAC	National Advisory Committee on Blood and Blood Products
NEBMC	National Emergency Blood Management Committee
P/T	Provincial/Territorial
P/TEBMC	Provincial/Territorial Emergency Blood Management Committee
PBCO	Provincial Blood Coordinating Office
RHA	Regional Health Authorities or alternate service providers/structure within a province.
SCIg	Subcutaneous immunoglobulin

Acknowledgements

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Executive summary

Canadian Blood Services manages a pan-Canadian formulary of approximately 50 brands of plasma protein products and synthetic alternatives. Globally, the use and demand for these products continue to rise. In particular, Ig utilization has more than doubled internationally over the past ten years. Ig is used to treat primary and secondary immune deficiency disorders, and autoimmune disorders including autoimmune neurological disorders and other diseases with an immune origin. In some cases, these are lifesaving treatments for which there are no alternative therapies.

The 2018 Expert Panel on Immune Globulin Product Supply and Related Impacts in Canada recommended the development of a national prioritized list of patient groups dependent on Ig and a process to allow appropriate allocation in the setting of a short-term or more prolonged shortage. Limitations in the supply of subcutaneous Ig (SCIg) in the summer of 2019 underscored the need for a dedicated national Ig shortage management plan. Subsequently, the CBS-P/TBLC identified the development of a national plan for managing Ig shortages as a priority project for the NAC.

NAC had initiated planning to develop a national Ig shortage plan but had not yet started the work when the COVID-19 pandemic struck in early 2020. The pandemic's potential impact on the global Ig supply chain highlighted the urgent need to have an Ig shortage management plan in place. Given that the development of a comprehensive plan would require significant time and resources, and that COVID-19 impacts to supply may emerge in the short- to medium-term, the NAC and CBS-P/TBLC recognized that proceeding with the development of an interim plan was required and tasked the NEBMC Secretariat with having an interim national plan in place within a 3-month time-frame by mid-July 2020.

The National Plan for Management of Shortages of Immunoglobulin Products (Ig) – Interim Guidance, henceforth known as the interim Ig plan, is intended as a response to potential

supply impacts on the near horizon and to remain in place while a full plan is developed. To expedite the development of the interim Ig plan, the NEBMC Secretariat leveraged existing documents including the Government of Quebec's *Nonspecific Immunoglobulin (Ig) Shortage Management Framework* and *The National Plan for Management of Shortages of Labile Blood Components*. In late May 2020, approximately 400 stakeholders, representing jurisdictions served by Canadian Blood Services, were invited to provide feedback on the criteria for use of Ig in a shortage as outlined in the Quebec document (see Appendix B for details on the consultation process).

The specific purpose of this interim Ig plan is to maximize the effectiveness of a response to any crisis which impacts the adequacy of the overall Ig supply in Canada. This interim Ig plan assumes that all efforts to increase the available supply of Ig (IVIg and/or SCIg) have been exhausted and addresses the allocation of the available scarce Ig supply.

This interim Ig plan provides a framework which will enable P/T ministries of health and hospitals/regional health authorities (RHA) to develop their own Ig shortage management plans in a manner that is congruent and complementary with the interim Ig plan. This approach is aimed at achieving the consistency and collaboration crucial to the effective management of an Ig shortage.

Based on a number of stated assumptions, the interim Ig plan addresses four phases of inventory availability – Green, Amber, Red and Recovery. Determination of the need to declare a shortage phase could apply to a single Ig brand or multiple brands in either SCIg or IVIg formulations.

- **Green** implies that normal Ig inventory levels exist and supply generally meets demand. This phase includes a broad range of inventory levels ranging from an ideal inventory to shortages that occur periodically and can be managed with existing Canadian Blood Services and hospital/RHA actions.
    - Green Advisory implies that Ig inventory levels are low, and that system wide inventory and utilization needs to be understood to inform the likelihood of crossing into Amber or Red Phase.
- **Amber** implies that the national Ig inventory is insufficient to continue with routine deliveries and hospitals/RHA will be required to implement specific measures, as outlined in this document, to reduce Ig usage.
- **Red** implies that Ig inventory levels are insufficient to ensure all patients will receive required Ig.
- **Recovery** implies that Ig inventory levels have begun to increase and are expected to be maintained at a level which would enable the return from Red to Amber and subsequently to Green Phase.

The roles and responsibilities of the principal participants, namely Canadian Blood Services, the P/T ministries of health and the Canadian hospitals/RHA, in each of these phases are described

in this document as well as the emergency blood management committees that would be required to successfully manage an Ig shortage.

The optimal management of an Ig shortage will depend upon the commitment of all stakeholders in the system served by Canadian Blood Services to work collaboratively to ensure scarce resources are used in a fair and equitable manner. This interim Ig plan is intended to provide a framework, which if followed, will ensure that optimization. It is nevertheless recognized that lessons will be learned in each shortage situation.

The development and implementation of this interim Ig plan and the resulting lessons learned will serve as a framework to directly inform the development of a full national Ig shortage management plan once this short-term supply risk is addressed. Work on the full plan is expected during the 12 to 24 months following final approval of the interim Ig plan. Revisions and the substantive change history of this interim Ig plan can be viewed in Appendix A.

1. Introduction

1.1 The Canadian blood system

Canada has two blood operators - Canadian Blood Services, which manages the blood supply system in all provinces and territories (except Québec); and Héma-Québec, which serves Québec. Canadian Blood Services and Héma-Québec collect blood donations from voluntary donors, prepare blood components and distribute them to hospitals in their respective jurisdictions. Canadian Blood Services and Héma-Québec are funded by the provinces and territories that they serve, but the management of the blood supply is entirely the responsibility of Canadian Blood Services and Héma-Québec within their respective jurisdictions. Both organizations are also responsible for managing the supply of commercially obtained plasma protein products (e.g. IVIg, SCIg, albumin and coagulation factor concentrates) and recombinant coagulation factors.

Within the ministry of health (ministries) in each province and territory served by Canadian Blood Services there is one identified person, the P/T blood representative, who has the primary responsibility for interactions between Canadian Blood Services and their province/territory. The P/T ministries of health select one jurisdiction, on a rotating basis, to act as the lead P/T on behalf of all jurisdictions for a period of two years.

The P/T blood representatives, together with selected representatives from the Canadian Blood Services executive and senior management teams, form a committee known as the CBS-P/T BLC. This committee is co-chaired by a Canadian Blood Services representative and the P/T blood representative for the lead province. This committee meets on a regular basis and constitutes the major forum for formal communications between Canadian Blood Services and its funders.

Canadian Blood Services solicits advice from various stakeholders through its advisory committees (as well as other ad hoc forums). One such committee is the National Advisory Committee on Blood and Blood Products (NAC), an advisory committee consisting of health care professionals with expertise in the field of transfusion medicine appointed by their respective P/T ministries, as well as Canadian Blood Services representatives. The NAC reports to the CBS-P/TBLC (current NAC membership and its terms of reference are available on www.nacblood.ca).

1.2 Immunoglobulins in Canada

Canadian Blood Services manages a pan-Canadian formulary of about 50 brands of plasma protein products and synthetic alternatives. The organization also stores, ships and delivers these drugs to hospitals and clinics across the country using a network already approved and funded as part of its national blood supply responsibilities. The plasma protein products program leverages the combined buying power of provincial and territorial health budgets to offer publicly funded blood products to those who need them at no direct cost to the patient. While Canadian Blood Services offers a substantial range of products, it has a managed formulary–not an open

formulary. Selective changes to product listings occur through product selection and tendering processes. While many of these drugs are administered in hospital, increasingly they are being manufactured in formulations that permit in-home administration, such as through subcutaneous injection.

Ig products are used to treat primary and secondary immune deficiency disorders, and autoimmune disorders including autoimmune neurological disorders and other diseases with an immune origin. Currently, Ig products account for 45% of all plasma protein products expenditures annually. Utilization continues to grow year over year and although there are jurisdictional guidelines available across the country, there is a recognized variation in use between provinces.

1.3 Purpose and scope

Currently, there is a national plan and framework to determine the equitable allocation of labile blood components in times of shortage. While many of the principles within *The National Plan for the Management of Shortages of Labile Blood Components* may also be applicable to a shortage of plasma protein products, the CBS-P/TBLC recognized that a national plan to specifically guide the allocation of Ig products in a short or prolonged shortage was needed and identified this as a priority task for NAC in 2019.

NAC had initiated planning to develop a national Ig shortage plan but had not yet started the work when the COVID-19 pandemic struck in early 2020. The pandemic's potential impact on the global Ig supply chain highlighted the urgent need to have an Ig shortage management plan in place. The NAC and CBS-P/TBLC recognized that proceeding with the development of an interim plan was required and tasked the NEBMC Secretariat with having an interim plan in place within a 3-month time-frame by mid-July 2020.

This interim Ig plan is intended as a response to potential supply impacts on the near horizon and to remain in place while a full plan is being developed. To expedite the development of the interim Ig plan, the NEBMC Secretariat leveraged existing documents including the Government of Québec's *Nonspecific Immunoglobulin (Ig) Shortage Management Framework* and *The National Plan for Management of Shortages of Labile Blood Components*.

The development of this interim Ig plan primarily focused on the clinical criteria for use and allocation of Ig products in times of shortage and is intended as a stopgap measure until a full national Ig shortage management plan is developed. It is reasonable to assume the development and implementation of this interim Ig plan and the resulting lessons learned will serve as a framework to inform the development of a full national Ig shortages management plan once this short-term supply risk is addressed.

1.4 Key participants and stakeholders

It is intended that the interim Ig plan will be used by key blood system participants who, for the purposes of the interim Ig plan, are defined to be Canadian Blood Services, regional health

authorities, hospitals, Ig prescribers, the provincial and territorial ministries of health, and the NAC. Some provinces have provincial blood coordinating offices; while not referred to specifically in the interim Ig plan, it is assumed that they, under the auspices of the corresponding ministry of health, will also play a key role in the implementation of the interim Ig plan. The interim Ig plan delineates roles and responsibilities for each of these participants.

Stakeholders for the interim Ig plan are these participants, as well as others potentially affected (or representing those potentially affected) by the interim Ig plan such as patient/blood recipient societies, health care professional societies, Héma-Québec, Health Canada, product vendors and others.

1.5 History of Ig shortages in Canada

Since Canadian Blood Services has been providing Ig products to hospital customers, there have been no shortages that would have met criteria to call a national Amber or Red phase in Canada for the overall Ig supply (including both IVIg and SCIg).

In 2019, Canadian Blood Services did experience a short-term supply constraint for SCIg due to unprecedented SCIg utilization and the NEBMC was subsequently convened to discuss the situation. In the absence of a national Ig shortages plan, the NEBMC, working with Canadian Ig prescribers and patient groups, leveraged principles and the framework from *The National Plan for Management of Shortages of Labile Blood Components* to guide decisions and communications. An Amber phase advisory was issued on May 8, 2019 which facilitated collaboration with stakeholders to implement mitigation measures to reduce risk and understand demand rates. This included ensuring known patients continued to receive SCIg. However, new patients diagnosed with a condition requiring Ig treatment may not have had the option of choosing intravenous versus subcutaneous administration in case demand outpaced available supply. Canadian Blood Services SCIg inventories recovered to levels allowing for discontinuation of the shortage by August 26, 2019.

In March 2020, in response to potential impacts of COVID-19 on the supply chain of Ig products, a Green Advisory phase was declared and remained active for 7 weeks before a return to Green phase.

2. Assumptions

The assumptions used in the development of this interim plan are as follows (per T*he National Plan for Management of Shortages of Labile Blood Components):*

A. **The interim Ig shortages management plan operates within the existing blood system structure, including the legislative and regulatory framework currently in place.**
   A basic principle of the Canadian blood system, as stated by Justice Horace Krever (*Commission of Inquiry on the Blood System in Canada Final Report, p.1047*) that is pertinent to this interim plan is the following:

A fundamental value that must guide the blood supply system in Canada is that blood is a public resource, given altruistically by persons in Canada for the benefit of other persons in this country. Profit should not be made from the blood that is donated in Canada. The operator of the blood supply system must act as a trustee of this public resource for the benefit of all persons in Canada.

With respect to the Canadian legislative and regulatory framework, the main features pertinent to the interim Ig plan are the following:

- provincial and territorial authority and responsibility for the delivery of the Canadian health care system, pursuant to the principles of the *Canada Health Act*: each province or territory therefore has a role in the management of blood delivery and blood utilization in its jurisdiction, including its role in hospital oversight;
- Canadian Blood Services' mission: "*Canadian Blood Services operates Canada's blood supply in a manner that gains the trust, commitment and confidence of all Canadians by providing a safe, secure, cost-effective, affordable and accessible supply of quality blood, blood products and their alternatives"*;
- regulation of the blood system by Health Canada, pursuant to the *Food and Drugs Act,* and adherence to a series of existing industry standards

B. The interim Ig shortages management plan assumes that all efforts to increase the available supply of Ig have been exhausted.

As indicated above (Section 1.2) and by the name of this document, the purpose of the interim plan is to optimize the allocation of Ig when the supply is severely compromised. It is not the purpose of the interim Ig plan to address mechanisms to increase the supply of Ig in the face of threats to that supply. Those aspects of emergency preparedness are important and must be addressed by Canadian Blood Services in their documents and plans regarding its management of the blood supply system. For the purposes of this interim Ig plan, it is assumed that in the instance of severe Ig shortage Canadian Blood Services has implemented such measures and in spite of this, the supply of Ig is insufficient to meet demand.

C. The interim Ig shortages management plan promotes collaboration.

The interim Ig plan is intended to promote the most efficient use of a limited supply of Ig in a situation of emergency, through collaboration by participants in the Canadian blood system, collectively achieving the benefits and bearing the risks of doing so. The optimal allocation of Ig in a time of shortage will depend upon the ability of all participants to act in a highly professional, collaborative and transparent manner.

D. The interim Ig shortages management plan is based upon established ethical principles.

During Ig shortages, difficult decisions will need to be made on how to ration Ig. Collaborative approaches that may transcend the needs of a single patient, health care professional or institution may need to be implemented. This could represent a paradigm

shift in decision-making for physicians—from a focus on individual patients to consideration of the “greater good”. Thus, in order to ensure acceptance and cooperation by all participants, a fair and transparent priority-setting process for rationing must be developed.

E. The interim Ig shortages management plan recognizes previous and ongoing work in this domain and represents an ongoing process.

The interim Ig plan was built upon existing documents including the Government of Quebec’s *Nonspecific Immunoglobulin* (*Ig) Shortage Management Framework* and *The National Plan for Management of Shortages of Labile Blood Components*. The interim Ig plan focuses on the clinical criteria for use and allocation of Ig products in times of shortage and is intended as a interim measure until a full national Ig shortage management plan is developed. It is reasonable to assume the development and implementation of this interim Ig plan and the resulting lessons learned will serve as a framework to inform the development of a full national Ig shortages management plan once this short-term supply risk is addressed. Work on the full plan is expected during the 12 to 24 months following final approval the interim Ig plan.

F. The interim Ig shortages management plan acknowledges potential legal concerns.

The interim Ig plan recognizes the potential for legal challenges on behalf of patients denied Ig in a shortage, where a decision not to administer Ig - a decision made pursuant to the agreed-upon protocols in the interim Ig plan - results in an adverse outcome. Legal and ethical representation was included in the development of the interim Ig shortage management plan. However, it is understood that jurisdictions have not conducted their own legal and ethical reviews of this interim plan; the intent is for jurisdictions to conduct individual legal and ethical reviews as may be desired or required as part of the development of the full national Ig shortage management plan. In terms of the interim Ig plan, it is recommended that, to the extent possible, protections be put in place for those who will be applying the interim plan and making real-time decisions pursuant to it. It is hoped that the development of a national Ig shortages management plan will, in and of itself, assist hospitals and physicians to make the most appropriate medical (and hence legal) decisions.

Finally, for a variety of reasons including legal considerations, careful record-keeping of decisions made pursuant to the interim Ig plan will be of paramount importance. It is recommended that preparations be undertaken to make the recording of such decisions, in the event of a crisis, as easy and efficient as possible.

G. The interim Ig shortages management plan assumes that all areas of the country served by Canadian Blood Services would be simultaneously affected in an approximately equal manner; however, provincial and/or regional differences can also be addressed the interim plan.

The interim Ig plan is written to address an Ig shortage with the assumption that the demand for Ig would be approximately equal across all jurisdictions served by Canadian Blood Services. However, given the large size of the country, it is possible that different scenarios

with respect to supply and demand could arise (e.g.- severe weather preventing temporary restock of local supply).

H. **The interim Ig shortages management plan acknowledges Canada's diverse geography and diverse expertise.**
The interim Ig plan acknowledges Canada's diverse geography, remote locations and the fact that there are many very small hospitals in rural locations that do not carry large Ig inventories. The reality is that there may be limited expertise in these remote and/or rural locations and this will need to be considered. Any reductions or recommendations will need to take these jurisdictions and their special needs into consideration.

I. **Provinces have some mechanism in place for Ig utilization monitoring to ensure there is appropriate utilization of Ig (see Appendix D for comparison of utilization guidelines by province).**

3. Plan structure – overview

In keeping with other plans to manage shortages, this interim Ig plan considers four phases of inventory availability, defined below. Roles and responsibilities for the participants (Canadian Blood Services, P/T ministries, and hospitals/RHA) are described in this section in general terms.

3.1 Phases of inventory availability

In keeping with *The National Plan for Management of Shortages of Labile Blood Components*, the interim Ig shortage management plan considers four phases of inventory availability, defined below. Roles and responsibilities for the participants (Canadian Blood Services, P/T ministries, and hospitals/RHA) are described in this section in general terms.

The interim Ig plan considers four phases of inventory availability – Green, Amber, Red and Recovery. Determination of the need to declare a shortage phase could apply to a single Ig brand or multiple brands in either SCIg or IVIg formulations. A number of considerations are critical for the NEBMC to make informed decisions regarding an Ig shortage, such as: overall product available in Canada, utilization rates, future supply outlook, effectiveness of clinical use guidelines, and allocation criteria. Standard data elements and availability of data in real time across the system are also essential and this interim Ig plan supports the further development of a mechanism and method for monitoring and forecasting utilization. With real time data, Canadian Blood Services and the NEBMC would be better equipped to determine appropriate actions required to manage a shortage.

3.1.1 Green Phase

Green phase implies that normal Ig inventory levels exist and supply generally meets demand. This phase includes a broad range of inventory levels ranging from an ideal inventory to temporary shortages that occur periodically and can be managed within the scope of existing Canadian Blood Services and hospital/RHA actions.

3.1.2 Green Advisory Phase

There could be brief situations where, while the overall inventory is in Green phase, a particular Ig brand may be in limited supply and require Canadian Blood Services to communicate with hospitals. Most of these situations should be brief, and Canadian Blood Services will communicate temporary inventory adjustments to hospitals through “business-as-usual” channels. Should Canadian Blood Services exhaust all options to balance brand availability (without requiring patient transition to a different Ig product) and should the situation persist, the Canadian Blood Services VP, Medical Affairs and Innovation will consult with the NAC Chair to convene the core and/or full NEBMC (within 24- 48 hrs) to determine if there are any changes to hospital inventory management practice which could assist with and/or improve the situation. If the situation cannot be improved with inventory management practices, then a Green Advisory Phase will be issued to hospitals per direction provided by the NEBMC.

The Green Advisory phase is typically when Ig inventory is low or there is a potential supply disruption being forecasting. This phase requires review of all hospital inventories and utilization to determine what the likelihood of entering Amber or Red phase. It would also be an advisory to hospitals and provinces to look at any potential conservation strategies that could help avoid a shortage. Hospitals/RHA will need to share inventory levels and any other utilization data within a specific timeframe to ensure that the NEBMC can assess what the phase would be. Ideally, inclusion of an estimate of daily demand over the next several days will be useful for decision making.

3.1.3 Amber Phase

Amber phase implies that Ig inventory levels are insufficient to continue with routine practice and hospitals/RHA will be required to implement specific measures to reduce Ig usage.

3.1.4 Red Phase

Red phase implies that Ig inventory levels are insufficient to ensure that all patients will receive the required product(s).

3.1.5 Canadian Blood Services inventory levels at Green, Amber, Red and Recovery Phases

It is not possible, a priori, to define concisely national inventory levels which would automatically trigger the declaration of an Amber or Red phase, partly because the inventory in patient homes is not considered in the national inventory. Critical levels will vary according availability of alternate product, shelf-life of all inventory and the anticipated length of a given shortage. Available Ig inventory at Canadian Blood Services is categorized as optimal through critical according to the number of ‘weeks on hand’ (defined as the number of weeks the inventory would last, based on average historical demand run rates over the last six months) which, as shown below, correspond approximately to inventory levels that could represent Green, Amber and Red phase inventories. The declaration of an Amber or Red phase would depend on the predicted ability of Canadian Blood Services to increase inventory. It is acknowledged that

hospitals and some patients (at home) also hold inventories of Ig products that may be available for patient use and would not be reflected in the phase declaration criteria.

Approximate Ig inventory levels that, if sustained, could lead to the declaration of Amber or Red phase are as follows:

Table 1. Ig Inventory – Canadian Blood Services and inventory held in country by vendors, accurate as of 2020-07-13

Ig	Green	Green Advisory*	Amber	Red
IVIg	> 11 WOH	8-11 WOH	5-8 WOH	< 5 WOH
SCIg	> 12 WOH	9-12 WOH	6-9 WOH	< 5 WOH

*Assumes brand availability is balanced
Weeks on hand (WOH) - It is the number of weeks the inventory would last (based on average historical demand run rates for the past 6 months.

3.1.6 Total inventory levels

The inventory levels presented in Table 1 represent a combination of product inventory held by Canadian Blood Services and the vendors within in-country facilities which is allocated to Canadian Blood Services. This represents only a part of the total Ig inventory within the blood system, inventory is also held in hospital/RHA blood banks and some patients also have SCIg inventory at their homes for self-administration.

3.1.7 Allocation of immunoglobulin in times of shortage

Refer to detailed table in Appendix C.

The provision of Ig to hospitals/RHA in times of shortages will be determined by Canadian Blood Services in consultation with national and P/T emergency blood management committees (described in Section 4) and will take into consideration usual requirements, the nature of the situation leading to the shortage, inventory requirements, and work done by hospitals/RHA as part of Green Phase activities.

During a shortage, Ig conservation strategies should be implemented at the hospital/ RHA level as a means to mitigate an increased shortage of Ig inventory. Ig conservation strategies should include any or all the actions suggested in Appendix C per inventory phase, and/or NEBMC directives, **including increasing the availability and the use of alternative therapies**. The NEBMC is responsible for assessing the level of shortage and the impacts, both short-term and long-term, the shortage may have on the Ig supply. A key element in inventory management during an Ig shortage is knowledge of the available Ig inventory, including in patient homes, at hospitals, and at Canadian Blood Services, and that which is available from product vendors.

3.2 Key Participant roles and responsibilities

This section outlines the general roles and responsibilities of the following stakeholders as they relate to Ig products only. Each stakeholder has a responsibility to develop emergency preparedness plans that include Ig shortage management as a key element and are appropriate to each respective agency/institution. Within all the categories listed below, there is the expectation that each representative to the NEBMC would ensure that they have identified a designate in the event that they are unavailable. This designate should be clearly communicated to the NEBMC Secretariat provided by the office of Canadian Blood Services VP, Medical Affairs and Innovation.

3.2.1 Canadian Blood Services

Canadian Blood Services manages the blood supply system in all provinces and territories except Québec. As part of this mandate, Canadian Blood Services currently engages in a number of activities to identify and avert potential shortages. Canadian Blood Services must actively participate in conversations pertaining to a national Ig shortage. Its main activity in this regard is the ongoing management of the Ig inventory as a single national inventory (as opposed to multiple regional inventories).

Canadian Blood Services has developed and continues to refine business continuity and business recovery plans to minimize the impacts of adverse events on the national Ig inventory. Canadian Blood Services has a *Business Continuity Management Program*, in which it is recognized that events/disasters could negatively affect the availability of Ig, Canadian Blood Services staff, equipment, information-technology systems, transportation systems and/or facilities upon which the maintenance of the national Ig inventory are critically dependent. Business continuity and recovery plans have been developed to mitigate disruptions to each of these critical dependencies.

With respect to the specific requirements of the interim Ig plan, Canadian Blood Services will have an active role in declaring the phase of Ig shortage and recovery from such shortages, as well as distributing Ig in accordance with the phase of shortage. These activities would occur in consultation with the NEBMC, (described in Section 4.1 below) and in consideration of its advice.

Canadian Blood Services will also coordinate communications as per the established process and will act as the secretariat for the NEBMC (Section 4.1).

3.2.2 CBS-P/T Blood Liaison Committee

The general mandate of the CBS-P/TBLC is to facilitate the work between the participating P/T Ministries of Health and Canadian Blood Services to support Canadian Blood Services in the provision of a safe, secure and affordable national Ig supply.

For the purposes of this interim Ig plan, the CBS-P/TBLC is responsible for establishing the NEBMC and its terms of reference, including membership and lines of communication that will

enable the rapid response and decision-making necessary for it to function effectively during an Ig shortage.

The CBS-P/TBLC is also responsible for reviewing this interim plan and a subsequent future Ig shortages management plan from time to time and ensuring that the NAC updates said plan as required.

3.2.3 Provincial and Territorial Ministries of Health

Given that the provision of health care and essential services falls under provincial/territorial jurisdiction, there are a number of ways in which the ministries of health and their staff will be involved in the execution of the interim Ig plan, **including access to alternative therapy for patients should Ig not be available or the NEBMC recommends the implementation of Ig conservation strategies.** Every provincial/territorial ministry of health is responsible for the development of detailed provincial/territorial plans to manage Ig shortages, including the establishment in each province/territory of a Provincial/Territorial Emergency Blood Management Committee (P/TEBMC) and its terms of reference. Provincial/territorial plans should comply with the requirements outlined in the interim Ig plan and should be linked to each province/territory's other emergency preparedness plans. It is strongly recommended that a standardized phasing system of inventory availability (Green, Amber, Red and Recovery as defined in this interim Ig plan) be adopted by all provinces/territories. Finally, the P/T ministry should play a leadership role in encouraging hospitals/RHA to comply with their provincial plan and this interim plan and, in collaboration with the P/TEBMC, to monitor the level of compliance in the institutions within their jurisdiction.

3.2.3.1 Provincial/Territorial Blood Representatives

The P/T blood representative in each province/territory is responsible to provide advice and support to the deputy minister and minister of health on issues affecting the blood system. In this capacity, P/T blood representatives will play central roles in the establishment of a Provincial/Territorial Emergency Blood Management Committee (P/TEBMC) and the development of their respective detailed provincial/territorial/hospital/RHA plans to manage shortages of Ig.

All P/T blood representatives will participate on the NEBMC, providing a link between national and P/T response plans to ensure a consistent and coordinated national response to an Ig shortage (see Section 4 below). In this capacity, P/T blood representatives will be responsible for ensuring the establishment of both internal and external lines of communications to enable consistency and coordination within and among P/T jurisdictions, hospitals/RHA and Canadian Blood Services.

3.2.3.2 Lead P/T Blood Representative

The P/T blood representative of the Lead P/T will play a leadership role in facilitating communications between the various participants/stakeholders and their respective provincial/territorial ministry.

3.2.4 National Advisory Committee on Blood and Blood Products

The NAC mandate is to provide medical and technical advice on the utilization management of blood and blood products to the P/T ministries and Canadian Blood Services. In light of this mandate, the CBS-P/TBLC asked NAC to develop an Ig shortages management plan. NAC had initiated planning to develop a national Ig shortage plan but had not yet started the work when the COVID-19 pandemic struck in early 2020. The pandemic's potential impact on the global Ig supply chain highlighted the urgent need to have an Ig shortage management plan in place. Given the development of a comprehensive plan would require significant time and resources, and that COVID-19 impacts to supply may emerge in the short- to medium-term, the NAC and CBS-P/TBLC recognized that proceeding with the development of an interim plan was required and tasked the NEBMC Secretariat with having an interim plan in place by mid-July 2020. The interim plan leverages existing documents including the *Government of Québec's Nonspecific Immunoglobulin (Ig) Shortage Management Framework* and *The National Plan for Management of Shortages of Labile Blood Components.*

The NAC plays a key role on the NEBMC; the Chair of the NAC will co-chair the NEBMC and all NAC members will be members of the NEBMC (see Section 4.1).

The NAC will review the implementation and outcomes of the interim Ig plan for ongoing refinement and modification of the interim plan and shall report these findings to all members of the NEBMC.

3.2.5 Hospitals/Regional Health Authorities

Each facility/region should establish a Hospital/RHA Emergency Blood Management Committee (H/REBMC) (see Section 4.3) and a hospital/RHA blood shortage management plan. The purpose of a hospital/RHA blood shortage management plan is to delineate lines of responsibility, decision-making processes, and effective communication to enable the H/REBMC to respond appropriately during a shortage. Such hospital/RHA plans should also define which staff members will participate in the H/REBMC and how a reduction in Ig usage will be achieved.

Hospital/RHA Ig shortage management plan should be based on, and comply with, the requirements outlined in this interim plan. It is strongly recommended that a standardized phasing system of inventory availability (Green, Amber, Red and Recovery as defined in the interim Ig plan) be adopted by all hospital/RHA Ig shortage management plans.

4. Emergency Blood Management Committees

4.1 National Emergency Blood Management Committee

The NEBMC is necessary to ensure the implementation of this interim Ig plan. Terms of reference and details regarding the NEBMC can be found in *The National Plan of the Management of Labile Blood Components*. Should the NEBMC be convened to discuss an emerging or current Ig inventory shortage, the committee will ensure appropriate clinical

representation includes those with interests and experience relevant to the use of Ig. To promote alignment, consistency and collaboration during a shortage or potential shortage, communications will be guided by the established framework and will be further reviewed as development of the full Ig shortages management plan proceeds.

4.2 Provincial/Territorial Emergency Blood Management Committees

It is the responsibility of the ministries of health of each province or territory to leverage its Provincial (or Territorial) Emergency Blood Management Committee (P/TEBMC) and its terms of reference for the purpose of managing an Ig shortage, which should include the following responsibilities:

- develop a response plan to minimize the provincial/territorial impact of Ig shortages;
- work in accordance with the guidelines outlined in this interim Ig plan;
- ensure that the recommendations of the NEBMC and resulting national decisions are appropriately communicated within its jurisdiction;
- solicit feedback on implementation of the interim Ig plan from the H/REBMC;
- provide the conduit for communications/feedback between the NEBMC and H/REBMCs;
- establish a process to monitor adherence to the interim Ig plan in times of Ig shortages;
- establish recommendations to manage non-adherence to the interim Ig plan in times of Ig shortages.

Thus, each P/TEBMC will work collaboratively as required with the NEBMC and its jurisdiction's H/REBMCs.

Provinces or territories may wish to consider having a core or an executive P/TEBMC and then an expanded membership depending upon the extent of the shortage including clinical representation reflective of Ig use. Details regarding mandatory and suggested membership are included within *The National Plan for the Management of Shortages of Labile Blood Components*.

4.3 Hospital/RHA Emergency Blood Management Committee

Each hospital or Regional Health Authority (RHA) has a responsibility to leverage its Hospital/RHA Emergency Blood Management Committee (H/REBMC) whose mandate is to develop an Ig shortage management plan in accordance with the guidelines outlined in this interim national plan and to ensure that these plans are appropriately communicated and adhered to in times of Ig shortages. H/REBMCs should also serve as the communication conduit to the P/TEBMC. In small provinces/territories it is possible that the P/TEBMC and H/REBMC would be one single body.

H/REBMC membership will vary from facility to facility and should include clinical representation reflective of Ig use. Details regarding suggested membership are detailed in *The National Plan for the Management of Shortages of Labile Blood Components*.

Appendix A. Approval and Revision History

Version 2020-07-27

The CBS-P/TBLC recognized that a national plan to specifically guide the allocation of Ig products in a short or prolonged shortage was needed and identified this as a priority task for NAC in 2019.

NAC had initiated planning to develop a national Ig shortage plan but had not yet started the work when the COVID-19 pandemic struck in early 2020. The pandemic's potential impact on the global Ig supply chain highlighted the urgent need to have an Ig shortage management plan in place. The NAC and CBS-P/TBLC recognized that proceeding with the development of an interim plan was required and tasked the NEBMC Secretariat with having an interim plan in place within a 3-month timeframe by mid-July 2020.

This interim Ig plan is intended as a response to potential short- to medium-term supply impacts and to remain in place while a full plan is developed. To expedite the development of the interim plan, the NEBMC Secretariat leveraged existing documents including the Government of Québec's *Nonspecific Immunoglobulin* (*Ig) Shortage Management Framework* and *The National Plan for Management of Shortages of Labile Blood Components.* Approximately 400 stakeholders were provided an opportunity to comment on proposed Ig allocation criteria in May 2020 and a final draft interim national plan was prepared and disseminated for stakeholder review in June 2020.

Version 2020-07-27 was endorsed by the National Advisory Committee on Blood and Blood Products, Canadian Blood Services, and the Provincial/Territorial Ministries of Health in jurisdictions served by Canadian Blood Services.

Appendix B. Stakeholder engagement

Stakeholder engagement is critical, prior to an actual shortage of Ig products, to gather support and objectively review and respond to proposed clinical allocation criteria for use during a shortage. The engagement process was an opportunity for stakeholders to provide feedback which informed revisions to the initially proposed clinical criteria leveraged from recently developed criteria used in *Québec's Nonspecific Immunoglobulin* (*Ig) Shortage Management Framework Immunoglobulin (Ig) Shortage Management Framework.*

The stakeholder engagement process included soliciting a broad range of perspectives. Approximately 400 individuals, organizations and societies were invited to participate, including patient groups, clinicians and others with interests and experience relevant to the use of immunoglobulin by Canadian patients to ensure development of a shortage management plan considering all perspectives.

Stakeholders were invited to attend online sessions as well as submit written feedback on the shortage plan inventory phases, and clinical allocation criteria for the use of Ig during a shortage. In total, 73 individuals participated in the consultation process; 49 participated in an online session and 47 provided written feedback. Some of these individuals provided feedback on behalf of organizations or groups. In addition to organizations and societies, these included various provincial blood coordinating offices/programs, hospitals and clinical service areas/programs (Figure 1).

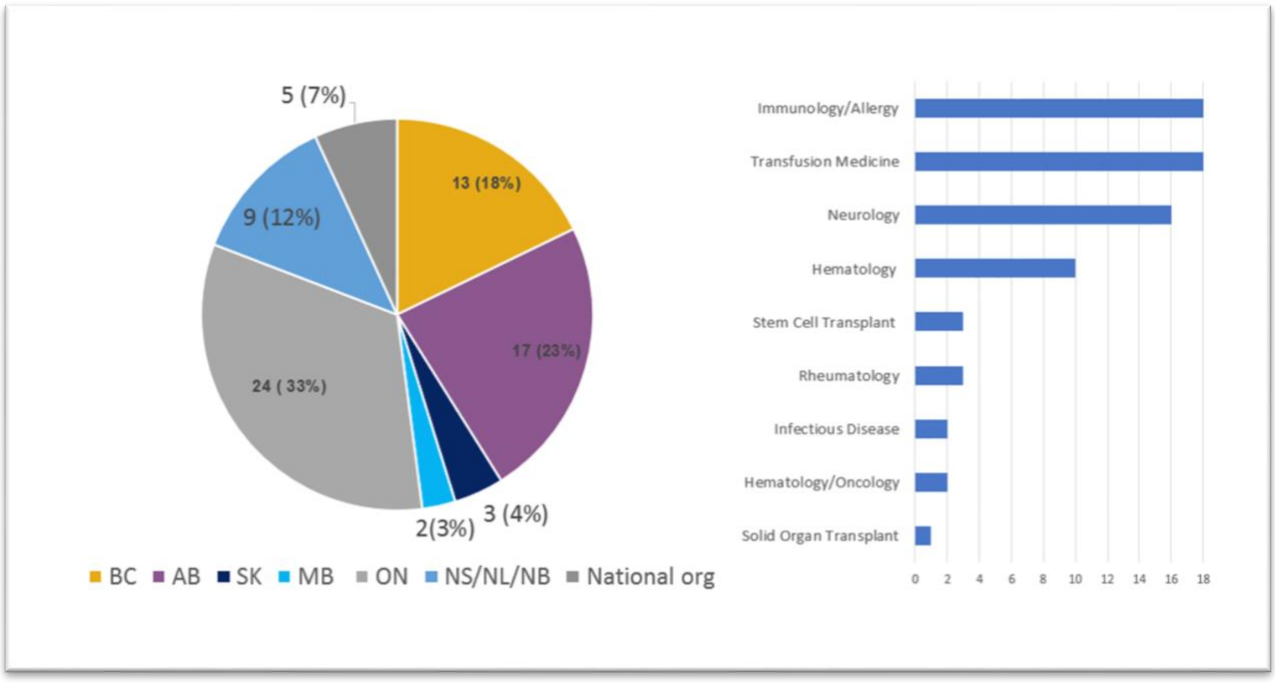

Figure 1: Total number of active participants in the consultation process represented geographically and clinically, including online session attendance and submission of written feedback

The following are lists of organizations and societies who were requested to participate in May-June 2020:

Stakeholder organization/society*	Online session participation	Written feedback received	Individual member response	Stakeholder official response
Myasthenia Gravis (MG) Society of Canada	Yes	Yes	Yes	Yes (President)
Immunodeficiency Canada	No	Yes	No	Yes (Chair)
Guillain Barre/Chronic inflammatory Demyelinating Polyneuropathy Foundation of Canada	Yes	Yes	Yes	Yes (Executive Director)
Canadian Immunodeficiency Patient Organization (CIPO)	Yes	Yes	No	Yes (Executive Director)
Cell Therapy Transplant Canada (CTTC)	Yes	No	Yes	No
Canadian Society of Allergy and Clinical Immunology (CSACI)	Yes	Yes	No	Yes (President)

The following organizations/societies did not provide comment or feedback: Canadian Pediatric Society, Canadian Society for Immunology, Canadian Neurological Sciences Federation, Canadian Hematology Society, Canadian Dermatology Association, Association of Medical Microbiology and Infectious Disease Canada, and the Canadian Society of Transplantation.

Feedback and input received was compiled and reviewed by the NEBMC Secretariat and Interim Immunoglobulin (Ig) Shortage Management Plan Steering Committee members. The inventory phase activities and clinical allocation criteria were revised with the approval of the steering committee. Perspectives provided regarding broader considerations were reviewed and incorporated into the interim plan where possible given the time limitation for the development of the interim shortage plan. Items or themes requiring further analysis and assessment, including specific stakeholder engagement beyond what was conducted are detailed in Appendix E.

For ease of review, main feedback received was categorized as follows:

- Positive feedback
- Legal implications / ethical considerations
- Adjudication process

- Equity of allocation
- Allocation criteria
- Reduction of use of Ig
- Alternative therapy
- Communication (includes inventory)
- Inventory phase activities

The stakeholder engagement resulted in extensive comments and feedback. Numerous comments from stakeholders were similar and repetitive and as a result, the NEBMC Secretariat/steering committee concluded that relevant comments and feedback for this interim Ig shortages plan have been captured and addressed appropriately. It is recognized that further engagement of the dermatology, solid organ transplant and infectious disease clinical stakeholders would provide additional valuable perspective. The need for ongoing refinement and revision as new data becomes available is vital and as such this interim Ig plan will be foundational to the development of a full comprehensive national Ig shortages management plan which will further address the requirement for provision of Ig products to Canadian patients during a shortage.

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Appendix C. Inventory phase activity and Ig allocation criteria

Section 1 Inventory Phases: Adapted (with input from results of the stakeholder consultation conducted May-June 2020) from the *Santé Et Services Sociaux Quebec. Appendix 3. Nonspecific Immunoglobulin (Ig) Shortage Management Framework*. March 2020.

The following table provides actions and activities the NEBMC would consider implementing per an inventory phase declaration. This is not an exhaustive list and other measures could be directed by the NEBMC in response to the inventory situation.

Inventory Level	Description and activities
Green	Ig supply/inventory meets demand. • Follow jurisdictional best practice recommendations for use of Ig (indications, optimal use guides, modality of administration, and doses). • Use the lowest Ig dose for the shortest duration required to achieve the desired outcome. • For ongoing therapy, ensure the achievement of measurable clinical outcomes; Ig should not be continued in patients with no demonstrable benefit. • Prior to starting Ig treatment, consider use of all other safe, effective, and accessible alternative therapies. • Where use is indicated, confirm that use aligns with the patient's goals of care. • Use a dose calculator based on adjusted body weight, and track Ig levels to adjust dose, as appropriate.

Green Advisory Phase	Ig supply/inventory levels are reduced or there are signs that short-term demand may outstrip capacity. **Reduce use by 10 to 20%:**
	• Continue to follow all the actions outlined in Green phase.
	• Round down Ig treatment doses and frequency. Re-assess all patients that are already on treatment to find the minimal effective dose and optimize the treatment for each individual.
	• Review stocking practices and maintain the minimum inventory level required.
	• Reduce the refill volume for patients on home infusion products
	• Consider the use of alternative therapies.
	• Consider increasing availability of alternative therapies
	• Initiate actions to prepare for the potential escalation to Amber and Red phase by:
	  ○ Identifying patients that can be switched to SCIg (in the event of an IVIg shortage) or IVIg (in the event of an SCIg shortage), or other alternative therapies.
	  ○ Initiating local and provincial processes to support an adjudication process in the event of a red phase advisory.

Amber	Ig supply/inventory levels are low for a short or prolonged period. **Reduce use by 20 to 50%:**
	• Continue to follow all the actions outlined in Green phase and Green Advisory phase.
	• Limit Ig use to clinical circumstances when there are:
	  ○ No viable alternatives; **and/or**
	  ○ the condition is life-threatening or there is a risk for irreversible disability as identified in the table below.
	• Use the lowest Ig dose for the shortest duration required to achieve the desired outcome.
	• Implement screening of all Ig orders within the hospital transfusion service/blood bank.

Red	There is a critical and prolonged Ig shortage. **Reduce use by over 50%:**
	• Limit Ig use to clinical circumstances when there are:
	  ○ No viable alternatives; **and/or**
	  ○ the condition is life-threatening or there is a risk for irreversible disability as identified in the table below.
	• Have each case and dose approved by a formally established peer committee as per local jurisdictional guidance*.
	• File a written copy of the decision in the patient's medical record and send another copy to Transfusion Medicine Services (blood bank).

*Provinces/territories will be responsible for determining the most appropriate mechanism for peer review, whether it be through an existing committee structure (ensuring adequate representation from clinicians with experience treating patients with Ig) or the formation of a new committee. This will be further explored as part of the work to develop the full national Ig shortage management plan.

Section 2 Criteria for Recognized Immunoglobulin (Ig) Indications: Adapted (with input from results of the stakeholder consultation conducted May-June 2020) from the Santé et Services Sociaux Quebec. Appendix 3. *Nonspecific Immunoglobulin (Ig) Shortage Management Framework*. March 2020.

This table was developed for use during an Ig shortage and should not to be interpreted as a clinical practice guideline. It is a framework to guide clinical decisions and triage in the event of an Amber or Red phase being declared when there is not enough Ig available for all patients and will be reviewed and updated during the development of the full Ig Shortages Plan.

The list of conditions and guidance is comprehensive but not exhaustive; there may be other clinical circumstances in which a condition is life-threatening (or there is a risk for irreversible disability) and all other therapeutic options have failed, are contraindicated or not tolerated. In these circumstances, Ig can be considered in amber and/or red phases. In red phase these will be approved during an adjudication process that will review these requests on a case-by-case basis.

	Condition	Amber Level	Red Level
IMMUNOLOGY	**Primary or secondary immunodeficiencies known to be associated with hypogammaglobulinemia or dysgammaglobulinemia for which Ig is necessary**[1]	• Preferential use • Should be based on the expert opinion of the physician, depending on the severity and frequency of infections and presence of additional immune dysregulation (e.g. autoimmunity, hyperinflammation) • For maintenance therapy, target IgG levels should be lowered to minimum clinically effective target (e.g., 5-7 g/L on Day 28 in adult patients with hypogammaglobulinemia on IVIg) • Increase or decrease target IgG on a case by case basis (i.e., based on factors such as clinical conditions or age)	
RHEUMATOLOGY	**Dermatomyositis**	• In cases of severe disease and failure, contraindication or intolerance to other therapeutic options[2]	
	Eosinophilic granulomatosis with polyangiitis (Churg Strauss syndrome)	• In cases of severe disease and failure, contraindication or intolerance to other therapeutic options[2]	
	Juvenile dermatomyositis	• In cases of severe disease and failure, contraindication or intolerance to other therapeutic options[2]	

	Condition	Amber Level	Red Level
RHEUMATOLOGY	**Kawasaki disease**	• First line therapy • Following the initial dose, maximum one additional dose may be given if there is ongoing inflammation	
	Macrophage activation syndrome (MAS)	• In cases of severe disease and failure, contraindication or intolerance to other therapeutic options[2]	
	Polymyositis	• In cases of severe disease and failure, contraindication or intolerance to other therapeutic options[2]	
HEMATOLOGY	**Acquired coagulation factor inhibitors**	• Should be considered only after adjunctive therapies (such as steroids) in urgent situations, as decided by experts at a hemophilia treatment centre	
	Allogeneic hematopoietic stem cell transplant	• In cases of hypogammaglobulinemia, acquired post-hematopoietic stem cell transplant (HSCT). See immunology section.	
	Autoimmune hemolytic anemia (AIHA)	• In cases of failure to first-line treatment, contraindication or intolerance of other therapeutic options in life-threatening cases.	
	Autoimmune neutropenia	• In cases of failure, contraindication or intolerance to other therapeutic options	• In cases of failure, contraindication or intolerance to other therapeutic options **AND one of the following:** • For severe, active infections • A history of severe infections that responded positively to treatment
	Catastrophic antiphospholipid syndrome	• In cases of severe disease and failure, contraindication or intolerance to other therapeutic options[2]	

	Condition	Amber Level	Red Level
HEMATOLOGY	**Fetal and neonatal alloimmune thrombocytopenia (FNAIT)**	• Treatment for mothers during pregnancy: permitted for use, maximum dose not to exceed 1 g/kg/week • Treatment for newborns: if there is potentially fatal bleeding or a platelet count below 30 x 10^9/L, when a platelet transfusion (whether selected for human platelet antigen [HPA] or not) is not possible	
	Hemolytic disease of the fetus and newborn (HDFN)	• Should be given only in consultation with neonatology and transfusion medicine: ○ Treatment for pregnant mothers: when there is a high risk AND intrauterine transfusion is contraindicated ○ Treatment for newborns: in cases of hyperbilirubinemia due to maternal alloimmunization if phototherapy fails	• Should be given only in consultation with neonatology and transfusion medicine: ○ Treatment for pregnant mothers: when there is a high risk AND intrauterine transfusion is contraindicated ○ Treatment for newborns: in cases of hyperbilirubinemia due to maternal alloimmunization if phototherapy fails and exchange transfusion cannot be done in a reasonable timeframe.
	Hyperhemolysis syndrome	• In cases of severe disease and failure, contraindication or intolerance to other therapeutic options[2]	
	Immune thrombocytopenia, acute	• Failure, contraindication or intolerance to steroids and anti-D Ig (if patient is Rh(D)-positive). Also consider early use of thrombopoietin receptor agonist or rituximab. **AND one of the following:** ○ When platelet count is <10 x 10^9/L ○ When <30 x 10^9/L and there is moderate to severe bleeding ○ Before urgent surgery and there is a need to rapidly raise the platelet count ○ There is life-threatening bleeding • Dose: Maximum of 1g/kg x 1 dose	• Failure, contraindication or intolerance to steroids and anti-D Ig (if patient is Rh(D)-positive). Also consider early use of thrombopoietin receptor agonist or rituximab. **AND one of the following:** ○ When the platelet count is <30 x 10^9/L and there is moderate to severe bleeding ○ Before urgent surgery and there is a need to rapidly raise the platelet count ○ There is life-threatening bleeding • Dose: Maximum 1g/kg x 1 dose

	Condition	Amber Level	Red Level
HEMATOLOGY	**Immune thrombocytopenia, chronic**	• Failure, contraindication or intolerance to steroids and anti-D Ig (if patient is Rh (D)-positive). • Alternative therapies (immunomodulators, thrombopoietin receptor agonist, rituximab) should be considered. **AND one of the following** ○ When the platelet count is <30 x 10^9/L and there is moderate to severe bleeding ○ Before urgent surgery and there is a need to rapidly raise the platelet count ○ There is life-threatening bleeding • Dose: Maximum 1g/kg x 1 dose	
	Immune thrombocytopenia during pregnancy	• Failure, contraindication or intolerance to steroids. **AND one of the following** ○ When the platelet count is <30 x 10^9/L and / or moderate to severe bleeding ○ In preparation for delivery to reach a platelet count ≥ 50 x 10^9/L in cases of failure, contraindication or intolerance to steroids ○ There is life-threatening bleeding	
	Post-transfusion purpura	• In cases of moderate to severe bleeding if plasma exchange is not feasible	
	Red cell aplasia caused by parvovirus B19	• In cases of severe disease and failure, contraindication or intolerance to other therapeutic options[2]	

	Condition	Amber Level	Red Level
NEUROLOGY	**Acute disseminated encephalomyelitis (ADEM)**	• In cases of severe disease and failure, contraindication or intolerance to other therapeutic options[2]	
	Autoimmune Encephalitis	• In cases of severe disease and failure, contraindication or intolerance to other therapeutic options[2]	
	Chronic inflammatory demyelinating polyneuropathy (CIDP)[1]	• Consider steroids and/or plasma exchange whenever possible • Initial and maintenance treatment in cases of failure, contraindication or intolerance to other forms of immunosuppressive therapy[2]	
	Graves' ophthalmopathy	• In cases of vision-threatening severe disease with failure, contraindications or intolerance to other therapeutic options	
	Guillain-Barré syndrome (GBS) or variants including Miller Fisher syndrome	• Preferential use for initial treatment of GBS if plasma exchange not available or feasible. • A second course of IVIG may be considered in patients with clearly demonstrated secondary deterioration, only after assessment by a specialist.	• In cases of failure, contraindication or intolerance to plasma exchange **OR** in cases where plasma exchange is not available.
	Lambert-Eaton myasthenic syndrome (LEMS)	• In cases of severe disease and failure, contraindication or intolerance to other therapeutic options[2]	
	Multifocal motor neuropathy (MMN)[1]	• For front-line therapy[2]	

	Condition	Amber Level	Red Level
NEUROLOGY	**Myasthenia gravis (MG)**	• In cases of severe exacerbation, myasthenic crisis or in preparation for urgent or semi-urgent surgery	• In cases of severe exacerbation, myasthenic crisis or in preparation for urgent or semi-urgent surgery with failure, contraindication, intolerance or lack of availability of plasma exchange or other therapeutic options.
	Opsoclonus-myoclonus syndrome	• In cases of severe disease and failure, contraindication or intolerance to other therapeutic options[2]	
	Pediatric autoimmune neuropsychiatric disorder associated with streptococcal infection (PANDAS)	• In cases of severe disease and failure, contraindication or intolerance to other therapeutic options[2]	
	Rasmussen's encephalitis	• In cases of severe disease and failure, contraindication or intolerance to other therapeutic options[2]	
	Refractory epilepsy	• In cases of severe disease and failure, contraindication or intolerance to other therapeutic options[2]	
	Relapsing-remitting multiple sclerosis	• In cases of severe disease and failure, contraindication or intolerance to other therapeutic options[2]	
	Stiff person syndrome (SPS)	• In cases of severe disease and failure, contraindication or intolerance to other therapeutic options[2]	

	Condition	Amber Level	Red Level
INFECTIOUS DISEASES	**Enterovirus meningoencephalitis**	• In severe cases in immunocompromised patients	
	Infectious gastroenterocolitis (such as *C. difficile* enterocolitis or rotavirus gastroenteritis in immunocompromised patients)	• Do not use	
	Invasive group A streptococcal disease or staphylococcal disease	• For severe invasive group A Streptococcal disease associated with hemodynamic compromise or Streptococcal or Staphylococcal toxic shock syndrome • IVIG is recommended in addition to surgical intervention, antibiotic therapy and other supportive measures	
	Lower respiratory tract infections caused by CMV or RSV in immunocompromised patients	• Do not use; preferential use should be made of specific antivirals +/- specific hyperimmune globulin (for CMV)	
	Neonatal sepsis	• In severe cases in cases of failure, contraindication or intolerance to other therapeutic options • Should not be used for prophylaxis	
	Measles post-exposure prophylaxis	• In pregnant women, infants and immune compromised/deficient individuals if IM injection is not an option because of weight 30 kg or greater or inability to receive IM injection	

	Condition	Amber Level	Red Level
DERMATOLOGY	**Bullous dermatitis (e.g.- pemphigus vulgaris, bullous pemphigoid)**	• Not permitted for use, apart from exceptional cases when disease is rapidly progressing, and other treatments are contraindicated. • First line therapy: corticosteroids. Second line: immunosuppressive agents. Third line: IVIG	• Do not use
	Pyoderma gangrenosum	• Not permitted for use, apart from exceptional cases when disease is rapidly progressing, and other treatments are contraindicated. • First line therapy: corticosteroids. Second line: immunosuppressive agents. Third line: IVIG	• Do not use
	Scleromyxedema	• Not permitted for use, apart from exceptional cases when disease is rapidly progressing, and other treatments are contraindicated. • First line therapy: corticosteroids. Second line: immunosuppressive agents. Third line: IVIG	• Do not use
	Stevens-Johnson syndrome and toxic epidermal necrolysis	• Not permitted for use, apart from exceptional cases when disease is rapidly progressing, and other treatments are contraindicated. • First line therapy: corticosteroids. Second line: immunosuppressive agents. Third line: IVIG	• Do not use

	Condition	Amber Level	Red Level
ORGAN TRANSPLANT	**Heart, lungs, liver, kidneys, pancreas** **(humoral rejection or pre-transplant HLA/ABO desensitization)**	• May be used as part of combination therapy with immunosuppressive therapy and/or plasmapheresis in selected cases.	• As part of combination therapy with immunosuppressive therapy and/or plasmapheresis, evaluated on a case-by-case basis by a peer committee. • For post-transplant treatment only, not new initiation of pre-transplantation desensitization protocol • Consult with transplant team required regarding potential delay in initiation of new transplants

Notes:

1. Preferential use should be made of SCIg for appropriate indications if available when there is an IVIg shortage.
2. For chronic conditions, when immunoglobulins are administered as maintenance treatment, try to find the minimal effective dose and optimize the treatment for each individual during Amber and Red phases.

Appendix D. Summary of Canadian Immunoglobulins Provincial Guidelines and Shortage Framework (Quebec and UK)

The table below summarizes the four provincial Ig guidelines (Ontario, Atlantic, British Columbia and Prairies) currently in place and highlights where there is disagreement on indications for Ig. The provincial guidelines are also compared to the shortage documents used in the Province of Quebec and the United Kingdom.

Disagreement among provincial recommendations

Recommendation provided in provincial guideline(s) but not in Quebec shortages plan

Provincial Guidelines

1. Recommended, indicated
2. Not recommended for routine use but some evidence that IG may be considered an option for therapy
3. Not recommended
4. Contraindicated

Indication	Comments	Provincial guidelines				Shortage documents		
						Quebec		UK
		ON	Atlantic	BC	Prairie	AMBER	RED	
Hematology								
Acquired pure red cell aplasia (PRCA)		2 Considered first line for PRCA associated with parvovrus B19 in immunocompromised patients. Option for immunologic PRCA if other therapies (steroids, cyclosporin) have failed	2 Immunocompromised patient with HPV-B19 pure red cell aplasia		1 Recommended for Immunocompromised patient with proven parvovirus B19 May be considered for other PRCA who have not responded other therapies	Yes. If failure, contraindications or intolerance to other therapeutic options.	No	Blue (note: Grey if not due to parvovirus B19)
Aplastic anemia				3				
Alloimmune thrombocytopenia								Red

Indication	Comments	Provincial guidelines				Shortage documents		
		ON	Atlantic	BC	Prairie	Quebec		UK
						AMBER	RED	
Autoimmune hemolytic anemia		2 May be considered one option among adjunctive therapies in urgent situations.	2 Patient must be resistant to steroids and exhibit symptomatic anemia		2 Not recommended for routine use, but may be considered as one of several options in urgent situations	Yes. In case of failure, contraindication or intolerance to other therapeutic options.	No	Blue
Autoimmune neutropenia		2 May be considered one option among adjunctive therapies in urgent situations.			2 May be considered as one of several options in rare circumstances when standard therapy fails	Yes. In case of failure, contraindication or intolerance to other therapeutic options.	Yes. In case of failure, contraindication or intolerance to other therapeutic options AND for severe infections or a history of severe infections that responded positively to treatment.	Grey
Coagulation factor inhibitors (allo and autoantibodies)	Acquired hemophilia, vWD, HA, HB	2 May be considered one option among adjunctive therapies, such as steroids, in urgent situations. Not recommended for routine use. Prescribed in consultation with specialized hemophilia care centre.	2 In consultation with Hematologist		2	Yes. On a case-by-case basis as decided by experts (inhibitors centre)	Yes. On a case-by-case basis as decided by experts (inhibitors centre)	Blue

Indication	Comments	Provincial guidelines				Shortage documents		
		ON	Atlantic	BC	Prairie	Quebec		UK
						AMBER	RED	
Fetal/neonatal alloimmune thrombocytopenia (F/NAIT)		1 Mother: first-line treatment (+/- steroids) for women with previously affected infant. Newborn: adjunct to provision of platelets for severe thrombocytopenia. In consultation with obstetrical medicine and Transfusion medicine	1 Mother: previously affected pregnancy or family history of F/NAIT or has been found to have platelet alloantibodies AND Treatment is under the direction of a MFM centre Newborns: treatment includes consultation with or is within a high-risk neonatal centre	1 Mother: previously affected pregnancy or family history of F/NAIT or found to have platelet alloantibodies. First-line. Newborn: provision of antigen-neg compatible platelets should be first line, IVIG is 2nd line Treatment under direction of high-risk obstetrical care with expertise in F/NAIT	1 Recommended for prevention or treatment of F/NAIT or hemorrhage. Should be under direction of specialist with expertise in high-risk obstetrics	Yes. Treatment for mothers during pregnancy permitted (not > 1g/wk). Treatment for newborns: potentially fatal bleeding or a platelet >30, when platelet transfusion (selected for HPA or not) is not possible.	Yes. Treatment for mothers during pregnancy permitted (not > 1g/wk). Treatment for newborns: potentially fatal bleeding or a platelet >30, when platelet transfusion (selected for HPA or not) is not possible.	
Hemolytic disease of the fetus and newborn (HDFN)		1 Total serum bilirubin (TSB) rising despite intensive phototherapy/hydration. In consultation with experts in FM medicine and transfusion medicine	1 TSB rising despite intensive phototherapy	1 Indicated only in infants with severe hyperbilirubinemia; i.e., TSB rising despite intensive phototherapy or TSB level within 34-51 mmol/L of the exchange level	1 May be considered in consultation with experts in FM medicine and transfusion medicine	Yes. Treatment for pregnant mothers: permitted for use when there is a high risk AND intrauterine transfusion is contraindicated. Treatment for newborns: permitted for use in cases of hyperbilirubinemia due to Rh incompatibility if phototherapy fails.	Yes. Treatment for pregnant mothers: permitted for use when there is a high risk AND intrauterine transfusion is contraindicated. Treatment for newborns: permitted for use in cases of hyperbilirubinemia due to Rh incompatibility if phototherapy fails and exchange transfusion can not be done within a reasonable time frame.	Red
Hemolytic transfusion reaction		2 May be considered as an option among supportive therapies for urgent situations						

Indication	Comments	Provincial guidelines				Shortage documents		
		ON	Atlantic	BC	Prairie	Quebec		UK
						AMBER	RED	
Hemolytic transfusion reaction in sickle cell disease (hyperhemolysis syndrome)		2 May be considered among the options for treatment of serious, life-threatening reactions			2 May be considered as one of several options in urgent situations	Yes	Yes	
Hemolytic uremic syndrome					2 Patient response should be documented			Grey
Heparin-induced thrombocytopenia					1 May be considered an option for severe HIT refractory to standard therapies			
ITP (acute and persistent) adult		1 Part of multimodal therapy for patients with platelet <30 and severe bleeding. May be considered: Planned surgery; patient with other concurrent risk factors for bleeding (e.g., anticoagulation therapy)	1 Major bleeding and platelets <10 OR Failed to respond to steroids after 3 days OR To produce an increase in platelet count to a level considered safe	1 Acute with bleeding: recommended as part of multimodal therapy for major or life-threatening bleeding complications and/or clinically important mucocutaneous bleeding Severe thrombo-cytopenia, no bleeding: No first-line therapy unless contraindications to steroids No/Slow response to steroids: may be considered as possible adjunctive therapy	1 Refractory ITP on recommendation of an appropriate clinical specialist OR Acute ITP with life-threatening hemorrhage or immediate high-risk for life-threatening hemorrhage OR Special circumstances (planned surgery, other risk factors for bleeding, platelets <20 where corticosteroid and immunosuppressives are contraindicated) OR HIV-assoc ITP and patient is unresponsive to antiviral therapy; platelet <20 or <50 with bleeding	Yes. Failure, contraindication or intolerance to steroids and anti-D AND platelet <10 or <30+ moderate-severe bleeding OR before surgery OR potentially fatal bleeding.	Yes. Failure, contraindication or intolerance to steroids, anti-D, Rituximab and TPO receptor agonists AND platelet <30 AND moderate-severe bleeding OR before urgent surgery OR potentially fatal bleeding.	Red

Indication	Comments	Provincial guidelines				Shortage documents		
		ON	Atlantic	BC	Prairie	Quebec		UK
						AMBER	RED	
ITP (chronic) adult		1 May be considered: Planned surgery; patient with other concurrent risk factors for bleeding (e.g., anticoagulation therapy)	1	1	1 Under the guidance of a clinical hematologist in addition to other therapies or where other therapies are ineffective or contraindicated	Yes. Failure, contraindication or intolerance to steroids and anti-D AND platelet <10 or <30+ moderate-severe bleeding OR before surgery OR potentially fatal bleeding.	Yes. Failure, contraindication or intolerance to steroids, anti-D, Rituximab and TPO receptor agonists AND platelet <30 AND moderate-severe bleeding OR before urgent surgery OR potentially fatal bleeding.	Grey
Preg-assoc ITP		1 When platelets < 30 or in preparation for delivery	1 Major bleeding OR Platelet <10 anytime in pregnancy or <10-30 during second or third trimester OR Rapid elevation of platelet count required before delivery		1 ITP and impending delivery	Yes. Failure, contraindication or intolerance to steroids AND plat <30 with moderate-severe bleeding; OR Failure, contraindication or intolerance to steorids to reach plt >50 before delivery; OR Potentially fatal bleeding	Yes. Failure, contraindication or intolerance to steroids AND plat <30 with moderate-severe bleeding; OR Failure, contraindication or intolerance to steorids to reach plt >50 before delivery; OR Potentially fatal bleeding	

Indication	Comments	Provincial guidelines				Shortage documents		
		ON	Atlantic	BC	Prairie	Quebec		UK
						AMBER	RED	
ITP pediatric		1 Moderate to severe mucosal and/or cutaneous bleeding and platelet < 30 May be used in chronic ITP for previous responders	1 Platelet < 50 and either major bleeding or surgery required OR Platelet <20 and treatment clinically indicated	1 May be considered initial therapy if platelet <20. Consultation with pediatric hematologist is advised. Recommended as part of multimodal therapy (with platelet transfusions and bolus IV MP) when patient has life-threatening bleeding. Not indicated if only mild bleeding. Chronic: may be considered	1 Platelet <20 as part of multimodal therapy when platelet has life-threatening bleeding or requires surgery			
Neonatal hemochromatosis					2 Consider for pregnant women who have had a previous affected pregnancy			
Neonatal thrombocytopenia secondary to maternal autoimmune disorders	Neonates of mothers with ITP		1 Platelets <50 OR Imaging evidence of ICH or other serious bleeding		1 Recommended in addition to other disorders in consultation with a neonatologist			
PTP		1 Standard first line therapy	1 No criteria		1 First line standard therapy for PTP with life-threatening bleeding	Yes. When there is moderate to severe bleeding.	Yes. When there is moderate to severe bleeding.	Blue
TTP					2			
Immunology								

Indication	Comments	Provincial guidelines				Shortage documents		
		ON	Atlantic	BC	Prairie	Quebec		UK
						AMBER	RED	
Chronic idiopathic urticaria			2 Failure to respond to or contraindications for high dose antihistamines AND Failed to respond to or has contraindications to Omalizumab (if covered)		2 May be considered as a last resort in patients with severe disease when conventional therapies are ineffective or contraindicated			Grey (severe, intractable)
Hematopoietic SCT in PID		1 Recommended			1 Recommended to reduce baseline community-acquired encapsulated gram-positive bacterial infections			Red
PID		1 Recurrent bacterial infections. Consultation with immunologist. Adult: trough >5 g/L (ideally > 7 g/L) and according to individual patient needs	1 Must be in consultation with immunologist Adult: Monitor IgG trough q5 months (7-10 g/L)	1 Hypogammaglobulinemia with recurrent bacterial infection.	1 Diagnosis must be established by immunologist with functional testing to establish diagnosis for: CVID and associated disorders; specific antibody deficiency; IgG subclass deficiency	Preferential use	Preferential use Target IgG on Day 28 5 g/L (may increase on a case by case basis) Increase time between doses if possible.	Red

Indication	Comments	Provincial guidelines				Shortage documents		
		ON	Atlantic	BC	Prairie	Quebec		UK
						AMBER	RED	
SID (any cause)		1	1 Adult: Recent life-threatening or recurrent clinically sig infection(s) related to low levels of polyclonal Ig Ped: Must be in consultation with immunologist	1 Hypogammaglobulinemia with recurrent bacterial infection.	1 Recommended for preventing recurrent, severe infection due to hypogammaglobulinemia (excluding paraprotein) related to other diseases or medical therapy At least one of: one invasive or life-threatening bacterial infection in previous year; recurrent severe bacterial infections; clinically active bronchiectasis confirmed by radiology' assessment by immunologist indicating significant antibody defect that would benefit from Ig replacement	No primary prophylaxis. Secondary prophylaxis (CLL, MM, NHL) permitted if patient has responded to treatment in the past after severe infection.	No	Blue
Specific antibody deficiency								Red
Thymoma with immunodeficiency								Red
Neurology								
Acute disseminated encephalomyelitis (ADEM)		2 Option when first-line therapy with high-dose corticosteroids fails or are contraindicated. Treatment of relapsing ADEM to eliminate steroid dependency or for those patients who fail to respond or have contraindications to steroids	2		1 Unresponsive to steroids of where steroids are contraindicated OR Recurrent or multiphasic ADEM unresponsive to steroid therapy or where steroid therapy has become intolerable or is contraindicated	Yes. In case of failure, contraindication or intolerance to other therapeutic options	Yes. In case of failure, contraindication or intolerance to other therapeutic options	Grey
Acute flaccid myelitis					2			

Indication	Comments	Provincial guidelines				Shortage documents		
		ON	Atlantic	BC	Prairie	Quebec		UK
						AMBER	RED	
Acute optic neuritis	See also neuromyelitis optica		2 Failed or contraindication to steroids (Autoimmune optic neuropathy)		3			
Adrenoleukodystrophy				3	3			
Aicardi-Goutieres Syndrome					2			
Alzheimer disease					3			Not recommended
Amyotrophic lateral sclerosis (ALS)				3	3			
Autism				3	3			
Autoimmune encephalitis NMDA		2 Option for treatment in conjunction with immunosuppressive medications and/or plasmapheresis. Requires expert consultation	2 Cared for in consultation with neurologist AND Used in conjunction with immune-suppressives and/or plasmapheresis		1 May be considered as an option with expert consultation			Grey
Autoimmune encephalitis (Rasmussen syndrome)		2 Option as a short-term, temporizing measure. Not recommended for long-term therapy	2 Short term, temporizing measure		2/3 Short-term, temporizing measure. Not recommended for longterm therapy	Yes. In case of failure, contraindication or intolerance to other therapeutic options.	Yes. In case of failure, contraindication or intolerance to other therapeutic options.	Blue
Childhood epilepsy, medically refractory/intractable	Including infantile spasms, Landau-Kleffner syndrome, Lennox-Gastaut syndrome			3	2 Consider only when conventional therapies are ineffective with full assessment by pediatric epileptologist			Grey
Chronic fatigue syndrome					3			Not recommended

Indication	Comments	Provincial guidelines				Shortage documents		
		ON	Atlantic	BC	Prairie	Quebec		UK
						AMBER	RED	
Chronic inflammatory demyelinating polyneuropathy (CIDP)		1 First-line therapy	1 Must be in consultation with a neurologist	1 First-line therapy If receiving it for chronic therapy, should be followed by neuromuscular specialist	1 First line treatment to be initiated when progression is rapid, walking is compromised or there is significant functional impairment	Yes. Initial treatment: Preferential use. Maintenance treatment in cases of failure, contraindication or intolerance to other forms of immunosuppressive therapy.	Yes. Initial treatment: Preferential use. Maintenance treatment in cases of failure, contraindication or intolerance to other forms of immunosuppressive therapy.	Red (short duration); Blue (long duration)
Critical illness polyneuropathy				3	3			
Diabetic amyotrophy					2			
Guillain-Barre Syndrome (GBS)	Including Miller-Fischer syndrome and other variants	1 Symptoms of grade 3 severity (able to walk with aid) or greater, or symptoms less than grade 3 that are progressing. Should be given within 2 weeks of symptom onset. Re-treatment for patients who do not respond may be considered	1 Within 2 weeks of symptom onset AND Hughes Disability score of 3 or more or less than 3 with symptoms progressing	1 Symptoms of grade 3 severity (able to walk with aid) or greater, or symptoms less than grade 3 severity that are progressing. Should be given within 2 weeks of symptom onset Diagnosis of GBS variants should be made by specialist with expertise in this area.	1 Recommended in patients with significant disability and progression	Preferential use	Yes. In cases of failure, contraindication or intolerance to plasma exchange.	Red
Hashimoto encephalopathy					2 May be considered in exceptional circumstances where there is progressive neurologic decline despite appropriate steroid therapy			
Inflammatory myopathies								Blue

Indication	Comments	Provincial guidelines				Shortage documents		
		ON	Atlantic	BC	Prairie	Quebec		UK
						AMBER	RED	
Lambert Eaton Myasthenic Syndrome (LEMS)		2 Option for treatment. Objective evidence of clinical improvement needed for sustained use	2 Must be in consultation with neurologist		1 Recommended as an option for initial treatment for indication and maintenance	Yes. In case of failure, contraindication or intolerance to other therapeutic options.	Yes. In case of failure, contraindication or intolerance to other therapeutic options.	Blue
Multifocal motor neuropathy (MMN)		1 First line treatment	1	1 Diagnosis should be made by neuromuscular specialist	1 First line treatment	Preferential use	Yes. In case of failure, contraindication or intolerance to other therapeutic options.	Blue
Multiple Sclerosis (MS) (relapsing/remitting)			2 Pregnant/immediate postpartum period when other immunomodulation is contraindicated OR Failure or contraindication to standard immunomodulatory therapies		1/3 First line short-term therapy for: Pregnancy and the immediate post-partum period when other immunomodulation is contraindicated; OR Young patients in whom other therapies are ineffective OR Severe relapse with no response to high-dose methylprednisolone Not recommended for long-term therapy	Yes. In case of failure, contraindication or intolerance to other therapeutic options.	Yes. In case of failure, contraindication or intolerance to other therapeutic options.	Not recommended
Myasthenia gravis (MG)		1 First-line treatment in moderate-severe MG or in myasthenic crisis. For refractory cases may be given in combination with immunosuppressive therapy	1 Acute exacerbation (myasthenic crisis) OR Optimization prior to surgery and/or thymectomy OR As maintenance therapy for moderate-severe MG in combination with immunosuppressive agents	1 Severe exacerbations of MG or myasthenic crises, or to stabilize patients before surgery Not recommended as maintenance therapy for patients with chronic MG	1/2 Alternate to plasma exchange in acute exacerbation (myasthenic crisis) or before surgery and/or thymectomy OR Maintenance therapy for moderate to severe generalized MG when other treatments are ineffective or have caused intolerable side effects	Yes. In cases of severe exacerbation, myasthenic crisis or in preparation for urgent or semi-urgent surgery	Yes. In cases of myasthenic crisis with failure, contraindication or intolerance to other therapeutic options (e.g., plasma exchange)	Blue

Indication	Comments	Provincial guidelines				Shortage documents		
		ON	Atlantic	BC	Prairie	Quebec		UK
						AMBER	RED	
Narcolepsy					2 May be considered in exceptional circumstances with expert consultation			
Neuromyelitis optica	Devic disease. See also acute optic neuritis		2 Failed or has contraindications to plasma exchange and/or steroids		2			
Neuropathic pain					3			Grey (chronic regional pain syndrome)
Neuropathy associated with IgM paraproteinemia					1/2/3 Recommended for neuropathy associated with IgM and features consistent with CIDP in the absence of anti-MAG ab Unclear if recommended if anti-MAG ab present Not recommended for axonal neuropathy			Blue
Opsoclonus-myoclonus ataxia, adult					2	Yes. In case of failure, contraindication or intolerance to other therapeutic options.	Yes. In case of failure, contraindication or intolerance to other therapeutic options.	Grey
Opsoclonus-myoclonus ataxia-pediatric					1 Recommended for acute and long-term treatment, in consultation with a neurologist in addition to other tumor therapies as applicable	Yes. In case of failure, contraindication or intolerance to other therapeutic options.	Yes. In case of failure, contraindication or intolerance to other therapeutic options	Grey

Indication	Comments	Provincial guidelines				Shortage documents		
		ON	Atlantic	BC	Prairie	Quebec		UK
						AMBER	RED	
PANDAS (Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections)		2 Requires expert consultation	2 Must be in consultation with pediatric neurologist		2 Utility may be limited to patients with a confirmed diagnosis, including evidence of recent streptococcal infection. Requires expert consultation.			Grey
Paraneoplastic or sporadic autoimmune encephalitis	Potassium channel antibody-associated encephalopathy				1 Should be considered as initial therapy and may play a role in maintenance therapy			Grey (if not known to be B- or T-cell mediated)
Paraneoplastic cerebellar degeneration and neurological syndromes			2 Treated within 1 month of symptom onset AND Used in conjunction with chemotherapy		2			Grey (if not known to be B- or T-cell mediated)
Paraprotein-associated demyelinating neuropathy				3 IgM variant				
POEMS syndrome				3	3			Grey
Post-polio syndrome					2			
Stiff person syndrome		2 Option GABAergic medications fail or contraindications to GABAergic	2 Failure or contraindications to GABAergic medications		1 Recommended for treatment of significant functional impairment, in consultation with a neurologist.	Yes. In case of failure, contraindication or intolerance to other therapeutic options.	Yes. In case of failure, contraindication or intolerance to other therapeutic options.	Blue
Susac syndrome					2			
Sydenham chorea			See PANDAS		1/2 Short-term therapy: use of a single dose in children with moderate to severe disease associated with significant impairment			
Transverse myelitis					2			
Dermatology								

Indication	Comments	Provincial guidelines				Shortage documents		
		ON	Atlantic	BC	Prairie	Quebec		UK
						AMBER	RED	
Atopic dermatitis					2 Most severe forms of eczema OR Immunodeficiency OR Contraindications to standard immunosuppressive therapies OR Recurrent or life-threatening infections			
autoimmune blistering disease	Pemphigus vulgaris, pemphigus foliaceus, pemphigoid, cicatricial pemphigoid, linear IgA disease, epidermolysis bollusa acquisita, pemphigoid gestionis	1 When no response or a contraindication to corticosteroids, immunosuppressive agents or biologics (e.g., rituximab). Considered 3rd line therapy (1st: steroids; 2nd immune-suppressive)	2 Disease is progressing rapidly AND Failed to respond or has contraindications to systemic steroids	1 Firm histiological and immunodiagnosis needed Consider when there is no response or a contraindication to corticosteroids and immune-suppressive agents	1 Recommended In addition to standard corticosteroids and/or immunosuppressive therapies for ALL severe forms	No, except in exceptional cases	No	Blue
Livedoid vasculopathy					2 May be considered in exceptional circumstances when patients do not respond to primary standard therapy			
Necrobiotic xanthogranuloma			2 Failed to respond or has contraindications to corticosteroids					
Pre-tibial myxedema			2 Failed to respond or has contraindications to corticosteroids					

Indication	Comments	Provincial guidelines				Shortage documents		
		ON	Atlantic	BC	Prairie	Quebec		UK
						AMBER	RED	
Pyoderma gangrenosum			2 Cared for in consultation with Dermatologist AND Failed to respond or has contraindications to systemic steroids		1 May be considered in patients with significant pyoderma gangrenosum when other therapies are ineffective or contraindicated Diagnosed by a dermatologist			Grey
Scleromyxedema			1 Failed to respond or has contraindications to corticosteroids		1 Consider in severe disease when other therapies are ineffective or contraindicated			
Toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome		2 When other treatments are contraindicated or when condition is life-threatening. Early intervention strongly recommended.			1 Early administration recommended as an option when other treatments are contraindicated and when the condition is life-threatening	No, except in exceptional cases	No	Red
Rheumatology								
Adult-onset Still's disease			2 Must be in consultation with a Rheumatologist					
Antiphospholipid antibody syndrome. catastrophic			2 Must be in consultation with a Rheumatologist		1 Recommended for C-APLAS characterized by widespread small vessel thrombosis leading to multiorgan failure	Yes. Failure, contraindication or intolerance to other therapeutic options.	Yes. Failure, contraindication or intolerance to other therapeutic options.	Grey
Antiphospholipid antibodies with cerebral infarction								Grey
Becet disease					3			
Congenital heart block, autoimmune (neonatal lupus)					2			Blue

Indication	Comments	Provincial guidelines				Shortage documents		
		ON	Atlantic	BC	Prairie	Quebec		UK
						AMBER	RED	
Dermatomyositis (adult)	1 Indicated as adjunctive therapy to corticosteroids and/or a steroid sparing agent in patients who have failed first line therapy or as clinically indicated in the management of severe disease		2 Has significant muscle weakness AND Failed to respond or has contraindications to corticosteroids		1 Adult: In cases who have not responded to first-line therapies. In severe or life-threatening situations, it may be first-line.	Yes. In case of failure, contraindication or intolerance to other therapeutic options.	Yes. In case of failure, contraindication or intolerance to other therapeutic options.	
Eosinophilia granulomatosis with polyangiitis (Churg-Strauss disease)					1 Patients with nervous system or cardiac disorders OR Who have not responded to primary standard therapy			
Grave's disease					2 May be considered in exceptional circumstances when steroids are ineffective or contraindicated	Yes. Cases of severe disease with failure, contraindications or intolerance to other therapeutic options.	No	Not recommended
Hemophagocytic lymphohistiocytosis (HLH) syndrome	Virus associated hemo-phagocytic syndrome (VAHS)	2 Not recommended for routine use. May be considered among the options for severe life-threatening VAHS	2 Must be in consultation with a Rheumatologist		2/3 Not recommended if no thrombocytopenia. With thrombocytopenia may be considered in exceptional circumstances with appropriate consultation			Blue

Indication	Comments	Provincial guidelines				Shortage documents		
		ON	Atlantic	BC	Prairie	Quebec		UK
						AMBER	RED	
Immune-mediated inflammatory myositis (Idiopathic inflammatory myopathy, includes dermatomyositis and polymyositis)	See individual entries	1 Indicated as adjunctive therapy to corticosteroids and/or a steroid sparing agent in patients who have failed first line therapy or as clinically indicated in the management of severe disease	2 Failed to respond or has contraindications to corticosteroids +/- immunosuppressive therapies AND/OR Presence of life-threatening disease					
Immune mediated uveitis					2 Consider for exceptional cases of immune-mediated, sight-threatening uveitis with persistent activity despite corticosteroid and immunosuppressive therapy			Blue
Inclusion body myositis				3	2/3 Not recommended if no dysphagia. May be tried in exceptional cases with dysphagia.			
Juvenile idiopathic inflammatory myopathy (Juvenile dermatomyositis [JD])		1 Recommended when there is a lack of response or contraindication to corticosteroids, methotrexate and/or azathioprine therapy	1 Glucocorticoids and other 2nd line agents are contraindicated or IVIG is part of early therapy in a critically ill child AND Cared for in consultation with a Rheumatologist	1 Lack of response or contraindication to corticosteroids, methotrexate, and/or azathioprine therapy	1 Should be considered in addition to corticosteroids and/or immune-suppressives at the outset of treatment or when response is suboptimal. Should be considered for persistent skin disease when muscle disease is otherwise well controlled.	Yes. In case of failure, contraindication or intolerance to other therapeutic options.	Yes. In case of failure, contraindication or intolerance to other therapeutic options.	
Kawasaki syndrome		1	1 (ped)	1 Validity of diagnosis must be established	1 (ped); 2 (adult)	Preferential use	Preferential use	Red
Macrophage activation syndrome					1 May be used in addition to other therapies			

Indication	Comments	Provincial guidelines				Shortage documents		
		ON	Atlantic	BC	Prairie	Quebec		UK
						AMBER	RED	
Polymyositis, adult		1 Indicated as adjunctive therapy to corticosteroids and/or a steroid sparing agent in patients who have failed first line therapy or as clinically indicated in the management of severe disease			1 Recommended for patients who do not respond to first-line therapies	Yes. In case of failure, contraindication or intolerance to other therapeutic options.	Yes. In case of failure, contraindication or intolerance to other therapeutic options.	
Polymyositis, pediatric					2	Yes. In case of failure, contraindication or intolerance to other therapeutic options.	Yes. In case of failure, contraindication or intolerance to other therapeutic options.	
Rheumatoid arthritis					3			Not recommended
Scleroderma					2 May be considered in exceptional circumstances when patients do not respond to primary standard therapy			
Sjogren's syndrome			2 Must be in consultation with a Rheumatologist		2			
Systemic lupus erythematosus (severe)			2 Failed to respond or has contraindications to corticosteroids		2 Exceptional circumstances when no other treatment options are effective or appropriate			Grey (without secondary immunocytopenias including juvenile)
Systemic vasculitic syndromes (including polyarteritis nodosa and livedoid vasculopathy)			1 Must be in consultation with a dermatologist		2 May be considered when primary standard therapy is ineffective or contraindicated			Grey

Indication	Comments	Provincial guidelines				Shortage documents		
		ON	Atlantic	BC	Prairie	Quebec		UK
						AMBER	RED	
Systemic onset juvenile idiopathic arthritis (adult Still Disease)			1 Resistant to other forms of therapy AND Cared for in consultation with Rheumatologist		2 Exceptional circumstances when patients do not respond to primary standard therapy			Grey
Infectious Disease								
Clostridium difficile colitis (severe or recurrent)					3			
Enterovirus meningoencephalitis						Yes. Immunocompromised patients in very severe cases.	Yes. Immunocompromised patients in very severe cases.	
HIV					3			Not recommended (immunodef secondary to ped HIV inf)
Infectious gastroenterocolitis (i.e., C. difficile or rotavirus in immunocompromised pts					2/3 Oral Ig should be considered for persistent, proven Norovirus or Rotavirus in immunosuppressed transplant recipients where reduction of immunosuppression is contraindicated	Do not use	Do not use	

Indication	Comments	Provincial guidelines				Shortage documents		
		ON	Atlantic	BC	Prairie	Quebec		UK
						AMBER	RED	
Measles post-exposure				1 To prevent post-exposure measles disease in pregnant women, infants, and immune-deficient or immune-suppressed patients in whom weight (>30 kg) or ability to tolerate IM preparations precludes the use of an IM preparation of hyperIg				Grey Post-exposure prophylaxis for viral or pathogenic infection if IM injection is contraindicated, or treatment with hyperIg are unavailable
Sepsis, neonatal					3 (proph)	Yes. Permitted for use in severe cases	Yes. Permitted for use in severe cases	Not recommended
Group A streptococcus necrotizing fasciitis (invasive disease)			1 Must be treated with combination therapy of antibiotics and IVIG	1	2 Insufficient evidence for patients without hemodynamic compromise (see TSS)	Preferential use	Preferential use	Blue
Staphylococcus aureus or Group A streptococcus toxic shock syndrome		1 Recommended when evidence of systemic inflammation and eng organ hypoperfusion with fever, tachypnea and hypotension	1 Must be treated with combination therapy of antibiotics and IVIG	1 Evidence of systemic inflammation and end organ hypoperfusion with fever, tachycardia, tachypnea and hypotension Consult with med micro or ID specialist before treatment	1 Recommended in addition to surgical intervention, antibiotic therapy, and other supportive measures	? preferential use (if considered with invasive group A strep disease)	? preferential use (if considered with invasive group A strep disease)	Blue
Varicella-zoster virus prophylaxis					3 Not recommended when VZV immune globulin is available			
Transplantation (solid organ and SCT) including ID in transplant patients								
								Blue (all solid organ)

Indication	Comments	Provincial guidelines				Shortage documents		
		ON	Atlantic	BC	Prairie	Quebec		UK
						AMBER	RED	
Community-acquired respiratory virus, URTI					1/2/3 May be considered for treatment of proven RSV in high risk patients			
Community-acquired respiratory virus, LRTI					2/3 May be considered in addition to antiviral therapy in high risk patients	Do not use; preferential use should be made of specific Ig (LRTI caused by CMV or RSV in immunocompromised patients)	Do not use; preferential use should be made of specific Ig (LRTI caused by CMV or RSV in immunocompromised patients)	
CMV prophylaxis	SCT and solid organ transplant				3			
EBV-associated PTLD	SCT and solid organ transplant				3			
GI viruses in solid organ transplant	Refractory and persistent norovirus or rotavirus diarrhea				2/3	See entry in infectious disease	See entry in infectious disease	
Heart: pre-transplant		1 For desensitization in selected heart transplant recipients who are highly sensitized, medically urgent and unlikely to receive a transplant otherwise				No, unless evaluated by peer review committee	No, unless evaluated by peer review committee	
HSCT CMV-induced pneumonitis		2 Used with appropriate antiviral			1 Recommended in addition to appropriate antiviral chemotherapy for proven or probably CMV-induced pneumonitis	Do not use; preferential use should be made of specific Ig (LRTI caused by CMV or RSV in immunocompromised patients)	Do not use; preferential use should be made of specific Ig (LRTI caused by CMV or RSV in immunocompromised patients)	
HSCT GVHD		2 High-risk (if hypogammaglobulinemia) for GVHD prevention			3 Not recommended for prevention of GVHD	Yes. For patients being treated with steroids for chronic GVHD or acute GVHD that becomes chronic	No	

Indication	Comments	Provincial guidelines				Shortage documents		
		ON	Atlantic	BC	Prairie	Quebec		UK
						AMBER	RED	
HSC allo (and recurrent infections)						Yes	No	
HSC haploidentical						Yes	No	
HSCT autologous					3 Not recommended unless the patient has established humoral deficiency			Not recommended
Kidney transplant from living donor to whom the patient is sensitized		1 Recommended to decrease donor-specific sensitization			1 Recommended when antibody(ies) might preclude transplantation. May be continued for up to 3 months post transplant	No, unless evaluated by peer review committee	No, unless evaluated by peer review committee	
Kidney, active antibody-mediated rejection prevention and management		1 First line for treatment			1 When other therapies are ineffective	No, unless evaluated by peer review committee	No, unless evaluated by peer review committee	
Kidney, acute/active T-cell mediated rejection management					2 May be considered in exceptional cases when other therapies are ineffective or contraindicated	No, unless evaluated by peer review committee	No, unless evaluated by peer review committee	
Kidney, non-active rejection management					2 May be considered in exceptional cases when other therapies are ineffective or contraindicated	No, unless evaluated by peer review committee	No, unless evaluated by peer review committee	

Indication	Comments	Provincial guidelines				Shortage documents		
		ON	Atlantic	BC	Prairie	Quebec		UK
						AMBER	RED	
Peri-transplant (heart, lung, kidney, pancreas)		1 First line for Donor-specific antibodies identified at time of transplant surgery			2 Highly sensitized patients awaiting transplantation OR Acute T-cell mediated rejection and clinical evidence of graft dysfunction OR As treatment or prophylaxis for rejection when conventional immunosuppressive therapy is contraindicated	No, unless evaluated by peer review committee	No, unless evaluated by peer review committee	
Post-transplant: Acute antibody-mediated rejection (organ other than kidney)		1 First line	1 Pathology proven acute antibody mediated rejection		1 Recommended in addition to plasma exchange	No, unless evaluated by peer review committee	No, unless evaluated by peer review committee	
Post-transplant: chronic antibody-mediated rejection		1				No, unless evaluated by peer review committee	No, unless evaluated by peer review committee	
Pulmonary GVHD					3			
Other								
Systemic capillary leak syndrome					1 May be considered for prophylaxis, in addition to other therapies			

UK Guidelines

- **Red**: Conditions for which treatment is considered the highest priority because of risk to life without treatment. The intention [is that] Trusts will protect supply for these high priority diseases in times of immunoglobulin shortage, particularly for patients with immunodeficiencies.
- **Blue**: conditions for which there is a reasonable evidence base for the use of Ig but other treatment options are available
- **Grey**: Immune-mediated disorders with limited evidence of immunoglobulin efficacy or presumed immune-mediated disorders with little or no evidence of efficacy. It is accepted that the lack of an evidence base may reflect the rarity of these diseases. Approval is required for Ig treatment on a case-by-case basis.

References

Provincial Guidelines:

- Atlantic Clinical Indications and Criteria for Intravenous and Subcutaneous Immunoglobulin (IVIG/SCIG) May 2018.
- Ontario Immune Globulin (IG) Utilization Management Guidelines. ORBCoN, Version 4.0; January 31, 2018
- Prairie Collaborative Immune Globulin Utilization Management Framework Project. Criteria for the clinical use of immune globulin. Alberta Ministry of Health, Shared Health Manitoba and Saskatchewan Ministry of Health; 2018.
- British Columbia PBCO. Intravenous Immune Globulin (IVIg) Utilization Management Program Recommendations. Version 5.0. Revision Date: 2019-07-25. https://pbco.ca/images/Programs/IVIG_Provincial_Program/UMIVIG0007_IVIG_Utilization_Management_Program_Guidelines_V42.pdf

Shortage Documents

- Sante et Services Sociaux Quebec. Appendix 3. Nonspecific Immunoglobulin (Ig) Shortage Management Framework. March 2020
- Department of Health. UK. Clinical Guidelines for Immunoglobulin Use. Second Edition update. July 2011
- Updated Commissioning Criteria for the use of therapeutic immunoglobulin (Ig) in immunology, haematology, neurology and infectious diseases in England, November 2019

Appendix E. Considerations for the development of a full national Ig shortages management plan

The development of the interim Ig shortages management plan was expedited considering a short-term supply risk due to impacts of COVID-19. This plan and its learnings will serve as a framework to directly inform the development of a full national Ig shortage management plan. To further maximize the effectiveness of a response to any shortage of the Ig supply in Canada, the following are considerations recommended for the development of the next iteration of an Ig shortage management plan:

- **Roles and responsibilities of all stakeholders:** Expand to include specific details and specificity of actions and expectations of each stakeholder group, including product vendors and the federal government. Assure input of affected patient organizations and expert physician organizations.
- **Data:** Detail a process and mechanism by which stakeholders will share data, including the provision of national, jurisdictional and hospital Ig inventory and utilization data.
- **Adjudication:** Explore adjudication options beyond the current framework (NEBMC, PEBMC, HEBMC, Triage teams, provincial/regional review panels).
- **Ethical framework:** Review and refresh the ethical framework (labile blood components and Ig), including adjudication considerations and to increase stakeholders' understanding of product availability and equitable allocation of Ig for patient treatment in Red phase. There would be value in determining specific exclusion criteria and provide direct guidance.
- **Allocation criteria:** Further consultation with clinical communities to garner additional support for the use of consistent criteria to guide use in times of shortage (specifically dermatology, solid organ transplant and infectious disease)
- **Medico-legal implications:** Confirm understanding of impacts of those tasked with making difficult clinical decisions in times of Ig shortage.
- **Effectiveness of inventory phase activities:** Conduct an assessment and review of proposed inventory phase activities to validate effectiveness if implemented in a declared shortage situation
- **Product switching:** Consideration of guidance on product switching for specific shortages of SCIg or IVIg or Total Ig.
- **Research:** Consideration of guidance as to the new and continued use of Ig in Canada for research purposes during a declared or pending shortage.

- **Alternative therapy:** Conduct an environmental scan of available alternative therapies for clinical conditions for which Ig is used, including ease of accessibility.
- **Tools for use:** Develop and/or identify appropriate tools (including technology) for use to document decisions (triage) regarding allocation of Ig.
- **Communications:** Review the communications plan framework and optimize for use during an Ig shortage