Position Statement - Immunoglobulin Replacement Therapy (IRT) for Primary Immunodeficiency (PID)

The aim of this document is to to improve health outcomes for people with PID by:

- Assisting GPs, paediatricians and other medical specialists to recognise early signs of PIDs and refer patients to a clinical immunologist to confirm diagnosis and initiate treatment, including IRT if required.
- Increasing awareness of IRT options for patients with PIDs - intravenous immunoglobulin (IVIg) or subcutaneous immunoglobulin (SCIg), and the pros and cons of IVIg versus SCIg.

Contents

This document is based on expert opinion, consensus and publications, reviewed by the ASCIA IRT/PID Working Party - members are listed at www.allergy.org.au/members/committees#wpai

A reference list that includes the publications is available at www.allergy.org.au/hp/papers#p4

This document is a source for ASCIA IRT e-training for health professionals, which is being developed as part of the National Prescribing Service (NPS) MedicineWise ViP Immunoglobulin project.

Key points

- PIDs are a diverse group of more than 400 potentially serious, chronic illnesses due to inherited absence or dysregulation of parts of the immune system.
- Because of their rarity, delays in diagnosis of PIDs are common, which are associated with further complications and reduced survival rates. As well as recognition of warning signs, improved access to specialist clinical and diagnostic laboratory services is required to improve early diagnosis and treatment.
- Early and correct diagnosis of PIDs leads to appropriate treatment, including IRT, which improves quality and length of life. This requires support from expert multi-disciplinary teams comprising of specialist medical, nursing and allied health professionals.
- IRT is the standard of care for patients with antibody deficiency due to a PID disease IRT should be readily available to these patients while under the active care of a clinical immunology/allergy specialist.The aim is to replace immunoglobulin to maintain normal Immunoglobulin G (IgG) levels, with the dose used individualised for each patient.
- IRT can be given as IVIg or SCIg and pharmacokinetics differ according to administration route. The choice of route (IVIg or SCIg) is dependent on multiple factors, including patient preference, medical conditions and lifestyle. The preferred route may vary at different times during a patient's life.

1. Overview of PIDs

PIDs are a diverse group of more than 400 potentially serious, chronic illnesses due to inherited absence or dysregulation of parts of the immune system.

Symptoms often appear in childhood, but many can first occur in adult life.

PIDs can lead to reduced quality of life and life expectancy due to recurrent, chronic or severe infections, swellings, autoimmune and inflammatory problems, and are a significant health burden.

PIDs are different from acquired immunodeficiencies (also known as secondary immunodeficiencies), which may be due to malignancy, cancer treatments, immunosuppressive medications, autoimmune diseases, or infections such as the human immunodeficiency virus (HIV), the latter causing acquired immunodeficiency syndrome (AIDS).

Individual PIDs are rare, with only a few patients identified in the world, whilst the more common PIDs affect between 1 in 10,000 and 1 in 1,000,000 people.

There are six main types of PIDs that affect the immune system in different ways:

- **Predominantly antibody deficiencies** such as common variable immunodeficiency (CVID).
- **Combined immunodeficiencies** such as severe combined immunodeficiency (SCID).
- **Phagocytic cell deficiencies** such as chronic granulomatous disease (CGD).
- **Immune dysregulation** such as autoimmune lymphoproliferative syndrome (ALPS).
- **Autoinflammatory disorders** such as familial Mediterranean fever (FMF).
- **Complement deficiencies** such as hereditary angioedema (HAE).

Note: A published classification of PIDs has been developed by the International Union of Immunological Societies (IUIS), which is regularly modified. The current version divides PIDs into nine categories and refers to PIDs as Inborn Errors of Immunity. For the purpose of this document, the more readily recognised term of primary immunodeficiencies (PIDs) is used.

Research and advances in therapies have resulted in improved health and a longer life for people with PIDs.

There are currently six main types of treatment options depending on the type of PID:

- **Antibiotics**
- **IRT - SCIg or IVIg**
- **Immunomodulation – including biologics**
- **HAE Treatments**
- **Haematopoietic Stem Cell Transplantation (HSCT)**
- **Gene Therapy**

The focus of this document is IRT (SCIg or IVIg) for patients with PID.

For further information about types of PIDs and treatments refer to Appendices A and B in the ASCIA Immunodeficiency Strategy for Australia and New Zealand which was first published in October 2020 and will be updated to include a preface prior to the official launch in February 2022.

2. Early recognition and referral of patients with PIDs

Because of their rarity, delays in diagnosis of PIDs are common, increasing the risk of further complications and reduced survival rates:

- For infants and very young children with severe PIDs, diagnostic delay leads to severe complications due to infections and early death.
- Early diagnosis is vital for severe PIDs, to allow curative treatment such as urgent HSCT, also known as bone marrow transplant
- For older children and adults with PIDs where curative treatment is not currently possible, delay in diagnosis can be associated with;
  - Infections, resulting in possible organ damage.
  - Increased morbidity.
  - Reduced life expectancy.
- Early and correct diagnosis will lead to appropriate treatment, including IRT, which improves quality and length of life. This requires support from expert multi-disciplinary teams comprising of specialist medical, nursing and allied health professionals.

As well as recognition of warning signs listed in this document, access to specialist clinical and diagnostic laboratory services is required to improve early diagnosis and treatment.

With targeted resources, patients with PID can be spared unnecessary interventions, and instead utilise available medical treatments to maximise their opportunities to lead productive and healthy lives.

The role of GPs, paediatricians and physicians in identifiying and managing patients with PIDs

GPs, paediatricians and adult medicine physicians, particularly respiratory medicine physicians and gastroenterologists, have an important role in identifying and managing patients with PIDs including:

- Recognition of early symptoms and signs of PIDs.
- Appropriate investigation and interpretation of test results.
- Appropriate and timely referral to a clinical immunologist.
- Appropriate follow up care in conjunction with a clinical immunologist.
- Management of general health issues, particularly assessment of growth and development in children in patients with PIDs.

When should patients be referred to a clinical immunologist?

Patients with suspected PID should be referred to a clinical immunologist when:

- They have early warning signs of PID.
- Results of initial testing suggests PID.
- Results of initial testing are confusing and diagnosis is unclear.
- Results do not confirm PID but there remains a high clinical suspicion for PID.

3. Warning signs of PID

Early diagnosis of other PIDs is important, since delayed treatment results in complications that can be chronic or life threatening.

Warning signs of PIDs are listed below. However, there is a broader range of symptoms and signs as some PID patients may not present with recurrent and severe infection but develop other features such as autoimmunity, autoinflammation or neoplasiaIf clinical concern exists patients should be referred to a clinical immunologist for further assessment.

CHILDREN	ADULTS
Four or more ear infections within one year	Two or more ear infections (otitis media) within one year
Two or more serious sinus infections within one year	Two or more sinus infections in one year in the absence of allergies
Two or more pneumonias within one year	Recurrent pneumonia
Recurrent, deep skin or organ abscesses	Recurrent, deep skin or organ abscesses
Two or more deep seated infections such as sepsis, meningitis or cellulitis	Infection with normally harmless tuberculosis-like bacteria
Persistent thrush in the mouth, skin or elsewhere after age one	Persistent thrush or fungal infection on skin or elsewhere
Two or more months on antibiotics with little effect	Persistent or recurrent viral infections (warts, herpes, EBV)
Need for intravenous antibiotics to clear infections	Need for intravenous antibiotics to clear infections
Failure to gain weight, grow at a normal rate, or chronic diarrhea	
Family history of PID	Family history of PID

This table is adapted from the ten warning signs developed by the Jeffrey Modell Foundation www.info4pi.org

4. IRT for PID

IRT is the standard of care for patients with antibody deficiency due to a PID disease. IRT is available to patients under the active care and follow up of a clinical immunology/allergy specialist. The aim is to replace immunoglobulin to maintain normal Immunoglobulin G (IgG) levels, and prevent infectious episodes. The dose used is individualised for each patient.

The introduction of IRT has greatly improved health related quality of life (QOL) for patients with PIDs. It is usually required lifelong for PID to prevent or alleviate infections and this therapy can be life saving. Access to IRT is guided by clear prescribing criteria to ensure clinically appropriate and economical use of immunoglobulin products.

Immunoglobulin products:

- Are made from pooled plasma from many healthy human donors, which is screened for hepatitis B, hepatitis C and HIV. They are treated with additional viral inactivation steps such as heat treatment, enzyme treatment, detergent treatment and nanofiltration.
- Contain 97-98% IgG specific antibodies against a broad spectrum of bacterial and viral pathogens, with traces of IgM and IgA
- Are plasma derived products and therefore a limited resource. Prescribing a dose that uses a partial vial results in unnecessary wastage so prescribers must ensure that doses are rounded to the full vial size. Vial sizes vary between products and this must be taken into account.
- Are available to patients meeting the prescribing criteria under the active care and follow up of a clinical immunology/allergy specialist.
- Can be given as IVIg or SCIg and pharmacokinetics differ according to administration route. There are multiple brands that may change from time to time and rates of administration may vary for different products. Both IVIg and SCIg:
    - Are effective at reducing infections and hospitalisations.
    - Preserve organ function and reduce long term damage from recurrent infections.
    - Are associated with significant benefits to patient quality of life.
    - Improve the lifespan of patients with PID.

5. IVIg or SCIg

IVIg replacement therapy:

- Is usually administered approximately monthly (three to four weekly) in hospital.
- Leads to a high peak of IgG after infusion.
- Levels decrease rapidly over few days then slowly decrease over next few weeks.
- Does not require patient training as it is usually hospital based.

The majority of side effects are mild and self-limiting and include headache, fever, chills, nausea, fatigue or flu-like illness. The frequency of side effects may be linked to the rate of infusion with more side effects seen with faster infusion rates. Serious adverse events are rare but include anaphylaxis, aseptic meningitis, renal impairment and thrombosis.

SCIg replacement therapy:

- Requires frequent administration (one to three times per week) by patients or carers at home.
- Involves slow diffusion of IgG from subcutaneous tissue
- More frequent small doses are associated with more consistent IgG levels.

Whilst systemic reactions to SCIg are much less common than with IVIg, local injection site reactions such as redness, itching, swelling, or discomfort are common, but improve with time.

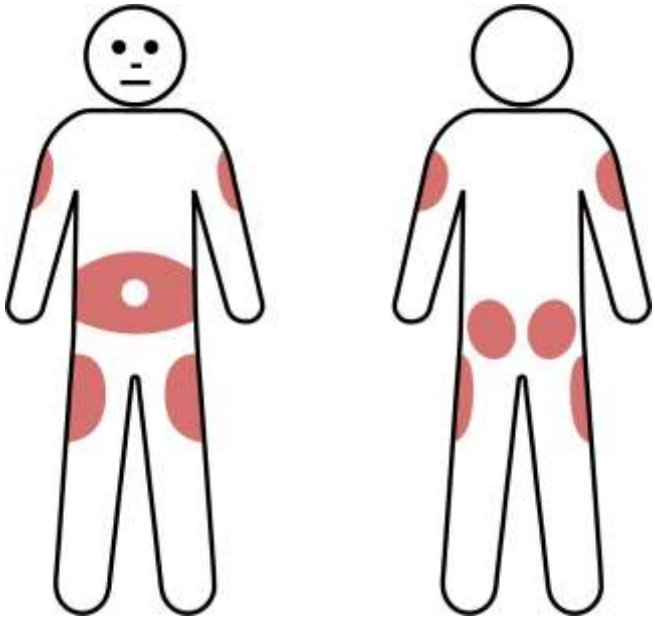

Figure 1. SCIg injections may be administered at multiple sites according to patient preference. Usually in the lower abdomen, but the outer edge of the thigh or back of the upper arm can also be used.

There are advantages and disadvantages for both IVIg and SCIg therapy and the preferred route may vary at different times during a patient's life, as shown in Table 1.

The decision on the route for IRT (IVIg or SCIg) depends on each patient's unique situation including medical history, response to treatment, compliance with therapy and lifestyle. Factors that may affect the choice of route for IRT (IVIg or SCIg) include:

- **Patient satisfaction –** this plays an important role in treatment decisions, particularly as patients with PID diseases require lifelong IRT.
- **Availability and resourcing of SCIg infusion pumps and consumables**.
- **Availability of SCIg products** - It is important that once a patient has been successfully established on a product there is ongoing supply of this product. Having multiple SCIg product options may be useful for patients who have tolerability problems with one or more products.
- **Other medical conditions** - SCIg therapy may be contraindicated in some patients with severe thrombocytopenia, bleeding disorders or for patients on anticoagulation therapy and may also be problematic for patients with widespread eczema.
- **Less frequent infusion procedures may be preferred for some young patients** - even though SCIg therapy has been shown to be well tolerated in infants and young children.
- **Limited subcutaneous tissue** – this may limit site options for SCIg infusions although it has been successfully administered to infants.

Table 1: Comparison of Pros and Cons of IVIg and SCIg therapy

	Pros	Cons
IVIg	• Less frequent infusion (monthly) • Rapid increase in serum IgG • Does not require patient training	• Usually hospital based • IV access required • Risk of immediate and systemic adverse effects • Adverse effects from high IgG levels in 12-48 hours post infusion • Symptoms related to wear off effects of IgG trough levels
SCIg	• Home based therapy • IV access not needed • Few systemic side effects • Can be used for patients with previous systemic reactions to IVIg or IV access difficulties - SCIg therapy may be the preferred treatment in these patients • Faster infusion duration • More consistent IgG levels with no wearing off effects related to IgG trough levels • Improved QOL of patient and family with flexibility, independence and empowerment • Reduced hospital costs • Reduced patient travel time and associated costs and inconveniences (e.g. time off school/ work, parking costs) • Patient can take treatment with them when travelling (e.g. on holiday)	• Frequent administration (1-3 times per week) • Local side effects (swelling, induration, local inflammation, itch), which are usually mild and transient • Some patients may require battery or spring driven pumps, although some patients may use the rapid push method which does not require a pump. • Requires treatment plan compliance

6. Resources

ASCIA Information for Patients, Consumers and Carers

Immunoglobulin replacement therapy

SCIg therapy - general information for patients and carers

Checklist - SCIg equipment

Checklist - SCIg infusions

Fast Facts about primary immunodeficiency

COVID-19 and Immunodeficiency

COVID-19, Immunodeficiency and School Attendance

Primary immunodeficiency (PIDs)

Severe combined immunodeficiency (SCID)

Common variable immunodeficiency (CVID)

ASCIA Subcutaneous Immunogobulin (SCIg) Information

SCIg therapy - general information for patients and carers

Guide - Setting up a SCIg service in a hospital

SCIg Treatment Plan

Transfer Care Plan for patients on IRT

Travel Plan for patients on SCIg

SCIg Position Statement

PID Patient Organisations

AusPIPS Inc	Australian Primary Immunodeficiency Patient Support www.auspips.org.au
HAE Australasia	Hereditary Angioedema Australasia www.haeaustralasia.org.au
IDFA	Immune Deficiencies Foundation Australia www.idfa.org.au
IDFNZ	Immune Deficiencies Foundation New Zealand www.idfnz.org.nz