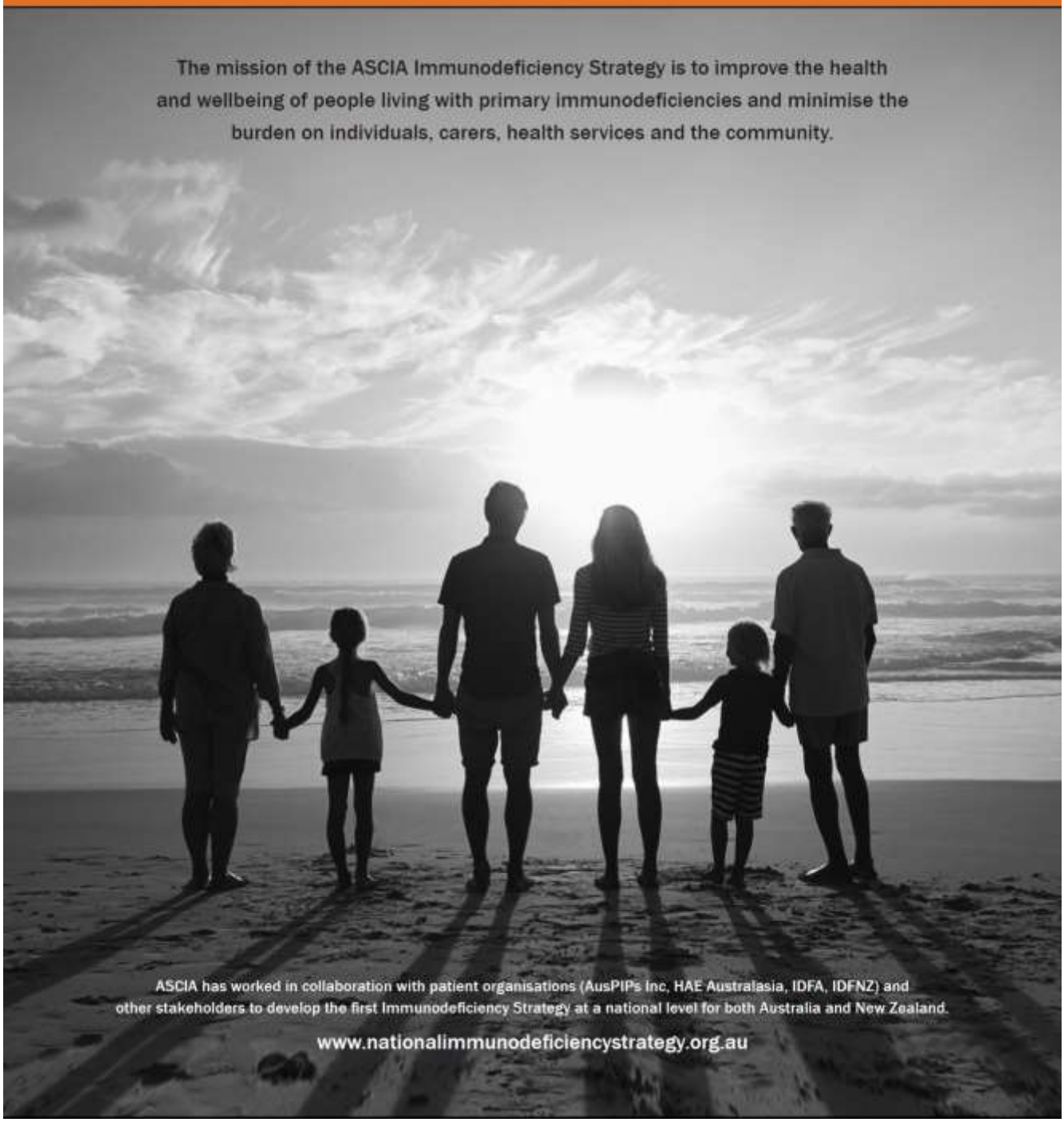
ascia

australasian society of clinical immunology and allergy

Immunodeficiency Strategy

for Australia and New Zealand

The mission of the ASCIA Immunodeficiency Strategy is to improve the health and wellbeing of people living with primary immunodeficiencies and minimise the burden on individuals, carers, health services and the community.



ASCIA has worked in collaboration with patient organisations (AusPIPs Inc, HAE Australasia, IDFA, IDFNZ) and other stakeholders to develop the first Immunodeficiency Strategy at a national level for both Australia and New Zealand.

www.nationalimmunodeficiencystrategy.org.au

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The Australasian Society of Clinical Immunology and Allergy (ASCIA) is the peak professional body of clinical immunology/allergy specialists in Australia and New Zealand.

ACKNOWLEDGEMENTS

The Australasian Society of Clinical Immunology and Allergy (ASCIA) was established in 1990 as the peak professional body of clinical immunology/allergy specialists in Australia and New Zealand.

Clinical immunology specialists are responsible for the management of patients in Australia and New Zealand with rare conditions known as primary immunodeficiencies (PIDs).

ASCIA has worked in collaboration with patient organisations (AusPIPs Inc, HAE Australasia, IDFA, IDFNZ) and other stakeholders (refer to Appendix E) to develop the first Immunodeficiency Strategy at a national level for both Australia and New Zealand.

The Strategy is available at www.nationalimmunodeficiencystrategy.org.au/

ASCIA looks forward to working in collaboration with patient organisations, governments and other stakeholders to implement the Strategy from 2021 onwards. A timeline and strategic action plan for implementation will depend on funding and agreement regarding priorities.

Development of the Strategy was coordinated by Jill Smith, ASCIA CEO, and led by the following ASCIA members:

- Dr Melanie Wong (NSW): Co-chair, ASCIA Immunodeficiency Strategy and past ASCIA President
- Professor Jo Douglass (VIC): Co-chair, ASCIA Immunodeficiency Strategy and past ASCIA President
- Dr Theresa Cole (VIC): Chair, ASCIA Immunodeficiency committee and ASCIA President Elect (2020-2022)
- Dr Jan Sinclair (NZ): Chair, Immunology/Allergy joint training committee
- Professor Connie Katelaris AM (NSW): Chair, ASCIA HAE working party and past ASCIA President
- Professor Michaela Lucas (WA): ASCIA President (2020-2022)
- Associate Professor Jane Peake (QLD): ASCIA Director (2020-2022)
- Dr Michael O'Sullivan (WA): ASCIA Director (2020-2022)

FINANCIAL SUPPORT

Unrestricted educational grants from CSL Behring and Grifols assisted ASCIA to host the ASCIA Immunodeficiency Strategy meeting held on Friday 8 March 2019, which involved 32 delegates (refer to Appendix E).

CSL Behring has provided another unrestricted educational grant to assist ASCIA in completing the ASCIA Immunodeficiency Strategy document.

The ASCIA Immunodeficiency Strategy document, meeting and outcomes are not influenced by this support.

FURTHER INFORMATION

If there are any queries regarding the ASCIA Immunodeficiency Strategy for Australia and New Zealand contact the ASCIA CEO, Jill Smith by emailing education@allergy.org.au

ASCIA is a Company limited by guarantee (ACN 608 798 241; ABN 45 615 521 452) and a Specialty Society affiliated with the Royal Australasian College of Physicians (RACP).

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INTRODUCTION

The ASCIA Immunodeficiency Strategy is focused on primary immunodeficiencies (PIDs), a diverse group of more than 400 potentially serious, chronic illnesses due to inherited absence or dysregulation of parts of the immune system, that can lead to reduced quality of life and life expectancy.

PIDs are different to 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), which causes acquired immunodeficiency syndrome (AIDS).

Many elements of the ASCIA Immunodeficiency Strategy will also benefit people with secondary immunodeficiencies in Australia and New Zealand, and other immune system disorders.

The mission of the ASCIA Immunodeficiency Strategy is to improve the health and wellbeing of people living with PIDs and minimise the burden on individuals, carers, health services and the community.

Issues listed below were identified at the ASCIA Immunodeficiency Strategy meeting held on Friday 8 March 2019 and following further consultations with stakeholders. This document includes suggested solutions related to each of the issues and goals.

Issue 1: Newborn screening for early diagnosis of severe PID
Goal: Enable early diagnosis of severe combined immunodeficiency (SCID) by newborn screening of the population.

Issue 2: Early diagnosis of other PIDs
Goal: Enable early diagnosis of other PIDs through recognition of early warning signs of PID, appropriate testing and treatment.

Issue 3: Improved access to genomic and immune testing for PID
Goal: Improve access to expert genetic diagnosis by using genomic and immune testing for patients with suspected or recently diagnosed PID, or people with a family history of PID.

Issue 4: Improved access to care for PID
Goal: Ensure equitable access to specialist and multi-disciplinary care for patients with PID, including those living in regional, rural and remote areas.

Issue 5: Improved access to funded and supported PID treatments
Goal: Ensure equitable access to treatments, that are appropriately supported and funded for patients with PID.

Issue 6: Support for PID education and training
Goal: Increase support for PID education and training for patients, carers and health professionals.

Issue 7: Support for PID research and collaborations
Goal: Increase support for multi-disciplinary clinical and laboratory PID research and collaborations.

Issue 8: PID in Indigenous Australian and Māori populations
Goal: Ensure that the priorities of Indigenous Australian and Māori populations are represented in PID diagnosis, care and research.

The ASCIA Immunodeficiency Strategy is based on expert opinion, consensus and publications.

Reference lists that include the publications are available at www.allergy.org.au/hp/papers#p4

ABOUT PRIMARY IMMUNODEFICIENCIES (PIDs)

Primary Immunodeficiencies (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.

Individual PIDs are rare, including many 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. However, taken together, the prevalence of PIDs is overall estimated to be 1 in 1,000 people.

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

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

Note: A published classification of conditions which cause 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:

- **Antibiotics**
- **Immunoglobulin Replacement Therapy (IRT**) - subcutaneous (SCIg) or intravenous (IVIg)
- **Immunomodulation** – including biologics
- **Hereditary Angioedema (HAE) Treatments**
- **Haematopoietic Stem Cell Transplantation (HSCT)**
- **Gene Therapy**

For further information about types of PIDs and treatments refer to Appendices A and B.

EARLY DIAGNOSIS AND SPECIALIST TREATMENT OF PID ENABLES PROFOUND BENEFITS

Because of their rarity, delays in diagnosis of PIDs are common, which is associated with 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 to allow curative treatment such as urgent haematopoietic stem cell transplantation (HSCT), also known as bone marrow transplant (BMT).

For older children and adults where curative treatment is not possible, delay in diagnosis is associated with reduced life expectancy.

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.

ISSUE 1: NEWBORN SCREENING FOR EARLY DIAGNOSIS OF SEVERE PID

Goal: Enable early diagnosis of severe combined immunodeficiency (SCID) by newborn screening of the Australian population.

Severe Combined Immunodeficiency (SCID) is a group of disorders that have impaired T cell function resulting in impaired B cell function and antibody (immunoglobulin) production.

The incidence of SCID is estimated at 1 in 58,000 births. Based on 311,000 live births in Australia in 2016, six new cases of SCID would be expected around the country every year. There were 60,000 live births in New Zealand in the same time period, and one new case per year would be anticipated.

Most patients (around 90%) with SCID have a genetically identifiable cause, and usually develop severe, recurrent, persistent and opportunistic respiratory and gastrointestinal infections within the first few months of life, with failure to thrive. **SCID is fatal in the first two years of life without definitive intervention.**

For infants with SCID to survive, urgent haematopoietic stem cell transplantation (HSCT), also known as bone marrow transplant (BMT) is required. HSCT provides a new source of stem cells obtained from donated bone marrow or blood. Stem cells are able to develop into all types of blood cells, including T cells and B cells. HSCT usually cures the underlying PID but is not without risk and must be performed in centres with suitable expertise in PID, with facilities to isolate and manage an infant with SCID, and experience with the specific protocols for HSCT in SCID.

Early diagnosis is vital to allow curative treatment such as urgent HSCT. Newborn screening (NBS) for SCID means that strategies can be used to try and prevent the infant developing infections, which can be life threatening. NBS for SCID allows early HSCT, with better outcomes in younger infants, before they develop infections that can be life threatening and cause complications.

A reliable NBS test is available for SCID based on proven technology, which identifies T cell receptor excision circles (TREC). Infants with SCID have impaired T cell development and will typically have significantly reduced numbers of thymically derived T cells, and therefore very low or absent TREC.

SCID NBS is NOT yet routinely available in Australia. SCID NBS is currently routinely performed in New Zealand, the United States, and in some European countries, and on a trial basis in all infants born in NSW, from 2018 to 2022.

SUGGESTED SOLUTION

- Implement newborn screening of the Australian population for severe combined immunodeficiency.

ISSUE 2: EARLY DIAGNOSIS OF OTHER PIDs

Goal: Enable early diagnosis of other PIDs through recognition of early warning signs of PID, appropriate testing and treatment.

Early diagnosis of PIDs is important since delayed treatment results in the accrual of disability and complications that can be chronic or life threatening. Warning signs of PIDs are listed in Appendix C. However, there is a broader range of symptoms and signs of PIDs. As well as recognition of warning signs, improved access to specialist clinical and diagnostic laboratory services is required to improve early diagnosis and treatment.

Due to their rarity, delays in diagnosis of PIDs are common, which is associated with 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.

For older children and adults where curative treatment is not possible, delay in diagnosis is associated with reduced life expectancy. The recent expansion of genomic technologies has the potential to transform care delivery to PID patients, informing early diagnosis and the delivery of precision medicine.

Correct diagnosis will lead to appropriate treatment, including immunoglobulin replacement therapy (IRT), improving quality and length of life. This requires support from expert multi-disciplinary teams comprising of specialist medical, nursing and allied health professionals.

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.

SUGGESTED SOLUTIONS

Early diagnosis and specialist treatment of PID enables profound benefits to patients, carers and the health system. Once recognised, PIDs are treatable, and in some cases curable. Untreated PIDs are often chronic, serious, or even fatal. Early and accurate diagnosis for PIDs requires:

- Improved access to specialised testing by diagnostic laboratories accredited by National Association of Testing Authority (NATA) or International Accreditation New Zealand (IANZ), with reference ranges for antibody levels and switched memory B cells established for paediatric and adult patients. Research laboratories will still play a role in investigating novel immunodeficiencies. Centres should have both specialised laboratory and clinical expertise.
- Improved access to paediatric and adult clinical immunology/allergy specialists, who are experts in the clinical and diagnostic evaluation of patients with suspected PID.
- Improved education for health professionals about recognising early warning signs of PID, and when to refer patients to specialists.

ISSUE 3: IMPROVED ACCESS TO GENOMIC AND IMMUNE TESTING FOR PID

Goal: Improve access to expert genetic diagnosis by using genomic and immune testing for patients with suspected or recently diagnosed PID, or people with a family history of PID.

Traditional diagnosis of PID is mainly through laboratory tests for immune function. Treatment for PID can be initiated or continued without a genetic diagnosis (using genomic testing) in patients where the clinical history and routine testing demonstrate a clear need for the therapy.

However, for an increasing number of PIDs, genetic diagnosis is required to make a definitive diagnosis. It also enables targeted therapies and counselling about outcomes based on what is known about that gene, and informed reproductive/family planning decisions.

The choice of genomic tests should be made by the clinical immunologist and the genomic medicine specialist based on the patient's clinical history and other investigations.

Genetic counselling should be provided before and after genomic testing with a clinical immunologist or genetic counsellor with expertise in PID.

Additional highly complex immune testing is often needed to work out whether or not changes in a gene found by genomic testing are likely to be the cause of PID in a particular patient.

In many cases, genomic testing for genetic diagnosis of PID, as well as associated complex immune testing, is currently:

- Unfunded and expensive,
- Often sent to overseas laboratories at considerable cost, or
- Performed in research laboratories, that are not accredited by National Association of Testing Authority (NATA) or International Accreditation New Zealand (IANZ).

Access to testing, funded or otherwise, varies considerably across regions, centres and in private versus public systems. There are well established collaborations e.g. AGHA. CIRCA, CPI, MGHA (refer to Appendix F for details), across Australia and New Zealand, which are attempting to provide services to meet these complex needs, but without adequate or ongoing resourcing.

SUGGESTED SOLUTIONS

Equitable access to funded and accredited genomic and immune testing for PID in Australia and New Zealand requires:

- Funding of diagnostic genomic testing performed by accredited diagnostic laboratories, including the introduction of a Medicare item number in Australia similar to those introduced in 2020 for identification of childhood dysmorphology syndromes and intellectual disability.
- Adequate staffing and resourcing of laboratories to ensure provision of results in a timely manner.
- Ensuring that genomic testing is supported by genomic medicine and genetic counselling expertise.
- Ensuring that highly complex specialised immune testing is funded and accessible to all patients with suspected PID in Australia and New Zealand.

ISSUE 4: IMPROVED ACCESS TO CARE FOR PID

Goal: Ensure equitable access to specialist and multi-disciplinary care for patients with PID, including those living in regional, rural and remote areas.

Once PIDs are diagnosed, only some PIDs are curable, but all are treatable. This requires specialist coordinated care delivery to minimise the acquisition of secondary disabilities.

Management of patients with PIDs is complex and requires specialist medical and nursing care, as well as multi-disciplinary care, to prevent complications and disabilities.

Recognition of the complex care that these patients need is required for hospital care priorities, funding models, e-health and coding.

Comprehensive principles of care for PIDs should therefore include:

- Access to specialist centres with expertise in clinical immunology.
- Sustained access to treatment options (listed in Appendix B) including availability and support for home based as well as hospital-based care.
- Allied health services including dietitians, physiotherapists, occupational therapists, psychosocial care, and genetic counselling in specialist centres.
- Coordination of care across disciplines and centres to the community and primary care, utilising electronic records where possible.
- Support and advocacy from patient organisations (AusPIPs Inc, HAE Australasia, IDFA and IDFNZ).

SUGGESTED SOLUTIONS

An evidence based standard/model of care for patients with PIDs needs to be developed (Cystic Fibrosis is an example of a model of care), to ensure that PID patients have access to appropriate and sustainable medical and support services.

The model of care should be divided into the following components:

- **Key service components** e.g. newborn screening, paediatric care, transition services, adult specialist clinical and diagnostic services.
- **Enablers for model of care** e.g. research, workforce development, role of specialised centres, benchmarking of multidisciplinary staffing needs and funding, registries, multinational research, health economics data to outline the cost benefit of strategies.
- **Community Care** e.g. upskilling of local services, education of allied health professionals on PIDs, allied health involvement at time of transplant/transition, role of patient organisations.

ISSUE 5: IMPROVED ACCESS TO FUNDED AND SUPPORTED PID TREATMENTS

Goal: Ensure equitable access to treatments, that are appropriately supported and funded for patients with PID.

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:

- Antibiotics
- Immunoglobulin Replacement Therapy (IRT) - subcutaneous (SCIg) or intravenous (IVIg)
- Immunomodulation – including biologics
- Hereditary Angioedema (HAE) Treatments
- Haematopoietic Stem Cell Transplant (HSCT)
- Gene Therapy

For further information about PID treatments refer to Appendix B.

SUGGESTED SOLUTIONS

Patients with PID require funded equitable access to all of the treatment options as listed above, and this requires:

- Treatments to be available to PID patients in rural, remote and regional centres, as well as urban areas.
- Supporting patient education resources, and training for treatment that can be administered at home.
- Prompt communication regarding treatment shortages or product changes.
- Prompt consideration given to access and funding of treatments such as new immunomodulatory agents (including biologics) and long term antibiotic therapy.
- Access and funding for treatment in all hospitals (public and private).
- Changes to improve the service model for provision of home based treatments (including SCIg), which can vary widely between centres and regions. These changes should be made in consultation with ASCIA and patient organisations.

ISSUE 6: SUPPORT FOR PID EDUCATION AND TRAINING

Goal: Increase support for PID education and training for patients, carers and health professionals.

Most patients with PID experience a delayed diagnosis, with recent Victorian data suggesting an average delay between symptom onset and diagnosis of nine years. This increases the risk of adverse patient outcomes and the acquisition of secondary complications.

Early recognition and diagnosis of PIDs is associated with increased survival. Education of health professionals and the public to recognise the warning signs of PID needs to be implemented to improve disease recognition and patient outcomes.

Immunoglobulin replacement therapy (IRT) is used to treat adults and children with PID and some other medical conditions. IRT is administered using intravenous immunoglobulin (IVIg) or subcutaneous immunoglobulin (SCIg). SCIg infusions are administered by slowly injecting purified immunoglobulin into tissue underneath the skin and can be administered at home by patients or carers. Sufficient patient and carer education, training and follow up is needed for effective and safe home based SCIg therapy.

Whilst ASCIA has been developing PID and SCIg resources since 2014, these are not funded and require ASCIA to subsidise development and updating. Some unrestricted educational grants have been obtained to go towards meeting costs, but these have not funded the development or updating of ASCIA resources, which assist nurse specialists, clinical immunologists and other health professionals in educating and training patients.

ASCIA resources provide accessible, consistent and evidence based information, training and resources that are regularly reviewed and updated. ASCIA resources include:

- Position Statements
- Patient/carer education
- PID e-training for health professionals, including a module on SCIg and IVIg
- Treatment plans and checklists

Surveys, clinical consensus, and published information have guided resource development and updating.

SUGGESTED SOLUTIONS

Increased financial support is required for the development and updating of ASCIA education and training resources about PIDs for health professionals, patients and carers, as listed below.

Education of:

- Physicians, including primary, secondary and tertiary care colleagues
- Allied health colleagues including dietitians, social workers and physiotherapists
- Patients and support groups

Training and education resources:

- For nurses supporting IVIg and SCIg administration
- Patient and physician information

Development of guidelines for:

- Referral pathways
- Transition from paediatric to adult care

ISSUE 7: SUPPORT FOR PID RESEARCH AND COLLABORATIONS

Goal: Increase support for multi-disciplinary clinical and laboratory PID research and collaborations.

Primary Immunodeficiencies (PIDs) are relatively rare and complex diseases. There is an urgent need to measure the prevalence, diagnosis and outcomes of patients with PID using genomic testing alongside conventional diagnostics to enable the delivery of appropriate care and to estimate resource utilisation.

The application of genomic technologies is changing this field and the benefits of this diagnostic advances will only be achieved in clinical and research centres with expertise in PID and translational genomics. It is important to continue to evaluate the impact of diagnosis through genomic testing, to ensure appropriate use of this testing.

It is also important that we understand more about the natural history and prognosis of PIDs. This requires support for registries to track the clinical course of PID, and collaborations between clinical immunology specialists and nurses with other health professionals and research collaborations.

ASCIA initiated the TAPID (Transplantation and PID) collaboration in 2013. TAPID is an important and ongoing expert collaboration facilitated by ASCIA, between clinical immunologists, stem cell transplant physicians and international experts. The main objective of TAPID is to enable complex PID and transplantation cases to be discussed in a confidential expert forum and to publish guidelines. It would be useful to expand TAPID to disseminate discovery research and knowledge rapidly across networks. www.allergy.org.au/about-ascia/ascia-initiatives/tapid

The ASCIA Immunodeficiency Register was launched in 2019, which requires further ethics approvals and coordinated promotion to expand its use. The Register will be a critical tool to build a broad and comprehensive knowledge base and improve outcomes for patients with immunodeficiencies, who are managed by clinical immunologists. Analysis of deidentified patient data collected in this Register will inform current and future practice https://idregister.ascia.org.au

An Allergy and Immunology Research Mission should be considered for inclusion in the Australian Government's Medical Research Future Fund (MRFF) and the New Zealand Government's research priorities.

SUGGESTED SOLUTIONS

Increased financial support is required for clinical research into PID and collaborations between clinical immunology specialists and nurses with other health professionals. More funding is needed to:

- Monitor numbers of affected individuals and trends in PIDs, through a comprehensive Immunodeficiency Register.
- Know the impacts of PIDs on patients, carers, health services and community.
- Understand more about the natural history and prognosis of PIDs.
- Improve collaboration between clinicians and researchers, to discuss cases and disseminate discovery research and knowledge rapidly across networks.
- Enable genomic patient testing, using accredited laboratories and a standardised consent process.
- Support rapid functional validation of results from accredited genomic testing, which are likely to be important.
- Establish PID centres of excellence, including virtual centres that provide expert advice.
- Facilitate the rapid translation of research-based tests to accredited tests performed by diagnostic laboratories, along with establishment and maintenance of a comprehensive test directory.

ISSUE 8: PID IN INDIGENOUS AUSTRALIAN AND MĀORI POPULATIONS

Goal: Ensure that the priorities of Indigenous Australian and Māori populations are represented in PID diagnosis, care and research.

ASCIA supports the objectives of the Closing the Gap Campaign and He Korowai Oranga, the Māori Health Strategy, to address health inequities between Indigenous Australian and Māori populations, and non-Indigenous people.

Severe, life threatening infections are more common in Indigenous Australian and Māori populations, than in the general population. Many factors contribute to this increased rate of infections, however the impact of PID on this area of health inequity should be considered.

Strategies to improve PID diagnosis, care and research have the potential to ensure health equity for Indigenous Australian and Māori populations, and the general population**.**

Genomic testing can be transformative for patients with PID and their families. Without a dedicated commitment to Indigenous genomics for PID there is a risk that Indigenous Australian and Māori populations will miss out on the benefits of these medical advances.

ASCIA commits to working in partnership with Indigenous Australian and Māori populations and other stakeholders to identify priority areas for improving PID diagnosis, care and research. This includes addressing inequity in access to genomic testing for PID.

SUGGESTED SOLUTIONS

- Address health inequities for Indigenous Australian and Māori populations as an overarching priority for all elements of this Strategy.
- Establish a consultation process that includes Indigenous Australian and Māori representation, to develop and implement a plan for improving PID diagnosis, care and research for Indigenous Australian and Māori populations.
- Consult and collaborate with existing programs with demonstrated leadership in health, research and genomics for Indigenous Australian and Māori populations.

APPENDIX A: TYPES OF PRIMARY IMMUNODEFICIENCIES

The body's immune system defends against infections from germs (e.g. bacteria, viruses, fungi, parasites) and other invaders (e.g. cancer cells), whilst protecting the body's own cells. The immune system is a complex network of organs, cells and proteins located throughout the body, which include:

White blood cells, also known as leukocytes

- Leukocytes develop from stem cells in the bone marrow and include phagocytes (neutrophils and macrophages) and lymphocytes (T cells, B cells and NK cells).

Antibodies, also known as immunoglobulins (Ig)

- Immunoglobulins are proteins produced by B cells, which are secreted into the bloodstream that recognise germs so they can be removed by the rest of the immune system.
- Long lasting protection against infections from germs is provided by immunoglobulin G (IgG), which can be measured in the blood.
- One of the most common forms of PID is antibody deficiency, which is treated with Immunoglobulin Replacement Therapy (IRT) to raise the levels of antibodies (IgG) to defend against infections.

Cytokines and chemokines, also known as signalling molecules

- Cytokines (such as interferons) switch on and off immune responses.
- Chemokines aid in the positioning of immune cells, drawing them to lymphoid organs or sites of infection where they can enact their effector function.
- Cytokines and chemokines bind to receptors that trigger signalling between cells.

Complement system

- The complement system contains over 20 different proteins and is named for its ability to "complement" the killing of germs (pathogens) by antibodies.

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

- **Predominantly antibody deficiencies** e.g. common variable immunodeficiency (CVID)
- **Combined Immunodeficiencies** e.g. severe combined immunodeficiency (SCID)
- **Phagocytic Cell Deficiencies** e.g. chronic granulomatous disease (CGD)
- **Immune Dysregulation** e.g. autoimmune lymphoproliferative syndrome (ALPS)
- **Autoinflammatory Disorders** e.g. familial Mediterranean fever (FMF)
- **Complement Deficiencies** e.g. hereditary angioedema (HAE)

ANTIBODY DEFICIENCIES

Antibodies, also known as immunoglobulins, are proteins made by specialised white blood cells, called B cells. Antibodies recognise germs so they can be removed by the rest of the immune system. The most common forms of PID are due to antibody deficiencies.

Common variable immunodeficiency (CVID) is the most common form of antibody deficiency and usually presents with recurrent chest and sinus infections. Symptoms can start at any age, although most cases are diagnosed in adults. Most individuals with CVID are more susceptible to other clinical symptoms, including autoimmune diseases, gastrointestinal disorders and cancers. People with CVID have a heightened prevalence of other immune disorders.

X-linked agammaglobulinaemia (XLA) is an antibody deficiency that is usually diagnosed in male infants. Common symptoms include frequent pus producing infections of the ears, lungs, sinuses and bones, chronic diarrhoea and poor growth.

Specific antibody deficiency occurs when the amount of antibody is normal, but it does not work very well. These patients are often less severely affected than CVID or XLA, but can nonetheless experience a significant burden of infection.

COMBINED IMMUNODEFICIENCIES

T cells (T lymphocytes) are specialised white blood cells that are essential for the functioning of the immune system. They kill infected cells (cellular immunity), help B cells make protective antibodies and can drive antibacterial and antiviral responses (humoral immunity). For this reason, most people with T cell problems have combined immunodeficiencies, because both B and T cell functions (cellular and humoral immunity) are affected.

Severe combined immunodeficiency (SCID) is the most serious of these disorders where neither the T or B cells work properly. In Australia SCID is usually diagnosed within the first year of life. SCID is diagnosed in the first months of life in New Zealand, the US and Sweden through newborn screening programs. Early diagnosis is critical for successful treatment by haematopoietic stem cell transplant (HSCT).

PHAGOCYTIC CELL DEFICIENCIES

Phagocytes (neutrophils and macrophages) are white blood cells that can eat and kill foreign invaders. Severe infections can occur if phagocytes are unable to kill germs or move to the site of an infection.

Chronic Granulomatous Disease (CGD) is a serious form of phagocytic cell deficiency. In people with CGD, neutrophils cannot kill germs effectively. They have frequent and severe infections of the skin, lungs and bones, usually with chronic abscess formation. They can also develop chronic inflammation, including inflammatory bowel disease (IBD).

IMMUNE DYSREGULATION

Immune dysregulation is a group of PIDs where the body's immune system is not regulated normally and may react against its own cells. People with immune dysregulation can have fever, damage to organs or blood cells, as well as increased risk of infection. Examples include immunodysregulation polyendocrinopathy enteropathy X-linked syndrome (IPEX), Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) and autoimmune lymphoproliferative syndrome (ALPS).

AUTOINFLAMMATORY DISORDERS

Autoinflammatory disorders are commonly due to defects of the innate (front line) immune system, and result in inflammation with fevers or damage to organs. Familial Mediterranean Fever (FMF) is the most common lifelong autoinflammatory disease in the Australian population. Patients get recurrent fevers every one to two months, as well as severe stomach pain, possibly arthritis and other features. If not properly treated the patients are at risk of getting a life-threatening disease called amyloidosis in the longer term, which can affect the kidneys, nerves and heart.

COMPLEMENT DEFICIENCIES

The complement system has an important role in the control of inflammation, killing of germs and clearance of damaged cells. Some complement deficiencies can increase the risk of autoimmune disease, whilst others result in severe infections such as meningitis or septicaemia.

Hereditary angioedema (HAE) is a unique PID due to the absence of a specific complement component called C1 esterase inhibitor. In people with HAE, the small blood vessels leak fluid into the tissues, causing non-itchy swellings known as angioedema. People with HAE can have unpredictable, debilitating and sometimes severe swellings (HAE attacks) throughout life, that may be life threatening.

APPENDIX B: TREATMENTS FOR PRIMARY IMMUNODEFICIENCIES

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:

- **Antibiotics**
- **Immunoglobulin Replacement Therapy (IRT)** - subcutaneous (SCIg) or intravenous (IVIg)
- **Immunomodulation** – including biologics
- **Hereditary Angioedema (HAE) Treatments**
- **Haematopoietic Stem Cell Transplantation (HSCT)**
- **Gene Therapy**

ANTIBIOTICS

Infections should be treated early, and antibiotics are often required. Some people may be prescribed long term antibiotics (prophylaxis) to reduce infections.

Medications against fungi, viruses and parasites may be needed to treat some conditions, and this may require long term access.

IMMUNOGLOBULIN REPLACEMENT THERAPY (IRT)

IRT is one of the most effective and commonly used treatments for some PIDs. IRT can be given using intravenous immunoglobulin (IVIg) that is injected into the vein, typically in a hospital setting, or given at home using subcutaneous immunoglobulin (SCIg) injected under the skin.

These products are derived from pooled blood (plasma), are in limited supply, and access is restricted. Doctors must follow specific guidelines to ensure that the product goes to people most in need.

IMMUNOMODULATION – INCLUDING BIOLOGICS

There is an increasing number of drugs (medications) used to increase or decrease immune function.

Medications include corticosteroids, biologics such as monoclonal antibodies, small molecule inhibitors and other immunosuppressive drugs.

Medications that specifically target pathways in genetically defined PIDs (known as targeted therapy or precision medicine) can be effective in some PIDs that have failed standard therapy.

However, many of these are not funded for PID indications. Therefore, they are not accessible unless funding for the affected individual can be negotiated through hospital drug committees or through compassionate access from the drug company.

HEREDITARY ANGIOEDEMA (HAE) TREATMENTS

There are two main treatments for severe, acute HAE attacks:

- Purified C1 esterase inhibitor for intravenous use in hospitals or at home; and
- Icatibant which can be self-administered at home.

Prophylactic treatment is increasingly important in the management of HAE as it restores quality of life to patients who otherwise live with the ever present threat of debilitating attacks.

- Older agents such as Tranexamic acid are available, but are not very effective in many people with HAE.

- Danazol has been useful for some people with HAE, however it has been discontinued in Australia and is difficult to obtain from overseas. It has many potential side effects in people with HAE who are using it long term.
- Newer agents are highly effective and have a very good safety profile.
  - C1 esterase inhibitor concentrate for IV and now SC use, is currently available but its use is very restricted to some people with very frequent HAE attacks.
  - Lanadelumab has been approved for use in Australia and New Zealand, but is not reimbursed. Clinical trials demonstrate its efficacy, safety and ease of use. Traditionally, it has taken years for such products to be made available to patients in Australia and New Zealand, so a more rapid process to allow access is needed.

Prophylactic management is rapidly evolving with a number of newer, more effective agents becoming available. Improved access to effective prophylaxis with be life-changing for many people with HAE.

HAEMATOPOIETIC STEM CELL TRANSPLANTATION (HSCT)

Current standard of care for definitive correction of SCID is HSCT, which must be performed urgently, as outcomes are best when performed at an early age with no active infection.

HSCT should only be undertaken in a specialist centre with suitable expertise and facilities to isolate and manage infants with SCID.

HSCT is also being used for other PID in adults and children and can be curative, such as CGD and some combined immune deficiencies.

However, this form of treatment requires specialist expertise in centres with recognition and experience in PID.

GENE THERAPY

Rather than replacing a person’s immune system using stem cells from a donor (bone marrow transplant), for a small number of PIDs with known gene defects, it is possible to treat patients using gene therapy.

This involves collecting stem cells from the affected individual, modifying them to include a healthy copy of the gene and returning them to the person to develop functioning immune cells.

Gene therapy is already commercially available in Europe for adenosine deaminase (ADA) SCID, with trials ongoing for several other PIDs.

It is important to develop clinical expertise in managing gene therapy, including the collection, chemotherapy and reinfusion elements similar to HSCT.

This is the model that has already been adopted for chimeric antigen receptor T (CAR-T) cell treatment in leukaemia, which is available in Australia.

APPENDIX C: WARNING SIGNS OF PRIMARY IMMUNODEFICIENCY

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 of PIDs.

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

CHILDREN	ADULTS
Four or more ear infections within one year	Two or more ear infections 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	One pneumonia per year for more than one year
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	Repeat viral infections (colds, herpes, warts, condyloma)
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	Chronic diarrhoea with weight loss
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

APPENDIX D: ASCIA AND PRIMARY IMMUNODEFICIENCY

The Australasian Society of Clinical Immunology and Allergy (ASCIA) is the peak professional body of clinical immunology and allergy in Australia and New Zealand. Established in 1990, ASCIA is a world leading, innovative and active professional society with strong leadership and sustainable operations.

ASCIA's mission is to advance the science and practice of allergy and clinical immunology, by promoting the highest standard of medical practice, training, education and research, to improve the health and quality of life of people with immune system disorders, including allergy and primary immunodeficiency (PID).

ASCIA is committed to providing high quality training, education and research to improve the health and wellbeing of all people in Australia and New Zealand with PID. This commitment is demonstrated by the following initiatives:

- Hosting of **ASCIA Annual Conferences** for the past 30 years, which provide an international standard of education for ASCIA members and other health professionals. The content of the three day ASCIA Annual Conference is at least one third based on PID.
- Continued development and updating of the **ASCIA website** for the past 20 years**,** which is a trusted and extremely well utilised source of information, with more than three million pageviews each year www.allergy.org.au
- Development of a range of **ASCIA PID resources** since 2010, including ASCIA PID e-training for health professionals, position statements, guidelines, treatment/management plans, checklists and patient information, particularly for subcutaneous immunoglobulin (SGIg) home based therapy. www.allergy.org.au/hp/papers/immunodeficiency
- **ASCIA established the Allergy and Immunology Foundation of Australasia (AIFA**) in 2013, to fund allergy and immunology research projects. This has included targeted PID research grants since 2019. www.allergyimmunology.org.au/projects
- **The TAPID (Transplantation and PID) collaboration as initiated by ASCIA in 2013**. TAPID is an important and ongoing expert collaboration facilitated by ASCIA, between clinical immunologists, transplant physicians and international experts. The main objective of TAPID is to enable complex PID and transplantation cases to be discussed in a confidential expert forum and to publish guidelines. www.allergy.org.au/about-ascia/ascia-initiatives/tapid
- The new **ASCIA Immunodeficiency Register** was launched in 2019. This requires further ethics approvals and coordinated promotion to expand its use. The Register will be a critical tool to build a broad and comprehensive knowledge base and improve outcomes for patients with immunodeficiencies, who are managed by clinical immunologists. Analysis of deidentified patient data collected in this Register will inform current and future practice. https://idregister.ascia.org.au
- Development of the **ASCIA Immunodeficiency Strategy** commenced in early 2019 and completed in November 2020. The Mission of the Strategy is to improve the health and wellbeing of people living with primary immunodeficiencies and minimise the burden on individuals, carers, health services and community.

APPENDIX E: ASCIA IMMUNODEFICIENCY STRATEGY MEETING

The following delegate list for the meeting held on 8 March 2019 includes representatives from:

- ASCIA membership - Clinical immunology specialists, nurses, dietitians, researchers
- Patient organisations - AusPIPS, HAE Australasia, IDFA, IDFNZ
- Major research centres – JMF Melbourne, ANU, WEHI, Garvan Institute
- Regulatory bodies - National Blood Authority (NBA), Jurisdictional Blood Committee (JBC)
- Supply channels - Australian Red Cross Lifeblood
- Other stakeholders - NPS MedicineWise

Bryant	Dr Vanessa	WEHI, JMF Melbourne, MGHA, AGHA	VIC
Cameron	Jo	NBA	ACT
Chan	Dr Samantha	Fellow	VIC
Cole	Dr Theresa	Specialist	VIC
Cook	Prof Matthew	ANU, AGHA, CPI (ANU)	ACT
Davies	Noelene	Nurse Consultant	SA
Douglass	Prof Jo	Specialist, MGHA, University of Melbourne, WEHI	VIC
Dunn	Rachael	Nurse Consultant	WA
Dunne	Geraldine	Nurse Consultant	NSW
Furey	Michael	JBC	VIC
Hissaria	Dr Pravin	Specialist	SA
Jackson	Amanda	Dietitian	VIC
Jeffrey	Christine	IDFA	NSW
Katelaris AM	Prof Connie	Specialist	NSW
Lindner	Robyn	NPS MedicineWise	NSW
London	Jane	NPS MedicineWise	NSW
Lucas	Prof Michaela	Specialist	WA
Murphy	Jackie	AusPIPS	VIC
Peake	A/Prof Jane	Specialist	QLD
Quinn	Dr Patrick	Specialist	SA
Simons	Janet	IDFNZ	NZ
Sinclair	Dr Jan	Specialist	NZ
Stephens	Simone	Nurse Consultant	NZ
Stone	Michael	NBA	ACT
Sullivan	Anna	Nurse Consultant	QLD
Tangye	Prof Stuart	Garvan Institute, CIRCA	NSW
van Dort	Ben	Nurse Consultant	VIC
van Zelm	A/Prof Menno	JMF Melbourne, Monash University	VIC
Wainstein	Dr Brynn	Specialist	NSW
Wilkinson	Anne	HAE Australasia	VIC
Wong	Dr Janet	ARC Lifeblood	NSW
Wong	Dr Melanie	Specialist	NSW

ASCIA staff who attended meeting: Jill Smith (CEO), Nadene Dorling, Rikki Dunstall, Michelle Haskard.

Meeting apologies: Dr David Gillis (QLD), Dr Paul Gray (NSW), Dr Miriam Hurst (NZ), Dr Alisa Kane (NSW), Dr Daman Langguth (QLD), Dr Andrew McLean-Tooke (WA), Dr Fiona Moghaddas (VIC), Dr Samar Ojaimi (VIC), Dr Michael O'Sullivan (WA), Dr Joanne Pink (NSW), Dr Charlotte Slade (VIC), Dr Joanne Smart (VIC), Fiona Wardman (HAE Australasia).

APPENDIX F: ORGANISATIONS, ABBREVIATIONS, WEBSITES

PID PATIENT SUPPORT ORGANISATIONS (Australia and New Zealand)

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

COLLABORATIONS AND OTHER ORGANISATIONS (mentioned in Appendix E)

AGHA	Australian Genomics Health Alliance https://www.australiangenomics.org.au/
ANU	Australian National University https://www.anu.edu.au/
ARC Lifeblood	Australian Red Cross Lifeblood https://www.donateblood.com.au/
ASCIA	Australasian Society of Clinical Immunology and Allergy www.allergy.org.au
CIRCA	Clinical Immunogenetics Research Consortium Australasia https://www.garvan.org.au/research/collaborative-programs/circa
CPI	Centre for Personalised Immunology https://www.cpi.org.au/
JBC	Jurisdictional Blood Committee https://www.blood.gov.au/jbc
JMF Melbourne	Jeffrey Modell Foundation Centre Melbourne https://www.jmf-melbourne.org.au/
MGHA	Melbourne Genomics Health Alliance https://www.melbournegenomics.org.au/
NBA	National Blood Authority https://www.blood.gov.au/
NPS MedicineWise	National Prescribing Service MedicineWise https://www.nps.org.au/
WEHI	Walter and Eliza Hall Institute https://www.wehi.edu.au/

PID CONDITIONS (mentioned in this document)

ALPS	Autoimmune lymphoproliferative syndrome
APECED	Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy
CGD	Chronic granulomatous disease
CVID	Common variable immunodeficiency
FMF	Familial Mediterranean fever
HAE	Hereditary angioedema
IPEX	immunodysregulation polyendocrinopathy enteropathy X-linked syndrome
PID	Primary immunodeficiency
SCID	Severe combined immunodeficiency
XLA	X-linked agammaglobulinaemia

PID TREATMENTS (mentioned in this document)

BMT	Bone marrow transplant (also known as HSCT)
HSCT	Haematopoietic stem cell transplantation (also known as BMT)
IRT	Immunoglobulin replacement therapy
IVIg	Intravenous immunoglobulin
SCIg	Subcutaneous immunoglobulin