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 Rimington, 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 predisposition 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 eczema, are predisposed to infections. This may involve multiple mechanisms, including loss of barrier, nutritional compromise, use of antibiotics, nosocomial infection 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.

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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 pathological 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 mucus rhinorhoea, 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 rule treatment of otitis media with effusion may require tympanostomy tubes. The allergic rhinitis should be treated separately.
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. The adaptive immune system consists of B and T 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.

These 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, secondary immune deficiencies

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 disorders

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

Phagocytic defects

A further group in the WHO classification is phagocytic defects, including leukocyte 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.

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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.

Recurrent infections in children

Name of the table: Recurrent infections in children

<table>
<thead>
<tr>
<th>Panel 1</th>
<th>Primary factors worldwide</th>
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<tbody>
<tr>
<td>• Allegra</td>
<td></td>
</tr>
<tr>
<td>• Exposure to tobacco smoke</td>
<td></td>
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<tr>
<td>• Prematurity (respiratory syncytial virus)</td>
<td></td>
</tr>
<tr>
<td>• Anatomical (generalised – burns, severe eczema; organ-specific – cystic fibrosis; location – gastro-esophageal reflux, adenoids, chronic tonsilitis)</td>
<td></td>
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<tr>
<td>• Malignancy</td>
<td></td>
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<tr>
<td>• Secondary immune deficiency disorders (diabetes, medications, HIV)</td>
<td></td>
</tr>
<tr>
<td>• Primary immune defects</td>
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</tbody>
</table>

WHO classification of PIDs (Table 1)

<table>
<thead>
<tr>
<th>Type</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>B cell defects</td>
<td>Bruton’s agammaglobulinaemia, CVID</td>
</tr>
<tr>
<td>T cell defects</td>
<td>DiGeorge syndrome</td>
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<tr>
<td>Combined defects</td>
<td>SCID, XHIM</td>
</tr>
<tr>
<td>Other well-defined disorders</td>
<td>Wiskott–Aldrich syndrome</td>
</tr>
<tr>
<td>Complement defects</td>
<td>(See Table 2)</td>
</tr>
<tr>
<td>Phagocytic defects</td>
<td>chronic granulomatous disease</td>
</tr>
<tr>
<td>Disorders of innate immunity</td>
<td>toll-like receptors</td>
</tr>
<tr>
<td>Autoinflammatory disorders</td>
<td>FMF, TRAPS</td>
</tr>
<tr>
<td>Disorders of apoptosis</td>
<td>ALPS</td>
</tr>
</tbody>
</table>

| Complement defects (Table 2) | |
| Early components | autoimmune manifestations |
| C3 | pyrogenic 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 leukocyte 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.

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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 bacte-
rial, fungal or viral infections. However, they can present to
a gastroenterologist with chronic diarrhoea, giardia or
cryptosporidiosis. Liver abscess is often the first presenta-
tion 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 si-
inusitis or recurrent otitis media or to endocrinologists with
nocutaneous candidiasis. Finally, haematology or oncol-
ogy specialists may see PID patients with autoimmune mani-
festations or malignancy.

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

The vast majority of PIDs can be treated effectively.
Furthermore, early diagnosis can potentially prevent disa-
bancing complications, particularly bronchiectasis (Notaran-
gelo 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
- an unusually large number of infections requiring treat-
ment
- 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 in-
fecions

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

With regard to an increased number of infections, as
indicated previously, it can sometimes be difficult to deter-
mine 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 pre-
dicted, 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
- counted. 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 help-
ful in identifying the majority of PIDs. Sometimes, these pa-
tients 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 immunisa-
tions 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 iso- or hamagglutinins,
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 con-
text. Some medications can cause hypogammaglobulinae-
mia, particularly anticonvulsants. There may be some slight
lab-to-lab variation in immunoglobulin levels also. All labo-
ratories are required to enroll in proficiency testing, which
minimises systematic measurement errors.

The age of the child is important. The initial IgG is pas-
sively 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
can be undertaken, including vaccine responses and flow
cytometry to examine markers on lymphocytes (Paul, 2002).
Electron microscopy can be helpful, particularly for neu-
traphil or phagocyte defects. Finally, molecular diagnosis
is also available in New Zealand (Ameratunga and Woos, 2009).

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.

References


Support organisations

Immune Deficiency 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