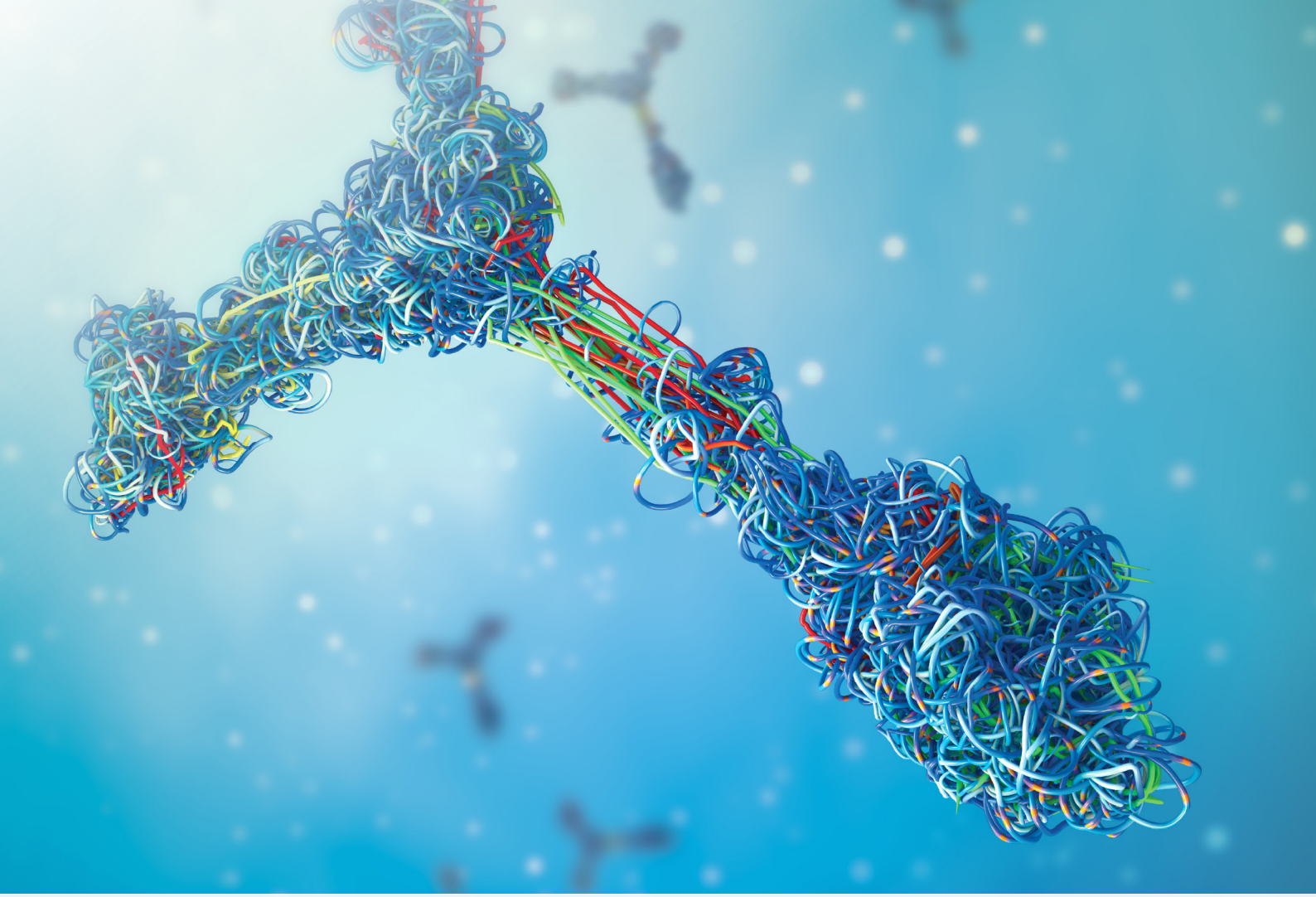
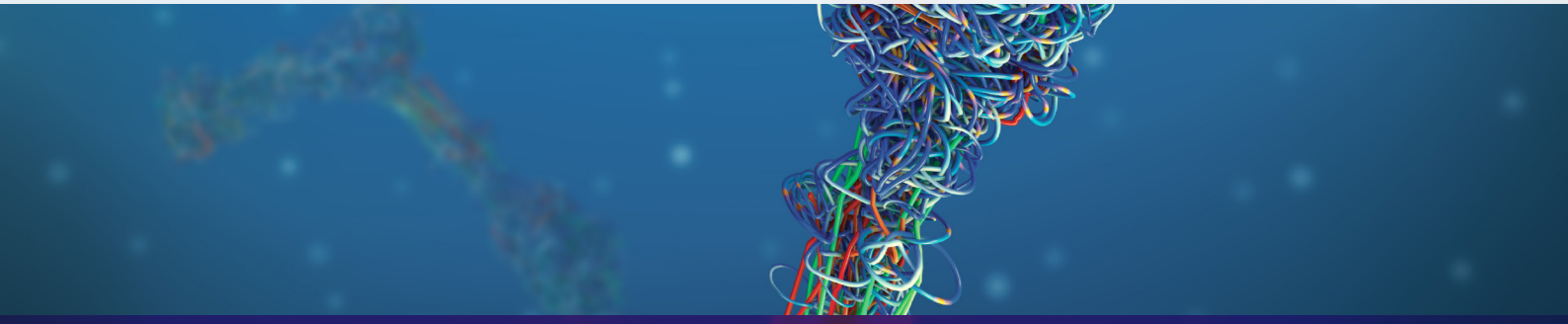


Immunoglobulin replacement therapy for acquired hypogammaglobulinaemia secondary to haematological malignancies and stem cell transplantation

CLINICAL GUIDANCE ARTICLE



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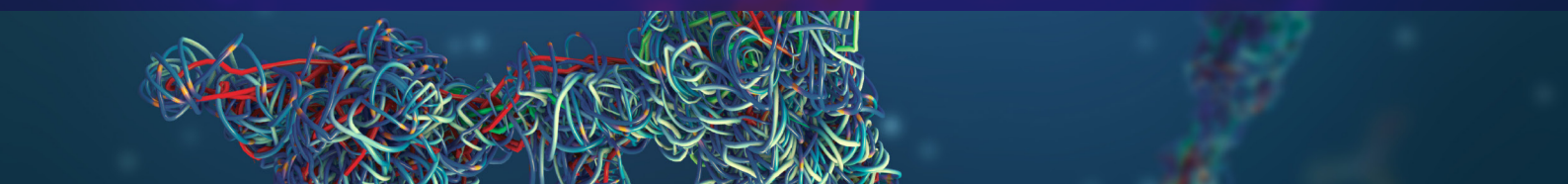

This clinical evidence summary has been developed as a part of the *Value in Prescribing – Immunoglobulin products* program. The program represents an evidence-based approach to fostering responsible stewardship of immunoglobulin (Ig) products, and ensure the viable and sustainable supply of Ig products in accordance with the National Policy, including the *Criteria for the clinical use of immunoglobulin in Australia*.

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ABBREVIATIONS

BloodSTAR: Blood System for Tracking Authorisations and Reviews

CLL: chronic lymphocytic leukaemia

Criteria: Criteria for the clinical use of immunoglobulin in Australia

Ig: immunoglobulin

IRT: immunoglobulin replacement therapy

IVIg: intravenous Ig

LifeBlood: Australian Red Cross LifeBlood

MM: multiple myeloma

NBA: National Blood Authority

NHL: non-Hodgkin's lymphoma

SCIg: subcutaneous Ig

CLINICIAN GUIDANCE

Immunoglobulin replacement therapy for acquired hypogammaglobulinaemia secondary to haematological malignancies and stem cell transplantation

Indications, advice, and evidence

Key points

- Immunoglobulin Replacement Therapy (IRT) can be used to prevent recurrent bacterial infections due to hypogammaglobulinaemia associated with haematological malignancies or post-haemopoietic stem cell transplantation.
- Immunoglobulin (Ig) can be administered intravenously (IVIg) or subcutaneously (SCIg). Both routes are effective and safe, and the most appropriate option depends on individual patient preferences and circumstances.
- Ig dosage should be tailored to the individual patient and delivered at the lowest effective dose based on the desired clinical outcome.
- Dosage should be continually reviewed to maximise efficacy while minimising risk of adverse events and costs.

BACKGROUND

In accordance with the *Criteria for the clinical use of immunoglobulin in Australia* Immunoglobulin Replacement Therapy (IRT) may be provided to patients with hypogammaglobulinaemia secondary to haematological malignancies and/or stem cell transplantation.

Malignancies of the B-lymphocyte lineage are among the most diagnosed haematological malignancies in clinical practice and are the most frequent haematological malignancies associated with symptomatic secondary hypogammaglobulinaemia. Multiple myeloma (MM) and its precursor condition, monoclonal gammopathy of undetermined significance (MGUS), account for approximately 12% of diagnoses, chronic lymphocytic leukaemia (CLL) and its precursor condition, monoclonal B lymphocytosis, account for approximately 9% of diagnoses, and non-Hodgkin's lymphoma (NHL, including diffuse large B-cell lymphoma, follicular lymphoma and marginal zone lymphoma) account for 14% of diagnoses.[1]

The cause of secondary hypogammaglobulinaemia in patients with these disorders is likely to be multifactorial, with the following factors implicated: specific defects in the underlying cell of origin for each different malignancy; disease-related immune dysfunction/dysregulation; and consequences of the therapies used to treat those malignancies.[2] Hypogammaglobulinaemia is the most common chronic immune defect in patients with lymphoproliferative disorders and has been reported to be present in up to 85% of patients with CLL and up to 90% of patients with MM at some point during the disease.[3,4] Bacterial, fungal, and viral infections are a leading cause of morbidity and mortality, contributing to 25–50% of deaths in those with CLL, 33% of deaths in those with NHL, and 30% of deaths in those with MM.[3,5,6]

An expanding range of treatment options is available for these diseases, although practices vary between countries and often between treating physicians. IRT is a common therapeutic intervention in patients with acquired hypogammaglobulinaemia, with a recent international survey of use in practice finding that one-quarter to one-third of patients with MM, CLL and NHL were receiving IRT.[2]

As Ig is a high-cost blood product with high demand and limited supply,[7] evidence-based approaches to its use are essential to ensuring it is administered to those who are most likely to benefit. This article considers the evidence around both primary and secondary prophylactic IRT for the management of immune dysfunction secondary to B-cell haematological malignancies and stem cell transplantation and outlines the criteria governing the use of IRT in Australia.

EVIDENCE SUMMARY

Evidence for use of IRT in patients with acquired hypogammaglobulinaemia is largely based on clinical trials performed 20–30 years ago and predates current therapeutic approaches. Most patients in these studies had CLL or MM with only one study including NHL patients with acquired hypogammaglobulinaemia, however the benefit for this group and transplant recipients has been inferred from these studies. The lack of information derived from cohorts treated using current clinical practice is due to the rapid development of new and more targeted therapies but is also reflective of the long natural history of many of these disease entities and the need for prolonged periods of observation.

A 2009 Cochrane systematic review and meta-analysis of nine randomised controlled trials compared IVIg prophylaxis with control treatment in patients with acquired hypogammaglobulinaemia secondary to haematological malignancy (including CLL and MM).[8] IVIg reduced the risk of developing clinically serious infections by 51% and reduced antibiotic use and hospitalisation. However, the meta-analysis showed no difference in all-cause mortality between those who received IRT and those who did not.

Subsequent studies have looked at the efficacy of IRT in a few selected cohorts such as patients with MM undergoing stem cell transplantation, and those with MM receiving SCIg with varying results.[9,10,11,12] Other more recent work has explored the association between immune deficiency and mortality in the modern treatment era, but there remains little in the way of current data to inform clinical practice.

Optimising IRT

Despite some variation between countries, most international guidelines suggest a role for IRT for patients with significant hypogammaglobulinaemia, recurrent bacterial infections, and/or a failure to mount an appropriate (>two-fold increase in serum immunoglobulin G [IgG] titres) response to vaccination.

In Australia, the National Blood Authority (NBA) recognises the role for IRT in the prevention of recurrent bacterial infections due to hypogammaglobulinaemia associated with haematological malignancies or following haemopoietic stem cell transplantation.[13] Patients with these conditions must meet one of the following specific criteria to qualify for Ig therapy:

- Serum IgG (excluding paraprotein) < 4 g/L regardless of the frequency and severity of infections,
- 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 two serious infections in the last 6 months requiring more than the standard courses of antibiotics.

Serum IgG levels should be measured on two separate occasions, at least 1 hour apart with at least one sample taken when the patient does not have an active infection. Baseline serum levels for immunoglobulin A (IgA) and immunoglobulin M (IgM) should also be measured to allow any future immune recovery to be assessed at review.

The NBA's *Criteria for the clinical use of immunoglobulin in Australia* should be referred to for a current list of conditions and circumstances for which government-funded Ig products can be accessed and considered clinically appropriate, as well as for further guidance.

Routes of administration

In Australia, IVIg is the most common route of administration[14] and is safe and well tolerated by most patients. IRT may also be administered via the subcutaneous route, usually as a 'slow injection' (SCIg). IVIg is administered every 4 weeks (or more frequently) in the hospital or clinic setting, whereas SCIg is typically self-administered weekly (or more frequently) in the home setting.[13]

There are advantages and disadvantages to each route of Ig administration.

IVIg is well validated in these groups of patients. It may however be associated with increased systemic adverse events,[15] such as headache, fever and anaphylactoid reactions, which occur in 2–27% of all infusions.[16] Adverse events are more commonly observed in patients new to treatment, and may occur up to 34% (all grades) of the time in patients receiving their first infusion.[17] Attention to maintenance of trough levels (see below) may obviate the risk of level 'wear-off' with its attendant risk of increased susceptibility to infection. Whilst IVIg is more time consuming and requires ambulatory care or clinic attendance, it may be the only option for patients who are unable or unwilling to use SCIg.

SCIg, which is widely used in patients with primary hypogammaglobulinaemia, can be administered at the place and time of the patient's choosing, and in much smaller doses. Since weekly SCIg injections produce consistent, steady-state serum IgG levels, trough levels may not be as marked as IVIg and 'wear-off' effects possibly avoided. Whilst the evidence for the efficacy of SCIg in patients with hypogammaglobulinaemia secondary to haematological malignancies is relatively scarce, a recent report has suggested SCIg may have a place in certain cohorts of such patients.[18] In addition, the smaller doses at each administration and the relatively gradual systemic absorption of SCIg have been reported to lead to significantly fewer systemic adverse reactions. Use of SCIg does however impose a variety of logistical issues such as training, supply, storage and the requirement for weekly self or assisted administration which may be a challenge for older patients or those with other comorbidities.[19,20]

Since both routes of administration have been shown to be effective and safe, the most appropriate option requires an assessment of the risks and benefits of each approach for a given patient, alongside patient preferences, availability of accredited SCIg programs and individual pharmacokinetics.

Optimising dosage

The appropriate Ig dosage, trough levels, and duration of treatment are all areas that currently lack robust clinical evidence.[2]

Several international guidelines advise an initial starting dose of 0.4 g/kg,[19,20,21] which is echoed by the NBA's *Criteria for the clinical use of immunoglobulin in Australia*. The Criteria allows a standard loading dose in individuals with serum IgG levels < 4 g/L of 0.4 g/kg.[22] 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.

Following the initial treatment, the dosage and interval between doses is then titrated to achieve an IgG trough level of, at minimum, the lower limit of the age-specific serum IgG reference range. BloodSTAR (Blood System for Tracking Authorisations and Reviews) includes a dose calculator that can be used to determine the Ig dose according to indication.

Ig dosage should be tailored to the individual patient and delivered at the lowest effective dose based on the desired clinical outcome. To reduce unnecessary wastage and oversupply, clinicians should ensure that specific adjustments in Ig dose are recorded in BloodSTAR. BloodSTAR will automatically round down to the closest vial size and there is an option to use ideal body weight rather that the patient's actual weight for dosage calculations. Note: ideal body weight is not suitable for patients younger than 18 years old, who are less than 152 cm tall or are pregnant.

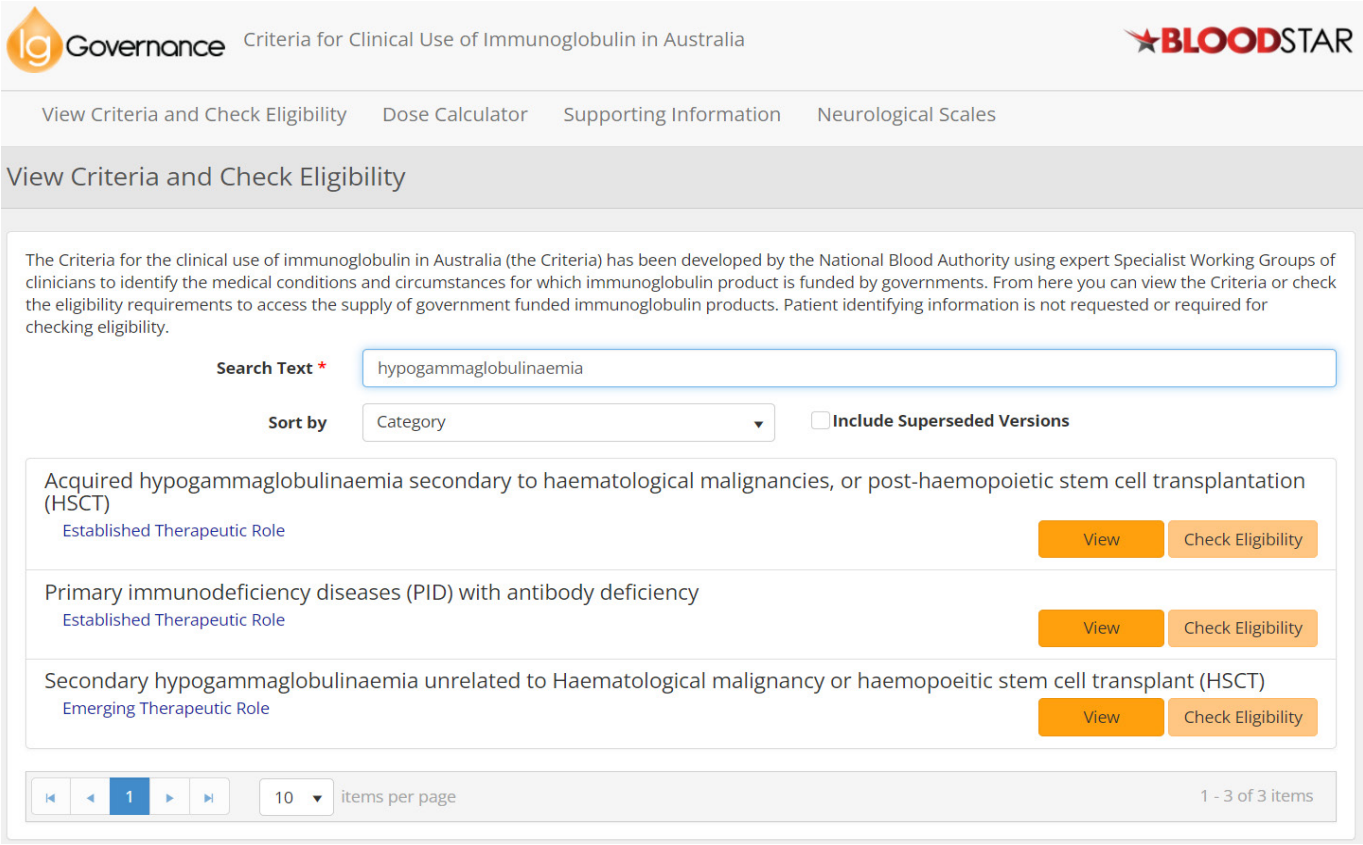

Image: BloodSTAR IG Governance web page search field

Access to Ig

In Australia, Ig products, like other blood products, are supplied at no direct cost to eligible patients under the National Blood Agreement (the Agreement),[23,24] and are managed by the National Blood Authority (NBA). The Agreement's primary objectives are:

- to provide an adequate, safe, secure, and affordable supply of blood products, blood-related products and blood-related services in Australia; and
- to promote safe, high-quality management and use of blood products, blood-related products and blood-related services in Australia.

Under the Agreement and related national blood arrangements, the NBA manages contracts with domestic and international suppliers of Ig to ensure demand for supply is met and manages a contract with the Australian Red Cross Lifeblood (Lifeblood) to collect blood and blood plasma from voluntary donors to support production and manufacture of Ig products for supply in Australia.

As collecting, manufacturing, and distributing Ig products is particularly expensive, and there is a limited supply, the NBA has a dedicated Ig Governance Program to manage Ig access, ensuring it is available for those who need it most. All healthcare professionals directly involved in the prescription, use and management of Ig have defined roles and obligations to ensure that Ig products are properly used and managed in line with the nationally agreed rules and obligations. Details are set out in The National Policy: Access to Government-Funded Immunoglobulin Products in Australia.

Rules governing patient eligibility for Ig funded under national blood arrangements are set out in the *Criteria for the clinical use of immunoglobulin in Australia*. The Criteria are evidence based and are developed and maintained by a national panel of health experts, in collaboration with federal, state and territory governments. They clearly articulate the medical conditions and circumstances for which the use of Ig funded under national blood arrangements is permitted, based on clinical appropriateness and the availability of safe, effective, and cost-effective alternative treatments.

To access Ig under the Agreement, a medical officer is required to submit an authorisation request through the national online system BloodSTAR, accessed through the NBA's online BloodPortal. The system is used to manage the authorisation request and review process and ensures that access to Ig products is consistent with the National Policy. Lifeblood is contracted by the NBA to review and authorise applications and provide advice on eligibility as required.

Patients that are ineligible to access Ig products under the Criteria may be able to access Ig through a Jurisdictional Direct Order at a cost to the approved health provider, or directly from suppliers at a personal cost.

Further information is available on the NBA's website at, https://www.blood.gov.au/Ig with online training courses available through BloodSafe eLearning at: https://learn.bloodsafelearning.org.au/categories#immunoglobulin-courses.

Ongoing patient review

All patients receiving IRT should be routinely reviewed by their haematologist. While the frequency of visits is determined by clinical status, there is a requirement for an initial review to assess clinical benefit within 6 months and annually thereafter to have continued access to government-funded Ig.[13] Reviews should include consideration of treatment efficacy and tolerability, history of infection and disease-specific considerations detailed in the Criteria.[13] Outcomes of each review should be recorded in BloodSTAR.

Ig therapy should continue at the lowest safe and effective dose for each patient.[13] If the patient continues to have significant infections, therapy should be titrated up by increasing the dosage or shortening the infusion interval.[25] As the risk of developing hypogammaglobulinaemia often increases the specific disease progress throughout the clinical course of a haematological malignancy, patients with normal Ig reference ranges at diagnosis should continually be monitored, with serum Ig levels checked every 6–12 months, as well as after significant infections or immunosuppressive therapy.[26]

Continuation of Ig therapy should depend on evidence of clinical benefit, including adequate replacement of antibodies (IgG) and history of infection. It is recommended that a trial of IRT cessation be considered after each 12 months of treatment in patients who are clinically well, free of infection and have serum IgG levels approaching normal levels.[13] Where possible, trial cessation should commence after the period of highest risk for respiratory infections, such as September or October when the circulation of seasonal respiratory viruses is lower.

Given the diverse symptoms and presentations associated with acquired hypogammaglobulinaemia, a coordinated approach to care should be taken that considers IRT alongside other therapeutic options. This includes the involvement of the patient's general practitioner with whom the patient can consult for routine issues between review appointments, as well as allied health professionals, such as physiotherapists, who can address organ-specific co-morbidities.[27]

This clinical guidance article outlines existing evidence on the use of immunoglobulin for immunodeficiencies secondary to B-cell haematological malignancies. This summary is not intended to be exhaustive and should not replace clinical judgement.

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