

Immunoglobulin replacement therapy for primary immunodeficiencies

CLINICAL GUIDANCE ARTICLE



NATIONAL BLOOD AUTHORITY
AUSTRALIA



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MEDICINEWISE

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](#).

Acknowledgement

The Value in Prescribing – Immunoglobulin products consortium would like to acknowledge Dr Andrew McLean-Tookey who has contributed his time and clinical expertise in the development of this document in collaboration with NPS MedicineWise and ASCIA.

Disclaimer: This document is a general guide to appropriate practice, to be followed subject to the circumstances, clinician's judgement, and patient's preferences in each individual case. It is designed to provide information to assist decision-making. Recommendations are based on the best-available evidence, current guidelines and informed by consensus. The relevance and appropriateness of the information and recommendations in this document depend on the individual circumstances. Moreover, the recommendations and guidelines are subject to change over time. Each of the parties involved in developing this document expressly disclaims and accepts no responsibility for any undesirable consequences arising from relying on the information or recommendations contained herein.

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NPS MedicineWise. Immunoglobulin replacement therapy for primary immunodeficiencies. Sydney: NPS MedicineWise, 2022.

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CONTENTS

Abbreviations.....	4
Overview	5
Evidence summary.....	6
Access to Ig.....	6
Approved indications for Ig in PID.....	6
Diagnostic challenges	7
Routes of administration.....	7
Optimising dosage	8
Considering body weight.....	9
Use of prophylactic antibiotics	10
Ongoing patient review.....	11
References.....	12

ABBREVIATIONS

BloodSTAR: Blood System for Tracking Authorisation and Reviews

Criteria: Criteria for the clinical use of immunoglobulin in Australia

CVID: common variable immunodeficiency

IBW: ideal body weight

Ig: immunoglobulin

IgA: immunoglobulin A

IgG: immunoglobulin G

IgM: immunoglobulin M

IRT: immunoglobulin replacement therapy

IVIg: intravenous Ig

LifeBlood: Australian Red Cross Lifeblood

NBA: National Blood Authority

PAD: primary antibody deficiency

PID: primary immunodeficiency disease

SCID: severe combined immunodeficiency

SCIg: subcutaneous Ig

TBW: total body weight

XLA: X-linked agammaglobulinemia

OVERVIEW

Key points

- ▶ Immunoglobulin replacement therapy (IRT) is the leading therapeutic approach for primary immunodeficiency disease (PID) with an antibody deficiency.
- ▶ Immunoglobulin (Ig) dosage should be tailored to meet individual patient needs.
- ▶ Prevention of infection, rather than achieving a particular immunoglobulin G (IgG) serum level, should be the goal of therapy for patients with PIDs.
- ▶ Dosage should be continually reviewed to maximise efficacy while minimising risk of adverse events and costs.

Primary immunodeficiency diseases (PIDs) are a group of more than 400 largely heritable genetic disorders characterised by an increased susceptibility to infectious diseases, autoimmunity, autoinflammatory diseases, allergy, and/or malignancy.¹ They may present alone or as part of a syndrome, with substantial heterogeneity within each disorder and high rates of potentially preventable morbidity.² PIDs typically present during infancy or childhood, but many present in adulthood.³ Once considered rare, PIDs are now collectively recognised to occur in 1/1000 to 1/5000 births.¹

PIDs may affect one or more components of the immune system, including defects or deficiencies in T-cells, B-cells, both T- and B-cells, phagocytic cells, or complement proteins.⁴ Deficiencies in antibody production are the most frequent, clinically significant PIDs,⁵ accounting for approximately 77% of all cases in Australia.²

Immunoglobulin replacement therapy (IRT) is the leading therapeutic approach for PIDs with an antibody deficiency (primary antibody deficiencies, PADs). However, Ig is a high-cost, high-demand blood product that is in limited supply.⁶ Evidence-based approaches to its use are essential to ensure it is administered to those who are most likely to benefit. Clinicians prescribing IRT should be familiar with the current clinical indications and levels of evidence in support of its use in these conditions.

There have been few well-designed clinical trials investigating IRT for PIDs. A review of the literature from the past decade identified only a single Australian study.⁷ Given the limited Australian research, the following evidence summary has been synthesised from current Australian guidelines^{8,9} for the treatment of PIDs in conjunction with international research.

EVIDENCE SUMMARY

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),^{10,11} 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](#) (Criteria). 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, medical officers are 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>.

Approved indications for Ig in PID

The aim of IRT is to reduce the incidence and severity of infections experienced by people with PIDs and to prevent long-term deterioration in organ function.¹² Ig products should be reserved for patients with PIDs who are most likely to benefit and for whom there are no safe and effective alternative treatments.

Lifelong IRT is universally indicated for all PIDs with significantly impaired antibody production. Accurate diagnosis to identify patients most likely to benefit from IRT is important.¹² For individuals with milder presentations, IRT may be initiated on a trial basis for a limited time period. In these cases it is important that there are clear discussions with the patient around the initial duration of treatment and expected outcomes.¹³

Clinical history is a critical aspect of determining a diagnosis of PAD.¹⁴ Laboratory assessment should be used to assess both the quantity (Ig levels) and quality (responses to vaccines) of antibody production. Examples include measuring serum levels of IgG, immunoglobulin A (IgA) and immunoglobulin M (IgM) and specific antibodies to tetanus, haemophilus and pneumococcus.¹⁵ However, functional antibody testing is not routine in all labs and may not be relevant in all conditions, such as X-linked agammaglobulinemia (XLA) or severe combined immunodeficiency (SCID).

The [Criteria](#) should be referred to for a current list of conditions and circumstances where the use of Ig products is considered to be clinically appropriate.

Diagnostic challenges

Individuals with PAD may present with a broad range of clinical features. The presence of non-infectious complications, such as autoimmune disease or malignancy, may precede hallmark clinical features such as a history of recurrent sinopulmonary bacterial infections. The variable clinical presentations may result in delayed diagnosis, as the underlying immunodeficiency diagnosis may be significantly delayed or missed.⁷ Indeed, a recent Australian cohort study found a median diagnostic delay of 9 years in adults with common variable immunodeficiency (CVID).⁷ Delayed diagnosis results in significant morbidity and an increased risk of mortality for individuals with PAD.¹⁶

The relative infrequency of PADs in primary care, and the accompanying lack of familiarity or consideration by primary care providers, further increases diagnostic delay.¹⁴ Molecular tests that identify pathogenic mutations may improve the accuracy and timeliness of PAD diagnosis, as well as long-term outcomes.¹⁷ A 2018 cohort study of Australian adults with PADs found that patients with an identified genetic contribution to their disease had a shorter time to a clinical diagnosis.⁷ However, clinical molecular genotyping is complex and expensive,¹⁸ and a next-generation sequencing approach is now recommended due to the genetic heterogeneity of PAD.¹⁹ Recent advances in sequencing methods may help improve the timeliness and accuracy of diagnoses and prediction of complications for patients with PAD.¹⁹ For example, initial screening using targeted whole exome sequencing panels that include hundreds of known PID genes are advantageous compared with the classical approach of sequencing selected candidate genes only due to variable disease penetrance and phenotypes, even in patients with identical genetics.²⁰

Routes of administration

IRT is administered via intravenous Ig (IVIg) or subcutaneous Ig (SCIg) infusion. IVIg is typically administered every 3–4 weeks in the hospital or clinic setting, whereas SCIg is typically self-administered weekly in the home setting. The most appropriate route of administration for a given patient requires an assessment of the risks and benefits of each approach, alongside patient preferences and individual pharmacokinetics. The best route may change for a patient across their lifetime.

In Australia, IVIg is the more common route of administration,²¹ and is generally considered to be safe and well tolerated. However, in comparison to SCIg, IVIg has higher rates of systemic adverse events, such as severe headache, fever and anaphylactoid reactions.^{22,23} Patients are more likely to experience adverse events during initial commencement of treatment: a prospective audit of 459 patients with PADs found that reactions occurred 34% of the time with the first infusion and decreased thereafter. All adverse events were either mild or moderate with no severe adverse events occurring.²⁴

Some patients receiving IVIg therapy may also note a diminished efficacy, with susceptibility to infection and decreased quality of life as IgG trough falls prior to the next dose (termed 'wear-off'). In a recent study, data from 177 patients with PIDs enrolled in three clinical trials were pooled in order to quantify subjective experiences of wear-off as well as rates of infection.²⁵ Compared with the first week of treatment, the probability of a first infection in the final week of the IVIg cycle increased by 26% and 55% for patients on a 3-week cycle and 4-week dosing cycles, respectively. Patients who experience wear-off effects often benefit from shortening the infusion interval or switching to SCIg.²⁶

In contrast to IVIg, SCIg can be self-administered at a place and time of the patient's choosing. Because weekly SCIg infusions produce more consistent, steady-state serum IgG levels, trough levels do not drop as low in comparison to IVIg and wear-off effects are avoided.²⁷ The smaller doses at each administration and the relatively gradual systemic absorption of SCIg also leads to significantly fewer systemic adverse reactions compared to IVIg. One study that included data from over 40,000 SCIg infusions (from several trials), showed that the overall incidence of systemic adverse events was only 0.43%.²⁸ However, patients receiving SCIg therapy were more likely to experience treatment-related infusion-site reactions (eg, erythema, swelling, warmth, induration, and soreness), which occurred in up to 75% of patients. These symptoms are usually self-resolving within 24–48 hours and don't require intervention.²⁶

For both routes of administration, most patients report satisfaction with their current therapy²⁹ and experience significant improvements in health-related quality of life.³⁰ However, significant differences in satisfaction have been observed between SCIg and IVIg. For example, self-infusion at home with SCIg decreases utilisation of the health care system and improves quality of life and mental health among paediatric and adult patients.^{31,32} It has also been demonstrated that the flexibility associated with home therapy results in greater independence, decreased periods of absence from social and school activities, decreased disruption to daily activities and improved convenience and comfort with therapy, compared with hospital-based IVIg treatment.^{29,33} Nevertheless, some patients with PADs perceive SCIg to be the less convenient route of administration and prefer to remain on IVIg, highlighting the importance of shared decision-making with the patient when determining the most appropriate therapeutic approach.

Optimising dosage

Ig dosage should be tailored to the individual patient and delivered at the lowest effective dose based on the desired clinical outcome. The optimal dosage of Ig varies according to the indication, patient weight and route of administration. For both IVIg and SCIg, and across all PADs, the standard loading dose for individuals with serum IgG levels < 4 g/L is 0.4 g/kg.¹¹ Following the initial treatment, the dosage and interval between doses is titrated in order to achieve an IgG trough level of, at minimum, the lower limit of the age-specific serum IgG reference range. To reduce wastage, doses should be rounded to the closest vial size. Ig doses requested in [BloodSTAR](#) are automatically rounded.

Several studies have demonstrated that higher serum IgG levels are associated with increased resistance to infection.¹² A 2010 meta-analysis of 17 clinical studies that included 2127 patient-years of follow-up found that, for patients with PADs treated with IVIg therapy, the risk of pneumonia decreased by 27% with each 100 mg/dL increase of trough IgG serum levels up to 1000 mg/dL.³⁴ Similarly, maintenance of trough levels greater than 500 mg/dL has been associated with fewer infections and improved clinical outcomes,^{35,36} while trough levels greater than 800 mg/dL have been associated with improved pulmonary outcomes.^{35,37}

However, a growing body of evidence is challenging the notion that a single therapeutic trough level will prevent infection in all patients. There is great variability in the dosing regimens required to maintain specific serum IgG levels, and the level of serum IgG required to protect individuals from recurrent or serious infections is likely to vary considerably across patients with PIDs.^{38,39} Not all patients will require the highest doses to reduce the risk of infections such as pneumonia.⁴⁰

For example, a prospective cohort study of 90 patients with confirmed CVID and XLA followed over 22 years showed that a wide range of serum trough IgG levels was associated with periods free of breakthrough infections. In this study, particular subsets of patients, such as those with bronchiectasis, enteropathy or XLA, required higher doses to reduce infections.³⁹ The study also found that there was a wide variation in trough IgG levels that were protective for infections, suggesting that trough IgG levels may be of little utility in predicting the prevention of future infections.

Given the large range of IgG levels in patients with PIDs, IRT dosage should be individualised rather than based on mean values from the normal population.^{41,42} Individualised treatment can be achieved by adjusting the recommended trough level for a given population until the 'biological' IgG trough level for an individual is reached – that is, the optimal trough level needed to keep that patient as infection-free as possible.^{38,40} Trough levels should be considered alongside a range of clinical and laboratory findings,¹² and prevention of breakthrough infections, rather than achieving a particular IgG serum level, should be the goal of therapy for patients with PIDs.

Considering body weight

For many PIDs, patient body weight determines the initial dosage, while maintenance therapy is determined according to the patient's response to therapy and IgG levels.¹⁰ However, there is considerable variability in approaches to measuring body weight.⁴³ While Ig dosage has historically been based on an individual's total body weight (TBW), this method may not be appropriate in patients who are obese (body mass index [BMI] > 30 kg/m²), as Ig accumulates disproportionately in fluids compared with body fat.^{44,45} For individuals whose actual body weight exceeds their ideal body weight (IBW), a common approach is to adjust Ig dosage for IBW.¹¹

The evidence for adjusting Ig dose using IBW is limited and mixed. A review of the literature identified a single, retrospective study that compared the effect of IBW-based dosing to TBW-based dosing on clinical outcomes and included PID.⁴⁶ This multi-centre trial compared data before and after implementing an IBW-based dosing strategy for IVIg over a 2-year period. The implementation of a standardised IBW dosing strategy led to the administration of smaller doses without increasing readmission rates or length of stay. However, only 17% of patients had an indication for IVIg for PID, and the desired power for the study was not achieved.

A retrospective audit of 107 patients with CVID across four centres in the UK did not find any relationship between annual dose and trough level despite normalising for weight and BMI.⁴⁷ Likewise, a US study of 173 patients with PID receiving SCIg found a similar increase in serum Ig concentration in both lean and obese patients proportional to the dose administered, leading the author to conclude that a dose adjustment in obese patients relative to lean patients was not justified.⁴⁸


While current evidence does not support a general recommendation to modify dosage based on weight status, clinicians should consider that obese patients may be receiving a large Ig dose while having multiple risk factors for complications associated with Ig.⁴⁹ Further research on IBW dosing and the impacts on patient outcomes is required to clarify the optimal method for calculating dosage.

Additionally, because the pharmacokinetics of IgG vary across patients, it is worth noting that a given dose may result in different trough levels in patients with similar body mass.⁴⁵ It is essential that both clinical and laboratory outcomes be taken into account when determining the appropriate dosage, and that doses are regularly reviewed as the patient's condition may change over time.⁴⁹

BloodSTAR includes a [dose calculator](#) that can be used to determine the Ig dose according to indication, and includes the option to adjust by IBW, where appropriate. In order to reduce unnecessary wastage and oversupply, clinicians should ensure that specific adjustments in Ig dose are recorded in BloodSTAR.

Dose Calculator

The dose calculator is intended to be used when determining the dose of immunoglobulin, based on the indication for use identified in the Criteria for the *Criteria for the clinical use of immunoglobulin in Australia*. An authorised dose will depend on the available product and presentation of that product.

Condition *	Primary immunodeficiency diseases (PID) ▼
Indication *	Replacement therapy in recognised primary immunodeficiencies for which immunoglobulin replacement is universally ir ▼
Patient Weight *	70.00 kg
Use Ideal Body Weight Adjusted Dosing	<input type="checkbox"/>  <p>Ideal body weight adjusted dosing is not recommended in patients who are: aged less than 18 years; less than 152cm in height; or pregnant. Where the Dose Determining Weight is greater than the patient's actual weight, use the patient's actual weight to calculate the Ig dose.</p>
Calculate	

BloodSTAR - Production - v3.6.0

Image: BloodSTAR Dose Calculator webpage

Use of prophylactic antibiotics

Prophylactic antibiotics are commonly used as an adjunct to IRT to prevent infection in patients with PIDs.^{50,51} The prophylaxis required varies according to the immune defect, and the pathogens or infections most commonly seen in that specific PID syndrome.⁵²

Antibiotic prophylaxis may be considered as the initial mode of therapy for patients with milder PAD phenotypes or transient hypogammaglobulinaemia of infancy alongside recurrent respiratory and/or ear infections.^{52,53} For CVID, therapy is with IgG replacement, antibiotic prophylaxis, or both.⁵³ Antibiotic prophylaxis may also be warranted in patients who experience recurrent breakthrough infections despite IRT and stable serum IgG levels.⁵³ Because IRT replaces IgG without correcting IgA defects or providing high levels of specific antibodies against all organisms, patients are still susceptible to infections, particularly those involving the sinopulmonary tract.¹³ In these instances, aggressive treatment of intercurrent infections with antibiotics is recommended.¹³

There is limited evidence supporting the use of antibiotic prophylaxis in PADs. A 2019 randomised, double-blind, placebo-controlled trial examined the effects of 3 years of low-dose azithromycin prophylaxis alongside IRT in 89 patients with PADs with associated infection-related pulmonary disease. Patients receiving azithromycin prophylaxis had a substantial reduction in respiratory exacerbation episodes per patient-year, with a consequent reduction in additional courses of antibiotics and risk of hospitalisation.⁵⁴ A 2010 prospective study followed 90 patients with CVID and 18 patients with XLA over 22 years of IRT and included an analysis of prophylactic antibiotics. Only three of 18 patients with CVID and one of eight patients with XLA who received prophylactic antibiotics for respiratory infections for more than 3 months had a reduction in the number of infections.³⁹

The decision to use prophylactic antibiotics should be based on clinical history, severity of infections, known risk of infections from specific organisms, the site of chronic infections, and the limitations of current therapies.⁵⁵ The drawbacks of prophylactic antibiotic use, including adverse effects and antibiotic resistance, should also be considered.⁵²

Ongoing patient review

All patients receiving IRT should be routinely reviewed by an immunologist. While the frequency of visits should be determined by clinical status, an initial review is required 3–6 months after starting treatment and then annually (at a minimum).¹⁰ An earlier initial review period should be considered in instances where a secondary illness is present.¹³

Reviews should include consideration of treatment efficacy and tolerability, history of infection and disease-specific considerations detailed in the Criteria.¹⁰ Measures of trough or steady-state IgG serum levels, as well as full blood cell count and results of liver and renal function, should be part of routine evaluation.^{13,26} Outcomes of each review should be recorded in [BloodSTAR, in accordance with the Criteria](#).

Therapy should continue at the lowest safe and effective dose for each patient.¹⁰ If the patient continues to have significant infections, therapy should be up-titrated by increasing the dosage or shortening the infusion interval.²⁶ As changes in weight and clinical status can alter serum IgG levels, dosage should be continually reviewed and optimised in order to maximise efficacy while minimising the risk of adverse events and cost.⁴⁹

Not all patients with PID require lifelong Ig therapy. Continuation of Ig therapy should depend on evidence of clinical benefit, including adequate replacement of antibodies. A trial of IRT cessation may be considered in cases where the ongoing need for IRT is uncertain.

Given the diverse symptoms and presentations associated with PIDs, a coordinated approach that considers IRT alongside other modalities of care should be taken. This includes the involvement of a general practitioner/physician who the patient can consult for routine issues between review appointments with the clinical immunologist, as well as allied health professionals, such as physiotherapists, who can address organ-specific co-morbidities.¹³

This clinical guidance article outlines existing evidence on the use of immunoglobulin for primary immunodeficiencies. This summary is not intended to be exhaustive and should not replace clinical judgement.

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Increasing the awareness and understanding amongst health professionals of access to immunoglobulin products in Australia, and improving health outcomes for patients through access to better health information to manage their health conditions. Funded by the Australian Government Department of Health through the Value in Prescribing Program: Immunoglobulins Products Grant.



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