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Investigation of recurrent infection

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Abstract
Repeated episodes of infection are required for the development of a competent immune system and, therefore, are an expected norm in early childhood. Although most children with recurrent infection have normal immunity and do not have serious underlying disease, early and accurate detection of immunodeficient children is essential for delivery of optimised care. This review aims to provide a framework for rational investigation.

Keywords antibody deficiency; HIV infection; immunodeficiency; infectious diseases; laboratory investigation; recurrent infection; severe combined immunodeficiency

Introduction
Development of effective childhood immunity requires that the host immune system successively meets and responds to a broad range of microbes. Each new host–microbe interaction can result in infection; and each infection should generate microbe-specific immunity, thus reducing the risk of later re-infection. However, each infection may also represent significant morbidity for the child, with worry and time off work for a parent. Therefore, while expected in children, recurrent infection is a common reason for seeking paediatric consultation.

Because infection is so common and recurrent infection tends to represent the end of a normal distribution, rather than a diagnostic category, appraisal of the patient with recurrent infection is 2-fold. First, we must consider the variety of specific risk factors contributing to the risk of infections; and second, whether there is an underlying explanatory diagnosis.

In the past, when infectious diseases were frequent and commonly fatal, virtually every child was exposed to virtually every infection and rates of infectious disease morbidity and mortality were high. Risk factors for infection were very important. A child’s survival was dependent on many different fundamental risk factors, such as age, nutrition and the degree of exposure to the infectious agent. Infectious disease is now less common, and we are moving toward a time when most significant infection will be understood primarily in the context of specific host immune factors.

Infection frequency in a population is best considered as a normal distribution: very few children escape infection in childhood, most have some infections and a small number have (too) many. Setting useful boundaries for the normal recurrence rate of infection in healthy children is difficult. As a screening device, ‘recurrent infection’ identifies mostly normal children. In concert with infection severity and peculiarity, clinical history and examination and a few further laboratory tests, important diagnoses can be made. The purpose of this review is to provide a reasoned basis for rational investigation.

Recurrent respiratory infection
Recurrent respiratory infection is common in young children. Although a preschool child can normally have up to five respiratory tract infections annually, as many as 6% of preschool children have more than six infections annually.1 Recurrent pneumonia (defined as more than 2 episodes in 1 year, or more than 3 episodes in a lifetime) has an incidence of 15–40/1000 and accounts for about 7.7–9% of childhood pneumonias.2 Two or more serious sinus infections or pneumonias within 1 year would be unusual.

Recurrent acute otitis media
Using the example of recurrent acute otitis media (RAOM), we can separately consider the contribution of specific risk factors and underlying diagnoses. Mathematically, in the clinic and in the population, risk factors explain many more cases than diagnoses. However, identification of relevant risk factors does not preclude important diagnoses. Risk factors for sinopulmonary infection include: environmental factors (the inhaled pathogen load and locally active irritants, such as cigarette smoke); local structural factors (such as the presence and quality of mucus or any airway malformations); and host factors (such as atopy and immunity).1 Specific risk factors for RAOM include day care attendance, family size, exposure to air pollution, parental smoking, upper respiratory tract infections, dummy use, craniofacial abnormalities and presence of adenoids.3 Most critically, day care attendance doubles the risk of RAOM. Within most UK populations, day care attendance is relatively high, while immunodeficiency is very rare. Even though RAOM is found commonly in human immunodeficiency virus (HIV)-infected children, for the paediatrician seeing cases of RAOM, day care attendance alone accounts for one in three cases, whereas one in 300 might have RAOM as a result of HIV infection. Our strategy for evaluation must identify both causes and risk factors as efficiently as possible.

Pneumonia
Figure 1 suggests an algorithm for the evaluation of children with recurrent pulmonary infection. From the history, examination and serial chest x-rays, clues to many important risk factors for recurrent pneumonia can be identified including asthma, gastroesophageal reflux, aspiration and airway abnormalities (foreign bodies, bronchiectasis, bronchial stenosis, compression resulting from lymph nodes, aberrant blood vessels or parenchymal...
tumours and parenchymal abnormalities, such as sequestration, cystic adenomatoid malformation and bronchogenic cysts). Where the recurrent infection particularly affects one lobe of the lung, or one nostril or one ear canal, foreign body should be considered and radiological followed by direct exploration are indicated; bronchoscopy will have a greater yield than other studies.

Cystic fibrosis, immunodeficiency, ciliary dyskinesia and certain airway disorders may not be suggested by these studies and so require more directed investigation. Cystic fibrosis has high frequency in children presenting with recurrent chest infection, demands lifelong specific therapy and is benefited from early intervention so should be excluded with a sweat test in all children presenting with recurrent chest disease. Ciliary dyskinesia is much rarer and unless findings are supportive (purulent sinusitis and situs inversus) is tested for less commonly (usually by cilial biopsy in a later round of investigation). Immunodeficiency should be considered in parallel with cystic fibrosis. Antibody deficiencies are most commonly found and in the infant may be primary or secondary. Primary antibody deficiencies encompass a broad range of conditions: from the genetically defined (e.g. X-linked agammaglobulinaemia) through common variable immunodeficiency to transient hypogammaglobulinaemia of infancy, which may just reflect delayed production of immunoglobulin (IgG) and maturation of antibody responses.\textsuperscript{4} Less common are complement deficiency, Neutropaenia and functional neutrophil defects.

Taking a comprehensive history and completing a detailed examination will provide the best grounds from which to determine the most appropriate strategy for investigation of each child. History and examination findings with particular value in the assessment of recurrent infection are highlighted in Table 1. In the same way, information regarding microbiological isolates can be helpful – particular organisms may suggest specific diagnoses (Table 2).

### Streptococcus pneumoniae
One specific respiratory tract pathogen deserving particular consideration is S. pneumoniae. Prior to current vaccination programmes, pneumococcal infections have been the predominant bacterial pathogen of childhood respiratory infections and a major contributor to the case mix with invasive bacterial disease. Following the introduction of immunisation for specific serotypes, infection is now less common in young children. For this reason, pulmonary pneumococcal infection should be regarded as interesting and a single episode of invasive pneumococcal infection should be regarded as highly significant, both as a marker for vaccine failure and also for possible underlying immunodeficiency. Invasive pneumococcal infection is found in patients without a spleen, without antibodies or with poor/delayed antibody

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**Table 1** Recurrent sinopulmonary or pyogenic infection.

<table>
<thead>
<tr>
<th>History and examination</th>
<th>Microbiology results</th>
<th>Histopathology results</th>
<th>Anatomical abnormality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, height and weight</td>
<td>Nose, throat, skin</td>
<td>Granulomata</td>
<td>CT chest, bronchoscopy (with cilia biopsy)</td>
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<tr>
<td>Daycare/family size</td>
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<td>Asthma/allergy</td>
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<td>Gastro-oesophageal reflux</td>
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<td>Aspiration</td>
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<td>Foreign body</td>
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<td>Family history</td>
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<td>Eczema</td>
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<td>Burns</td>
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<td>Malignancy</td>
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**Table 2**

<table>
<thead>
<tr>
<th>FBC</th>
<th>IgGAM</th>
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<tbody>
<tr>
<td>Lymphopaenia</td>
<td>Low IgGAM</td>
</tr>
<tr>
<td>Neutropaenia</td>
<td>High IgM</td>
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<tr>
<td>Neutrophilia</td>
<td>High IgE</td>
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<tr>
<td>Eosinophilia</td>
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</tbody>
</table>

- **FBC**
  - Less than 2.8 is abnormal in infants: perform lymphocyte subset analysis
  - Autoantibodies, anti-neutrophil antibodies, bone marrow, (may need serial neutrophil counts)
  - Leucocyte-adhesion deficiency syndrome (LAD) confirmed by aberrant expression of CD11b/CD18
  - Suggests a TH2 skew, found in parasitic infection, atopy and some defects of T cell immunity

- **IgGAM**
  - Check specific antibodies (Hib, tetanus, pneumococcus), boost/vaccinate and repeat. Perform lymphocyte subset analysis
  - Boost/vaccinate and repeat. Perform lymphocyte subset analysis
  - Look at B cell phenotype (class switching). If IgG is low, check CD40L and CD40 expression
  - Found in atopy and Hyper-IgE syndrome

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1. [Link to Table 1]
2. [Link to Table 2]
responses, lacking complement components or mannose binding lectin and those with defects in the Toll-like receptor signalling pathways.\(^5\)

Specific antibody immune deficiencies have been described with poor pneumococcal polysaccharide-specific antibody responses, and a proportion of these have defined deficiencies, such as NF-\(\kappa\)B essential modulator (NEMO) deficiency and interleukin-1 receptor-associated kinase (IRAK4) deficiency. The finding of dampened inflammatory responses in the face of invasive disease specifically suggests these two conditions.

### Recurrent meningitis

Recurrence of meningitis is abnormal (except after inadequate therapy) and an underlying cause should be sought, as suggested in Figure 2. If specific bacteria have been isolated, investigation of the underlying cause may be directed: *Pneumococcus* and *Haemophilus* suggest cranial dural defects; *Coliforms* suggest spinal dural defects, whereas *Meningococci* suggest immunologic deficiency. Dural defects can be frustrating to identify, as it is uncommon to identify a site of cerebrospinal fluid leakage or another local indicator to suggest a lesion site. Detailed and extensive scanning is required.

Both meningococcal and pneumococcal infection may result in meningitis as well as septicaemia. Asplenia or immunodeficiency (such as complement or immunoglobulin deficiency) may cause recurrent meningitis but rarely without history of frequent infection elsewhere.

### Recurrent urinary tract infections

Urinary tract infections (UTIs) are very common in children of all ages. Recurrence is found in at least 20% of cases, where recurrence is defined as two or more episodes if one episode is acute pyelonephritis, or three episodes of cystitis.

UTI is most likely to recur in children with ‘voiding dysfunction’. Children who ‘hold on’ to delay voiding, or ‘posture’ to prevent incontinence during detrusor contraction, or who are constipated are all at higher risk of recurrence of UTI.

Other risk factors include anatomical abnormalities or bladder neuropathies,\(^5\) use of broad-spectrum antibiotics that disturb periurethral flora, and there is evidence that in young women, various innate immune functions may play a role (such as non-secretor genotype).

Investigation should identify evidence of obstruction and history will tell whether the pattern of micturition is normal or if
voiding dysfunction is likely. No further specific investigations are required. There is no identified link between recurrent UTIs and immune deficit.

Recurrent gastroenteritis

Primary immune deficiency with strong association

**Streptococcus pneumoniae and Haemophilus influenzae**
- IgG2 deficiency
- Deficiencies of early components of classical pathway complement system (C1, C4, C2, C3, factors I and D)
- IRAK4 deficiency
- Defects of NEMO-dependent NF-κB activation (X-EDA-ID)
- Asplenia
- MHC-I deficiencies (due to TAP-1 or TAP-2 deficiencies)

**Staphylococcus aureus**
- Hyper-IgE syndrome
- CGD
- Neutropaenias
- LAD
- Chediak-Higashi syndrome
- IRAK4 deficiency
- XL- and AR-agammaglobulinemia
- IPEX syndrome

**Mycobacterial infections**
- Defects of Interleukin (IL)-12/IL-23-Interferon (IFN)γ axis
- All SCID types
- Idiopathic CD4 lymphocytopenia
- Defects of NEMO-dependent NF-κB activation (X-EDA-ID)
- CGD

**Pneumocystis jiroveci**
- All SCID types
- MHC-II deficiency
- ZAP-70 deficiency
- CD4 lymphocytopenia
- Hyper-IgM syndrome (CD40L and CD40 deficiency)

**Candida infections**
- APECED
- Other forms of chronic mucocutaneous candidiasis
- Hyper-IgE syndrome
- SCID
- MHC-II deficiency
- Idiopathic CD4 lymphocytopenia
- Defects of NEMO-dependent NF-κB activation (X-EDA-ID)
- Wiskott-Aldrich syndrome

**Aspergillus fumigatus**
- Chronic granulomatous disease
- Hyper-IgE syndrome
- LAD
- Idiopathic CD4 lymphocytopenia

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**Characteristic associations between specific microbes and immunodeficiencies**

<table>
<thead>
<tr>
<th>Organism</th>
<th>Primary immune deficiency with strong association</th>
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<tbody>
<tr>
<td><strong>Streptococcus pneumoniae</strong> and <strong>Haemophilus influenzae</strong></td>
<td>IgG2 deficiency, Deficiencies of early components of classical pathway complement system (C1, C4, C2, C3, factors I and D), IRAK4 deficiency, Defects of NEMO-dependent NF-κB activation (X-EDA-ID), Asplenia, MHC-I deficiencies (due to TAP-1 or TAP-2 deficiencies)</td>
</tr>
<tr>
<td><strong>Staphylococcus aureus</strong></td>
<td>Hyper-IgE syndrome, CGD, Neutropaenias, LAD, Chediak-Higashi syndrome, IRAK4 deficiency, XL- and AR-agammaglobulinemia, IPEX syndrome</td>
</tr>
<tr>
<td><strong>Mycobacterial infections</strong></td>
<td>Defects of Interleukin (IL)-12/IL-23-Interferon (IFN)γ axis, All SCID types, Idiopathic CD4 lymphocytopenia, Defects of NEMO-dependent NF-κB activation (X-EDA-ID), CGD</td>
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<tr>
<td><strong>Pneumocystis jiroveci</strong></td>
<td>All SCID types, MHC-II deficiency, ZAP-70 deficiency, CD4 lymphocytopenia, Hyper-IgM syndrome (CD40L and CD40 deficiency)</td>
</tr>
<tr>
<td><strong>Candida infections</strong></td>
<td>APECED, Other forms of chronic mucocutaneous candidiasis, Hyper-IgE syndrome, SCID, MHC-II deficiency, Idiopathic CD4 lymphocytopenia, Defects of NEMO-dependent NF-κB activation (X-EDA-ID), Wiskott-Aldrich syndrome</td>
</tr>
<tr>
<td><strong>Aspergillus fumigatus</strong></td>
<td>Chronic granulomatous disease, Hyper-IgE syndrome, LAD, Idiopathic CD4 lymphocytopenia</td>
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Viral infections

<table>
<thead>
<tr>
<th>Primary immune deficiency with strong association</th>
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</thead>
<tbody>
<tr>
<td>All forms of SCID, MHC-II deficiency, Idiopathic CD4 lymphocytopenia, Complete STAT-1 deficiency (homozygous patients), XL- and AR-agammaglobulinemia (enteroviruses), X-linked lymphoproliferative syndrome (EBV)</td>
</tr>
<tr>
<td>XLA, X-linked agammaglobulinemia, CVID, IgA deficiency, Hyper-IgM syndrome (CD40L and CD40 deficiency), MHC-II deficiency, Defects of NEMO-dependent NF-κB activation (X-EDA-ID), APECED</td>
</tr>
<tr>
<td>Hyper-IgM syndrome (CD40L and CD40 deficiency), MHC-II deficiency</td>
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**Giardia lamblia**

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<tbody>
<tr>
<td>XL-agammaglobulinemia, CVID, IgA deficiency, Hyper-IgM syndrome (CD40L and CD40 deficiency), MHC-II deficiency, Defects of NEMO-dependent NF-κB activation (X-EDA-ID), APECED</td>
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**Cryptosporidium parvum**

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<th>Primary immune deficiency with strong association</th>
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<tr>
<td>Hyper-IgM syndrome (CD40L and CD40 deficiency), MHC-II deficiency</td>
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**Table 2**

voiding dysfunction is likely. No further specific investigations are required. There is no identified link between recurrent UTIs and immune deficit.

**Recurrent gastroenteritis**

Recurrent gastroenteritis primarily reflects the degree of pathogen exposure. Children who frequently encounter gastrointestinal pathogens in their drinking water or in their diet will more frequently experience diarrhoeal disease. In the hygiene-focused world in which we now live, recurrent diarrhoeal disease is less commonly reported than persistent diarrhoea. Persistent diarrhoea has a host of causes, and is commonly found in children with immunodeficiency. The full assessment of persistent diarrhoea is beyond the scope of this review, however, when seen in combination with any recurrent infection, persistent diarrhoea should strongly suggest a defect in cell-mediated immunity or neutrophil function.

The host response to infection of the gastrointestinal tract is principally diarrhoea. Diarrhoea must be considered one of the most essential innate immune defences, as deficiency states are fatal.

Bacterial infection of the gastrointestinal tract includes *Salmonella, Shigella, Campylobacter, Escherichia coli, Yersinia* and *Vibrio cholera*. Recurrence of these bacterial infections is seldom reported, except in HIV-infected people living in endemic regions. Viral infections of the gastrointestinal tract include...
rotavirus, norovirus, adenovirus, enteroviruses, and caliciviruses amongst many others. Rotavirus has many serotypes and recurrent infections with different serotypes have been reported in normal children, but only as part of a surveillance study. In children at particular risk of gastrointestinal viral infections, the problem is usually persistent diarrhoea, rather than recurrent diarrhoea. Recurrent infection with *Giardia lamblia* is seen in children who are antibody deficient, while recurrent infection with other protozoa suggests repeated exposure and possibly deficient cell-mediated immunity (Table 2).

*Clostridium difficile* is carried asymptomatically in the gut of up to 3% of healthy adults and 66% of infants. *C. difficile* toxin mediated diarrhoea is the most common laboratory identified cause for recurrent diarrhoeal episodes. Although its role as an aetiological agent in children is poorly understood, it is not commonly a problem for children. Recurrence is a major problem in adults, with risk factors including hospital residence, frequent antibiotic use and age. While hypogammaglobulinaemia has been shown to be an independent risk factor for the development of *C. difficile* associated diarrhoea in patients following cardiac transplantation, there is no evidence to suggest that any hypogammaglobulinaemic child has been identified because of recurrent *C. difficile* identification. No specific tests of immunological or gastroenterological function are indicated.

In children with inflammatory bowel disease, infections are known to trigger clinical decompensation. It is possible that recurrent diarrhoeal episodes may represent the first presentation of Crohn’s disease or ulcerative colitis. The history and examination will usually direct further investigation.

**Recurrent abscesses or skin infection**

Children, more than adults, commonly develop pyogenic bacterial skin infections. Risk factors relate to the integrity of the epithelial surface and to the bacterial load on the skin surface. Eczema and other skin-damaging conditions produce considerable attributable risk for skin infection. In the absence of such an obvious underlying condition, continued bacterial colonisation should be considered. This often results in repeated episodes of abscesses secondary to *Staphylococcus aureus*. Eradication of carriage will often eliminate the problem. Certain immunodeficiencies also predispose to skin sepsis including Hyper-IgE syndrome, chronic mucocutaneous candidiasis and chronic granulomatous disease (CGD). Patients with CGD may present with *S. aureus* liver abscess, hence the evaluation of skin infection also requires the evaluation for abscesses anywhere, as the immune disorders predisposing to abscesses will also usually have history of skin infection.

**Recurrent bone and joint infection**

Incomplete treatment of bacterial infection will often result in recurrence of the original disease. This is particularly so, where either too short a course of antibiotic is prescribed, or where there is a focal nidus of infection that cannot be easily eradicated by antibiotic therapy. The treatment of bone infection demonstrates this problem where, despite long treatment courses, recurrence may occur if antibiotics are not continued for long enough or when a sequestrum of ischaemic bone is formed.

Immune defects predisposing to bone and joint infection include hypogammaglobulinaemia, neutropaenia, CGD and HIV infection. Alternative diagnoses should be considered in cases where treatment for bacterial osteomyelitis is presumptive and recurrence is a problem. These include the following autoinflammatory conditions: chronic recurrent multifocal osteomyelitis and synovitis, acne, pustulosis, hyperostosis and osteitis (SAPHO). At present both are diagnoses of exclusion and deserve the attention of a specialist with interest in this field.

**Recurrent infections in different organ systems**

In practice, patients most commonly present with unusually severe or protracted infection, on the background of recurrent infection or failure to thrive. Children in whom there is concern regarding an underlying cause for infections, not uncovered by a systematic history and examination, deserve evaluation for immunodeficiency.

Worldwide, the most common immune deficiencies result from malnutrition, HIV and immunosuppressive drug therapy. These three immune deficiencies will probably account for more episodes of infection in our patients than the single gene defects. The immunodeficiencies resulting from HIV and iatrogenic immunosuppression are predictable and well understood. Malnutrition has a close and complex relationship with infectious diseases and although certainly the major attributable risk factor for global infectious disease mortality, the mechanisms underlying this relationship remain elusive.
Investigation

Patients presenting with recurrent infection can be divided into different groups for the purpose of planning investigation and securing a diagnosis of immunodeficiency. Investigations are directed at the most likely underlying cause, as outlined above. Thus, knowledge of probable diagnoses for common clinical scenarios is essential in ordering investigations. The first group, children who have either recurrent sinopulmonary or pyogenic infection can be investigated following the algorithm in Figure 1. Most of these children will have normal immunity, but those with suggestive family history should have immunodeficiency excluded as a priority. In children with no other cause found for their recurrent sinopulmonary infections, about 10% have been found to have specific antibody deficiencies.12 Initial screening, therefore, aims to rule out antibody deficiency and neutropaenia by performing a full blood count (with differential and platelet volume) and immunoglobulins (IgGAME).

Absent immunoglobulins (GAM) suggest XL- and AR-agammaglobulinaemia and should precipitate evaluation of lymphocyte subsets by flow cytometry. Abnormalities of lymphocyte subset numbers or phenotype should be urgently discussed with an immunologist. However, alternative causes such as drugs, immunoglobulin loss (in urine or in faeces) or lymphoid malignancy also need to be considered.

Selectively absent IgA is the most common problem detected, although most are asymptomatic and the finding is only relevant in the context of recurrent infection if other humoral deficiencies are also detected. Raised IgM is significant especially when noted with low IgG and IgA and suggests the possibility of CD40 (ligand) deficiency, which can be identified by flow cytometry. Raised IgE is found in atopy and as a result of cytokine imbalance (sometimes found in combined immunodeficiencies).

Where immunoglobulins are low, further investigations are necessary. Specific functional responses to primary vaccinations should be measured. If low, boosted vaccine responses help to determine the quality of the humoral immune response. If results are normal, the European guidelines suggest re-evaluation after 3–6 months.13

If there are no significant risk factors, microbiological data and completion of the screening tests are unhelpful, further tests can be considered. These should include a HIV test, functional assessment of neutrophils by performing an oxidative burst to exclude CGD; functional classical and alternate complement pathway

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Figure 3 Recurrent infection with intracellular organisms.
conclusions

parents are often concerned that their children suffer frequent infections. where growth and development progress normally and interval period health is normal, an underlying diagnosis to explain recurrent infection is unlikely. where infections are limited to a single organ system, the likelihood of identifying an organ-specific underlying cause is greater, but still small, and is often suggested by findings in the history and examination. children with immunodeficiency commonly have significant clinical findings in addition to recurrent infection that assist in choosing the most efficient strategy for investigation. strategies focus on identifying defects in cell-mediated immunity, humoral immunity, phagocytic function or inflammatory responses.

references

Practice points

- Recurrent infection is common in young children
- Recurrent infection is more likely to be clinically important if infection has been severe, protracted, is in an unusual site or is caused by an unusual organism

- Identification of risk factors for recurrent infection helps in the management of further risk
- Screening for immunodeficiency relies upon history, examination and a few select laboratory tests
- Particular pathogens and illness patterns provide important clues to underlying causes
- Lymphopaenia is a critically important finding in infants with recurrent infection
- Investigations should be tailored to the likely causes and a HIV test should be considered early