About the Authors

Oksana Prokopchuk-Gauk, MD, FRCPC, DRCPSC

Dr. Oksana Prokopchuk-Gauk is the Provincial Transfusion Medicine Clinical Lead with the Saskatchewan Health Authority and an adult hematologist with the Saskatchewan Bleeding Disorders Program based at Royal University Hospital, Saskatoon. Dr. Prokopchuk-Gauk actively participates in provincial and national transfusion medicine committees, including the National Advisory Committee on Blood and Blood Products. Her research interests include identifying strategies to improve transfusion safety and blood utilization, and optimizing perioperative care in patients with inherited bleeding disorders.

Affiliations: Department of Pathology and Lab Medicine, Saskatchewan Health Authority; College of Medicine, University of Saskatchewan, Saskatoon, Saskatchewan.

Kathryn E. Webert, MD, MSc, FRCPC

Dr. Kathryn Webert is a Medical Director and Special Advisor with Canadian Blood Services and an Associate Professor with the Department of Pathology and Molecular Medicine at McMaster University in Hamilton, Ontario. Dr. Webert's clinical interests include transfusion medicine, benign hematology, and hemostasis and coagulation. Dr. Webert's areas of research interest include the utilization of blood and blood products and bleeding in patients with bone marrow failure.

Affiliations: Canadian Blood Services and Division of Pathology and Molecular Medicine, McMaster University, Hamilton, Ontario.

Jennifer Grossman, MD, FRCPC

Dr. Grossman is a Hematologist with the Department of Medicine and Assistant Professor at the University of Calgary. Following her hematology residency, she completed a Fellowship in adult primary immune deficiencies at the National Institutes of Health in Bethesda, Maryland. Dr. Grossman launched a clinic specifically for this patient population in Calgary, which has evolved to become the Collaborative Immunohematology Program, and includes the Subcutaneous Immunoglobulin program.

Affiliations: Division of Hematology and Hematologic Malignancies, University of Calgary, Calgary, Alberta.

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Rational Use of Immunoglobulin in Adult Patients with Secondary Hypogammaglobulinemia in the Setting of Hematologic Malignancy: A Canadian Perspective

Oksana Prokopchuk-Gauk, MD, FRCPC, DRCPSC
Kathryn Webert, MD, MSc, FRCPC
Jennifer Grossman, MD, FRCPC

Introduction

Hypogammaglobulinemia is identified by the detection of low serum immunoglobulin (Ig) levels. Secondary hypogammaglobulinemia (SHG) is an acquired state in which circulating Ig levels are reduced due to suppressed antibody production or increased antibody loss.[1,2] Specifically, SHG most commonly refers to low circulating total IgG levels. In contrast, primary hypogammaglobulinemia (PHG) is due to an underlying inborn error of immunity contributing to low or defective Ig production and frequent and/or severe infections.

In patients with hematologic malignancies, it is important to evaluate baseline Ig (IgG, IgM, IgA) levels at the time of diagnosis. However, it may be challenging to distinguish whether low Ig levels are attributable to PHG or SHG, if antibody defects are identified in the context of hematologic malignancies (including chronic lymphocytic leukemia [CLL], lymphoma, and multiple myeloma), even before initiation of immunosuppressive treatment,[3] PHG should be considered, especially in younger patients presenting with a hematologic malignancy who have a history of recurrent, severe infections.[1,3]

Treatment of several hematologic malignancies includes anti-CD20 B cell-depleting therapy, which is known to cause the development of SHG. Advancements in lymphoma and myeloma management now incorporate bispecific antibody therapies and chimeric antigen receptor T-cell (CAR T-cell) therapies, which have revolutionized care for patients with disease refractory to conventional treatments. However, the risk of SHG is significant, with rates of ≥70% with bispecific antibody treatments and 20–46% with CAR T-cell therapies.[4,5] Thus, patients with hematologic malignancies have a high rate of SHG attributable to both the underlying disease and associated treatment.

Pooled immunoglobulin products, including intravenous immunoglobulin (IVIg) and subcutaneous immunoglobulin (SCIg), are a source of exogenous IgG that can be administered to replace IgG in patients who have deficient levels. Due to a continuing increase in global demand and a supply dependent on volunteer human donors (most of whom are compensated financially), it is prudent to ensure appropriate stewardship of Ig products. Canada has the third largest consumption of Ig per capita, narrowly trailing behind Australia and the United States,[6] with the annual demand of all countries continuing to increase. Supply sufficiency is a real concern for Canadians who are dependent on American donors and Ig manufacturers to provide approximately 75%–80% of the Ig utilized for patient care.[7]

In this context, we aim to provide a concise summary of when Ig may be considered for the management of SHG in adult patients with hematologic malignancies. Further, we highlight potential risks of adverse reactions due to Ig, the challenges with health system cost and global Ig supply constraints, and areas where further research is required.

Measured serum IgG level

Hypogammaglobulinemia: measured serum total IgG level <7 g/L
• Total IgG level subcategory stratification:
  ◦ IgG 4.0–6.9 g/L
  ◦ IgG 2.0–3.9 g/L
  ◦ IgG <1.9 g/L
• Evaluation of IgG subclasses is not recommended
Duration of low IgG levels subcategory stratification:
• Transient: 3–6 months, 6–12 months, or 12–24 months
• Persistent: more than 24 months

Clinically significant infections:
***Severe infection*—an infection requiring:** • An emergency room visit or hospitalization, and • Intravenous antibiotics, or • A prolonged course or more than 1 course of antibiotic/antiviral/antifungal therapy for the purposes of treatment (not prophylaxis). ***Recurrent* – any of the following occurring in 1 year:** • ≥2 new ear infections, or • ≥2 new sinus infections in the absence of allergy, or • ≥1 pneumonia (for more than 1 year), or • Deep abscesses of the skin or internal organs.

Table 1. Proposed definition of SHG, based on serum IgG levels and clinical infection frequency in adults.[1,8]

SHG Definition

There is a prominent lack of a standardized definition of SHG in the literature, which leads to difficulty in interpreting reported rates of SHG. Serum immunoglobulins that may be measured include IgG (total; subclasses may also be measured), IgA, IgM, and IgE. At present, only IgG-containing replacement therapies are available in Canada. In the context of SHG, limited evidence exists regarding the clinical impact and management strategies of acquired deficiencies of IgG subclasses, as well as total IgA and IgM levels.[1]

In 2022, a standardized definition of SHG, specifically referring to low serum IgG levels and criteria for clinical infection, was proposed by the American Academy of Allergy, Asthma, and Immunology (AAAAI) Primary Immunodeficiency and Altered Immune Response Committees to aid in standardizing future work.[1] Based heavily on primary immunodeficiency (PID) literature, these are summarized in **Table 1**. The listed criteria for severe and recurrent infection are adapted from the Jeffery Modell Foundation's *10 Warning Signs of Primary Immunodeficiency in Adults*, rather than in pediatrics.

In addition to Ig production, vaccination testing has been used as a functional test of the humoral immune system, in which serotype titers are measured before and 4–6 weeks after vaccination. As a pure polysaccharide vaccine, the polyvalent pneumococcal vaccine (Pneumovax 23) has been recognized as provoking a T cell-independent response and has long been used by immunologists.

Unfortunately, Pneumovax 23 is gradually being replaced by a protein-polysaccharide vaccine (Prevnar 20) in many countries, which does not evoke the same type of humoral response. Most other common vaccines, including those against diphtheria and tetanus, are protein-polysaccharide conjugate vaccines and therefore not useful in strictly assessing humoral response. The immunology community is still grappling with how to address this impending void in functional testing.[9]

In the context of SHG due to hematologic malignancy, vaccination testing is not routinely performed. If there is uncertainty around the patient's immune function and vaccination testing is a consideration, consultation with an immunology specialist is recommended.

Ig Replacement Therapy

The decision regarding when to start Ig replacement therapy (IgRT) in the setting of SHG varies, as there are no clear criteria as to when it should be initiated. Published recommendations generally recommend consideration of multiple patient factors, including low IgG levels and a history of serious or recurrent bacterial infections.[1,2] There is no evidence to support the use of IgRT in patients with low IgM or IgA in the context of a hematologic malignancy. It is important to make the distinction between bacterial and viral infections, as the efficacy of IgRT in preventing viral infections has not been proven.[10]

IgRT may include subcutaneous Ig (SCIg) or intravenous Ig (IVIg), and the decision regarding the administration modality must be considered based on resource availability, cost, and individualized patient factors. The cost of IVIg and SCIg is relatively equivalent per gram of IgG. SCIg self-administration at home may be a more convenient option for the patient and has been demonstrated to have a markedly lower health system cost impact than IVIg infusions in an ambulatory care setting, with the average administrative cost of SCIg per patient year being about $5,500 lower than IVIg administered in a hospital clinic.[11] A shared decision-making approach between the patient and multidisciplinary clinical care team is essential, given that the decision to initiate IgRT can be complex.[1]

There is even less clarity around the decision to initiate IgRT as primary versus secondary infection prophylaxis.[1,2] With the advances in hematologic malignancy treatments for relapsed and refractory disease, it remains unclear whether Ig should be initiated as a means of primary infection prophylaxis (i.e., before the development of any infections in the setting of documented low IgG levels), or if daily antibiotics may confer an equivalent protection in certain settings.[12] IgRT has most commonly been used for secondary prophylaxis (ie, to prevent additional severe or recurrent infection development), though proposed criteria to standardize IgRT eligibility based on IgG levels and clinically significant infection have been relatively recent.[1,8] Furthermore, if IgRT is initiated, an optimal IgG level required to achieve adequate infection prophylaxis has not been determined, especially if Ig is initiated prior to the development of a clinically significant infection.[2]

The half-life of total IgG from IVIg administration has been reported to be 26 days[13]; thus, it is not fully eliminated until at least 5 months after administration. Following baseline serum Ig monitoring at the time of disease diagnosis, monitoring of trough IgG levels should occur immediately prior to the next IVIg administration, or at any time during SCIg administration (steady-state) levels. Although a precise target IgG level in this context has not been defined, extrapolating from PID literature, an IgG level of 7–8 g/L is likely reasonable to mitigate against severe or recurrent bacterial infection. Expert opinion suggests that an even lower target trough IgG level in some patients with SHG may be adequate.

Assessment of individual patient factors is necessary to determine when a trial of an IgRT taper or discontinuation may be undertaken. To determine the endogenous patient Ig baseline, circulating Ig levels should be checked no sooner than 3 months following the last IgG dose. By 6 months after the last Ig dose, all replacement IgG will have been eliminated to reflect the patient's baseline Ig levels.[14]

Within Canadian jurisdictions, evidence-based clinical criteria for accessing IgRT have been developed to improve stewardship of this publicly funded resource. A summary of clinical criteria for accessing IgRT in the setting of SHG with hematologic malignancies is presented in **Table 2**.[15-19] A reference comparison of clinical criteria from Australia and the United Kingdom is included in **Table 3**.[20-21] All clinical criteria documents endorse using adjusted body weight (ABW) IgRT dosing.

Ig Preparations and Procurement

Human-source, purified preparations predominantly contain a polyclonal blend of IgG (no clinically significant replacement amount of IgM or IgA protein is included in preparations of IgRT available in Canada). The decision to initiate IVIg versus SCIg depends on the clinical indication for which IgRT is necessary, patient values, an informed discussion about the risks and benefits, and the administration modality related to each product. All brands of IVIg and SCIg available in Canada are approved for IgG replacement in the setting of SHG in adults.

Canadian Jurisdiction (*year published*)*	Criteria for Prescribing Ig Replacement Therapy (*summary*)	Dosing Recommendations	Review Criteria for Assessing the Effectiveness of Ig Use
British Columbia (2024)	Prevention of recurrent bacterial infections due to hypogammaglobulinemia associated with hematological malignancies or post-HSCT. **Qualifying Criteria** • Serum IgG must be measured on two separate occasions (at least one sample taken when the patient does not have an active infection, ideally for 4-6 weeks) Baseline serum levels of IgA and IgM should be obtained with the second IgG for assessment of immune recovery Consider pre-existing primary immunodeficiency, if not excluded previously, especially if there is a family history or other non-immunoglobulin deficiency infectious findings Significant hypogammaglobulinemia with serum IgG <5g/L. If paraprotein confounds the serum IgG level (such as in MM), then the indication for starting Ig can exclude the serum IgG level **AND EITHER:** 1. At least one life threatening bacterial infection in the last 12 months (ICU admission) 2. At least two serious bacterial infections in the last 6 months requiring more than standard courses of antibiotics (e.g., hospitalization, intravenous or prolonged antibiotic therapy) **WITH BOTH:** 1. Infections unrelated to chemo/radiotherapy, including neutropenia or mucosal/epithelial toxicity 2. Infections confirmed to be due to encapsulated bacteria and/or are clinically consistent with encapsulated bacteria	Antibiotic therapy may be indicated in addition to Ig therapy. **Loading Dose (IVIg)** - One loading dose of 0.4 g/kg (ABW) in the first month of therapy (in addition to the maintenance dose) is permitted if the serum IgG level is <4 g/L. **Maintenance Dose (IVIg)**- 0.4–0.6g/kg (ABW) every 4 weeks or more frequently, to achieve IgG trough level of at least the lower limit of the age-specific serum IgG reference range initially. Trough levels are to be measured within a week before the next infusion, with target trough IgG levels generally at 7-10 g/L (and/or the minimal dose required for clinical effectiveness). SC administration of Ig should be considered as an alternative to IVIg allowing homecare rather than a medical daycare unit or infusion clinic. **Maintenance Dose (SCIg) -** 0.1-0.15g/kg every week or more frequently, to achieve IgG trough level of at least the lower limit of the age-specific serum IgG reference range initially.	Ig should only be continued or renewed if there is a demonstrated clinical benefit. Documentation of clinical effectiveness is necessary for continuation of Ig therapy. The lowest dose possible that achieves the appropriate clinical outcome for each patient is to be used. The goal of Ig in immune deficiency is to minimize infections, as completely eliminating risk of infections is not a feasible target.

Canadian Jurisdiction (*year published*)*	Criteria for Prescribing Ig Replacement Therapy (*summary*)	Dosing Recommendations	Review Criteria for Assessing the Effectiveness of Ig Use
Prairie Collaborative (Saskatchewan, Manitoba, Alberta) (2022)	Ig replacement is recommended for secondary prevention of recurrent, severe infection due to hypogammaglobulinemia (excluding paraprotein) related to other diseases or medical therapy in patients who have a history of infections. It is not recommended for routine replacement of Ig as primary prophylaxis against infections in the setting of an isolated low IgG level without infection. The decision to use Ig should be made in consultation with a physician with recognized expertise in immunodeficiency disorders. Hypogammaglobulinemia secondary to underlying disease or medical therapy (including HSCT) with all of the following: • Serum IgG less than the lower limit of the reference range on two separate occasions **AND** **At least one of the following:** • One invasive or life-threatening infection (e.g., pneumonia, meningitis, sepsis) in the previous year • Recurrent, severe infections • Clinically active bronchiectasis confirmed by radiology • Assessment by a physician specializing in immunodeficiency indicating a significant antibody defect that would benefit from Ig replacement	**Maintenance:** 0.4 to 0.6 g/kg adjusted body weight IVIg every 4 weeks, or SCIG 0.1-0.15 g/kg (ABW) weekly, modified to achieve an IgG trough level of at least the lower limit of the age-specific serum IgG reference range, or as needed to achieve clinical effectiveness. **Loading:** One additional dose of 0.4 g/kg (ABW) may be given in the first month of therapy if the serum IgG level is markedly reduced. *Chronic suppurative lung disease:* 0.4 to 0.8 g/kg (ABW) IVIg or equivalent SCIg dose may be given if chronic suppurative lung disease is not adequately controlled at an IgG trough level at the lower limit of the age-specific serum IgG reference range. *Disseminated enterovirus infection:* One dose of 2 g/kg (ABW) (IVIg or SCIg) divided over 2 to 5 days at any stage is permitted (in addition to the maintenance dose).	Continued use of Ig should be based on objective measures of effectiveness established at the outset of treatment. The following outcome measures should be recorded: • IgG level every 3 to 6 months; AND • number of infections and hospital admissions for infection If clinical effectiveness has not been achieved, Ig treatment should be discontinued. Cessation of Ig treatment may be possible depending on the status of the underlying disease.

Canadian Jurisdiction (*year published*)*	Criteria for Prescribing Ig Replacement Therapy (*summary*)	Dosing Recommendations	Review Criteria for Assessing the Effectiveness of Ig Use
Ontario (2025)	Hypogammaglobulinemia acquired secondary to hematological malignancies. Ig replacement is recommended for secondary prevention of recurrent, severe infection due to secondary hypogammaglobulinemia (excluding paraprotein) in patients who have a history of infections. It is not recommended for routine replacement of Ig as primary prophylaxis against infections in the setting of an isolated low IgG level without infection. **Qualifying Criteria** • Hypogammaglobulinemia secondary to underlying disease or medical therapy (including HSCT) with all the following: • Serum IgG less than the lower limit of the reference range on two separate occasions **AND** **At least one of the following:** • One invasive or life-threatening infection (e.g., pneumonia, meningitis, sepsis) in the previous year • Recurrent, severe infections • Clinically active bronchiectasis confirmed by radiology • Assessment by a physician specializing in immunodeficiency indicating a significant antibody defect that would benefit from Ig replacement	**Maintenance:** 0.4-0.6 g/kg (ABW) IVIg every 4 weeks, or SCIg 0.1-0.15 g/kg (ABW) weekly, modified to achieve an IgG trough level of at least the lower limit of the age-specific serum IgG reference range, or as needed to achieve clinical effectiveness. **Loading:** One additional dose of 0.4 g/kg (ABW) may be given in the first month of therapy if the serum IgG level is markedly reduced. *Chronic suppurative lung disease:* 0.4-0.8 g/kg (ABW) IVIg or equivalent SCIg dose may be given if chronic suppurative lung disease is not adequately controlled at an IgG trough level at the lower limit of the age-specific serum IgG reference range. *Disseminated enterovirus infection:* One dose of 2 g/kg (ABW) (IVIg or SCIg) divided over 2 to 5 days at any stage is permitted (in addition to the maintenance dose).	**Review Criteria** The following outcome measures should be recorded: • IgG level within 3 to 6 months; and number of infections and hospital admissions for infection • Cessation of Ig treatment may be possible depending on the status of the underlying disease.
Atlantic Provinces (Nova Scotia, New Brunswick, Newfoundland and Labrador, Prince Edward Island) (2022)	Patient has/had recent life-threatening or recurrent clinically significant infection(s) related to low levels of polyclonal Ig.	**IVIg dose:** 0.4-0.7 g/kg every 3 to 4 weeks. **SCIg dose:** 0.1-0.23 g/kg every week.	None.

Canadian Jurisdiction (*year published*)*	Criteria for Prescribing Ig Replacement Therapy (*summary*)	Dosing Recommendations	Review Criteria for Assessing the Effectiveness of Ig Use
Québec (2025)	Secondary hypogammaglobulinemia due to a hematological cancer or its treatment. **Secondary prophylaxis if the following 3 criteria are met:** • IgG <4 g/L OR on a case-by-case basis if IgG is ≥4 g/L and <6 g/L; • Biologically active cancer treatment OR incomplete immune reconstitution; • Severe, unusual, or recurrent infections	**Initial dosage:** • **IVIg dose:** 0.4 to 0.6 g/kg. • IVIg is generally administered every 3 to 4 weeks. **Maintenance dosage:** Adjust to achieve a residual IgG level at least equal to the lower limit of the reference range according to age or based on clinical efficacy. **Subcutaneous Immunoglobulin (IgSC) and Facilitated Subcutaneous Immune Globulin** **Initial dosage:** 0.1 to 0.2 g/kg. IgSC can be administered daily, weekly, or every two weeks. Facilitated IgSC can be administered weekly initially, then the dose should be gradually adjusted to achieve administration every 3 to 4 weeks. **Maintenance dosage:** Adjust to achieve a residual IgG level at least equal to the lower limit of the reference range according to age or based on clinical efficacy. **Note:** In the case of a severe or life-threatening infection, the initial dose may be higher.	**Duration:** until remission OR immune reconstitution, depending on the clinical situation. **Discontinuation:** yes, after confirmation of remission OR immune reconstitution, depending on the clinical situation.

Table 2. Comparison of approved jurisdictional criteria to access immunoglobulin replacement therapy (IgRT) in the setting of hypoammaglobulinemia secondary to hematologic malignancies within Canadian provinces and territories.[15-19] Prescribers are required to include the indication for IgRT on forms that are reviewed in accordance with provincial policy to ensure Ig request compliance with Ministry of Health-endorsed criteria within each jurisdiction. The territories have not yet endorsed the use of a specific IgRT criteria document; *courtesy of Oksana Prokopchuk-Gauk, MD, FRCPC, DRCPSC, Kathryn Webert, MD, MSc, FRCPC, and Jennifer Grossman, MD, FRCPC.*

*The most current versions of the criteria for prescribing IgRT are included in this summary. However, as documents may periodically be updated, prescribers should confirm the most current version of criteria for accessing IgRT within their jurisdictions when prescribing Ig for patient care.

Abbreviations: ABW: adjusted body weight; **HSCT:** hematopoietic stem cell transplantation; **ICU:** intensive care unit; **Ig:** immunoglobulin; **IVIg:** intravenous Ig; **MM:** multiple myeloma; **SCIg:** subcutaneous Ig.

International Criteria (*year published*)*	Criteria for Prescribing Ig Replacement Therapy (*summary*)	Dosing Recommendations	Review Criteria for Assessing the Effectiveness of Ig Use
Australian National Blood Authority (NBA) (2025)	Prevention of recurrent bacterial infections due to hypogammaglobulinemia associated with hematological malignancies or post-HSCT. **Qualifying Criteria** • Serum IgG to be measured on two separate occasions (at least one sample taken when the patient does not have an active infection). Baseline serum levels of IgA and IgM should be provided to allow assessment of immune recovery at review. • Significant hypogammaglobulinemia with serum IgG <4 g/L (excluding paraprotein) regardless of the frequency and severity of infections **OR** • Serum IgG (excluding paraprotein) >4 g/L but less than the lower limit of the age-related reference range with at least one life threatening infection in the last 12 months **OR** • Serum IgG (excluding paraprotein) >4 g/L but less than the lower limit of the age-related reference range with at least 2 serious infections in the last 6 months requiring more than standard courses of antibiotics (e.g., hospitalization, intravenous or prolonged antibiotic therapy) Antibiotic therapy may be indicated in addition to Immunoglobulin therapy.	**Loading Dose (IVIg and SCIg):** one loading dose of 0.4 g/kg in the first month of therapy (in addition to the maintenance dose) is permitted if the serum IgG level is <4 g/L. **Disseminated Enterovirus Dose (IVIg and SCIg):** one dose of 2 g/kg at any stage is permitted (in addition to the maintenance dose) in the management of disseminated enterovirus infection. **Maintenance Dose (IVIg):** 0.4–0.6g/kg every 4 weeks or more frequently, to achieve IgG trough level of at least the lower limit of the age-specific serum IgG reference range. More frequent dosing to achieve IgG trough level of up to 9 g/L is permitted if chronic suppurative lung disease is not adequately controlled at an IgG trough level at the lower limit of the age-specific serum IgG reference range. A total dose of up to 1 g/kg may be given over any 4-week period. **Maintenance Dose (SCIg):** 0.1-0.15 g/kg every week or more frequently, to achieve IgG trough level of at least the lower limit of the age-specific serum IgG reference range. More frequent dosing to achieve IgG trough level of up to 9 g/L is permitted if chronic suppurative lung disease is not adequately controlled at an IgG trough level at the lower limit of the age-specific serum IgG reference range. A total dose of up to 1 g/kg may be given over any 4-week period. **Supplementary Dose (IVIg and SCIg):** One additional dose of 0.4 g/kg is permitted at any stage (in addition to the maintenance dose) if the serum IgG level is <4 g/L. The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.	Initial review is required within 6 months by any specialist with ongoing reviews at least annually to assess clinical benefit. In principle, Ig should be continued or renewed only if there is a demonstrated clinical benefit; therefore, documentation of clinical effectiveness is necessary for continuation of Ig therapy. Clinical effectiveness of Ig therapy may be assessed by monitoring of serum immunoglobulin levels (IgG, IgA, and IgM) and any history of infection. There should be regular consideration of a trial period of cessation of Ig (at least every 12 months) for the purposes of immunological evaluation unless medically contraindicated on safety grounds (such as neutropenia, immunosuppressant medication, active bronchiectasis, and/or suppurative lung disease) or severe hypogammaglobulinemia persists where no significant improvement has occurred in the underlying condition. Trial cessation is best commenced in September or October.

International Criteria (*year published*)*	Criteria for Prescribing Ig Replacement Therapy (*summary*)	Dosing Recommendations	Review Criteria for Assessing the Effectiveness of Ig Use
National Health Service Blood and Transplant (NHSBT), UK (2025)	**Qualifying Criteria** • Underlying cause of hypogammaglobulinemia cannot be reversed, or reversal is contraindicated. **OR** • Hypogammaglobulinemia associated with drugs, including emerging bispecific antibody therapies, therapeutic monoclonals targeted at B cells and plasma cells (rituximab and other anti-CD20/CD19 agents, daratumumab, etc.) post-HSCT, NHL, CLL, MM or other relevant B-cell malignancy confirmed by hematologist **AND** • Recurrent or severe bacterial infection despite continuous oral antibiotic therapy for 6 months • IgG <4 g/L (excluding paraprotein) • Documented failure of serum antibody response to unconjugated pneumococcal or other polysaccharide vaccine challenge **Notes:** • In patients developing hypogammaglobulinemia associated with B-cell aplasia as a consequence of CAR T-cells targeted against B cell or plasma cell antigens, the prophylactic use of Ig in the absence of a burden of severe infections and vaccine challenge may be appropriate • Use of Ig post-CAR T-cell therapy in B-ALL: because of the severity of B-cell aplasia and the longer time required for reconstitution, it is anticipated that virtually all patients (children and adults) with B-ALL will initially require Ig replacement following CAR T-cell therapy. As with the use of Ig post-CAR T-cell therapy in B-cell lymphoma, continued use of IVIg should be reviewed at regular intervals based on B-cell recovery, serum immunoglobulins and burden of infection • Use of Ig post-CAR T-cell therapy in B-cell lymphoma: The need for Ig replacement in patients receiving CAR T-cell therapy for B-cell lymphoma is variable, ranging between 31% and 64% in published studies, highlighting faster B-cell recovery in this group in contrast to patients with B-ALL • Use of Ig at inception of bispecific antibody treatment in patients with myeloma and B-cell lymphoma: many patients in these disease groups will have a low serum IgG at baseline due to previous chemo-immunotherapy, including CD20 and CD38-depleting agents. The prophylactic use of Ig would be appropriate in patients with a serum IgG <4g/L at the time of commencement of a bispecific antibody	0.4–0.6 g/kg/month modified to achieve an IgG trough level of at least the lower limit of the age-specific serum IgG reference range	6 monthly reviews (compared to baseline) • Raised trough IgG level • Reduction in number of infections • Reduction in number of treatment courses of • antibiotics • Reduction in number of days in hospital

Table 3. Comparison of criteria to access immunogbulin replacement therapy (IgRT) in the setting of hypoammaglobulinemia secondary to hematologic malignancies from selected countries where Ig products are funded through public healthcare arrangements.[20,21] Prescribers are required to comply with these criteria to access IgRT within their jurisdictions; *courtesy of Oksana Prokopchuk-Gauk, MD, FRCPC, DRCPSC, Kathryn Webert, MD, MSc, FRCPC, and Jennifer Grossman, MD, FRCPC*.

Abbreviations: B-ALL: B-cell acute lymphoblastic leukemia; **CAR-T:** chimeric antigen receptor T cell; **CLL:** chronic lymphocytic leukemia; **HSCT:** hematopoietic stem cell transplantation; **Ig:** immunoglobulin; **IVIg:** intravenous Ig; **SCIg**: subcutaneous Ig; **MM:** multiple myeloma; **NHL:** non-Hodgkin lymphoma

In Canada, Ig products are procured by Canadian Blood Services for all provinces and territories except Québec, which receives products from Hema-Québec. A Request for Proposal process is executed to determine Ig supply vendors for defined periods, to ensure the lowest feasible product cost. IgRT is funded through provincial/territorial tax dollars as a part of the Canadian universal healthcare system. Thus, IgRT utilization appropriateness is carefully monitored within Canadian provinces and territories to ensure accountability.[22] All Ig products are expected to meet utilization appropriateness criteria as defined by respective regional guidelines endorsed by provincial/territorial Ministries of Health.[23] IgRT preparations currently available in Canada are considered equivalent in terms of their potency and efficacy based on concentration, regardless of indications listed within the approved product monograph.[24] The list of currently available Ig products from Canadian Blood Services is listed in the **EFormulary**, and products available in Québec are listed on the **Héma-Québec website**.

Potential Adverse Reactions to Ig

As human blood product concentrates, IgRT products may cause potential adverse transfusion reactions. Expressed informed consent must be obtained by authorized prescribers prior to the administration of IgRT products.

Infection transmission from Ig products is considered theoretical, given the extensive donor screening, testing, and pathogen reduction manufacturing processes. Significant non-infectious risks of Ig must be discussed with the patient as a part of the informed consent process. Risks of IVIg administration and rates occurrence include[25]:

- Non-serious flu-like symptoms (chills; headache; chest, back, or abdominal pain; nausea/vomiting) and hypotension or hypertension in up to 1:5 recipients[26];
- Clinically significant red blood cell hemolysis in up to 1:5 non-group O recipients (due to passive anti-A and anti-B), occurring with within 10 days of IVIg infusion[27];
- Thromboembolic events in up to 1:100 recipients[28];
- Aseptic meningitis in 1:1500 recipients[29]; and
- Anaphylaxis in less than 1:1000 recipients

The risk of local site injection reactions is more common with SCIg (pain, local site irritation). Systemic reactions are less common overall in comparison to IVIg, making SCIg a safer option from the perspective of adverse reaction risk.

Isolated reactions may be idiosyncratic, associated with the blend of donor proteins within a particular product lot number, which do not recur with exposure to a different lot number of the same brand. Recurrent reactions to the same Ig brand may be associated with non-Ig components of the product and warrant trial of a brand switch. Consultation with the local Transfusion Medicine Physician is recommended to discuss product options if serious or recurrent reactions to Ig develop.

SHG and IgRT in Specific Hematologic Malignancies

Multiple Myeloma (MM)

Patients with MM may have SHG at the time of diagnosis as a consequence of their disease. However, in the setting of relapsed or refractory MM, there is a further increased risk of SHG due to both the underlying MM pathology and therapeutic exposures.[30]

Bispecific antibody and CAR T-cell therapies are now available to patients who have received at least 3 prior lines of treatment. Infections are common with bispecific antibody therapy, with rates reported to be 32–76% (any grade), and severe Grade 3–4 infections reported in up to 45% of cases.[31] This infection risk may be related to the bispecific antibody dose and frequency, as dose reductions appear to confer a reduction in infectious risk.[32]

The overall infection risk in patients receiving CAR T-cell therapy for MM was comparable to that of bispecific antibody therapy, with rates of 9–70% reported (any grade); however, the risk of severe grade 3 or higher infections was lower, reported in up to 30% of cases.[4] Interestingly, IgG levels were not measured in all CAR T studies; in the

two studies where IgG levels were measured, SHG with IgG levels under 4 g/L was observed in up to 23.5% of patients.[33,34]

The preventative role of Ig in patients undergoing MM therapy is an area of ongoing investigation. It is prudent to check IgG levels at diagnosis (excluding the monoclonal protein total). Due to the high infection risk with bispecific antibody therapy, current consensus guidelines recommend routine monitoring of IgG levels for SHG. It would be reasonable to check IgG levels every 6 months and whenever significant or recurrent infections occur.[1] Initiation of prophylactic IgRT replacement may be considered if serum IgG levels are under 4 g/L during treatment and thereafter, or in the setting of severe or recurrent infections with higher IgG concentrations.[31] A dose of 0.4 g/kg IVIg administered every 4 weeks[4] or 0.1 g/kg SCIg weekly may be considered with the intent to achieve a minimum effective dose.

Chronic Lymphocytic Leukemia (CLL)

SHG is a well-known complication of CLL in the context of this underlying B-cell disease, with evaluation of baseline serum Ig levels recommended at diagnosis as a part of routine patient work-up.[35] Treatments, including immunosuppressive regimens and B cell-targeted therapies have the potential to exacerbate the degree and duration of SHG; thus, experts have recommended that clinical follow-up of infection history and serum Ig level evaluation should occur at a minimum every 6 months.[36]

There is a strong body of literature demonstrating that IgRT confers a decrease in the frequency of bacterial infections, including major bacterial infections in patients with CLL and SHG. However, no survival benefit with IVIg use has been demonstrated.[37] Clinical practice guideline recommendations vary, though there is consensus to initiate IgRT in patients with SHG with repeated infections at immune replacement doses, including 0.4 g/kg IVIg or 0.1 g/kg SCIg; prophylactic use of IgG to prevent primary infection is not endorsed.[38,39]

Lymphoma

The prevalence of SHG appears to be lower in patients at the time of B-cell lymphoma diagnosis than in patients with MM and CLL. Thus, confirming patient serum Ig levels at the time of lymphoma diagnosis is appropriate to establish a baseline. The risk of SHG is known to increase with B-cell-targeted therapy, including rituximab.[1] SHG has been observed in nearly 40% of patients after a rituximab-based therapy; however, only a minority are of clinical significance (non-neutropenic infections requiring IgRT).[40] Variability in definitions of SHG, inconsistencies in the measurement frequency of IgG levels among lymphoma trial participants, and the evolution of lymphoma diagnosis and treatment has led to challenges in the evaluation and management of SHG in this population.

Management of more intensive diffuse large B-cell lymphoma may include autologous stem cell transplantation, bispecific antibody therapy, and CAR T-cell therapies. More intensive treatments like bispecific antibody therapy and CAR T-cell therapies may increase the risk of SHG in patients with relapsed or refractory disease, but its incidence and duration can be variable.[41,42]

Presently, there is no definitive role for prophylactic IgRT during lymphoma treatment, regardless of the underlying diagnosis and measured serum IgG levels, in the absence of severe or recurrent infections.

Recommendations regarding the frequency of Ig measurement in patients receiving lymphoma treatment are not specific, though it may be reasonable to consider evaluating serum IgG levels every 6 months or as required based on recurrent or severe infections.[1] A precise management strategy for SHG in the context of lymphoma treatment has not yet been clearly defined due to the lack of randomized, controlled trial data.[1,5] Following CAR T-cell therapy, it is reasonable to consider IgRT in adults with serious or recurrent infections with encapsulated organisms and IgG levels under 4 g/L.[42] An immune supportive dose of 0.4 g/kg IVIg or 0.1 g/kg SCIg may be initiated in this context. At this time, no clear role for prophylactic IgRT has been defined in adult CAR T-cell therapy recipients who have not developed an infection.

Hematopoietic Stem Cell Transplantation (HSCT)

To date, a definitive clinical benefit of Ig replacement for prevention against bacterial infections in the setting of autologous and allogeneic bone marrow transplantation has not been demonstrated. Establishing a pre-transplant IgG level is prudent to establish a baseline. Monitoring for infection is essential throughout the patient's treatment course.

In 2018, Canadian and American HSCT experts collaborated to develop five Choosing Wisely recommendations with the aim of reducing unnecessary healthcare resource utilization while providing optimal patient care. Given the absence of high-quality evidence demonstrating infection prevention and overall survival, plus commentary that IgRT may predispose patients to a higher risk of complications and adverse effects, the recommendation "*don't routinely give Ig replacement in adult HSCT recipients in the absence of recurrent infections regardless of Ig level*" was included.[43]

European bone marrow transplant best practice recommendations reaffirm that late infection prevention (more than 100 days following transplantation) against encapsulated bacterial infection includes oral antibiotic prophylaxis as a first-line strategy. Initiation of IgRT may also be considered at an immune supportive dose in patients with serum IgG levels of less than 4 g/L. Finally, vaccination should be initiated with immune recovery.[44]

A Proposed Approach to SHG Management in Hematologic Malignancies

The decision to initiate Ig prophylaxis in patients with SHG with hematologic malignancies is complex and multifactorial. We have adapted a framework recently proposed by experts[14], based on current literature (with an acknowledgement of existing limitations)[27], as summarized in **Figure 1**. Shared decision-making between patients and healthcare providers remains an essential component of determining the right time to initiate Ig replacement therapy, balancing the risks and benefits of this treatment, relative to potential alternative strategies for infection prevention, in the context of potential global Ig supply limitations.

Future Ig Sustainability

In Canada, the demand for Ig is expected to increase by approximately 10% each year for the next 5 years. SHG is expected to be the fastest-growing area for immunoglobulin use in Canada, with the potential for growth for this indication estimated to be closer to 15% over the next 5 years. This growth is mostly due to factors such as the increased availability and use of new immunosuppressant therapies, the increasing prevalence of diseases such as leukemias, MM, and lymphoma, and the fact that patients who may require IgRT are living longer with disease due to improvements in treatments and supportive care.[45]

This rapid growth in demand for Ig products is also seen internationally, in both developed and developing countries, leading to global shortages and related impacts on pricing. This has prompted many jurisdictions to significantly increase the collection of plasma, the critical material from which Ig drugs are made, to meet population needs. In Canada, Canadian Blood Services and Héma-Québec are exploring ways to expand and accelerate plasma collection and promote immunoglobulin production within domestic borders.

While Canadian patients' needs for IgRT are currently being met, the ongoing global shortage of Ig has raised concerns about sustainability and the possibility of a Canadian Ig shortage. Because of this, the *Canadian National Advisory Committee for Blood and Blood Products*, through the support of Health Canada and provincial/ territorial Ministries of Health, recently developed the *National Plan for the Management of Shortages of Immunoglobulin Products (The Ig Plan)*.[46] The specific purpose of the national Ig Plan is to maximize the effectiveness of a response to any crisis that impacts the adequacy of the overall Ig supply in Canada. The Ig Plan acknowledges that difficult decisions will need to be made about allocating Ig product in the event of a shortage. It also emphasizes the use of alternative therapies to Ig, where applicable. Criteria to guide clinical decisions and triage of Ig products, as well as an ethical framework, are provided to guide decision making and to assist with doing as little harm as possible.

Additional high-quality studies that utilize standard definitions for SHG and severe or recurrent infection are needed in the setting of hematologic malignancies to better understand the role of IgRT for primary or secondary infection prevention. Currently, there are limited data to inform when IgRT should be started, when it can be stopped, how it should be dosed, and the role of alternatives like antibiotic use for infection prevention. The RATIONAL platform trial at several sites in Canada is aimed at helping answer some of these questions. This investigator-initiated, international (Australia, New Zealand, Canada), Phase II/III randomized controlled trial has three domains: the START domain will compare prophylactic antibiotics to standard dose IgRT for patients eligible to start IgRT; the STOP

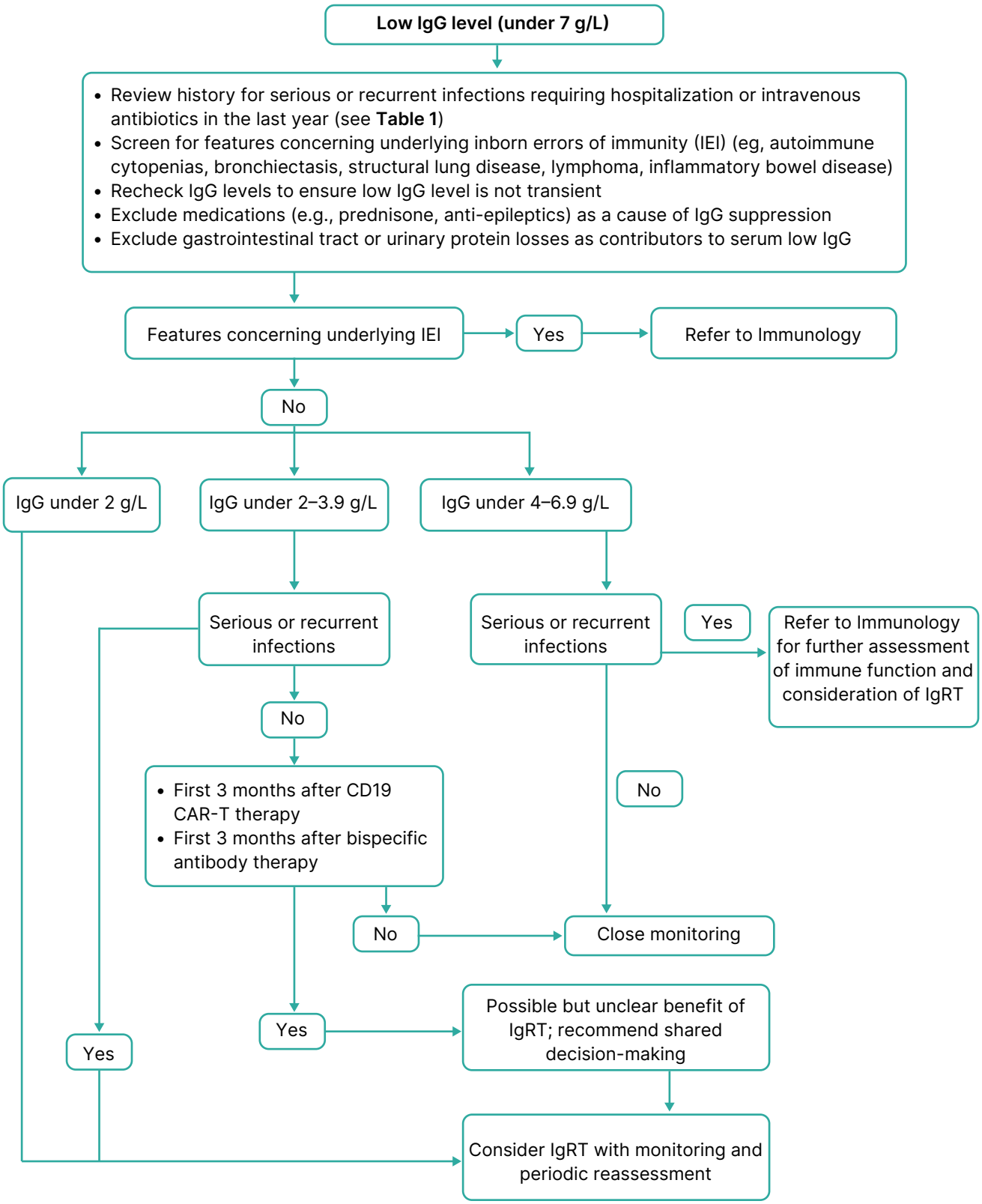

Figure 1. A proposed approach for evaluating SHG in hematologic malignancies, based on presented evidence; *adapted from Pendergrast et al., 2021.*[27]

Abbreviations: CAR-T: chimeric antigen receptor T cell; **Ig:** immunoglobulin; **IgRT:** Ig replacement therapy.

domain will compare stopping IgRT with either prophylactic antibiotics or antibiotics on demand, to continuing standard dose IgRT; and the DOSE domain will compare low dose and standard dose IgRT.[47]

Summary

The decision to initiate IgRT in patients with hematologic malignancies is complex and must consider both patient and healthcare system impacts. To obtain IgRT, clinicians in provinces and territories are required to comply with the clinical criteria for Ig, endorsed within their regional jurisdictions. Current evidence supports close patient monitoring and IgRT initiation at immune supportive doses in the setting of severe or recurrent infections with documented significantly reduced IgG levels. SCIg is an important IgRT option that is more convenient and less resource-intensive. Additional guidance is needed to better understand when to decrease or stop IgRT. It is essential to maintain stringent Ig use, as current product utilization trends will be unsustainable into the future. Exploration of alternatives to Ig for infection prevention in the setting of SHG must be prioritized.

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Correspondence

Oksana Prokopchuk-Gauk, MD, FRCPC, DRCPSC
Email : oksana.prokopchuk-gauk@saskhealthauthority.ca

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References

1. Otani IM, Lehman HK, Jongco AM, Tsao LR, Azar AE, Tarrant TK, et al. Practical guidance for the diagnosis and management of secondary hypogammaglobulinemia: A Work Group Report of the AAAAI Primary Immunodeficiency and Altered Immune Response Committees. J Allergy Clin Immunol. 2022;1949:1525-60.
2. Monahan R, Otani IM, Lehman HK, Mustafa SS. A second look at secondary hypogammaglobulinemia. Ann Allergy Asthma Immunol. 2025;134:269–278
3. Dhalla F, Misbah SA. Secondary antibody deficiencies. Curr Opin Allergy Clin Immunol. 2015;15:505-13.
4. Ludwig H, Terpos E, van de Donk N, Mateos M, Moreau P, Dimopoulos M, et al. Prevention and management of adverse events during treatment with bispecific antibodies and CAR T cells in multiple myeloma: a consensus report of the European Myeloma Network. Lancet Oncol. 2023;24(6):e255-e269.
5. Wat J, and Barmettler S. Hypogammaglobulinemia after Chimeric Antigen Receptor (CAR) T-cell therapy: characteristics, management, and future directions. J Allergy Clin Immunol Pract. 2022;10(2):460–466. doi:10.1016/j.jaip.2021.10.037.
6. Mikulic M. Immunoglobulin consumption in select countries in 2017. Statista. [Internet]. https://www.statista.com/statistics/1055466/immunoglobulin-consumption-in-select-countries/ Accessed June 15, 2025.
7. Protecting Access to Immune Globulins for Canadians. Health Canada. 2018-05-16. https://www.canada.ca/en/health-canada/programs/expert-panel-immune-globulin-product-supply-related-impacts-canada/protecting-access-immune-globulins-canadians.html Accessed June 15, 2025.
8. Jeffrey Modell Foundation "10 Warning Signs of Primary Immune Deficiency in Adults" https://info4pi.org/library/educational-materials/. Accessed July 21, 2025.
9. Orange JS, Ballow M, Stiehm ER, Ballas ZK, Chinen J, De La Morena M, et al. Use and interpretation of diagnostic vaccination in primary immunodeficiency: A working group report of the Basic and Clinical Immunology Interest Section of the American Academy of Allergy, Asthma & Immunology. J Allergy Clin Immunol. 2012;130(3 suppl):S1-24.
10. Kainulainen L, Vuorinen T, Rantakokko-Jalava K, Osterback R, Ruuskanen O. Recurrent and persistent respiratory tract viral infections in patients with primary hypogammaglobulinemia. J Allergy Clin Immunol. 2010;126(1):120-6.
11. Ritchie B, Martins KJB, Tran DT, Blain H, Richer L, Klarenback SW. Economic impact of self-administered subcutaneous versus clinic-administered intravenous immunoglobulin G therapy in Alberta, Canada: a population-based cohort study. Allergy Asthma Clin Immunol. 2022;18(1):99. doi: 10.1186/s13223-022-00735-6.
12. McQuilten ZK, Weinkove R, Thao LTP, Crispin P, Degelia A, Dendle C, et al. Immunoglobulin replacement vs prophylactic antibiotics for hypogammaglobulinemia secondary to hematological malignancy. Blood Adv. 2024;8(7):1787-95.

13. Mankaruious S, lee M, Fischer S, Pyun KH, Ochs HD, Oxelius VA, et al. The half-lives of IgG subclasses and specific antibodies in patients with primary immunodeficiency who are receiving intravenously administered immunoglobulin. J Lab Clin Med. 1988;112(5):534-40.
14. Otani IM and Ballow M. If and when to consider prophylactic immunoglobulin replacement therapy in secondary hypogammaglobulinemia. J Allergy Clin Immunol Pract. 2025;13(3):511-21.
15. British Columbia Provincial Blood Coordinating Office. Immunodeficiency Ig Resources. Secondary Immunodeficiency. Accessed on June 24, 2025 at https://www.pbco.ca/index.php/programs/immunodeficiency/secondary-immunodeficiency.
16. Prairie Collaborative Immune Globulin Utilization Management Framework Project. Criteria for the clinical use of immune globulin. Second Edition. Alberta Ministry of Health, Shared Health Manitoba, and Saskatchewan Ministry of Health; 2022. Accessed on June 24, 2025 at https://ihe.ca/public/uploaded/Prairie%20Ig%20Final%20Guideline%20 09.02.22.pdf.
17. Ontario Immune Globulin Utilization Management. Version 5.0. Ontario Regional Blood Coordinating Network (ORBCoN). 2025 Accessed on June 24, 2025 at https://transfusionontario.org/en/category/ivig-scig/utilization-management-guidelines/ .
18. Atlantic Blood Utilization Strategy Working Group (2021) Atlantic Clinical Indications and Criteria for Intravenous and Subcutaneous Immunoglobulin (IVIG/SCIG) Version 2.0 Halifax, NS. (IVIG/SCIG). April 2022. Accessed on June 24, 2025 at https://www.gov.nl.ca/hcs/files/Atlantic-Clinical-Indications-and-Criteria-for-Intravenous-and-Subcutaneous-Immunoglobulin-IVIG-SCIG.pdf .
19. Usage optimal des immunoglobulins. Institut national d'excellence en santé et en services sociaux Québec. (2025). Accessed on July 24, 2025 at https://www.inesss.qc.ca/publications/repertoire-des-publications/publication/usage-optimal-des-immunoglobulines.html
20. Clinical Commissioning Policy for the use of therapeutic immunoglobulin (Ig) England (2025). Accessed on June 24, 2025 at https://www.england.nhs.uk/wp-content/uploads/2021/12/ccp-for-the-use-of-therapeutic-immunoglobulin-england-2025.pdf
21. Criteria for immunoglobulin products. National Blood Authority, Australia. Accessed on June 24, 2025 at https://www.blood.gov.au/supply-system/governance-immunoglobulin-products/criteria-immunoglobulin-products.
22. Clinical Guide to Transfusion – Chapter 1. https://professionaleducation.blood.ca/en/transfusion/clinical-guide/vein-vein-summary-blood-system-canada Accessed June 15, 2025.
23. NAC Ig Utilization Statement. https://nacblood.ca/en/resource/immunoglobulin-utilization-statement Accessed June 15, 2025.
24. NAC Statement on Clinical Equivalency of Select Fractionated Plasma Protein Products. https://nacblood.ca/en/resource/nac-statement-clinical-equivalency-select-fractionated-plasma-protein-products Accessed June 15, 2025
25. Callum JL, et al. Bloody Easy 5.1 (2023). Ontario Regional Blood Coordinating Network. p. 110. https://transfusionontario.org/en/bloody-easy-5-blood-transfusions-blood-alternatives-and-transfusion-reactions-a-guide-to-transfusion-medicine-fifth-edition-handbook/ Accessed June 16, 2025.
26. Souayah N, Hasan A, Khan HMR, Yacoub HA, Jafri M. The safety profile of home infusion of intravenous immunoglobulin in patients with neuroimmunologic disorders. J Clin Neuromuscul Dis. 2011;12(Suppl 4):S1-S10.
27. Pendergrast J, Armali C, Callum J, Cserti-Gazdewich C, Jiwajee A, Lieverman L, et al. A prospective observational study of the incidence, natural history, and risk factors for intravenous immunoglobulin-mediated hemolysis. Transfusion. 2021;61(4):1053-1063.
28. Ammann EM, Jones MP, Link BK, Carnahan RM, Winiecki SK, Torner JC, et al. Intravenous immune globulin and thromboembolic adverse events in patients with hematologic malignancy. Blood. 2016;127(2):200-207.
29. Bharath V, Eckert K, Kang M, Chin-Yee IH, Hsia CC. Incidence and natural history of intravenous immunoglobulin-induced aseptic meningitis; a retrospective review at a single tertiary care centre. Transfusion. 2015;55(11):2597-2605.
30. Giralt S, Jolles S, Kerre T, Lazarus HM, Mustafa SS, Papanicolaou GA, et al. Recommendations for management of secondary antibody deficiency in multiple myeloma. Clin Lymphoma Myeloma Leuk. 2023;23(10)719-32.
31. Rodríguez-Otero P, Usmani S, Cohen AD, van de Donk NWCJ, Leleu X, Perez-Larraya JG, et al. International Myeloma Working Group immunotherapy committee consensus guidelines and recommendations for optimal use of T-cell-engaging bispecific antibodies in multiple myeloma. Lancet Oncol. 2024;25(5):e205-e216.
32. Usmani SZ, Karlin L, Benboubker L, Nahi H, San-Miguel J, Trancucci D, et al. Durability of responses with biweekly dosing of teclistamab in patients with relapsed/refractory multiple myeloma achieving a clinical response in the majesTEC-1 study. Proc Am Soc Clin Oncol 2023;41(suppl):8034.
33. Munshi NC, Anderson LD Jr, Shah N, Madduri D, Berdeja J, Lonial S, et al. Idecabtagene vicleucel in relapsed and refractory multiple myeloma. N Engl J Med. 2021;384(8):705–16.
34. Chen W, Fu C, Fang B, Liang A, Xia Z, He Y, et al. Phase II study of fully human BCMA-targeting CAR-T cells (zevorcabtagene autoleucel) in patients with relapsed/refractory multiple myeloma. Blood. 2022;138(suppl 1):4564–65.

35. Eichhorst B, Robak T, Montserrat E, Ghia P, Hillmen P, Hallek M, et al. Chronic lymphocytic leukaemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2015;26(Suppl 5):v78-84.
36. Lachance S, Christofides AL, Lee JK, Sehn LH, Ritchie BC, Shustik C, et al. A Canadian perspective on the use of immunoglobulin therapy to reduce infectious complications in chronic lymphocytic leukemia. Curr Oncol. 2016;23(1):42-51.
37. Raanani P, Gafter-Gvili A, Paul M, Ben-Bassat I, Leibovici L, Shpilberg O. Immunoglobulin prophylaxis in chronic lymphocytic leukemia and multiple myeloma: systematic review and meta-analysis. Leuk Lymphoma. 2009;50(5):764-72.
38. Hallek M, Cheson BD, Catovsky D, Caligaris-Cappio F, Dighiero G, Dohner H, et al. iwCLL guidelines for diagnosis, indications for treatment, response assessment, and supportive management of CLL. Blood. 2018;131(25):2745-2760.
39. Walewska R, Parry-Jones N, Eyre TA, Follows G, Martinez-Calle N, McCarthy H, et al. Guideline for the treatment of chronic lymphocytic leukaemia. Br J Haematol. 2022;197(5):544-557.
40. Casulo C, Maragulia J, Zelenetz AD. Incidence of hypogammaglobulinemia in patients receiving rituximab and the use of intravenous immunoglobulin for recurrent infections. Clin Lymphoma Myeloma Leuk. 2013;13(2):106-11.
41. Gerhard GM and von Keudell G. Bispecific antibody therapy for lymphoma. Best Practice & Research Clinical Haematology. 2024;37(4):101598.
42. Hayden PJ, Roddie C, Bader P, Basak GW, Bonig H, Bonini C, et al. Management of adults and children receiving CAR T-cell therapy: 2021 best practice recommendations of the European Society for Blood and Marrow Transplantation (EBMT) and the Joint Accreditation Committee of ISCT and EBMT (JACIE) and the European Haematology Association (EHA). Ann Oncol. 2022;33(3):259-75.
43. Bhella S, Majhail NS, Betcher J, Costa LJ, Daly A, Dandoy CE, et al. Choosing Wisely BMT: American Society for Blood and Marrow Transplantation and Canadian Blood and Marrow Transplant Group's List of 5 Tests and Treatments to Question in Blood and Marrow Transplantation. Biol Blood Marrow Transplant. 2018;24(5);909-13.
44. The EBMT Handbook: Hematopoietic Cell Transplantation and Cellular Therapies. Sureda A, et al (Editors). Springer Nature Switzerland AG. 2024. p. 317. https://www.ebmt.org/education/ebmt-handbook
45. An ZY, Fu H, He Y, Zhu X, Huang Q, Wu J, et al. Projected global trends in hematological malignancies: incidence, mortality, and disability-adjusted life years from 2020 to 2030. Blood. 2023;142(Supplement 1):3810.
46. National Advisory Committee of Blood and Blood Products. The National Plan for Management of Shortages of Immunoglobulin (Ig) Products. 2024. Accessed on June 25, 2025 at https://nacblood.ca/en/blood-shortage.
47. Wood EM, Chai KL, Reynolds J, Griffiths J, Beaton B, Callum J, et al. Optimizing immunoglobulin replacement therapy for patients with B-cell malignancies and hypogammaglobulinemia: the investigator-initiated, international, randomized phase II/III rational platform trial, and the rationalise (stop IGRT) domain. Blood. 2023;142(Supplement 1):1295.

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