

HOW TO TREAT

Detailed treatment updates for common conditions

recurrent infections in childhood

Children who have repeated infections are a common scenario in general practice. This article aims to assist GPs in identifying the small number of children who may have a serious underlying host immune system defect. The article provides a summary of the differential diagnosis for recurrent infections in children and was written by Rohan Ameratunga, an adult and paediatric immunologist at Auckland Hospital and Quay Park Specialist Centre, Auckland. Rohan was formerly a paediatric immunologist at Starship Hospital. He has completed a paediatric allergy and immunology fellowship at Johns Hopkins University Medical School and his PhD was on the molecular pathology of hyper-IgM syndrome.

Small proportion have immune defect

Recurrent infections in children are a frequent problem in clinical practice. On one hand, frequent infections are very common, while on the other there are a small number of children who have a serious underlying host immune system defect. These children require urgent diagnosis and referral for treatment to prevent imminent death or to prevent long term disability.

Worldwide, there are many potential contributors to recurrent infections. Malnutrition, chronic diarrhoea, malaria and vaccine preventable diseases are probably the most important causes, and they carry significant morbidity and mortality. The vast majority of child deaths are due to infections, many of them vaccine preventable and others amenable to treatment.

Patients with protein and calorie malnutrition are severely immune suppressed and have impaired T cell function, which may predispose to tuberculosis and other infectious disease. Therefore, in developing countries, children who do not have congenital immune dysfunction may be susceptible to recurrent infections.

In developed countries, to a large extent, the number of "normal" infections depends upon the socioeconomic status of the family. There is, however, no generally agreed number of infections beyond which a host defect may become a significant possibility. The American Academy of Allergy, Asthma and Immunology (AAAAI) does provide a guideline to work to, which is discussed later.

The number of expected infections depends, of course,



on factors such as overcrowding, number of siblings, number of siblings attending daycare or school, birth order and access to medical care. All of these are relevant in predisposing to recurrent infections in otherwise healthy children.

Primary immune deficiency disorders (PIDs) are congenital defects of the immune system.

The only study of the prevalence of PIDs in New Zealand (Kirkpatrick and Riminton, 2007) is consistent in its findings with overseas studies. It suggests a prevalence of one in 25,000 general population for common variable immune deficiency, the most common symptomatic PID.

Milder immune deficiency disorders are much more common. Overseas serological surveys suggest IgA deficiency may be as common as one in 700 blood donors. Most of these IgA-deficient patients are asymptomatic although they are at risk of blood transfusion reactions as a result of reacting to IgA in blood products.

In spite of increased awareness, some symptomatic patients are not diagnosed as having a PID for several years. Data from the Immune Deficiency Foundation survey in the US show about 5 per cent of patients with a PID have had 21 or more hospitalisations for infections prior to diagnosis. Recent New Zealand data suggest a major improvement in the diagnosis, such that most patients are tested and diagnosed within a year of symptom onset.

The diagnosis of a PID can help the patient to deal with the sequelae of chronic disease, which can affect work or school. Because many of these disorders are inherited single gene defects, there are profound implications for family members.

In the survey undertaken by the Immune Deficiency Foundation, there was major improvement in health status after PID was diagnosed and treated.

Do you need to read this article? Try this quiz

- 1 Allergic rhinitis is unlikely to cause chronic sinus disease in children. **True/False**
- 2 Bronchiectasis in children is not associated with exposure to passive smoking. **True/False**
- 3 Severe antibody deficiency cannot be diagnosed until one year of age. **True/False**
- 4 IgA levels reach adult levels by two years of age. **True/False**
- 5 Malignancy is a possible complication of primary immune deficiency. **True/False**

Answers on page 35

Factors increasing rates of infection

Several causes need to be simultaneously considered in children with an increased number of infections (Panel 1).

Allergy, especially untreated upper respiratory tract (URT) allergy, is an important cause of recurrent infections. There are many potential reasons why allergies predispose to recurrent infections, including the expression of inflammatory receptors such as intercellular adhesion molecule 1 (ICAM-1), the receptor for respiratory viruses.

Furthermore, the increased mucus production and impaired drainage of mucus may also predispose to repeated bacterial infections (Case study 1).

Exposure to tobacco smoke has also been shown to predispose to infections. Induced ciliary dysfunction is one possible explanation for this. Studies have shown a predis-

position to Mycoplasma and rhinovirus infections with parental smoking. Again, inflammation of the airways may be the explanation for the predisposition.

Prematurity results in an immune deficient state. Most IgG is transferred in the third trimester. Therefore, a preterm newborn has a reduced level of IgG through passive transfer, and these children are hypogammaglobulinaemic until they start producing antibody. During this time, they are predisposed to infections, particularly respiratory syncytial virus in the first year. Predispositions in preterm infants to other infections are less well characterised.

Anatomical defects predispose to recurrent infections, which may be generalised or localised.

Patients with a major skin defect, such as a burn or ecze-

ma, are predisposed to infections. This may involve multiple mechanisms, including loss of barrier, nutritional compromise, use of antibiotics, nosocomial infections and immobility. Frequently, infections occur in multiple anatomical areas and may occur with multiple species of bacteria.

Organ-specific defects, such as cystic fibrosis, can lead to lung infections. Cystic fibrosis is usually identified in New Zealand by neonatal screening. However, it can present later, and children may appear relatively well.

Nasal polyps in children may suggest cystic fibrosis and require further investigation. Sometimes, these children present with a chronic cough, sputum production and bronchiectasis. If cystic fibrosis is suspected, sweat testing and genetic testing need to be considered and the child referred for specialist evaluation.

Other localised anatomical factors predisposing to recurrent infections include enlarged adenoids resulting in frequent repeated URT infections and chronic otitis media with effusion. If suspected, the patient should be referred for ENT evaluation and tympanostomy tubes, if indicated.

Localised areas of infection, such as chronic tonsillitis, can lead to recurrent sore throats. If suspected, the patient should have a specialist ENT review, and tonsillectomy if indicated. Chronic tonsillitis is a cause of ill health, recurrent URT symptoms and, possibly, abdominal symptoms.

Localised anatomical defects, such as obstruction to a bronchus, may result in infections in the same organ system as well as the same location. These infections can be slow to respond to treatment due to impaired drainage, and there may be localised complications, such as bronchiectasis. In this situation, investigations and treatment are directed at correcting the anatomical defect. Other localised problems include gastro-oesophageal reflux, which may predispose to recurrent respiratory infections.

Most IgG is transferred in the third trimester. Therefore, a preterm newborn has a reduced level of IgG

Advanced malignancy can also severely compromise the immune system. Malignancy predisposes to infections via multiple mechanisms, including anatomical obstruction, malnutrition and immune suppression. Immune system compromise can result from bone marrow infiltration or, secondarily, from chemotherapeutics. Malnutrition is another significant factor in predisposing to secondary immune deficiency. Infections with cancer may be worse with haematological rather than solid organ malignancies.

The above disorders can usually be identified and treatment is generally directed at the underlying cause.

Recurrent infections due to allergy (Case study 1)

Presentation and history

Five-year-old James has had recurrent mucopurulent nasal discharge needing up to 12 courses of antibiotics a year. His symptoms are worse in winter and he has frequent sneezing and rhinorrhoea, consistent with allergy rhinitis.

Investigations

Other family members are atopic and James has strongly positive tests to dust mites and cats.

Management

The GP prescribes a combination of budesonide and loratadine and advises the parents to undertake house dust mite prevention measures. Sinus lavage with saline is also recommended.

Outcome

James sees an improvement in his hay-fever symptoms. He also begins allergen-specific immunotherapy. With better control of his allergic rhinitis, there is a significant reduction in infection frequency.

Comment

A study of children presenting at an ENT clinic in the UK showed the vast majority were atopic compared with the general population. Therefore, atopy predisposes to recurrent ear infections and chronic otitis media with effusion. It is important to note treatment of otitis media with effusion may require tympanostomy tubes. The allergic rhinitis should be treated separately.

Primary, secondary immune deficiencies

If anatomical, defects, malignancy and the other predisposing factors already discussed have been excluded in a child with recurrent infections, primary and secondary immune deficiency disorders must be considered.

Secondary immune deficiency disorders

Secondary immune deficiency disorders tend to affect multiple components of the immune system. Usually, there is no specific anatomical pattern to the infections and the treatment is directed towards the underlying disorder.

Secondary immune defects include patients receiving high doses of steroids or cytotoxic drugs, or who have HIV or poorly controlled diabetes. Those with diabetes are predisposed to infection not only by high glucose levels but also if there are ischaemic complications due to vasculopathy, particularly in adults. Sometimes, drugs or viruses can induce an immune defect that is very similar to PIDs (Smith et al, 2004; Ameratunga et al, 2009).

A brief overview of the normal immune system

While discussing immune deficiency disorders, it is useful to briefly review normal immune function. The primary functions of the immune system are to:

- recognise self from non self
- react to non self (failure results in immune deficiency)
- avoid reacting to self (to do so causes autoimmunity)
- avoid reacting to harmless antigens (to do so leads to allergy)
- react to altered self (to respond to malignancy).

The immune system is traditionally divided into the innate immune system and the adaptive immune system.

The innate immune system consists of the protein complement cascade, phagocytic cells and natural killer cells. The innate immune system has some elements of recognition and generally is the first line of defence, particularly for a new type of infection. Defects of innate immunity can result in PIDs.

In contrast, the adaptive immune system is antigen specific and this specificity is conferred by surface receptors of the T and B lymphocytes. Pathogen destruction is specific and there is amplification on re-exposure as well as a shorter lag period on re-exposure. This results from T and B cell memory.

Those precursor B cells destined to produce antibody travel to the bone marrow and undergo maturation. If they come into contact with antigen, further differentiation occurs and they enter the germinal centres within the lymphatic system.

The germinal centre reaction in the lymph nodes and spleen is where immature B cells undergo class switching as well as somatic hypermutation, resulting in either memory B cells or antibody-secreting plasma cells.

A further series of complex interactions occurs between B cells and T cells and follicular dendritic cells in the germinal centres. Initially, IgM is expressed and secreted by the immature B cells. Following the germinal centre reaction and "T cell help", other immunoglobulin isotypes, including IgA, IgG and IgE, can be secreted by plasma cells.

T cells also undergo maturation in the thymus, during which there is initially positive selection for T cells which have productively rearranged their receptors and are able to recognise antigen presented by Class 1 or Class 2 molecules. Class 1 and Class 2 molecules reside on the surface of antigen-presenting cells such as macrophages, dendritic cells and B cells. This is followed by negative selection, whereby T cells which have an excessively high affinity for self Class 1 and Class 2 molecules are deleted, to remove autoreactive clones. T cells then exit the thymus as either CD4 helper cells or CD8 cytotoxic cells.

In parallel to the innate and adaptive immune systems, there is also a mucosal immune system where antigens are sampled by cells within Peyer's patches and other mucosal surfaces. Gut-associated lymphocytes then undergo recirculation and home back to various parts of the mucosal immune system.

Primary immune deficiency disorders: classification of defects

Primary immune deficiency disorders are congenital defects of the immune system. Most are inherited as single gene defects. The 2007 classification of PIDs by the Expert Committee of the World Health Organization is one of several currently used (Table 1).

B cell defects

The first group is B cell defects, which include Bruton's agammaglobulinaemia as well as common variable immune deficiency (CVID). B cell defects tend to predispose to bacterial, protozoal and viral infections and, in general, these patients tend to have normal growth unless they have severe bronchiectasis.

T cell defects

The second group is T cell defects. T cell disorders include conditions such as DiGeorge syndrome, but of course HIV needs to be considered in the differential diagnosis, even though it is not a PID. T cell defects in children are often associated with impaired growth and patients are predisposed to viral, fungal and parasitic infections.

Combined defects

The third group in the WHO classification includes combined defects such as severe combined immune deficiency (SCID) and X-linked hyper-IgM syndrome where there are significant T and B cell defects. Patients with combined defects have the gamut of infections and often present with other associated features.

Other well-defined defined disorders

A fourth group consists of well-categorised disorders such as Wiskott-Aldrich syndrome, where both lymphoid and haematopoietic cells are affected.

Complement defects

A fifth group is those with complement defects. Complement defects can affect any of the complement components.

The classical, lectin and alternative pathways converge on the complement C3 convertase. Activation of the final common pathway (membrane attack complex) from C5-C9 leads to a doughnut shaped lesion on the pathogen cell membrane, leading to osmotic lysis of the pathogen.

The classical pathway is usually triggered by immune complexes. The alternative pathway is triggered by bacterial cell surfaces. The lectin pathway has elements of both the classical and alternative pathways.

The clinical manifestation of complement deficiency depends on the component affected (Table 2). Patients who have a deficiency of early classical pathway complement proteins may have autoimmune manifestations. A significant proportion of patients with systemic lupus erythematosus, particularly those who are antinuclear antibody negative, have C4 deficiency.

C3 deficiency is very rare but tends to present with pyogenic infections, rather similar to an antibody defect.

If a patient has had more than one episode of meningococcal septicaemia, there is a high probability he or she may have a complement defect and should be referred to a specialist for further testing and evaluation. The patient may have a defect of the membrane attack complex or the alternative pathway.

Those with defects of the alternative pathway tend to have autoimmune manifestations as well as recurrent neisserial infections.

Patients with C1 inhibitor deficiency present with recurrent angio-oedema (not associated with urticaria). This is an autosomal dominant disorder and there does not appear to be an increased risk of infections.

Recurrent infections in children (Panel 1)

Primary factors worldwide

- Malnutrition
- Malaria
- Vaccine-preventable disease
- Diarrhoea

Primary factors in developed countries

- Allergy
- Exposure to tobacco smoke
- Prematurity (respiratory syncytial virus)
- Anatomical (generalised – burns, severe eczema; organ-specific – cystic fibrosis; localised – gastro-oesophageal reflux, adenoids, chronic tonsillitis)
- Malignancy
- Secondary immune defects (diabetes, medications, HIV)
- Primary immune defects

WHO classification of PIDs (Table 1)

Type	Example
B cell defects	Bruton's agammaglobulinaemia, CVID
T cell defects	DiGeorge syndrome
Combined defects	SCID, XHIM
Other well-defined disorders	Wiskott-Aldrich syndrome
Complement defects	(See Table 2)
Phagocytic defects	chronic granulomatous disease
Disorders of innate immunity	toll-like receptors
Autoinflammatory disorders	FMF, TRAPS
Disorders of apoptosis	ALPS

ALPS, autoimmune lymphoproliferative syndrome; CVID, common variable immune deficiency; FMF, familial Mediterranean fever; SCID, severe combined immune deficiency; TRAPS, TNF-receptor-associated periodic syndrome; XHIM, X-linked hyper-IgM syndrome

Complement defects (Table 2)

Early components	autoimmune manifestations
C3	pyogenic infections
Alternate pathway	autoimmune features and neisserial infections
Late components	neisserial infections
C1 inhibitor	angio-oedema

Phagocytic defects

A further group in the WHO classification is phagocytic defects, including leucocyte adhesion deficiency and chronic granulomatous disease. Neutrophil defects can lead to bacterial and fungal infections and sometimes there are cold abscesses. Periodontitis can be a significant feature in some forms of neutrophil defects.

Newly added defect categories

There are three recently added categories to the WHO classification, which include defects of innate immunity, such as toll-like receptor defects, and two categories including those with autoinflammatory disorders, such as familial Mediterranean fever or TNF-receptor-associated periodic syndrome (TRAPS), and finally disorders of apoptosis such as the autoimmune lymphoproliferative syndrome.

Presentation of PIDs and testing

Patients with PIDs typically present with recurrent bacterial, fungal or viral infections. However, they can present to a gastroenterologist with chronic diarrhoea, giardia or cryptosporidiosis. Liver abscess is often the first presentation of chronic granulomatous disease, which needs to be considered in any patient with a staphylococcal liver abscess, even if they present in adulthood.

Patients with PIDs can present to a chest clinic with bronchiectasis or chronic bronchitis, or to a rheumatologist with connective tissue disorders or monoarthritis. They can present to ear, nose and throat specialists with chronic sinusitis or recurrent otitis media or to endocrinologists with mucocutaneous candidiasis. Finally, haematology or oncology specialists may see PID patients with autoimmune manifestations or malignancy.

Most patients are diagnosed because they have repeated infections. They can, however, be identified through a family history of PID or other manifestations.

The vast majority of PIDs can be treated effectively. Furthermore, early diagnosis can potentially prevent disabling complications, particularly bronchiectasis (Notarangelo et al, 2007).

In rare cases of SCID, early diagnosis can be life saving. These infants present with the gamut of infections, including treatment-resistant candidiasis, after three months of age.

When to suspect a PID

It is worthwhile considering PID in a child when there is present:

- an unusually large number of infections requiring treatment
- infection in unusual places
- a child who does not grow or put on weight as expected
- any other unusual symptoms related to infections
- infection caused by unusual types of organism
- infection that does not respond to treatment as expected
- family history of an immune deficiency or abnormal infections.

None of these are specific but the combination may potentially alert clinicians to a host defect.

With regard to an increased number of infections, as indicated previously, it can sometimes be difficult to determine how many per year is considered abnormal.

If a child or adult has an unusual organism, such as *Pneumocystis jirovecii*, or an infection in an unusual site, such as a liver abscess, or if the patient fails to respond as predicted, there may be a host defect.

If there is failure to thrive in children in the context of

recurrent infections, again, an immune deficiency needs to be considered. There may be other clinical features such as eczema and bruising in a boy who has Wiskott-Aldridge syndrome or there may be a relevant family history, which may point to the diagnosis.

Testing for immune defects

Screening tests for PID are very simple and inexpensive (Empson et al, 2004). A full blood count, immunoglobulins and erythrocyte sedimentation rate (ESR) can be very helpful in identifying the majority of PIDs. Sometimes, these patients have a normal ESR in the face of a severe infection because of the muted inflammatory response, and this may be a clue to an underlying B cell defect.

The blood film can be helpful in identifying a neutrophil abnormality. Likewise, reduced immunoglobulin levels can identify the majority of individuals who have a B cell defect.

Most patients have received the standard immunisations and, therefore, specific responses to proteins can be measured in the form of tetanus, diphtheria or hepatitis B antibodies. Specific antibodies to carbohydrates can be identified in the form of blood group isohaemagglutinins, providing the patient is not blood group AB. An HIV test might also be appropriate.

It is very important to remember that immunoglobulin levels need to be interpreted in the appropriate clinical context. Some medications can cause hypogammaglobulinaemia, particularly anticonvulsants. There may be some slight lab-to-lab variation in immunoglobulin levels also. All laboratories are required to enroll in proficiency testing, which minimises systematic measurement errors.

The age of the child is important. The initial IgG is passively acquired. There is a nadir at approximately six months of age for IgG, before the patient starts making his or her immunoglobulin. Prematurity will decrease the levels, and concurrent infections may artificially increase levels as part of the inflammatory response.

Most patients do not produce adult levels of IgA until at least five years of age. IgA deficiency, therefore, may not be identifiable until middle childhood (Figure 1).

If a patient is suspected of having an immune deficiency and is referred to an immunologist, other advanced tests may be undertaken, including vaccine responses and flow cytometry to examine markers on lymphocytes (Paul, 2002). Electron microscopy can be helpful, particularly for neutrophil or phagocyte defects. Finally, molecular diagnosis is also available in New Zealand (Ameratunga and Woon, 2009).

Child with a PID (Case study 2)



Presentation and history

Alex is two years of age. He presents with recurrent chest infections since six months of age. The family history is remarkable in that two uncles had died at one year of age.

Investigations

Alex has no tonsils. His immunoglobulins show markedly reduced IgG, IgM and IgA levels. When he was immunised for diphtheria and tetanus there was no response in the form of antibody. Flow cytometry shows an absence of B cells.

Diagnosis

Sequencing of the *btk* gene confirmed Bruton's agammaglobulin-aemia.

Management

Subsequently, Alex receives long term intravenous immunoglobulin. There is a dramatic improvement in his health, with fewer lower respiratory tract infections and reduced sputum production. Other family members are advised to seek genetic counselling and testing given the X-linked nature of the disorder.

Criteria for referral (Panel 2)

- More than eight new infections in a year.
- Requires more than six courses of antibiotics per year (and perhaps more than two or three for adults).
- More than four new ear infections after four years of age.
- More than three episodes of bacterial sinusitis in a year or chronic sinusitis.
- Requires prophylactic antibiotics to decrease the number of infections.
- Two or more months of antibiotic treatment with no response.
- An unusually severe infection or infection that does not cause problems in most patients of that age.
- At least two episodes of pneumonia over any period of time, or more than two episodes of pneumonia within a year.
- Recurrent deep-seated skin infections or organ abscesses.
- Persistent thrush after one year of age.
- Requires intravenous antibiotics to clear infections.
- Failure to gain weight or to thrive by an infant, especially in the context of recurrent infections.
- A family history of immune deficiency – testing should be undertaken.

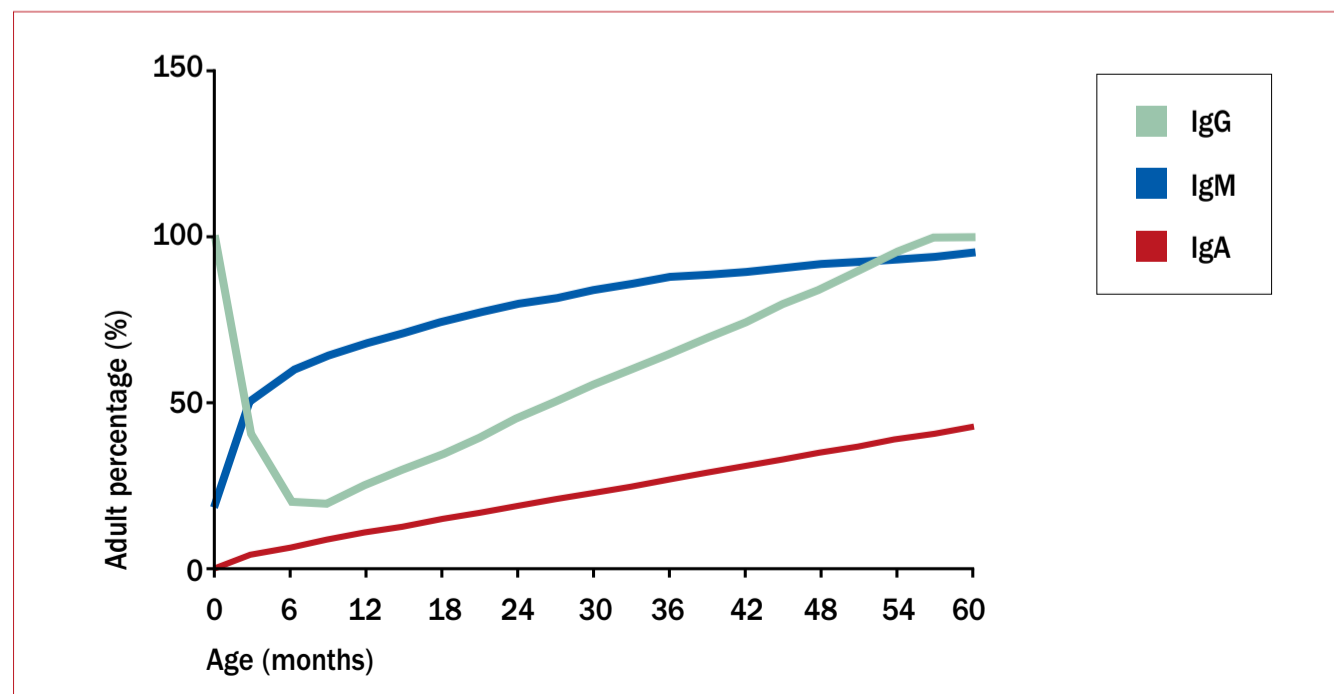


Figure 1. Maturation of B cell function and immunoglobulin production

Clinical approach to the patient

When evaluating a patient with a suspected host defect, it is very important to document the number of infections experienced. It is also important to ask whether the infections have been localised to one organ system.

- Are they localised to the one anatomical location within the organ system (eg, a segment of a lung)?
- Are there any other predisposing factors including exposure to tobacco smoke?
- Is there failure to thrive/growth retardation in children?
- Are there any unusual features of the infections?
- Is there a relevant family history of recurrent infections or unexplained deaths in childhood?

AAAAI recommendations for immunology referral

The AAAAI suggests a number of criteria whereby a child should be considered for further investigation (Panel 2).

Treatment of patients with immune defects

For severe antibody defects, the treatment of choice is long term intravenous immunoglobulin, and this results in a significant improvement in health. In addition, immunoglobulin can be given as a subcutaneous infusion on a weekly basis, and patients can self-administer it.

A variety of other treatments may be appropriate, including long term antibiotic prophylaxis or bone marrow transplant.

Generally, patients with severe T cell or neutrophil defects require bone marrow transplantation. These children are often severely ill and need urgent referral to a specialised unit

so further investigations and treatment can be undertaken.

Given the specialised nature of the problem, patients with a PID should be under the care of an immunologist. Identification at an early age, before irreversible lung damage has occurred, is critical for long term prognosis. Appropriate treatment results in a significant improvement in the quality of life.

Once the child has been evaluated, it is very important for the GP to work closely with the child's paediatrician and immunologist to ensure infections and other complications are quickly diagnosed and treated. Given the host defect, there should be a low threshold for investigation and institution of antibiotics. Many patients carry their own supply of antibiotics so treatment can be rapidly initiated. **D**



It's very important to document the number of infections

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Support organisations

Immune Deficiencies Foundation of New Zealand
www.idfnz.org.nz

Immune Deficiency Foundation (US)
www.primaryimmune.org

QUIZ ANSWERS

1. True. 2. True 3. False. 4. False. 5. True