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Information
FOR HEALTH PROFESSIONALS

Primary immunodeficiencies (PID) Clinical Update

This Clinical Update complements ASCIA primary immunodeficiencies (PID) e-training for health professionals. The main purpose of this document and the ASCIA PID e-training course is to:

- Increase awareness of PID assist health professionals, particularly general practitioners, paediatricians and general physicians.
- Promote early recognition and referral to a clinical immunologist to improve the management and quality of life for patients with PID in Australia and New Zealand.

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For further information register at https://immunodeficiency.ascia.org.au/ to complete the ASCIA primary immunodeficiencies (PID) e-training for health professionals, which includes a final assessment.

1. Immunodeficiency overview

How does the immune system work?

The immune system is a collection of tissues (e.g. bone marrow, thymus, lymph nodes and spleen), cells (e.g. lymphocytes, neutrophils and macrophages) and molecules that can be broadly divided into two parts, the innate and adaptive immunity. There can be significant overlap between these 2 systems.

Innate immune responses:

- Are present before there is contact with pathogens
- Are limited in specificity
- Have no memory or long lived protection
- Are mediated by cells (e.g. neutrophils, natural killer [NK] cells) and circulating molecules (e.g. complement proteins)

Adaptive immune responses:

- Are slower to initiate
- Respond specifically to antigens
- Result in immunological memory
- Are mediated by cells (T cells, B cells, dendritic cells) and circulating molecules (antibodies)

Effects of age on the immune system

Whilst newborns have maternal antibodies that crossed the placenta during pregnancy, their adaptive immune systems are still developing. Serum immunoglobulin (Ig) levels normally drop as maternal antibodies wane, before recovering as the newborn's immune system develops.

With advanced age the immune system weakens, particularly the adaptive system, resulting in less efficient responses by T cells and less efficient B cells with less diversity in the immune system. This makes older patients more prone to infection and non-infectious diseases, such as cancer.

What are immunodeficiencies?

Immunodeficiencies are a heterogeneous group of disorders in which there is a defect in the normal function of the immune system. Delayed recognition and diagnosis of immunodeficiencies leads to poor health outcomes and potentially premature death.

Infections are the predominant feature of immunodeficiency, particularly infections that may:

- be unusually persistent, severe, recurrent or resistant to treatment.
- involve unusual organisms or organisms of usually low virulence.
- involve body sites not usually prone to infection or multiple organs.

Immunodeficiencies may present at any age and are associated with an increased risk of certain types of autoimmune conditions and malignancies.

There are 2 types of immunodeficiencies:

- **Primary Immunodeficiencies (PIDs)** - There are more than 250 different PIDs and these are mostly caused by inherited defects of the immune system. This document focuses on PIDs.
- **Secondary Immunodeficiencies (SID)** - These are usually caused as part of another disease or illness (e.g. severe burns, haematological malignancy), as a consequence of certain medications (e.g. chemotherapy) and some infections (e.g. HIV). SIDs are more common than PIDs and lead to an increased incidence of infection, malignancy or autoimmune disease, similar to PIDs.

Primary immunodeficiencies (PIDs) overview

PIDs are inherited defects that affect development and/or function of the immune system and result in increased susceptibility to infection, autoimmunity and malignancy.

More than 250 different immunodeficiency syndromes are now described and whilst individually PIDs are rare, collectively they make up a significant chronic disease. The prevalence of PIDs is estimated to be 1 in 1200 but is variable depending on specific disorder (e.g. IgA deficiency occurs in 1 in 500 whilst other PIDs occur in 1 in 10,000 – 1:1,000,000 people.

More severe forms of PIDs typically become apparent in early life, such as severe combined immunodeficiency (SCID), with only a short asymptomatic period after birth. Early recognition of severe PIDs is critical as successful treatment outcomes are dependent on early diagnosis.

PIDs may present at a later age, with some PIDs such as common variable immunodeficiency (CVID) more commonly diagnosed in adults.

Despite major advances in molecular characterisation over the last 20 years, many patients remain undiagnosed or are diagnosed late, with adverse effects on morbidity and mortality. Treatment options for PIDs include prophylactic antibiotics, immunoglobulin replacement therapy (IRT) and in some PIDs, haematopoietic stem cell transplantation (HSCT), such as bone marrow transplantation (BMT).

PID and the immune system

Although PIDs vary in many ways, they all result from a defect in one or more elements of immune system regulation or function, as shown in the following table.

Classification	Immune defect	Examples
Combined immunodeficiencies	T cells and B cells	Severe combined immunodeficiencies (SCID) e.g. X-linked SCID, RAG 1 and 2 deficiency
Combined immunodeficiencies with associated or syndromic features	T cells and B cells with other features	Ataxia-telangiectasia, DiGeorge syndrome, Wiskott-Aldrich syndrome (WAS), Hyper-IgE syndromes (HIES), DOCK-8, NEMO
Predominantly antibody immunodeficiencies	B cells or plasma cells	X-linked agammaglobulinaemia, common variable immunodeficiency (CVID), specific antibody deficiency
Diseases of immune dysregulation	Susceptibility to haemophagocytosis or defects in regulation of immune system	Chediak-Higashi syndrome, familial haemophagocytic lymphohistiocytosis (HLH, FLH), X-linked lymphoproliferative syndrome
Congenital defects of phagocytes	Phagocytes number or function	Severe congenital neutropaenia, leukocyte adhesion deficiency, chronic granulomatous disease (CGD)
Defects of innate immunity	Innate immune system	IRAK-4 and MyD88 deficiencies, WHIM syndrome, TLR3 and UNC93B1 deficiencies, chronic mucocutaneous candidiasis
Autoinflammatory disorders	Cytokine overproduction	Familial Mediterranean fever, Hyper-IgD syndrome, Muckle-Wells syndrome, familial cold autoinflammatory syndrome
Complement immunodeficiencies	Complement components	Deficiencies of components of the classic or alternate complement pathway (e.g. C5 or C6 deficiency), C1 inhibitor deficiency / hereditary angioedema (HAE)
Phenocopies of PID	Arise from acquired mechanisms	(a)Phenocopies associated with somatic mutations e.g. autoimmune lymphoproliferative syndrome (ALPS-SFAG) (b) Phenocopies associated with autoantibodies e.g. chronic mucocutaneous candidiasis due to IL-17 autoantibody, adult-onset immunodeficiency due to INF-gamma autoantibody, pulmonary alveolar proteinosis due to Granulocyte-macrophage colony-stimulating factor (GM-CSF) autoantibody

2. Recognition, diagnosis and management of PIDs

There are 7 early warning signs of PIDs

1. **An unusually large number of infections requiring treatment including:**
   - Frequent middle ear infections (>8 per year)
   - More than one serious sinus infection per year
   - More than one pneumonia infection per year
   - Chronic suppurative sinus or lung disease in adults

2. **Infections caused by unusual or opportunistic types of organisms including:**
   - Organisms of low pathogenicity

3. **Infections in unusual places including:**
   - Perianal abscesses
   - Organ abscesses

4. **Infections that do not respond to treatment as normally expected, including:**
   - Infections refractory to antibiotic treatment
   - Rapid recurrence of infections after ceasing antibiotic treatment
   - Persistent unexplained oral thrush after one year of age
   - Severe infections (e.g. meningitis, osteomyelitis, pneumonia) requiring IV antibiotics
   - Middle ear infections asssociated with a persistent purulent discharge
   - Recurrent serious sinus infections
   - Persistent production of purulent sputum

5. **A child that does not grow or put on weight as expected or weight loss in adults**

6. **A family history of immunodeficiency or abnormal infections, particularly if there is:**
   - Shared kinship of parents
   - A family history of fatal infective complications or unexplained infant deaths

7. **Any other unusual symptoms related to infections, including:**
   - Persistent diarrhoea
   - Unusual infection related sequelae or syndromes

Other features of PIDs (these mainly occur in adult patients with CVID) include:

- Autoimmune cytopenias
- Granuloma formation at any site (often misdiagnosed as sarcoidosis)
- Chronic enteropathy unresponsive to gluten withdrawal from diet
- Unexplained hepatomegaly especially in adults
- Unexplained splenomegaly in children or adults
- Lymphoid interstitial pneumonitis

Delay in diagnosis is common

Severe PIDs may be recognised in early childhood. However, many PIDs are undiagnosed into adolescence or adulthood. According to a survey by the Immue Deficiencies Foundation (IDF) in 2007 amongst 1,300 people with PID, the average time from symptom onset to diagnosis is 12.4 years.

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, particularly assessment of growth and development in children
- Management of general health issues of patients with PIDs

Expected frequency of infections in childhood

The burden of infectious disease is high in children, even in individuals with healthy immune systems. In Australia normal healthy toddlers can have up to 4-8 minor infections each year. The number of infections can be increased up to 12 if the child attends childcare, has older siblings or has parents who smoke.

PIDs should be considered in patients with recurrent infections (more than expected for age), severe infections or infection with unusual or opportunistic organisms.

Frequency of infections in general childhood population

Age (yrs)	Infections/yr
0-2	6
3-4	5
5-9	4
10-14	3

Ref: Gray et al, JPCH 2010

Testing for PIDs

Initial evaluation always starts with a thorough clinical history and physical examination.

Prediction of specific PIDs on the basis of a particular organism is difficult. However, identification of certain types of microbial organisms may help provide clues as to the underlying defect in the immune system, as shown in the following table.

Infections associated with PIDs

PID	Infections	Organisms
Cellular (combined T and B cell) immunodeficiencies	Systemic viral infections, intracellular bacteria, fungal infections	Bacteria: Pyogenic bacteria Viruses: All Mycobacteria: Non-TB including Bacillus Calmette-Guerin (BCG) Fungi: Candida, Aspergillus Protozoa: Pneumocystis jiroveci pneumonia (PJP), cryptosporidium
Antibody (B cell) deficiencies	Upper and lower respiratory tract infections, GI tract infections	Bacteria: Streptococcus pneumonia (pneumococcus), Haemophilis influenzae**,** Moraxella catarrhalis, Campylobacter Viruses: Enteroviruses Protozoa: Giardia
Phagocytic immune defects	Respiratory tract, cellulitis, skin abscesses, liver abscesses	Bacteria: Staphylococcus aureus, Pseudomonas aeruginosa Mycobacteria: Non-TB including BCG Fungi: Candida, Aspergillus
Complement immunodeficiencies	Meningitis, systemic bacterial infections	Bacteria: Neisseria, Streptococci

Antibody (B cell) deficiencies

Antibody deficiencies are the most common type of immunodeficiency and are associated with decreased ability to produce protective antibodies against pathogens. They usually present from 3 months after birth, once maternal antibodies transferred across the placenta have gone.

Patients with antibody or humoral deficiencies generally have more frequent and/or prolonged infections compared to healthy individuals. Typically these patients suffer recurrent or severe bacterial infections of ears, sinuses and lungs, particularly with encapsulated organisms (e.g.pneumococcus, meningococcus, haemophilus).

Evaluation of antibody (B cell) deficiencies

- Antibody function can be tested both quantitatively and qualitatively.
- Quantitative serum immunoglobulin (Ig) tests are used to detect abnormal levels of the 3 major classes of Ig – IgG, IgA and IgM.
- A low level of IgG is termed ‘hypogammaglobulinaemia’ and its presence should be confirmed on repeat testing. Any underlying secondary causes of hypogammaglobulinaemia should be considered before referral to a clinical immunologist.
- Cellular immune testing for B cells should be performed in consultation with a clinical immunologist.
- Assessment of specific antibody responses (e.g. tetanus and pneumococcus) may be required, usually in consultation with a clinical immunologist, in less severe forms of hypogammaglobulinaemia or when

the clinical history is suggestive of an antibody deficiency disorder. Specific antibodies need to be correlated with vaccine history and age of patient.

Patients with abnormal results or patients with normal results who are of ongoing clinical concern should be referred to a clinical immunologist.

Cellular (combined T and B cell) immunodeficiencies

Cellular immunodeficiencies are much less common than antibody immune defects and are often present with defects of B cells and other immune cells. Therefore they are sometimes called combined immunodeficiencies. Primary T cell deficiencies present early in life, with failure to thrive, opportunistic infections, candida and chronic diarrhoea.

If a cellular immunodeficiency is suspected, live vaccines need to be withheld and patient should be referred to a clinical immunologist for an urgent consultation.

Evaluation of cellular (combined T and B cell) immunodeficiencies

Tier 1 (GPs, paediatricians)

- Full blood count
  - Particularly in children, transient lymphopenia is common. Persistent or profound lymphopenia should be followed up.
  - T cells comprise two thirds of lymphocytes in blood, therefore decreased T cells are typically associated with lymphopenia on a full blood count but normal T cells does not rule out cellular immunodeficiency.
- Quantitative serum Ig tests are used to assess humoral immunity.

Tier 2 (Clinical immunologists and/or paediatricians)

- Flow cytometry for T cells, B cells and NK cells.
- HIV testing should be performed to exclude HIV.
- Additional testing may be indicated.

Severe T cell immunodeficiencies such as SCID are medical emergencies and patients need to be urgently referred to a clinical immunologist for continuation of diagnosis and treatment.

Phagocyte immune defects

Phagocyte abnormalities are due to defects in neutrophils or monocytes/macrophages and are commonly present with recurrent pyogenic or fungal skin infections and/or abscesses.

Evaluation of phagocyte immune defects

Tier 1 (GPs, paediatricians)

- Full blood count with blood film can assess for neutropenia although multiple time points are needed to exclude conditions with fluctuating neutrophil counts.
- Blood films may show disorders associated with abnormal granules inside phagocytes.

Tier 2 (clinical immunologists)

- If neutrophil numbers are normal, nitroblue tetrazolium (NBT) and/or dihydrorhodamine (DHR) tests may be used to assess for function.
- Additional testing may be indicated.

Complement immunodeficiencies

Complement immunodeficiencies may be due to deficiencies in any on the components of the 3 complement pathways. Clinical indications include bacterial infections (especially Niesseria), autoimmunity and recurrent angioedema.

Evaluation of complement immunodeficiencies

Initial screening should include C3, C4, AH50 and CH50. In patients with recurrent angioedema C4 and C1 esterase levels should be tested. Additional testing including individual components may be indicated in consultation with a clinical immunologist.

When should patients be referred to a clinical immunologist?

Patients should be referred to a clinical immunologist when:

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

Additional testing includes specialised molecular and genetic tests, that may be needed to confirm a diagnosis.

General care of PID patients

Management of patients with PID requires a multidisciplinary team.

Issues include:

- Monitoring growth and ensuring adequate nutrition in children
- Optimising exercise, sleep and stress management.
- Ensuring good general hygiene (e.g. hand washing, dental hygiene)
- Providing information about patient support organisations:
  - Immune Deficiencies Foundation Australia (IDFA) – www.idfa.org.au
  - Immune Deficiencies Foundation New Zealand (IDFNZ) – www.idfnz.org.au
  - HAE (Hereditary Angioedema) Australasia – www.haeaustralasia.org.au

Specific therapies for PIDs

The following therapies need to be individualised according to the type of PID:

- Prophylactic antibiotics, antifungals, antivirals
- Immunoglobulin replacement therapy (IRT)
- Immune modulatory drugs
- Gamma interferon
- Haemotopoetic stem cell transplant (HSCT)
- Bone marrow transplantation (BMT)

- Gene therapy
- Others – granulocyte-colony stimulating factor (G-CSF), polyethylene glycol-conjugated adenosine deaminase (PEG-ADA)

Infections in PID patients

Infections should be investigated and treated aggressively. It is important to:

- Notify microbiology laboratory to consider atypical or opportunistic infections
- Treat patient with broad spectrum antibiotics until organism is identified
- Consider fungal, mycobacterial, viral and protozoan therapy, according to specific condition

Serology is not useful if patient is unable to make antibodies or is on immunoglobulin replacement therapy (IRT).

Curative therapies

Haemotopoetic stem cell transplant (HSCT)
Potential sources of stem cells include bone marrow, peripheral blood or umbilical cord blood

Gene therapy
This therapy is still experimental and is therefore not routinely available. It involves the use of viral organisms to replace the missing genes and correct the abnormality

PID and vaccinations

If a PID is suspected or confirmed, live attenuated vaccines should **not** be routinely administered as they may cause disease in immunodeficient patients. Issues regarding immunisation of these patients should be discussed with a clinical immunologist.

Potential live vaccines include:

- MMR
- Varicella
- BCG (given to at risk populations)
- Rotavirus
- Yellow fever

Meningococcal, pneumococcal and Haemophilus Influenza vaccines are recommended for patients with complement immunodeficiencies.

Current immunisation guidelines:
www.immunise.health.gov.au/internet/immunise/publishing.nsf/Content/Handbook10-home

Vaccination information for patients on immunoglobulin repacement therapy (IRT):
www.immunise.health.gov.au/internet/immunise/publishing.nsf/Content/Handbook10-home~handbook10part3~handbook10-3-3#3-3-4

3. Immunoglobulin replacement therapy in PIDs

Immunoglobulin replacement therapy (IRT)

Replacement of serum immunoglobulin with human gamma globulin fraction is the standard treatment for most patients with hypogammaglobulinaemia and some with specific antibody deficiencies. The aim is to replace immunoglobulin to maintain normal IgG levels. The dose used is individualised for each patient.

IRT may be given as intravenous immunoglobulin (IVIg) or subcutaneous immunoglobulin (SCIg) and pharmacokinetics differ according to administration route. There are multiple brands that may change from time to time and rates of administration vary for different products.

Immunoglobulin products

Immunoglobulin products are made from pooled plasma from many healthy human donors. Plasma donors and plasma pools are screened for hepatitis B, hepatitis C and HIV. Additional viral inactivation steps such as heat treatment, enzyme treatment, detergent treatment and nanofiltration are performed.

Despite differences in manufacturing, all IgG products contain 97-98% IgG specific antibodies against broad spectrum of bacterial and viral pathogens, with traces of IgM and IgA.

Long term benefits of immunoglobulin replacement therapy

Both intravenous immunoglobulin (IVIg) and subcutaneous immunoglobulin (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

Intravenous Immunoglobulin (IVIg) replacement therapy

Intravenous immunoglobulin (IVIg) replacement therapy:

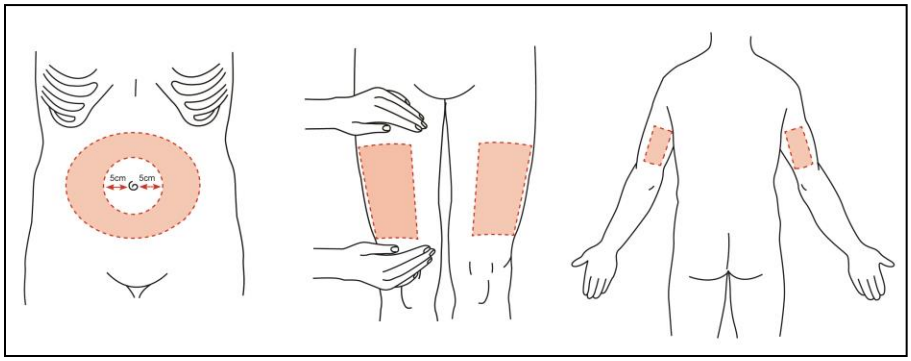
- Is usually administered 3-4 weekly in hospital
- Leads to a high peak of IgG after infusion
- Levels decrease rapidly over few days then slowly decrease over next few weeks.

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

Subcutaneous Immunoglobulin (SCIg) replacement therapy

Subcutaneous immunoglobulin (SCIg) requires frequent administration (1-3 times per week) by patients or carers at home. SCIg involves slow diffusion of IgG from subcutaneous tissue and the small and more frequent doses are associated with more consistent IgG levels. Whilst systemic reactions to SCIg are much less common than with IVIg, local injection site reactions (e.g. redness, itching, swelling, discomfort) are common but improve with time.

SCIg injections may be administered at multiple possible sites according to patient preference. Usually the lower abdomen will be used. However, the outer edge of the thigh or back of the upper arm can also be used for SCIg infusions. The shaded areas below can be used for insertion of the needle.



IVIg versus SCIg replacement therapy

The choice of route (IVIg or SCIg) is dependent on multiple factors. Treatment is tailored to patient preference, medical conditions and lifestyle. The preferred route may vary at different times during a patient's life.

Comparison of Pros and Cons of IVIg and SCIg therapy *Source: Adapted from APIIEG*

	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 • More consistent IgG levels with no wear 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 • 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 transient • Some patients may require battery or spring driven pumps (although some patients may use the push method which does not require a pump) • Requires treatment plan compliance

4. Severe combined immunodeficiency (SCID)

Severe combined immunodeficiency (SCID) is a rare inherited condition, with 6-8 new patients diagnosed in Australia and New Zealand each year.

SCID is:

- The most severe form of PID and has a high mortality, especially if diagnosis is delayed.
- Usually fatal within the first 2 years without treatment.
- Caused by genetic defects affecting the number or function of T cells.
- Characterised by absence or dysfunction of T lymphocytes affecting both cellular and antibody mediated immunity. Depending on the type of SCID, B cells and NK cells may be present or absent.
- A syndrome caused by mutations in one of at least 10 genes affecting T cell development.

The only cure routinely available for SCID is Haemotopoetic stem cell transplant (HSCT). Gene therapy trials are in progress.

Approximately half of all SCID cases are X linked due to mutations in the common gamma chain. Other forms of SCID include deficiency of the enzyme adenosine deaminase (ADA) and a variety of other genetic defects. Atypical SCID patients with partial function of genes typically associated with classical SCID may occur and may present at later ages.

Infants affected by SCID generally appear well at birth but are usually symptomatic within the first few months of life. Symptoms include:

- Recurrent severe infections, which may be life-threatening
- Chronic diarrhoea
- Poor growth and failure to thrive
- Recurrent or persistent oral thrush, viral respiratory and gastrointestinal infections
- Opportunistic infections, particularly PJP or disseminated BCG
- Extensive skin rashes such as erythroderma or eczema
- Absent lymphoid tissue

Early diagnosis of SCID is important

Early diagnosis of SCID is critical as early treatment is associated with improved outcomes. In some countries (not currently Australia or New Zealand) early diagnosis is facilitated by newborn screening programmes.

Tests for diagnosis of SCID include:

- Full blood count to assess for lymphopenia (normal result does not rule out SCID).
- Flow cytometry for enumeration of T cells, B cells and NK cells.
- Quantitative serum Ig tests are used to assess antibody mediated immunity.
- Chest X-ray may show absence of thymic shadow.
- HIV testing should be performed to exclude HIV.
- Additional testing may be indicated including naïve and memory T cells, in vitro T cell proliferation to mitogens and specialised cellular and molecular tests, which should only be requested after discussion with a clinical immunologist.

SCID is a medical emergency and patients need to be urgently referred to a clinical immunologist in a specialist centre for assessment and treatment.

Management of SCID

Management of patients with SCID includes:

- Aggressive search and treatment of infections
- Protective isolation, usually in hospital
- Immunoglobulin replacement therapy (IRT)
- Prophylaxis regime designed to prevent opportunistic bacterial, viral and fungal infection:
  - Cotrimoxazole for PJP
  - Fluconazole for fungal infections
  - Acyclovir for viral infections

Other issues:

- Live vaccines should not be given to the patient or their family
- Breastfeeding should be withheld until mother's Cytomegolovirus (CMV) status is known.
- Additional nutritional support may be required.
- All blood products must be irradiated, leukodepleted (GVHD) and CMV negative.
- For ADA deficiency enzyme replacement with pegylated-ADA is possible although this is not curative.

Curative therapy

- **Haematopoetic stem cell transplant (HSCT)** is currently the treatment of choice and a successful procedure is generally curative.
- **Gene therapy** is available in a few specialised centres as part of clinical trials.

Haematopoetic stem cell transplant (HSCT)

HSCT provides a new source of normal lymphocytes, especially T cells. Stem cell sources used include bone marrow, peripheral blood and umbilical cord blood.

The success of HSCT varies according to the:

- Type of SCID.
- Number of infections, especially around the time of the transplant.
- Type of treatment the stem cells has to receive to reduce the risk of being rejected, such as removal of the T cells (or 'T cell depletion').
- Need for conditioning, whereby the bone marrow of the patient with SCID is suppressed prior to transplantation, to improve the ability of the new marrow to grow properly (or 'take').
- Source of the stem cells - transplantation of bone marrow cells from a family member with identical 'tissue typing' of human leukocyte antigens (HLA) gives best results.

Some patients may not achieve B cell engraftment and may require lifelong IRT.

5. Antibody deficiency disorders

Common variable immunodeficiency (CVID)
- Most frequent clinically symptomatic PID.
- Mixed group of disorders with similar presentation.
- Relative prevalence between 1:10 000 and 1:50 000.
- Affects both males and females equally.
- Generally be sporadic with <10% of cases familial.
- Some genes have been identified but most cases remain unidentified.

CVID characteristics
- Clinical features variable and infections, autoimmunity, granulomatous disease and lymphadenopathy
- Have low immunoglobulins of at least 2 isotypes (IgG and either IgA or IgM).
- Associated with poor specific antibody responses:
    - Poor antibody response to vaccines and/or absent isohaemagluttinins.
- Disease onset may occur at any age:
    - Most patients present with symptoms between ages of 20-40 years.
    - ~20% diagnosed in childhood.
- Delayed diagnosis common: 4-9 years between symptom onset and diagnosis is usual.
- Usually normal B cell numbers but may be low.
- Variable T cell abnormalities in some.

CVID diagnosis
Diagnosis of CVID can be given to a patient if the patient is over 4 years of age and has **all** of:
- Consistent clinical features (infections, autoimmunity, granulomatous disease and lymphadenopathy)
- Marked decrease of IgG and marked decrease of IgA and/or IgM levels
- Poor response to vaccines (and/or absent isohaemaglutinins)
- Secondary causes of hypogammaglobulinaemia have been excluded

Clinical features of CVID
- Infections – most common (90%) with sinopulmonary, ear and gastrointestinal infections.
- Gastroenterological (up to 50%) – chronic diarrhoea, malabsorption.
- Lymphophadenopathy or splenomegaly (50%).
- Autoimmunity (30%).
- Granulomas (10-30%) – lungs, liver, other.
- Splenomegaly (20%).
- Malignancy – increased incidence of lymphoma and stomach cancers.

CVID treatment options
- Regular and sufficient substitution with immunoglobulins: 90% of CVID patients require either IVIg or SCIg.
- Dose of immunoglobulin to maintain normal serum IgG levels and keep patient infection free.
- Prophylactic antibiotics in patients with chronic suppurative lung disease or frequent infections.
- Targeted antibiotic treatment of (breakthrough) infection.
- Antibiotic treatment may need to be higher dose and longer duration than normal healthy individuals.
- Appropriate treatment of complications (e.g. bronchiectasis, sinusitis, enteropathy, autoimmunity).
- Surveillance for autoimmune disease including cytopaenias, granulomatous disease and adenopathy.
- Surveillance for malignancy, particularly including lymphoproliferative disease and gastric cancer.

Differential diagnosis of hypogammoglobulinaemia

Genetic Disorders	Drug Induced	Infectious Diseases	Malignancy	Systemic Disorders
Ataxia Telangiectasia	Antimalarial agents	HIV	Chronic Lymphocytic Leukemia	Immunodeficiency caused by hypercatabolism of immunoglobulin
Autosomal forms of SCID	Captopril	Congenital Rubella	Immunodeficiency with Thymoma	Immunodeficiency caused by excessive loss of immunoglobulins (nephrosis, severe burns, lymphangiectasia, severe diarrhea)
Hyper IgM Immunodeficiency	Carbamazepine	Congenital infection with CMV	Non Hodgkin's lymphoma	
Transcobalamin II deficiency and hypogammaglobulinemia	Glucocorticoids	Congenital infection with Toxoplasma gondii	B cell malignancy	
X-linked agammaglobulinemia	Fenclofenac	Epstein-Barr Virus		
X-linked lymphoproliferative disorder (EBV associated)	Gold salts			
X-linked SCID	Penicillamine			
Some metabolic disorders	Phenytoin			
Chromosomal Anomalies	Sulfasalazine			
Chromosome 18q-Syndrome				
Monosomy 22				
Trisomy 8				
Trisomy 21				

Ref: www.esid.org/Working-Parties/Clinical/Resources/Diagnostic-criteria-for-PID2#Q5

Selective IgA deficiency

- Is common with a frequency of 1:500 of the general population.
- Thought to result from failure of differentiation of IgA producing B cells.
- Defined as undetectable IgA (usually <0.07 g/L) with normal other immunoglobulins in a patient aged over 4 years.
- Majority of patients (85-90%) are asymptomatic and identified incidentally.
- Further investigation is warranted in the small proportion of patients who have:
  - Increased infections, especially recurrent sinopulmonary infections.
  - GI tract disease including infections (Giardia) and coeliac disease.
  - Autoimmune disease.
- Symptomatic IgA deficient patients may have other immune deficits (e.g. specific antibody deficiency).
- Patients may be at higher risk of severe reactions to blood products due to presence of antibodies against IgA, although reaction rates are low and patients can usually be safely transfused.
- Treatment includes preventative measures to reduce infection and treatment of complications.

X-linked and autosomal recessive agammaglobulinaemia

- Most common form is X-linked due to mutation in btk protein normally required for B cells to mature in the bone marrow.
- Deficiency results in absent or low numbers of B cells in blood and lymphoid tissue:
  - No tonsils or palpable lymph nodes.
  - Results in severe deficiency of all immunoglobulin isotypes (agammaglobulinaemia).
- Presents in males with recurrent or severe bacterial infections of ears, sinuses and lungs, particularly with encapsulated organisms.
- Presents at about 6 months of age as maternal IgG antibodies acquired transplacentally are lost.
- Diagnosis often delayed with average age of diagnosis of 3-5 years.
- Mainstay of treatment is immunoglobulin replacement therapy (IRT) and aggressive treatment of infections.

Hyper-IgM immunodeficiency syndrome

- Hyper IgM syndromes are a group of disorders which may be X-linked or autosomal recessive.
- Disorders cause defect of B cells in switching from making IgM to B cells making IgG, IgA and IgE.
- Most common cause (70%) due to deficiency of CD40 ligand (CD40L) which is X-linked.
- Typically have normal to high serum levels of IgM but low other immunoglobulin classes.
- Often associated with neutropenia at presentation.
- In some cases, this may also be associated with susceptibility to opportunistic infections such as pneumocystis and cryptosporidium and patients should therefore only drink cooled, boiled water.

Treatment options include:

- Prophylactic immunoglobulin replacement therapy.
- Antibiotic prophylaxis, particularly against pneumocystis.
- Haematopoetic stem cell transplant.

Specific antibody deficiency (SAD)

- This is an incompletely defined disorder affecting patients with normal serum IgG levels who fail to produce a normal IgG antibody response following antigen challenge, particularly to polysaccharide antigens (most commonly unconjugated pneumococcal vaccine i.e. Pneumovax®).
- These patients may require antibiotic prophylaxis.
- Immunoglobulin replacement therapy may be considered where there is evidence of recurrent or persistent infection or suppurative lung disease.

6. Complement disorders (including HAE)

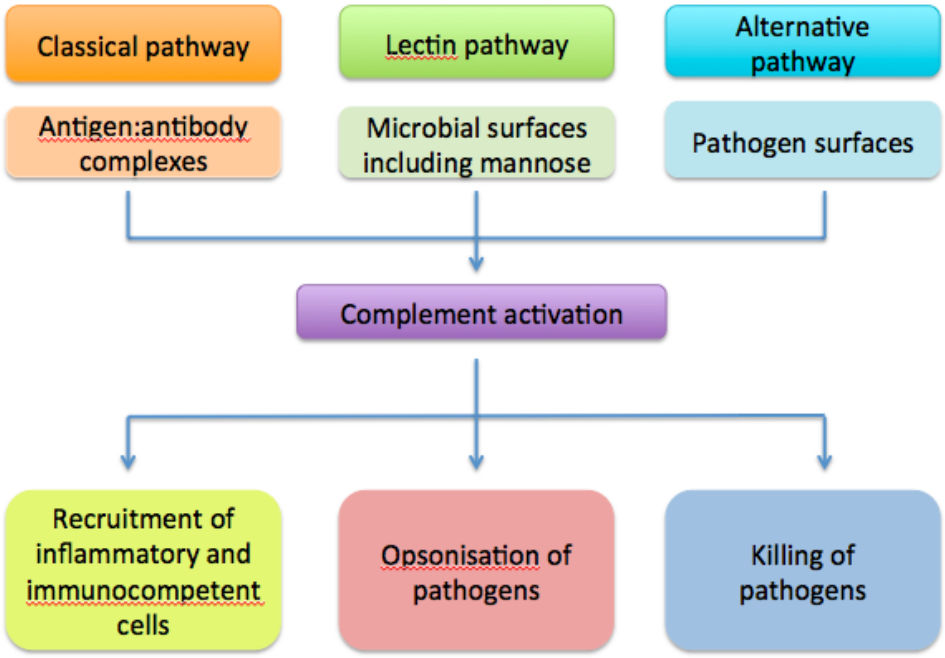
Overview

Complement deficiencies represent 1% of PIDs in Australia and New Zealand.

- They are most commonly caused by C1, C2 and C4 deficiencies and C1 inhibitor deficiency.
- Clinical indications for investigation include recurrent bacterial infections, autoimmunity and recurrent angioedema.
- Complement pathway consists of 3 main pathways: classical, alternative and mannose binding lectin pathway.
- All pathways converge on one common final or terminal pathway which generates membrane attack complex.

Infection associated/typical PID

There are a group of complement disorders that present with similar frequent infections as with other PIDs. However, HAE does not present with the classic PID frequency of infection.



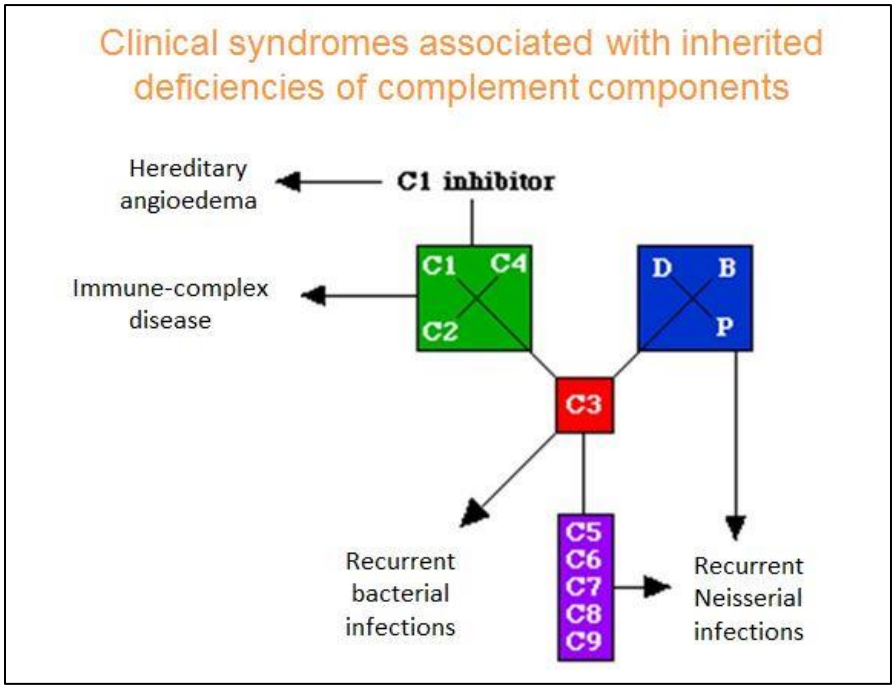
Deficiencies in classical pathway

- Classical pathway important in clearing of immune complexes and dead/dying cells.
- Primary deficiency of C1, C2 or C4 is linked to development of SLE.
- C2 deficiency most common complement deficiency in 1:20 000.
- Hereditary angioedema (HAE) due to C1 inhibitor deficiency, a control protein of classical pathway.

Deficiencies in alternative pathway

- Factor B and D deficiency are exceedingly rare.
- Properidin deficiency is X linked and associated with increased susceptibility to Niesserial infections.

- Deficiencies of alternative pathway control proteins may cause consumption of complement and increase risks of infection and autoimmunity.



Deficiencies in mannose lectin pathway

- MBL binds to carbohydrates on microbes or unwanted material and triggers the activation of the lectin pathway.
- No consensus on the clinical relevance of MBL deficiency.
- The majority of individuals with low MBL levels are asymptomatic.
- However, increased susceptibility to infection with MBL deficiency appears to occur when there are other concomitant factors impairing the immune system.

Deficiencies in common final pathway

- Major feature in this group is recurrent infections.
- Generates membrane attack complex.
- Infection with Neisseria meningitides particularly common. Rare serotypes such a W135 and Y may cause disease.

Investigation of complement deficiency

- Clinical indications for investigation include recurrent bacterial infections and autoimmunity.
- HAE patients do not present with recurrent infections (refer next slide).
- Investigation of complement deficiency in consultation with clinical immunologist/specialist:
  - Initial screen for complement is C3, C4 levels and CH50 and may include AH50.
  - CH50 assesses classical pathway and final common pathway.
  - AH50 assesses alternative and final common pathway.
  - Low CH50 alone suggests deficiency of C1, C2 or C4.
  - Low AH50 alone suggests deficiency of Factor B, Factor D or Properidin.
  - Low AH50 and CH50 suggests deficiency of C3 or final common pathway.

Hereditary Angioedema (HAE)

- Rare autosomal dominant genetic disorder due to deficiency of C1 inhibitor (C1 INH) protein.
- Patients suffer unpredictable and recurrent episodes of angioedema involving skin, gut and airway. Angioedema results from excessive production of bradykinin, a potent vasodilatory mediator.
- Histamine and other mast cell mediators are not directly involved, which explains the lack of response to antihistamines.
- An acquired form of C1 INH deficiency may be seen in older patients without a family history of angioedema and is associated with underlying disorders and autoantibodies in most cases. Acquired C1-INH deficiency is not discussed further in this module.

Types of HAE

Type 1

- Type 1 HAE most common (85%) due to low levels of the C1 inhibitor (C1-INH).
- Upon testing, **protein (antigenic) and functional levels are both low.**

Type 2

- Type 2 HAE (remaining 15%) due to normal levels but abnormal function of C1-INH.
- Upon testing **normal or elevated protein** levels **but functional levels are low**.

Type 3

- Distinguished from other types of HAE due to normal levels and function of C1 inhibitor.
- Some cases associated with mutations of Factor XII

In both Type 1 and Type 2 cases, C4 levels are usually low due to consumption of complement.

Indications for screening

Indications for screening of C1 inhibitor disorders include the presence of one or more of the following:

- Recurrent angioedema without urticaria.
- Unexplained recurrent episodes of self-limited, colicky, abdominal pain.
- A family history of angioedema.
- Unexplained laryngeal oedema (even a single episode).
- Low C4 levels, especially in the setting of angioedema.

Diagnosis

- C1 Inhibitor protein (antigenic) and functional levels should be assessed.
- Abnormal results should be repeated to confirm.
- Low C4 level would be supportive.
- All diagnosed patients should be referred to a clinical immunologist with experience in managing HAE patients.
- Genetic testing is not required to confirm the diagnosis in adults.
- C1-INH levels are difficult to interpret in children younger than one year.

Testing family members

- Once a diagnosis of HAE has been made, testing of the patient's children, parents, and siblings (if parents carry the mutation) should be encouraged.
- Although autosomal dominant approximately 25% of cases result from *de novo* mutations, so may not always have affected family members.
- Affected individuals may be asymptomatic, especially early in childhood.

HAE attacks

- Attack frequency is variable.
- Untreated patients may have attacks up to every 1-2 weeks.
- Swelling usually builds up over 24 hours, and may last 3 to 4 days or longer.
- Manifestations:
  - Abdominal pain – nausea, vomiting, dehydration, diarrhoea or constipation.
  - Swelling – face, limbs, genitals.
  - Oropharangeal swelling – less frequent, **but life threatening.**
  - No itching or urticaria.
- Does **not** respond to adrenaline, antihistamine or corticosteroids.

Prodromal symptoms

Occurs in up to 50% of HAE patients:

- Fatigue.
- Flu-like symptoms.
- Indigestion.
- Tingling or "tightness" sensation at site where swelling then occurs.
- About 25% of patients will have a flat, non-itching, blotchy, red rash before and during the attack.

Triggers of HAE include:

- Anxiety and stress
- Minor trauma or injury
- Some surgical and dental procedures
- Oestrogens
- ACE inhibitors
- Infections
- Sometimes no trigger factor can be identified

Treatment options for HAE

Drug	Action	Route
Acute treatment		
Berinert Cinryze*	C1-inhibitor concentrate	IV
Firazyr (icatibant)**	B2 bradykinin receptor antagonist	SC
Prophylaxis		
Danazol	Anabolic steroid	Oral
Cinryze*	C1-inhibitor concentrate	IV
Tranexamic Acid	Antifibrinolytic	Oral

*Not registered in NZ
** Not licensed for children below 12 years

Ongoing care

- Education about HAE is very important, particularly in newly diagnosed patients.
- Trigger avoidance – triggers vary, but generally avoidance of trauma particularly to the face and upper respiratory tract and recognition and prompt treatment of oral and dental infections.
- Planning for acute treatment – all patients should be equipped with:
  - Medical information jewellery.

  - An ASCIA Action Plan for HAE www.allergy.org.au/health-professionals/papers/hereditary-angioedema
- Vaccinations – patients should be vaccinated against hepatitis B in case they require blood-derived products in the future.

Indications for prophylaxis

Short term prophylaxis should always be administered if intubation, oral surgery or general surgery is planned, as oral surgery is one of the most predictable triggers for HAE attacks.

Long term prophylaxis is given to decrease the overall number of attacks.

Further information

- ASCIA HAE position statement and action plan
  www.allergy.org.au/health-professionals/papers/hereditary-angioedema

- HAE Australasia (patient support organistion)
  www.haeaustralasia.org.au/

7. Other PID syndromes

DiGeorge Syndrome

DiGeorge syndrome:

- Is due to defective embryonic development of the 3rd and 4th pharyngeal pouches, with the classic features of conotruncal abnormalities, thymic hypoplasia and hypoparathyroidism.
- Is often associated with 22q11.2 deletion (which affects 1:4000 live births) but absence of 22q22.1 deletion does not exclude DiGeorge syndrome.
- May present with a wide phenotypic spectrum.

The spectrum of immune defect in patients with DiGeorge syndrome varies widely and is not related to other clinical features:

- Most commonly mild to moderate decrease in T cells, and patients are not clinically immunodeficient.
- Antibody deficiencies can sometimes be seen, and may necessitate antibiotic prophylaxis or immunoglobulin replacement therapy.
- Autoimmunity can also be seen.
- Complete DiGeorge syndrome affects <1% of patients, who have complete absence of thymus. These patients have no T cell function and present with SCID phenotype, requiring HSCT or thymic transplant.
- Hypoplasia of parathyroid glands is associated with hypocalcaemia.
- Contruncal cardiac defects may occur including Tetralogy of Fallot, Ventricular septal defect and interrupted aortic arch.
- Patients almost always show abnormal facial features but may be subtle.
- 50% of patients will have ‘non typical’ malformations including opthalimic, renal, endocrine and musculoskeletal anomalies.

Diagnosis of DiGeorge syndrome involves karotyping and fluorescent in-situ hybridization (FISH) to look for 22q11.2 deletion.

Treatment of DiGeorge syndrome is dependent upon specific clinical features:

- Hypocalcaemia may require calcium supplements.
- Surgical correction of congenital heart defect usually needed.
- Immune reconstitution is not recommended for milder immunological defects.
- IVIg and antibiotic prophylaxis may be indicated dependent on immune function.

Wiskott-Aldrich Syndrome (WAS)

Wiskott-Aldrich (WAS) is an X-linked recessive disease due to mutation in the Wiskott-Aldrich Syndrome Protein (WASP) gene, which is important in cytoskeletal organisation of cells. Mutations can result in a wide spectrum of disease:

- Classic WAS was originally described as a triad of immunodeficiency, thrombocytopenia with small platelets and eczema.
- Severe disease results in a broad immunodeficiency (affecting both T and B cells, which may worsen with time), autoimmunity and malignancy.
- These patients may present with early opportunistic infection (e.g. PJP).
- Milder forms include isolated thrombocytopenia (XLT) or neutropenia (XLN).

Investigations typically show thrombocytopenia with small platelets, low serum IgM and poor pneumococcal antibody responses.

Treatment may include:

- Immunoglobulin replacement therapy and antibiotic prophylaxis may be indicated dependent on immune function.
- Bleeding problems may require platelet transfusions.
- Patients with severe disease require HSCT.

Transient hypogammaglobulinaemia of infancy (THI)

Development of immunoglobulins through infancy and early childhood follows a predictable pattern, with IgM reaching adult normal ranges in the first year of life, IgG by middle childhood, and IgA by adolescence. However, in some infants and young children the production of immunoglobulins is delayed. These children may present with recurrent mild infections particularly in the first 1-2 years of life. The diagnosis of transient hypogammaglobulinaemia of infancy (THI) can only be securely made once immunoglobulin levels normalise, and these children need exclusion of more significant immunodeficiency.

Management for most children with THI involves periodic monitoring (e.g. 6 monthly) of immunoglobulin levels. Prophylactic antibiotics may be needed, and rarely a defined period of immunoglobulin replacement may be considered, with a plan to reevaluate with time.

Chronic Granulomatous Disease (CGD)

Chronic Granulomatous Disease (CGD) is a rare disorder where neutrophils are able to ingest organisms but cannot kill them, resulting in granuloma formation. CGD is due to mutations in nicotinamide adenine dinucleotide phosphate **(**NADPH**)** oxidase complex which normally generates microbicidal respiratory bursts. CGD can present at any age, but most commonly during early childhood.

Patients with CGD are susceptible to recurrent and persistent infections with organisms which are resistant to non-oxidative killing. An X-linked mutation in gp91 component accounts for 65% of cases. Other causes are autosomal recessive, therefore girls can also be affected.

Patients with CGD usually present with:

- Infections - frequent first manifestations including pneumonia, cellulitis and skin abscesses, liver abscesses and osteomyelitis (usually caused by Staphylococcus aureus).
- Fungal infections with Aspergillus may be seen as well as infections with unusual organisms such as mycobacteria and burkholderia.
- Development of granulomas in the skin, gastrointestinal (GI) tract, and genitourinary (GU) tract.
- Granulomatous inflammation of bowel which may cause granulomatous colitis, Crohns-like inflammatory bowel disease (IBD) or bowel obstruction.

Investigations include nitroblue tetrazolium (NBT) and/or Dihydrorhodamine (DHR) tests for neutrophil oxidase activity. Specialised protein or genetic tests are useful to establish subtype and genetic inheritance pattern. Treatment options for CGD include:

- Antibacterial and antifungal prophylaxis
- Gamma Interferon
- Haematopoetic stem cell transplant (HSCT)

Hemophagocytic lymphohistiocytosis (HLH)

Hemophagocytic lymphohistiocytosis (HLH) is a life threatening syndrome of excessive immune activation.

HLH:

- May occur as a primary (familial/hereditary) or secondary (non-familial/hereditary) disorder.
- Is characterised by hereditary or acquired impaired cytotoxic function of NK cells and cytotoxic T-cells.
- Impaired killing of target cells results in excess pro-inflammatory cytokine release (IFN-γ, TNF-α, GM-CSF) from activated T cells and macrophages (cytokine storm).
- Presentation of primary HLH is often triggered by infections (especially EBV or CMV) or other metabolic/immune stress.
- Common genetic causes of primary HLH - Familial HLH (FHL) types 2-5 (perforin, MUNC13-4, syntaxin 11, syntaxin binding protein), X-linked lymphoproliferative syndrome (SAP (XLP1) or XIAP (XLP2)), Chediak-Higashi syndrome, Griscelli syndrome type 2, Hermansky-Pudlak syndrome type 2).
- Primary HLH usually develops during the first 1-3 years of life but late-onset cases can present at any age.
- Secondary HLH develops in association with infection, autoimmune / rheumatological conditions and malignancy.
- Molecular mechanisms involved in secondary HLH are unknown but may be predisposed to by polymorphisms in or carrier status of genes associated with primary HLH.
- Early diagnosis is important.
- Typical presentation with persistent fever, hepatic and/or renal dysfunction, pancytopenia, splenomegaly, hemorrhagic diathesis, neurological symptoms.

Diagnostic criteria for HLH

A. Molecular diagnosis consistent with HLH: pathologic mutations of *PRF1, UNC13D, Munc18-2, Rab27a, STX11, SH2D1a, or BIRC4*

or

B. Five of the 8 criteria below are fulfilled:

1. Fever ≥ 38.5°C
2. Splenomegaly
3. Cytopenias (affecting at least 2 of 3 lineages in the peripheral blood):
   Hemoglobin <9 g/dL (in infants <4 weeks: hemoglobin <10 g/dL)
   Platelets <100 x 10^3/ml Neutrophils <1 103/ml
4. Hypertriglyceridemia (fasting, >265 mg/dL) and/or hypofibrinogenemia (<150 mg/dL)
5. Hemophagocytosis in bone marrow, spleen, lymph nodes or liver
6. Low or absent NK-cell activity
7. Ferritin >500 ng/mL
8. Elevated sCD25 (α-chain of sIL-2 receptor)

HLH treatment

- Early aggressive supportive therapy and treatment of infection essential.
- Immunosuppressive therapy to control the hypercytokinemia with steroids, cyclosporin, intravenous immunoglobulin +/- etoposide or anti-thymocyte globulin (especially if primary HLH) - commonly used protocols are HLH-94 and HLH-2004.
- Allogeneic hematopoietic stem-cell transplantation (HSCT) recommended for primary HLH or refractory secondary disease.
- High morbidity and mortality:
  - death during acute phase in 10%-15%,
  - <10% 3 year survival if untreated,
  - 21-26% 5 year survival with treatment,
  - 43%-92% 3 year survival post HSCT.

8. References and further information

Patient Organisations

HAE (Hereditary Angioedema) Australasia Ltd	www.haeaustralasia.org.au
Immune Deficiencies Foundation Australia (IDFA)	www.idfa.org.au
Immune Deficiencies Foundation New Zealand (IDFNZ)	www.idfnz.org.nz

Publications

Gray PE, Namasivayam M, Ziegler JB. Recurrent infection in children: when and how to investigate for primary immunodeficiency? J Paediatr Child Health. 2012 Mar;48(3):202-9.

Waleed Al-Herz et al. Primary immunodeficiency diseases: an update on the classification from the International Union of Immunological Societies Expert Committee for Primary Immunodeficiency. Frontiers in immunology. 2014 April.