Assessment of the child with recurrent chest infections

Jon Couriel
Respiratory Unit, Royal Liverpool Children’s Hospital, Liverpool, UK

The child with recurrent chest infections presents the clinician with a difficult diagnostic challenge. Does the child have a simply-managed cause for their symptoms, such as recurrent viral respiratory infections or asthma, or is there evidence of a more serious underlying pathology, such as bronchiectasis? Many different disorders present in this way, including cystic fibrosis, a range of immunodeficiency syndromes, and congenital abnormalities of the respiratory tract. In some affected children, lung damage follows a single severe pneumonia: in others it is the result of inhalation of food or a foreign body.

The assessment of these children is demanding: it requires close attention to the history and examination, and in selected cases, extensive investigations. Early and accurate diagnosis is essential to ensure that optimal treatment is given and to minimise the risk of progressive or irreversible lung damage.

The aim of this chapter is to examine the causes of recurrent chest infections and to describe how this complex group of children should be assessed and investigated.

Recurrent chest infections are a common reason for children to be seen by their general practitioner (GP) or a paediatrician. Recurrent or persistent cough may be the only symptom, but often there is also a history of wheeze, breathlessness, sputum production or general ill-health. A number of disorders can present with these features (Table 1). Many of these children are simply having the repeated viral upper respiratory tract infections that are a normal part of growing up. In others, the symptoms are the first manifestations of asthma. But, in an important minority there is a clear history of persistent or recurrent episodes of pneumonia, or of chronic sputum production, indicating more severe pathology.

The challenge for the clinician is to distinguish between the child with self-limiting or minor problems and the child with serious, perhaps progressive, lung disease. To do this, it is necessary to assess the severity and to diagnose the cause of the symptoms. This depends very much on taking a detailed history, on detecting any abnormal physical signs, and in selected cases, on the use of appropriate investigations. There needs
Incidence of respiratory infections in children

Acute respiratory infections are the commonest illnesses of childhood. In Britain, they account for a third of all consultations between GPs and children and 8–18% of acute hospital admissions\(^1\,^2\). Most involve only the upper respiratory tract, but in 10–30% the lower respiratory tract is also affected. It is common for children to have 6–10 upper respiratory tract infections (URTIs) in a year\(^3\,^4\). The peak incidence is at 6–12 months of age, with an increase when the child first mixes with large numbers of children at nursery or school.

Most respiratory infections are mild, self-limiting and caused by viruses. The commonest viral pathogens are rhinoviruses, coronaviruses, the respiratory syncytial virus (RSV), influenza and parainfluenza, and adenoviruses. \textit{Streptococcus pneumoniae} (pneumococcus) and other streptococci, \textit{Haemophilus influenzae}, \textit{Mycoplasma pneumoniae}, \textit{Chlamydia pneumoniae} and \textit{Moraxella catarrhalis} are the commonest non-viral pathogens for lower respiratory infections\(^3\,^5\). Co-infection with more than
one type of bacteria or virus is present in 8–30% of pneumonia\textsuperscript{3,5}. In many cases, no pathogen can be identified.

The incidence of lower respiratory tract infections (LRTIs) such as pneumonia, bronchiolitis and bronchitis has been assessed in prospective studies\textsuperscript{5,6}. Wright showed a cumulative incidence of acute LRTIs of 33% in the first year of life in a birth cohort of 1179 infants in Tucson\textsuperscript{7}. RSV was the commonest of the 12 pathogens identified and acute bronchiolitis accounted for 60% of episodes. Murphy, in an 11 year community-based study, showed a peak incidence for LRTIs at the end of the first year of life: a quarter of these LRTIs were pneumonia\textsuperscript{8}. Jokinen found an incidence of radiologically proven pneumonia of 36 per 1000 children per year below the age of 5 years, and 16 per 1000 children per year in 5–14-year-olds, in a large Finnish study\textsuperscript{9}. The overall hospitalisation rate for pneumonia was 4/1000 children/year between the ages of 1 month and 15 years, but 5 times higher in children aged below 2 years\textsuperscript{10}. No community studies have reported the incidence of recurrent pneumonia, but 10% of over 2900 children admitted to Toronto’s Hospital for Sick Children with pneumonia had two or more episodes\textsuperscript{11}.

Factors influencing the incidence of lower respiratory infection

When assessing children who present with repeated chest infections, it is important to recognise the factors that affect the incidence of these infections in children (Table 2)\textsuperscript{3}.

The child’s age influences the type and frequency of all respiratory infections. The normal fall in the incidence of LRTIs with age reflects the pattern of exposure to infection and the development of the child’s immunity. Some infections occur only in children within a specific age band. For example, acute bronchiolitis occurs almost exclusively in infants aged 1–8 months, although many affected children have recurrent cough, wheeze and breathlessness for months or years afterwards. Age also affects severity and two-thirds of childhood deaths due to respiratory infections occur in infancy\textsuperscript{3}. Lower respiratory infections are more common in boys than girls, for reasons that are not understood.

<table>
<thead>
<tr>
<th>Table 2 Risk factors for lower respiratory infections in children</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
</tr>
<tr>
<td>Male sex</td>
</tr>
<tr>
<td>Prematurity</td>
</tr>
<tr>
<td>Parental smoking</td>
</tr>
<tr>
<td>Large family size, overcrowding</td>
</tr>
<tr>
<td>Congenital abnormalities</td>
</tr>
<tr>
<td>Immunodeficiency</td>
</tr>
</tbody>
</table>
Infants born prematurely, and particularly those who develop broncho-pulmonary dysplasia (chronic lung disease of prematurity) after ventilation, frequently require hospital admission for respiratory infections in early childhood. The mortality from infection in these infants is higher than in term infants.

The immunoprotective effect of breast feeding against respiratory infections is most important in non-industrialised countries, but is also evident in industrialised societies. Parental smoking increases the risk of all respiratory illnesses and symptoms, and particularly lower respiratory tract infection, in children. The effect is greater in infants than in older children, is related more to maternal than paternal smoking, and is dose-related. Both maternal smoking during pregnancy and postnatal passive exposure predispose the children of smokers to recurrent respiratory infections and symptoms.

Exposure to other children influences the number of infections children develop. Infants with older siblings or from over-crowded homes, have more frequent respiratory infections. When children first attend school or nursery, the number of infections they contract rises.

Children with congenital defects of the respiratory tract, such as tracheoesophageal fistula or sequestration, and children with congenital heart disease, are at increased risk of recurrent respiratory infection. Neurologically handicapped children are particularly vulnerable. Recurrent or persistent chest infections are a common presenting feature of cystic fibrosis, the commonest cause of bronchiectasis in children. Infections in all of these groups of children are not only more common but also more severe than in normal children, with a greater risk of respiratory failure and death.

Some children with recurrent or persistent chest infections have a defect in the complex system of defence mechanisms which normally protect the lungs from a hostile microbiological environment. These include physical and physiological defences, cellular defences, and secretory defences.

<table>
<thead>
<tr>
<th>Physical and physiological defences</th>
<th>Secretory defences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Airway filtration of particles</td>
<td>Immunoglobulins G, A, M and E</td>
</tr>
<tr>
<td>Cough</td>
<td>Collectins</td>
</tr>
<tr>
<td>Sneezing</td>
<td>α1-Antitrypsin and α2-macroglobulin</td>
</tr>
<tr>
<td>Bronchoconstriction</td>
<td>Lysozyme</td>
</tr>
<tr>
<td>Mucociliary clearance</td>
<td>Lactoferrin</td>
</tr>
<tr>
<td>Airway mucus</td>
<td>Complement</td>
</tr>
<tr>
<td>Respiratory cilia</td>
<td>α and β Defensins</td>
</tr>
<tr>
<td>Alveolar fluid movement</td>
<td>Interferon</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cellular defences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphocytes (T- and B-cells)</td>
</tr>
<tr>
<td>Pulmonary macrophages</td>
</tr>
<tr>
<td>Neutrophils</td>
</tr>
</tbody>
</table>
defences such as cough and mucociliary clearance, circulating and resident cellular defences, and a range of humoral or secretory mechanisms (Table 3). Collectively, their function is to prevent the entry or to remove foreign material from the lung. Detailed accounts of the organisation and properties of these defences are given elsewhere in this issue and in review articles 15–18.

**Differential diagnosis of recurrent chest infections**

Most children referred with recurrent respiratory infections have normal immune and other respiratory defences. They are simply at one end of the normal distribution of acute respiratory infections, often because of their age or environment. Rubin 19 has described these children as ‘normal but unlucky’. Characteristically, they are growing and developing normally, the examination and chest X-ray are normal between episodes, there is no family history of severe infections, and no serious extrapulmonary infections. Reassurance is all that is required.

**Asthma**

Despite recent advances in care, many children referred with ‘recurrent chest infections’ or a ‘persistent cough’ will be shown to have undiagnosed asthma. Closer attention to the history reveals that most, but not all, have recurrent episodes of cough, wheeze and breathlessness, often with the characteristic trigger factors of URTIs, exercise, cold air, emotional upset, or exposure to pets and other aero-allergens. There is often a personal or family history of other atopic conditions such as eczema or allergic rhinitis. They may have responded to bronchodilators or anti-inflammatory therapy. Examination is often normal at the time of consultation, but spirometry may indicate airways narrowing and bronchodilator responsiveness. There is no agreed clinical definition or pathognomonic test for childhood asthma and making the diagnosis can be difficult, particularly in children below the age of 3 years 20. Furthermore, in some children, asthma co-exists with another disorder, such as a specific antibody deficiency. Signs which suggest an alternative or additional diagnosis include asymmetric or focal chest signs, finger clubbing, failure to thrive or the features of systemic disease. A cough productive of purulent sputum is not a feature of asthma.

**Post-infective cough**

Some parents clearly describe a cough which first appeared with an acute infection and which has persisted for weeks or months since. This
is common after *Bordetella pertussis* (whooping cough) and *M. pneumoniae* infections\(^1\). With these pathogens the cough, which may be paroxysmal, may yield clear or white mucus. It is the result of the bronchial hyper-reactivity and impaired mucociliary clearance that follow the inflammation that occurs with these infections. The cough normally subsides within 2–6 months. Episodes of wheeze, cough and breathlessness, which may recur for months or years, are common in infants who have been admitted to hospital with RSV bronchiolitis\(^21,22\). The pathophysiology of this ‘post-bronchiolitis syndrome’ is complex, involving abnormalities of both immune function and airway growth.

**Inhaled foreign body**

The possibility of an inhaled foreign body should be considered in any young child who develops a persistent productive cough, particularly if there has been an acute onset after an episode of choking. Some intrabronchial foreign bodies, notably peanuts, evoke severe inflammation of the bronchial mucosa which quickly leads to airways obstruction and distal infection. Even after the diagnosis of a foreign body has been made and it has been removed bronchoscopically, there may be persistent localised airway damage, abnormal lung function and a persistent cough\(^23\).

**Chronic suppurative lung disease**

In a minority of children who present with recurrent chest infections, the cardinal symptom is a persistent or recurrent loose cough that is productive of yellow or green sputum. This suggests chronic suppurative lung disease (Table 1) and possibly bronchiectasis, which is defined as cylindrical or saccular dilatation of the subsegmental bronchi. The incidence of these conditions is unknown\(^24\). Some children with chronic suppurative lung disease present with recurrent or persistent pneumonia: while any normal child can have one episode of pneumonia, recurrent or poorly resolving episodes often indicate an underlying abnormality. Some of these children will also have recurrent ear or sinus infections. Wheeze and chest pain are present in over a fifth of children with bronchiectasis\(^24\). As the differential diagnosis includes several inherited conditions (for example, cystic fibrosis, ciliary dyskinesia and some immunodeficiencies), it is important to take a detailed family history of severe or recurrent respiratory or systemic infections in childhood. As certain acute infections, such as adenoviral pneumonia, can lead to bronchiectasis, it is vital to obtain a detailed history of the first episode
of symptoms. A history of swallowing difficulties or choking with feeds, or of gastro-oesophageal reflux, should be sought as recurrent aspiration of feeds is an important cause of recurrent pneumonia\textsuperscript{11} and chronic suppurative lung disease, particularly in children with neuro-developmental problems\textsuperscript{25,26}. The acute onset of symptoms after an episode of choking is highly suggestive of an inhaled foreign body in young children.

The clinical examination may reveal important signs such as wheeze, crackles, hyperinflation, finger clubbing, hepatosplenomegaly, nasal disease, skin lesions and failure to thrive. A plain chest X-ray may show either focal or wide-spread changes such as atelectasis, hyperinflation, consolidation or abnormal patterns of the airways. The left lower, lingula and right middle lobes are the most commonly affected\textsuperscript{24}.

**Cystic fibrosis**

Cystic fibrosis is the commonest cause of chronic suppurative lung disease in children, affecting one in 2500 births in Caucasians. Most affected children present with recurrent chest infections in early childhood and over 90\% also have malabsorption and failure to thrive due to pancreatic insufficiency. About 10–20\% present with neonatal intestinal obstruction due to meconium ileus. Others are diagnosed because of a family history of this autosomal recessive condition or by neonatal screening.

Viscid mucus in the small airways predisposes to chronic infection, initially with *Staphylococcus aureus* or *H. influenzae*, but later with *Pseudomonas aeruginosa* (see elsewhere in this issue). The infection, and the inflammatory response to it, lead to progressive damage of the bronchial wall, bronchiectasis, cystic lesions and eventually lung fibrosis. Cystic fibrosis must always be considered early in the differential diagnosis of recurrent chest infections.

**Bronchiectasis following acute pneumonia**

In the past, many cases of childhood bronchiectasis followed acute lower respiratory tract infections with pertussis, measles or tuberculosis. This is now rare. Virtually all children with normal immune function will make a full recovery from pneumonia or bronchiolitis, even if the acute episode was severe. However, there are important exceptions to this rule. Adenovirus serotypes 3, 4, 7, and 21 can all cause severe bronchiolitis, pneumonia and death\textsuperscript{27,28}. Up to 40–70\% of survivors are left with permanent damage to the airways (bronchiolitis obliterans).
with segmental or lobar atelectasis, areas of hyperinflation and impaired 
lung function. A quarter of children with bronchiolitis obliterans sub-
sequently develop bronchiectasis. Typically, these children are left with 
persistent wheeze (which responds poorly to bronchodilators), a persistent 
cough (which is initially dry but then becomes productive of purulent 
sputum), and the characteristic radiological changes of bronchiolitis 
obliterans. Swyer-James or MacLoed’s syndrome, where there is a small 
hyperlucent lobe with impaired perfusion and ventilation, has also been 
described after these infections. Similar damage can follow severe myco-
plasmal pneumonia. Co-infection with both adenovirus and *M. pneumoniae* 
is particularly devastating.

Although most children make a full recovery from bacterial pneumonia, 
in some there is slow or incomplete resolution, with persisting localised 
clinical signs and atelectasis or inflammation on the chest X-ray. This may 
be due to obstruction of a bronchus by a plug of mucopus or localised 
damage to the bronchus and the adjacent lung parenchyma, but in some 
cases it reflects an underlying abnormality of the lung anatomy or defences 
or an inhaled foreign body. The cough continues and may become 
productive of sputum: there may be exacerbations with fever. These 
children need detailed assessment.

**Immunodeficiency disorders**

The respiratory tract is the organ system most commonly involved in 
immunodeficiency disorders. There is often a delay of years between the 
onset of symptoms and the diagnosis being made: this delay increases 
the risk of bronchiectasis and irreversible lung damage occurring before 
appropriate treatment is given.

An immune defect should be considered in any child who has respiratory 
infections that are unusually severe, recurrent, unresponsive to 
conventional treatment, or atypical. Common associated features include 
failure to thrive, which is often secondary to gastrointestinal disease, severe 
atopic disease such as eczema, and occasionally, auto-immune disease. Some children with certain syndromes, such as DiGeorge and Down’s 
syndromes, have abnormalities of their immunity as well as cardiac, facial 
and other anomalies. As many immunodeficiencies are inherited, a family 
history of severe infection or early death or consanguinity should be 
sought. As well as respiratory infections, there may be severe infections of 
the skin, gastrointestinal tract and soft tissues, and lymphadenopathy. The 
clinical examination is often abnormal in children with immunodeficiency. 

Immunodeficiencies are classified as primary (congenital) or secondary 
(acquired). In the past, secondary immunodeficiencies were most often 
the result of disorders such as malignancy, immunosuppressive therapy,
measles, or malnutrition, but in many countries HIV infection is now the commonest cause of acquired immunodeficiency.

Over 80 different primary immunodeficiencies have been identified. These can be classified on the basis of which of the four sections of ‘the immune orchestra’ (antibodies, T-lymphocytes, phagocytes or the complement system) is involved, but disorders in which there are abnormalities in more than one section are common. For example, in the severe combined immunodeficiencies (SCID), which are the most severe disorders, there are defects in both cell-mediated (T-lymphocyte) and antibody (B-lymphocyte) function. Defects of humoral (antibody) immunity account for 50% of primary immunodeficiencies, combined humoral and cellular deficiencies constitute 20–30% of cases, phagocyte defects approximately 18% and complement defects less than 2%.

As one would expect, the younger the child when infections first appear, the more severe the immune defect is likely to be. Most defects involving cell-mediated immunity present within the first 6 months of life, frequently with the triad of pneumonia, intractable diarrhoea and mucocutaneous candidiasis. Antibody deficiencies such as X-linked agammaglobulinaemia (XLA), often cause recurrent respiratory infections between the ages of 4 months – when levels of maternally derived IgG have fallen – and 2 years of age, but there is often a delay of 2–5 years before the diagnosis is made. Phagocyte and the rare complement defects can also present at this stage.

Table 4 lists the major categories of immunodeficiency and gives some examples of disorders within each category that can present with severe, recurrent, persistent or unusual chest infections. As the nature of the immune defect determines the susceptibility to particular microorganisms, identifying the pathogen is not only important in deciding what treatment is appropriate, but it may also indicate which part of the immune system is defective. For example, identification of Pneumocystis carinii and cytomegalus virus (CMV) in bronchial lavage fluid from a child with interstitial pneumonia would suggest a defect of T-cell function, whilst recurrent cavitating staphylococcal pneumonia, which is refractory to appropriate antibiotics suggests a neutrophil defect, such as chronic granulomatous disease.

**Defects of antibody production**

Antibody deficiencies are the commonest of immunodeficiencies. There are many different types of antibody deficiency, ranging from severe deficiencies of all immunoglobulins (X-linked agammaglobulinaemia, Bruton’s disease) to milder deficiencies of specific antibodies in children with normal immunoglobulin levels. They may occur as an isolated
defect or as part of a wider immunodeficiency. It is not possible to give a comprehensive review of all of these defects and only some of the commonest types which present with chest problems in children are described here.

The normal term infant has undetectable serum levels of IgM and IgA at birth and these rise progressively in the first 2–3 years of life\textsuperscript{32,33}. The maternal IgG which crosses the placenta into the fetus disappears within 5–7 months. The infant’s own IgG appears at significant levels at 4–8 months and rises for 2–3 years. Anti-protein antibodies are produced in the first few months of life, but the ability to produce IgG antibodies against polysaccharide antigens, such as the capsules of certain bacteria, matures much more slowly and is only effective after 2 years. IgG has four sub-classes (1–4) which differ in concentration, structure and function. Antibodies against protein are mainly of the IgG1 and IgG3 subclasses and those against polysaccharides are predominantly of the IgG2 subclass.

### Table 4 Classification of primary immunodeficiencies

<table>
<thead>
<tr>
<th>Immunodeficiency and examples</th>
<th>Major pathogens in this group</th>
<th>Investigations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ANTIBODY (B-CELL) DEFICIENCY</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>X-linked agammaglobulinaemia (XLA)</td>
<td>H. influenzae</td>
<td>Immunoglobulins (G, A, M, E)</td>
</tr>
<tr>
<td>IgA, IgG subclass deficiency</td>
<td>Strep. pneumoniae</td>
<td>IgG subclasses</td>
</tr>
<tr>
<td>Specific antibody deficiency</td>
<td>Giardia lamblia</td>
<td>Specific antibodies</td>
</tr>
<tr>
<td>Common variable immunodeficiency</td>
<td>ECHO virus</td>
<td>B-cell populations</td>
</tr>
<tr>
<td></td>
<td>Salmonella spp.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>M. pneumoniae</td>
<td></td>
</tr>
<tr>
<td><strong>DEFECTIVE CELLULAR IMMUNITY (T cell deficiency) and SEVERE COMBINED IMMUNODEFICIENCIES (SCID)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenosine deaminase (ADA) deficiency</td>
<td>Herpes simplex, zoster</td>
<td>White cell differential</td>
</tr>
<tr>
<td>Hyper IgM syndrome</td>
<td>CMV, EBV, measles, RSV</td>
<td>Chest X-ray (thymic shadow)</td>
</tr>
<tr>
<td>Major histocompatibility complex deficiency</td>
<td>Pn. carinii</td>
<td>Lymphocyte populations</td>
</tr>
<tr>
<td>Wiskott-Aldrich syndrome</td>
<td>Streptococci, H. influenzae</td>
<td>Mitogen responses</td>
</tr>
<tr>
<td></td>
<td>Candida, Aspergillus</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mycobacteria (typical and atypical)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cryptosporidium</td>
<td></td>
</tr>
<tr>
<td><strong>PHAGOCYTE DEFECTS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic granulomatous disease (CGD)</td>
<td>Staph. aureus</td>
<td>White cell differential</td>
</tr>
<tr>
<td>Familial, cyclical or auto-immune neutropenia</td>
<td>Streptococci</td>
<td>Chemotaxis, phagocytosis</td>
</tr>
<tr>
<td>Leukocyte adhesion defects</td>
<td>Candida, Aspergillus</td>
<td>Nitroblue tetrazolium test</td>
</tr>
<tr>
<td>Hyper IgE syndrome (Job’s syndrome)</td>
<td>Enteric Gram-negative bacteria</td>
<td></td>
</tr>
<tr>
<td><strong>COMPLEMENT DEFICIENCY</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mannose-binding protein</td>
<td>Strep. pneumoniae, H. influenzae</td>
<td>C3, C4, CH 50 levels</td>
</tr>
<tr>
<td>C3 or C5 deficiency</td>
<td>Neisseria meningitidis</td>
<td></td>
</tr>
</tbody>
</table>

This is not an exhaustive or complete classification. The investigations are for disorders of that component of the immune system and not the specific disorders.
It is now recognised that many children with recurrent chest infections have abnormalities in their ability to produce specific antibodies to common respiratory pathogens such as the *Strep. pneumoniae* or *H. influenzae* which is commonly isolated from their sputum. Many of these children are diagnosed as suffering from asthma and are receiving high doses of inhaled steroids and other asthma therapies. Important clues to the diagnosis include the lack of response to high doses of asthma treatment, the presence of a productive cough and coloured sputum, and improvement with courses of antibiotics. There may be a history of recurrent upper respiratory infections, such as otitis media or tonsillitis. If an antibody deficiency is suspected, total serum levels of IgG, IgM, IgA and IgE should be measured. As the normal ranges of these proteins change during childhood, the measured values must be compared to the age-appropriate normal values, ideally from the same laboratory. There is controversy about the value of also measuring IgG sub-class levels as not all children with ‘deficient’ sub-classes have evidence of an increased susceptibility to infection. Nevertheless, IgG subclass deficiency, and particularly IgG2 deficiency, can be associated with severe bronchiectasis and many clinicians still measure IgG subclasses.

It is important to measure serum levels of specific antibodies against protein antigens (tetanus and diphtheria toxoids) and polysaccharide antigens (*H. influenzae* type b [Hib] and *Strep. pneumoniae*). A key element of the evaluation of humoral immunity is the assessment of the child’s ability to produce normal levels of specific antibodies in response to the routine childhood immunisations or 4 weeks after test vaccinations with Hib and polyvalent pneumococcal vaccines (Pneumovax®). Care is needed in the interpretation of these tests as the child’s age profoundly influences the response to these immunisations. For example, a persistently low level of anti-pneumococcal antibodies after Pneumovax® in a 10-year-old suggests a pathological defect in antibody production, whereas low levels and the lack of a response in a 2–3-year-old is normal and simply indicate physiological immaturity. It is difficult to make a definite diagnosis of a specific anti-pneumococcal antibody deficiency in a child aged less than 5–6 years.

Selective IgA deficiency is the commonest immunodeficiency with an incidence of 1:400–700. Many affected individuals are asymptomatic, but others, and particularly those who have an associated IgG subclass or specific antibody deficiency, suffer from recurrent sinopulmonary infections. As serum IgA levels are low in healthy children and do not reach adult levels until the age of 8 or 9 years, a diagnosis of IgA deficiency should not be made in children below the age of 4 years.

In another important antibody deficiency, X-linked agammaglobulinaemia, there are low or undetectable levels of all the major immunoglobulins due to abnormalities of the BTK gene and B-cell differentiation in
affected boys. There may be an associated neutropenia. Pyogenic infections such as pneumonia first appear after 6–12 months. Unless treated with regular intravenous or subcutaneous immunoglobulin therapy and aggressive antibiotic treatment of acute infections, this progresses rapidly to chronic bacterial bronchitis and irreversible lung damage with bronchiectasis.

**T-cell deficiencies**

T-lymphocytes are essential not only in controlling viral, fungal, mycobacterial and protozoal infections, but also in aiding B-cells to produce immunoglobulins. Children with T-cell deficiencies can present with severe bacterial infections as well as the classic opportunistic infections. Primary T-cell deficiencies are rare inherited disorders. Children with severe combined immunodeficiency (SCID) have profoundly defective T-cell and B-cell function. Although they can present with recurrent chest infections, these are often associated with other severe acute infections, including septicaemia, severe and refractory mucocutaneous fungal infections and enteropathies. Most untreated children die in infancy and the only cure is bone marrow or stem-cell transplantation.

Many children with DiGeorge syndrome, in which there is a microdeletion of chromosome 22q11.2, have a milder T-cell deficiency, with reduced lymphocyte and T-cell numbers and poor in vitro T-cell proliferation responses to mitogens such as phytohaemagglutinin or poke weed mitogen. These defects often improve as the child grows older, but affected children may have recurrent chest infections and bronchiectasis in early childhood.

**Phagocyte disorders**

Primary disorders of phagocyte numbers or function are relatively uncommon in children. Recurrent sinopulmonary, gastrointestinal and soft tissue infections due to *Staph. aureus, Burkholderia cepacia, Serratia marascens* and fungi are the usual mode of presentation. In boys with chronic granulomatous disease (CGD), the commonest serious phagocytic disorder, in which there is defective killing of ingested micro-organisms, cavitating pneumonia which responds poorly to antibiotic therapy is a common presentation. Severe pneumonias, empyemas and bronchiectasis are common in children with the hyper-IgE (Job) syndrome, who have a wide variety of defects of neutrophil, lymphocyte and humoral function as well as very high levels of serum IgE.

**Disorders of ciliary function**

In healthy children, the microcilia of the respiratory epithelium beat in a regular co-ordinated manner, propelling mucus proximally to the
opharynx where it is swallowed or expectorated. The mucus provides both a physical and a chemical barrier to pathogens.\textsuperscript{15,38}

The estimated prevalence of primary ciliary dyskinesia (PCD) is 1:16,000–20,000.\textsuperscript{38} Recent developments in high speed digital imaging have led to the identification of an increasing number of congenital defects of ciliary structure, beat pattern and frequency when used in conjunction with electron microscopy studies of nasal epithelial brush biopsies.\textsuperscript{15} Many cases of PCD are undiagnosed\textsuperscript{38} reflecting poor awareness of the spectrum of the clinical patterns of these disorders and the difficulty in making an accurate diagnosis. Most cases are autosomal recessive, but other patterns of inheritance have been reported – the affected genes have not yet been identified. Males and females are equally affected.

Children with primary ciliary dyskinesia have abnormal mucociliary clearance. PCD may present in new-born infants with tachypnoea or pneumonia, sometimes associated with nasal obstruction and a mucopurulent discharge. In the older infant and child, it typically presents with a persistent productive cough, atypical asthma, or occasionally severe gastro-oesophageal reflux, and later with the features of bronchiectasis. As the upper respiratory tract is also affected, chronic purulent rhinitis, sinusitis, and chronic secretory otitis media with effusion and conductive deafness are often also present.\textsuperscript{38} Half of children with classical Kartagener’s syndrome have situs inversus and dextrocardia in addition to these features and there is an increased incidence of congenital heart disease, hydrocephalus and oesophageal atresia. Most affected males are infertile because of immotile spermatozoa and affected women can be subfertile.

Making the diagnosis of primary ciliary dyskinesia is technically difficult. It depends on the assessment on ciliary structure and function using the specialised techniques mentioned above and few centres have the ability to produce reliable results. False negatives and false positives do occur. Abnormal ciliary function is also seen in asthma, cystic fibrosis and after certain viral and bacterial infections (secondary ciliary dyskinesia). Traditional tests of mucociliary clearance, such as the saccharin test, are not reliable in children. Nasal nitric oxide is lower in children with PCD than in healthy controls or children with asthma and other forms of bronchiectasis and this may prove to be a useful screening test for this group of conditions in the future.\textsuperscript{39}

**Congenital abnormalities of the lung**

Recurrent or persistent chest infections are common in children with congenital abnormalities of the airways, lung parenchyma and pulmonary
vascularity. For example, repeated episodes of pneumonia are often the presenting feature of lobar sequestration, bronchial stenosis and bronchomalacia, and cystic adenomatoid malformations of the lung. Such an abnormality should be suspected if one lobe is repeatedly infected or if there is incomplete resolution after treatment. Computerised tomography and magnetic resonance scanning are helpful in defining the anomaly prior to surgical excision.

Children born with oesophageal atresia and tracheo-oesophageal fistula often have repeated episodes of pneumonia and bronchitis in early life as a result of persisting abnormalities of airway and oesophageal function. The condition has an incidence of 1:3000 and associated vertebral, anal, cardiac, renal or limb defects (VACTERL anomalies) are seen in up to 50% of affected children. In one series of 334 survivors of tracheo-oesophageal fistula with oesophageal atresia, 31% had had one or more episodes of pneumonia in the first 5 years of life and 5% had been admitted on more than 5 occasions. Many more had recurrent ‘bronchitis’ in childhood. The rates of pneumonia and bronchitis fall as the children grow older. Gastro-oesophageal reflux, oesophageal dysmotility and strictures all predispose to recurrent aspiration pneumonia in these children. Some require further oesophageal surgery to prevent progressive lung damage and to allow adequate nutrition. Both restrictive and obstructive patterns of lung dysfunction are present in 18–60% of survivors.

**Tuberculosis**

Tuberculosis should be considered in any child with a persistent productive cough, particularly if there are systemic features such as fever, weight loss or general malaise. Since most tuberculous infections are transmitted by inhalation, primary lesions occur in the lungs in over 95% of infected children. As with adults, there are several different clinical and radiological patterns of lung disease that can develop from the primary complex. These include effusions, cavitation, bronchial obstruction due to mediastinal lymphadenopathy with atelectasis or distal emphysema, tuberculous pneumonia, endobronchial tuberculosis, or miliary disease. Post-tuberculous bronchiectasis is rare nowadays. Extrapulmonary manifestations, of which meningitis is the most serious, are more common in children than in adults. The diagnosis depends on a high index of suspicion, tuberculin skin testing, radiology, and microbiology of sputum and gastric washings.

**Investigation of the child with chronic suppurative lung disease**

It is impossible to overemphasise the importance of the clinical history and examination in the assessment of these children.
The plain chest X-ray is valuable in assessing the severity and distribution of lung involvement. Wide-spread changes such as bronchial wall thickening or inflammation involving several lobes suggests a systemic disorder such as cystic fibrosis, ciliary dyskinesia or an immunodeficiency disorder. Focal changes are more common if there is a congenital abnormality, an inhaled foreign body or bronchial obstruction for some other reason. High resolution computerised tomography (HRCT) is more sensitive than plain radiographs at revealing bronchiectasis: it has largely replaced bronchography. It can also show localised areas of gas-trapping (hyperinflation) and interstitial fibrosis not evident on the chest X-ray, for example in children with bronchiolitis obliterans. CT scanning and magnetic resonance imaging are both helpful for assessing congenital anatomical abnormalities, such as sequestration or cystic adenomatoid malformations. Isotope scans provide useful evidence about regional ventilation and perfusion.

All children with persistent cough should have their sweat electrolytes measured. The sweat test remains the standard diagnostic test for CF, although CF gene mutation studies are being used increasingly. Other investigations include bacteriological studies on sputum if this can be produced; viral and mycoplasmal antibody levels; tuberculin skin testing; and in selected cases, immune function tests. All children should have a full blood count and white cell differential: persistent lymphopenia or neutropenia may be present even when the child is well.

Which immune tests are performed will depend on the nature and severity of the respiratory symptoms. For example, in the child who has repeated episodes of cough with purulent sputum containing Strep. pneumoniae or H. influenzae, but who is otherwise well with no clinical or radiological evidence of lung damage, measurement of immunoglobulin and immunoglobulin subclass levels, and specific antibody levels against pneumococcus, tetanus and Hib would be appropriate, as a specific antibody deficiency is the most likely diagnosis. Children with low Hib and anti-pneumococcal antibody levels should be immunised with Hib vaccine and (over the age of 4 years) Pneumovax® and have their antibody levels repeated 4–6 weeks later. By contrast, a child with severe opportunistic pneumonia demands a detailed assessment of cellular and humoral immune function (Table 4). This should be planned with a clinical immunologist.

Flexible fibre-optic bronchoscopy is now established as a key investigation in the assessment of children with chronic lung sepsis or suspected immunodeficiency. Microbiological and cellular specimens can be obtained by suction, by the use of a protected brush, or by broncho-alveolar lavage. Bronchoscopy also allows a detailed evaluation of the tracheobronchial anatomy and dynamics and identification of unsuspected foreign bodies.

If recurrent aspiration is suggested by the history, this may be detected by isotope milk scans. Incoordinate swallowing, which is most commonly
seen in children with severe neurodevelopmental problems, such as cerebral palsy or severe myopathies, should be assessed by video fluoroscopic barium swallow\textsuperscript{26}. Although oesophageal pH monitoring can give both false positive and false negative results, it remains the best test for assessing the frequency and severity of gastro-oesophageal reflux. Respiratory ciliary studies require referral to a specialist centre.

**Organisation of care**

The assessment and management of children with chronic suppurative lung disease or recurrent severe infection is complex. It requires the involvement of several disciplines, including respiratory paediatricians, paediatric radiologists, immunologists, physiotherapists and microbiologists. The multidisciplinary team approach that has been so successful in improving the care and prognosis of people with cystic fibrosis is now being adopted for the care of this demanding group of patients in some specialist paediatric centres, including the Royal Liverpool Children’s Hospital. Concentrating the experience of many rare conditions within a specialised team allows the development of a more methodical approach to the clinical care of these children. It also has the potential for the clinical research that is clearly required to establish the optimal care of these children.

**Key points for clinical practice**

- There are many different causes of recurrent chest infections in children. The clinician has to distinguish between children with self-limiting or easily managed conditions, such as recurrent acute viral infections or asthma and those with more severe, often progressive, diseases
- It is important to understand the epidemiology of acute respiratory infections in children and the factors that influence the pattern of these common infections
- A chronic or recurrent cough productive of purulent sputum, or repeated episodes of pneumonia, suggest chronic suppurative lung disease and the possibility of bronchiectasis. These children require detailed and specialist assessment
- The commonest causes of suppurative lung disease are cystic fibrosis, immune deficiencies, congenital lung and ciliary abnormalities, and lung damage caused by acute pneumonia. Other causes include an unsuspected foreign body or recurrent aspiration
- Although a meticulous history and examination are vital in assessing these children, specialist investigations including sweat tests, immune and ciliary
function tests, and bronchoscopy are often indicated. Plain radiology, CT and MR scanning can all help define the site and severity of any abnormalities such as bronchiectasis, atelectasis or congenital anomalies. A multidisciplinary team approach to the assessment and care of this demanding and complex group of children has many advantages

References

Respiratory tract infections due to direct and reflux aspiration in children with neurodisability. Dev Med Child Neurol 1999; 41: 329–43