IPOPI
INTERNATIONAL
PATIENT ORGANISATION
FOR PRIMARY IMMUNODEFICIENCIES

PRIMARY **IMMUNODEFICIENCIES**

A GUIDE FOR **GENERAL PRACTITIONERS**

ABBREVIATIONS

GCSF	Granulocyte colony stimulating factor
GP	General practitioner
HIV	Human immunodeficiency
HSCT	Haematopoietic stem cell transplantation
IG	Immunoglobulin
IPOPI	International Patient Organisation for Primary Immunodeficiencies
IV	Intravenous
PID	Primary immunodeficiency
SC	Subcutaneous
SCID	Severe combined immunodeficiency

Primary immunodeficiencies: a guide for general practitioners (1st edition).

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INTRODUCTION

This booklet explains how general practitioners (GPs) can play a crucial role in identifying patients with primary immunodeficiencies (PIDs) and discusses key aspects of patient care.

PIDs are an important group of conditions that most GPs will encounter during their career. To date, over 280 different PIDs have been identified. While some PIDs are very rare (e.g. severe combined immunodeficiency or SCID), others are more common (e.g. selective immunoglobulin A deficiency). Together, diagnosed PIDs may affect around one person in 1200.

PIDs have widely differing presentations: some are relatively mild, while others are life-threatening. Some develop over time and worsen as late manifestations or complications take effect. Generally, compared with healthy people, people with PIDs are more susceptible to infections, allergies, autoimmunity, malignancies and complications due to infections and inflammation. PIDs can be difficult to recognise because many of the symptoms are non-specific (such as recurrent respiratory tract infection and fatigue) and because the clinical presentation of particular PIDs can vary between patients and even within patients over time.

The most severe forms of PIDs are diagnosed in childhood. However, others are frequently recognised during adulthood because of their late onset and because they have been misdiagnosed or undiagnosed. Many patients with PIDs go undiagnosed for several years, during which time they are often treated several times with antimicrobials. Often this is because doctors focus on treating specific symptoms rather than identifying the underlying cause, as it can be difficult to see the pattern in their progress. Untreated, PIDs are chronic, serious diseases that can be fatal.

Crucially, once recognised, PIDs are treatable and in some cases curable. Early recognition of PIDs, based on the clinical signs and symptoms, is therefore essential, because the right treatment can often prevent the development of further complications. GPs have a crucial role in identifying patients with suspected PIDs and in referring them for specialist diagnosis, assessment and care. It is vital therefore that GPs are alert to the warning signs and recognise the pattern. It is important that GPs are able to refer patients with suspected PIDs to specialists and that they understand the appropriate initial steps in assessment and referral in these patients.

This booklet has been designed to help GPs identify patients with PIDs and to provide key information about the specialist care these patients need.

Early identification of PIDs is vital — the key is to consider the possibility.

IDENTIFYING PIDs

SIGNS AND SYMPTOMS OF PIDS

The typical symptoms of PIDs are frequent, severe and/or unusual infections, and failure to thrive (in children). Some patients display immunological symptoms such as autoimmunity (e.g. autoimmune haemolytic anaemia or idiopathic thrombocytopenia), autoinflammation, or certain malignancies in both children and adults. Long standing diarrhoea, severe eczema, weight loss or bronchiectasis may also be warning signs of a PID. GPs should also be aware of the potential diagnosis of a PID in patients with infections, inflammation or autoimmunity who do not respond to normal treatments. Patients with infections or symptoms localised to a specific organ should be examined for an anatomical cause before a PID is considered.

Warning signs that should prompt doctors consider PIDs are shown in the table on page 5. PIDs can present in diverse ways, and up to one third of patients with PIDs may not show the above symptoms. Therefore, a PID diagnosis should not be ruled out based on the absence of these signs. Specific attention should be paid to the family medical history. For children, additional information should be collected, including records of weight and height since birth, as failure to thrive is an important sign of serious disease.

Patients suspected of having a PID should be referred to a specialist, typically a clinical immunologist or a specialist in infectious disease medicine (for adults) or a paediatrician (for children). If a severe PID is suspected in a child, referral should not be delayed pending blood test results. In such cases the child should be referred immediately to the appropriate paediatrician.

Family history is a vital clue to the diagnosis of a PID.

WARNING SIGNS OF PIDS	
CHILDREN	**ADULTS**
Known PID in the family	Known PID in the family
Failure to thrive	
Infections with an unusual course	
Chronic candidiasis after the age of 3 months or cutaneous candidiasis	Persistent oral candidiasis or fungal skin-infections
Refractory pneumonia	One or more episode of pneumonia per year for more multiple years
Invasive infections such as osteomyelitis, meningitis, sepsis or organ abscesses	Bronchiectasis, abscesses, recurrent sinusitis
Six or more sequences of middle-ear infections per year or otitis associated with mastoiditis or perforation of the tympanic membrane	Two or more middle ear infections within a year
Two or more sequences of sinusitis per year	Two or more episodes of sinusitis within a year (in the absence of allergy)
Chronic diarrhoea, weight loss and abdominal pain	Unusual infections or infections by unusual causes
Recurrent and/or severe virus infection	Recurrent and/or severe virus infection
Recurrent need for IV antibiotics to treat infections	Recurrent need for IV antibiotics to treat infections
Recurrent abscesses in the skin or in organs	Recurrent abscesses in the skin or in organs
Invasive infection with normally inoffensive mycobacteria	Invasive infection with normally inoffensive mycobacteria

LABORATORY TESTS

PIDs cannot be excluded on the basis of normal blood test results alone. Rather, the diagnosis has to be made taking into consideration the complete clinical picture with due regard to other cases of PIDs in the family.

The specific tests that GPs can perform before referring a patient with a suspected PID to a specialist vary between countries, depending on the organisation of the healthcare service and laboratory facilities. Many tests are simple and inexpensive. For example, the following tests may be considered, during a time when there is no evidence of infection, before referral:

- Blood cells: leukocytes (with differential count of subtypes, especially the lymphocytes to detect the most severe forms of PID in infants, e.g. SCID), thrombocytes, haemoglobin
- Serum immunoglobulins: main classes, i.e. G (eventually subclasses 1–4), A, M (immunoglobulin E can be done as a second step marker)
- Human immunodeficiency virus (HIV) test
- Blood chemistry: e.g. creatinine, sodium, potassium, albumin.

Further, more expensive tests include an immunoarray, genetic testing for abnormalities known to cause PIDs, and testing for specific protein defects. These tests should be performed by a PID specialist according to clinical need.

TREATMENT FOR PIDs

The treatment for PIDs depends on the part of the immune system affected. Patients with PIDs should be managed in specialist PID centres. They may need specialist care from a variety of disciplines, including radiology, respiratory medicine, haematology, internal medicine, gastroenterology, hepatology, dermatology and clinical genetics.

IMMUNOGLOBULIN REPLACEMENT THERAPY

Most PIDs cause a deficiency in antibodies, i.e. immunoglobulins (IG). Among these, immunoglobulin G has the highest concentration in blood and body fluids and is critical for protection against infection. IG replacement is the essential cornerstone of therapy for most patients with PIDs. IG replacement therapy aims both to prevent bacterial infections and to avoid organ damage that leads to chronic disease and poor quality of life. It is life-saving and usually needs to be continued for life.

A variety of IG products are marketed worldwide. These contain varying concentrations of IG purified safely from donated human plasma, together with certain excipients. Important differences exist between IG brands — they are not interchangeable. Patients must remain on the correct prescribed product and treatment should not be interrupted.

IG replacement therapy can be given by intravenous (IV) or subcutaneous (SC) infusion. Treatment is started under supervision by experienced staff at a hospital or clinic. Once the patient is stabilised on treatment, SC infusions can often be given at home by patients themselves, or by parents or carers, once they have been trained appropriately. 'Rapid push' SC administration is preferred by some patients, as it can offer even greater convenience and flexibility than infusions using a pump.

Some patients are able to receive IG replacement therapy without side effects. A few patients may need medicines (e.g. non-steroidal anti-inflammatory drugs and antihistamines) to treat mild side effects. A very few (1%) may have more troublesome side effects, but serious reactions are very rare indeed.

With the variety of products and infusion options available almost all patients can be treated successfully with IG replacement. However, no single product or method of administration is suitable for all PID patients and hence therapy must be chosen on an individualised basis according to the patients' clinical situation and preferences. Different IG products are not interchangeable or mixable.

Immunoglobulin replacement therapy, individualised for each patient, is the cornerstone of care for most PIDs.

OTHER TREATMENTS AND ASPECTS OF CARE

Haematopoietic stem cell transplantation (HSCT): HSCT from blood or bone marrow is the only cure for severe, otherwise fatal, cellular lymphocyte disorders that present in infancy or early childhood. For example, all paediatric patients with SCID should have access to this life-saving therapy, regardless of where they live.

Antimicrobials: patients with PIDs may require antimicrobials for infection prophylaxis, as well as for the treatment of acute infections.

Granulocyte colony stimulating factor (GCSF): This may be used to treat neutropenia in selected patients with some PIDs.

Gamma-interferon: This is sometimes used to treat chronic granulomatous disease.

Gene therapy: This has been performed for certain PIDs in some situations, but it remains an experimental therapy and research tool.

Autoimmune manifestations: Patients with PIDs often require treatment for autoimmune symptoms affecting various parts of the body, e.g. the blood, lymph system, lungs, gastrointestinal tract, liver, kidney, musculoskeletal system, endocrine system and skin. Immunosuppressive drugs can be necessary in selected situations.

Vaccination: Most patients with PIDs who are receiving IG replacement therapy do not need vaccines. Nevertheless, vaccinations should be considered: as part of routine childhood immunisation programmes; where a bacterial or influenza infection might make the underlying condition worse; and when international travel is planned. Recommendations vary between patients and specialist advice should always be sought before receiving any vaccinations. Patients with severe PIDs (especially T cell disorders) should not be given live-attenuated vaccines, as these can cause infections. Inactivated vaccines can often be given without harm even to patients with PIDs, but they may not have any effect. Generally, the families of people with PIDs should normally be vaccinated in order to protect patients catching infections from them. **However, important considerations necessitate specialist advice.** Family members should be careful with regard to live-attenuated vaccines, as there can be a risk of infecting the PID patient. Please refer to the International Patient Organisation for Primary Immunodeficiencies (IPOPI) booklet entitled, 'Vaccines and primary immunodeficiencies' (2013) for further information (**www.ipopi.org**).

Lifestyle measures: Patients should be advised to maintain good personal hygiene to help prevent infections. Exercise and recreational activities should be encouraged, subject to certain restrictions for some conditions and patients. As always, good nutrition and sleep are important for overall health.

Holistic aspects: Patients with PIDs, and parents or carers, may need support to deal with the psychological impact of the disease (e.g. stress, anxiety and depression), as well as fatigue and disability. PIDs can be particularly challenging during adolescence and hence specific support and transitional care, where available, is important. Patients can obtain advice and support from PID patient organisations that exist in many countries (**www.ipopi.org**).

FURTHER READING

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FURTHER INFORMATION AND SUPPORT

This booklet has been produced by the International Patient Organisation for Primary Immunodeficiencies (IPOPI). Other booklets are available in this series. For further information and details of PID patient organisations in 56 countries worldwide, please visit **www.ipopi.org**.

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Provided by

PID UK
Supporting families affected by primary immunodeficiencies

IPOPI National Member Organisation for the UK

Our website www.piduk.org provides useful information on a range of conditions and topics and explains the work we do to ensure the voice of PID patients is heard.

Please contact us at hello@piduk.org or **0800 987 8986** where you can leave a message.

Support us by becoming a member at www.piduk.org/register and get monthly newsletters.

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