

# Immune deficiencies in children: an overview

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## ABSTRACT

Primary immune deficiencies (PIDs) are disorders of the immune system that result in increased susceptibility to infectious disease, autoimmunity and malignancy. They are challenging to paediatricians as they can present anytime from birth to adolescence with a wide variety of signs and symptoms. It is important to diagnose PIDs promptly, especially more severe forms to prevent significant morbidity and mortality. However, significant challenges exist in deciding which children to investigate and when. We aim to give a basic understanding of the human immune system, the different presentations in a child that should alert a paediatrician about the possibility of PID and the possible underlying diagnosis. Additionally, we have developed a framework for a stepwise approach to investigating these children.

## INTRODUCTION

Immune deficiencies in children are a heterogeneous group of disorders in which there is a defect in the normal function of the immune system. This leads to increased susceptibility to infection, autoimmunity or malignancy. Immune deficiencies can be either primary or secondary to an underlying disorder, for example, severe burns. There are over 180 defined primary immune deficiencies (PIDs), and increasing numbers are being recognised.<sup>1</sup> There is particular increasing recognition of 'non-classical' forms of immune deficiency where defects in the immune system may predispose patients to a narrow range of pathogens (rather than multiple pathogens seen in classical PID). These may present in childhood but then improve and may be affected by environmental factors.<sup>2</sup> The clinical expression of immune deficiency is therefore a spectrum from 'normal' to severe forms of disease and is a rapidly developing field. The incidence of all currently recognised paediatric PIDs taken together is

approximately 1:2000;<sup>3</sup> however, more severe forms such as severe combined immune deficiency (SCID) are rare (approximately 1 in 70 000).<sup>4</sup> Early recognition of a child with PID, especially the severe forms such as SCID is important as successful treatment outcomes are dependent on early diagnosis.

The majority of children that present with signs or symptoms raising suspicion of an underlying immune dysfunction will in fact have a normal immune system. However, consideration of the possibility of a PID is the key to diagnosis and reduction of morbidity and mortality.<sup>5</sup> General paediatricians, alongside general practitioners and paediatric specialists, play an essential role in identifying children that require further investigation. Sixty-five per cent of children with PIDs will be referred initially to a general paediatrician.<sup>6</sup> Although the time taken to diagnose PID has decreased in recent years, the average delay in diagnosis is 1.9 years for adults and children resulting in significant morbidity and mortality.<sup>6</sup> The challenge for these clinicians is to differentiate normal children who require reassurance; children that require further screening investigations due to a differential of PID and follow-up; and children that have clinical signs and symptoms consistent with PID and require further diagnostic evaluation. Clinicians also need to be aware of the presenting features and have a low threshold for suspecting PID. This article aims to give a background of immune deficiency, when to consider immune deficiency and a pragmatic approach to initial investigation of immune deficiency in children.

## THE HUMAN IMMUNE SYSTEM—WHAT CAN GO WRONG IN IMMUNE DEFICIENCY?

For simplicity, the human immune system can be thought of as acting on three

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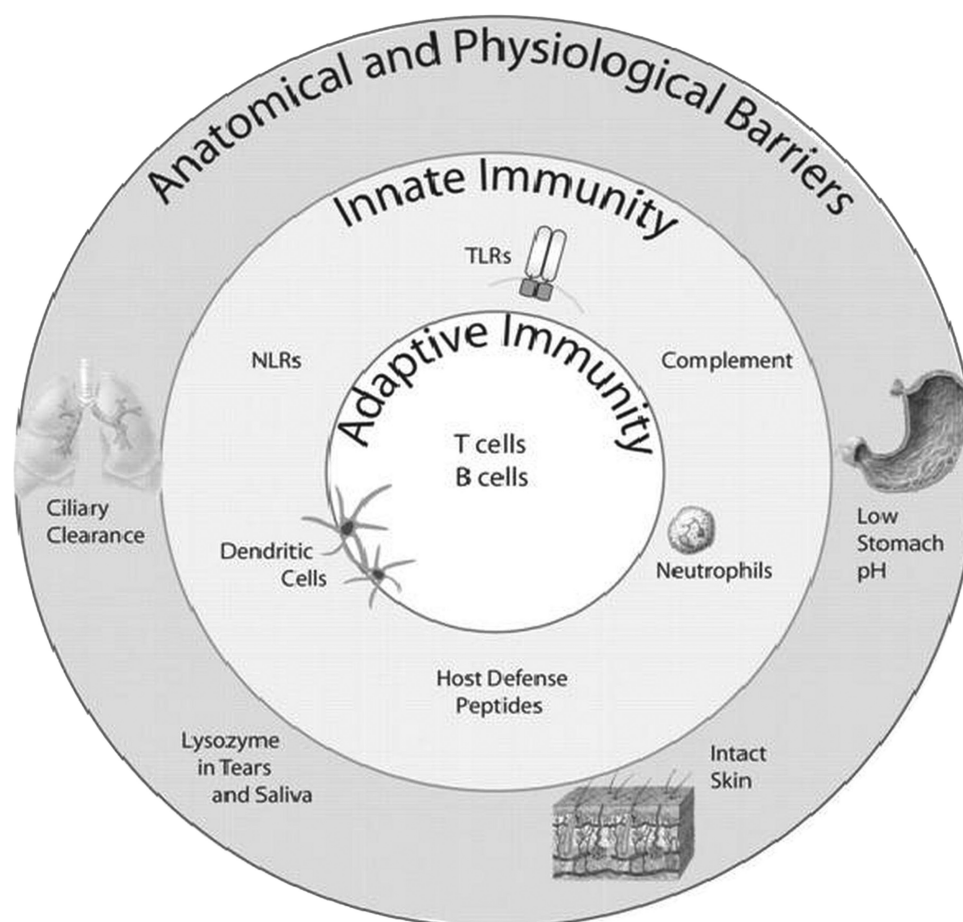


**Figure 1** Three levels of human defence against infection. (reproduced after permission from Turvey).<sup>7</sup>

levels<sup>7</sup> as shown in figure 1. These levels do not act independently of one another, and their interactions can be complex. Immune deficiencies, primary and secondary, affect the immune system at any one or a combination of these three levels.

1. Anatomical and physiological barriers: Skin and mucous membranes provide the important first line of defence. These include intact skin, vigorous mucociliary clearance mechanisms, low stomach pH and bacteriolytic lysosomes in secretions such as tears and saliva. Defects in these barriers, such as burns, patients with central lines or endotracheal intubation result in an increased susceptibility to infection.
2. Innate immunity: Macrophages/monocytes, eosinophils and neutrophils are important in the defence against many microorganisms.<sup>8</sup> They also have an important role in the initiation and direction of the adaptive immune response and removal of pathogens targeted by the adaptive immune response. The innate immune system recognises unopsonised microorganisms as foreign by pattern recognition receptors (eg, Toll-like receptors), which bind to glycosylated proteins on bacterial cell surfaces. Genetic defects in these, for example, neutrophil development or toll-like receptor signals, or their pathways, result in immune deficiencies. Cells of the innate immune system can also recognise, with better

avidity, opsonised pathogens coated in antibody, often acting as the final mechanism in the adaptive immune pathway.

3. The adaptive immune system is made up of T (CD4 and 8) and B lymphocytes (CD19) and is designed to provide a specific defence and increase protection against subsequent re-infection with the same organism by the development of a memory response.<sup>8</sup> The body's response to vaccination is an example of the adaptive response and is more rapid, stronger, better targeted and IgG or CD8 mediated with repeated challenges. SCID, the most severe forms of PID, has defects in B- and T-cell functions.

### THE NORMAL CHILD

Normal children, especially those less than 2 years old, have a relatively immature immune system. Some of the reasons that infants particularly are at a greater risk of infection are detailed below.

Despite T and B lymphocyte counts being generally higher in children than in adults throughout the first years of life, the majority are naïve cells that slowly form a pool of memory cells.<sup>9</sup> T lymphocytes produce less interleukin and interferon and induce less IgG production from neonatal B lymphocytes.<sup>9</sup>

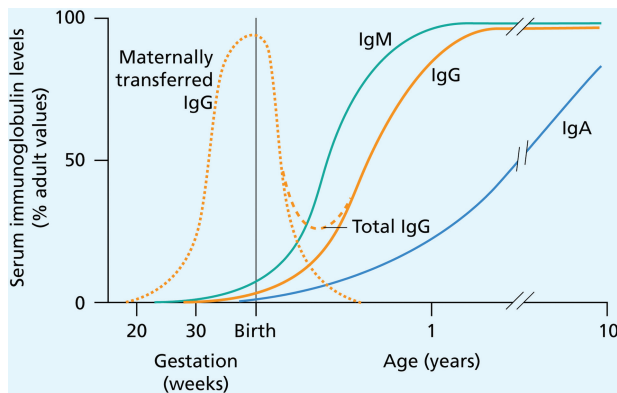


**Figure 2** Serum immunoglobulin levels and age.<sup>10</sup>

Immunoglobulin G (IgG) production slowly increases during the first months of life. This, coupled with waning maternal transplacental IgG from birth, means that by 6 months infants have a transient immunoglobulin deficiency. Preterm babies start with lower maternal IgG levels, and therefore, have lower trough levels and reach immune competence later after birth. Changes in serum immunoglobulin levels with age are shown in figure 2. This relative antibody deficiency coupled with neutrophil numbers that are more easily depleted during infections, particularly in neonates, and the complement that does not reach adult function for a number of months make infants more prone to severe infections.

Children under the age of 2 years are also often unable to mount a T-cell-independent response to polysaccharides. They are more susceptible to polysaccharide encapsulated organisms such as pneumococcus, meningococcus and haemophilus B.<sup>8</sup> These responses generally mature between 2 and 5 years. Conjugate forms of vaccines such as Hib, meningococcal C and Prevenar 13 need to be given under this age rather than plain polysaccharide vaccines.

A maturing immune system alongside frequent first contact with numerous infections makes young children prone to developing common infections. The frequencies of these infections vary enormously; up to 11 respiratory infections/year in infancy, 8 in pre-school years and 4 in school aged children,<sup>11</sup> which can last 8–14 days<sup>12</sup> and result in a cumulative ‘sick period’ of 3–5 months per year for infants and 1–2 months per year for preschool/school children. This means that the differentiation of these ‘normal’ children from those with PID is often difficult.

### WHEN TO SUSPECT AN IMMUNE DEFICIENCY

The most common presenting symptoms to general practitioners and paediatricians in children with suspected immune deficiency are recurrent upper and lower respiratory tract infections.<sup>6</sup> In children, most of these infections will be viral in origin; they usually recover completely and are otherwise well. These

infections are also common in children with PID. However, children with PID can also present with other features, for example, failure to thrive, skin manifestations and autoimmune conditions, which may give clues to the underlying diagnosis. Rates vary, but about 50% of children referred with recurrent infections will be normal, 30% will have atopy, 10% will have a chronic illness and only 10% will have PID.<sup>13</sup> It is important to recognise that immune deficiency and atopy can coexist and children who are atopic also have increased risk of respiratory infection.<sup>14</sup> Children with chronic illness that compromises the immune system, such as hypotonia causing poor cough and uncoordinated swallow, indwelling catheters, pelvico-ureteric obstruction and skin breakdown, will be more susceptible to recurrent infection.

Various groups have developed models to permit the differentiation of PID from non-PID patients. These are generally based upon the assumption that children with PID compared with normal children are more likely to have a Serious infection (eg, meningitis, peritonsillar abscess), and/or a Persistent infection (eg, does not improve with appropriate treatment), and/or an Unusual infection (eg, Burkholderia cepacia or Pneumocystis jiroveci), and/or a Recurrent infection (appear to have resolved but re-appear). An accurate history of ‘SPUR’ infections can be difficult to ascertain in practice but can be a useful tool to raise a suspicion of possible PID and should prompt a closer detailed history, focused examination and consideration of first-line investigations.

The ‘10 warning signs’ model (table 1) was developed by the Jeffrey Modell Foundation<sup>15</sup> and has been used for a number of years to help clinicians identify those at possible risk of PID. This model was based upon expert guidance. Two recent reviews of patient cohorts have demonstrated that these warning signs have low sensitivity and specificity. A review into cases of children evaluated for PID at a referral centre revealed that of 140 children investigated for PID, 23% were diagnosed with PID.<sup>14</sup> The majority of those had antibody deficiency, with one case of

**Table 1** The 10 warning signs for paediatric primary immune deficiency<sup>15</sup>

|                                                                      |                                                        |
|----------------------------------------------------------------------|--------------------------------------------------------|
| ≥4 new ear infections within 1 year                                  | Recurrent deep skin or organ abscesses                 |
| ≥2 serious sinus infections within 1 year                            | Persistent thrush in mouth or fungal infection of skin |
| ≥2 months of oral antibiotic treatment with little effect (possibly) | Need for IV antibiotics to clear infections (possibly) |
| ≥2 episodes of pneumonia within 1 year (depending on organism)       | ≥2 deep-seated infections, including septicaemia       |
| Failure of an infant to gain weight or grow normally                 | A family history of PID                                |

PIDs, primary immune deficiencies.

congenital neutropenia and one 22q11.2 deletion syndrome. The '10 warning sign model' had a sensitivity of 63% and a specificity of 23% in this cohort.<sup>14</sup> Over one-third of children with PID did not have any early warning signs present. Another study looking at 430 children with PID compared to 133 matched controls who had severe or unusual infections but did not have PID identified three important factors in the diagnosis of PID: a family history of PID, use of intravenous (IV) antibiotics and failure to thrive.<sup>16</sup> Final diagnoses in these children were T-cell defects (56%), antibody deficiency (21%), phagocyte defects (17%) and complement deficiency (5%). Together, these three features were able to correctly identify PID in over 96% of patients with neutrophil and complement PID, 86% of T-cell PID and 60% antibody PID. Worryingly in this cohort, in children with more severe PID (including SCID), waiting for the appearance of two or more warning signs would have delayed the diagnosis in over one-third patients. Consequently the '10 warning signs' are a less than

ideal method for early detection of PID and are currently being reviewed.

### Clinical patterns of presentation

It can be useful to consider immune deficiencies presenting in recognisable patterns of clinical presentation, which give clues to the underlying diagnosis and can guide initial investigations.

The European Society for Immunodeficiencies (ESID) have produced guidelines to assist non-immunologists in evaluating patients with possible PID, updated in 2011, by grouping them into seven clinically recognisable patterns of presentation<sup>17</sup>; table 2 incorporates these guidelines.<sup>17 21</sup>

### Age at presentation

In general, age at presentation outside of the neonatal period is not particularly useful in guiding the diagnosis or raising the possibility of PID. The more severe PIDs, such as SCID, usually present in the first 3–6 months although some types of 'classical' SCID can

**Table 2** The European Society for Immunodeficiencies (ESID) clinical guidelines grouping by clinical patterns of presentation (modified from de Vries E<sup>17</sup>)

| Presentation                                                | Possible further clues (adapted from 17)                                                                                                                                                                                     | Possible immune deficiency                                                                                                                         | Differential                                                                                                                                                                |
|-------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Recurrent ENT and airway infection (majority of cases)      | Bronchiectasis particularly associated with antibody deficiency. <sup>18</sup><br>Single isolated episodes of bacterial rhinosinusitis in children do not require screening for PID. <sup>19</sup>                           | Antibody deficiency<br>Phagocyte deficiency<br>HIV<br>Wiskott-Aldrich Syndrome<br>Complement deficiency                                            | Normal child (majority of cases)<br>Asthma, allergy<br>Adenoidal hypertrophy<br>Gastro-oesophageal reflux<br>Inhaled foreign body<br>Cystic fibrosis<br>Ciliary dyskinesias |
| Failure to thrive from early infancy                        | Particularly when associated with chronic diarrhoea, rash, Candida                                                                                                                                                           | T-lymphocyte deficiency (SCID)<br>HIV                                                                                                              | Wide variety                                                                                                                                                                |
| Recurrent pyogenic infections                               | Including granulomatous inflammation and poor wound healing<br>Invasive Aspergillus or Burkholderia raises possibility of chronic granulomatous disease (CGD)<br>May be associated with inflammatory bowel disease (CGD)     | Neutrophil defects                                                                                                                                 | Skin barrier breach, for example, eczema<br>Staph aureus carriage, especially if PVL toxin positive<br>Neutropenia<br>Malignancy                                            |
| Unusual infections or unusually severe course of infections | Invasive pneumococcal disease when isolated from CSF or a serotype covered by the vaccine<br>A single episode of Herpes Simplex Encephalitis in a child should be investigated for innate immune defect (TLR3) <sup>20</sup> | T-lymphocyte deficiency (SCID)<br>HIV<br>Wiskott-Aldrich Syndrome<br>Defects of innate immunity                                                    | Secondary immunodeficiency<br>Malignancy, malnutrition, chronic disease, immunosuppressive disease                                                                          |
| Recurrent infections with the same type of pathogen         | Recurrent episodes meningococci or other encapsulated bacteria or infection with uncommon serotype (W135 or Y in UK).                                                                                                        | Encapsulated—antibody deficiency or complement deficiency<br>Candida—T-lymphocyte deficiency<br>Mycobacteria—macrophage—T-cell interaction problem | Increased exposure<br>Inadequate first-line treatment or drug resistance<br>Anatomical defects, for example, recurrent aspiration, blocked Eustachian tube or CSF fistula   |
| Autoimmune or chronic inflammatory disease                  | Increasingly recognised as a feature of PID                                                                                                                                                                                  | Common variable immunodeficiency (CVID)<br>Haemophagocytic lymphohistiocytosis (HLH)                                                               | Other auto-immune disease<br>Systemic Lupus erythematosus                                                                                                                   |
| Syndrome characteristic combinations of clinical features   | PID is increasingly being diagnosed in more genetically determined diseases                                                                                                                                                  | DNA repair defects<br>Hyper IgE syndrome<br>Microdeletion 22q11 (DiGeorge)                                                                         |                                                                                                                                                                             |

CSF, cerebrospinal fluid; ENT, ear, nose and throat; PIDs, primary immune deficiencies; PVL, Pantan-Valentine leukocidin; SCID, severe combined immune deficiency; SLE, systemic Lupus erythematosus.

present later in childhood (eg, hypomorphic mutations of recombination activating genes). O'Sullivan and Cant suggest particular warning signs within the first year of life that require prompt initial investigation and discussion with an immunologist<sup>21</sup>:

1. Oral thrush, chronic diarrhoea or failure to thrive in the first months of life
2. Recurrent infections with bacterial pathogens, opportunistic organisms and viruses
3. Pneumonitis that does not clear
4. Extensive skin lesions, such as rashes with erythroderma or eczema that do not resolve with simple therapy
5. Delayed umbilical cord detachment (more than 30 days)
6. Hepatosplenomegaly, lymphadenopathy
7. Congenital heart defects, particularly conotruncal anomalies
8. Family history of PID or deaths in infancy
9. Laboratory findings of lymphopaenia (lymphocyte count <3400 cells/mL), other cytopenias or leukocytosis without infection, immunoglobulin M (IgM) less than 0.2 g/L, IgA less than 0.05 g/L or hypocalcaemia.
10. Absence of thymic shadow on radiograph

Immune deficiencies that classically present in the late teens or early adulthood include common variable immune deficiency (CVID), although this is increasingly being recognised as a paediatric disease, possibly as an extension of transient hypogammaglobulinaemia of infancy.

## EXAMINATION OF A CHILD WITH SUSPECTED IMMUNE DEFICIENCY

Physical examination provides important information when evaluating a child for immune deficiency. Examination of the general health, growth, skin and lymphoid tissue are particularly important and may suggest features of recurrent infection, allergy, chronic disease or specific immune deficiencies. Several immune deficiencies are associated with eczema including SCID, Omenn syndrome, hyper IgE and Wiskott-Aldrich syndrome. Non-healing sores, cutaneous granulomas and impetigo may suggest underlying immune deficiency. Immune deficiencies can either lead to paucity or overgrowth of lymphoid tissues (eg, lymph nodes, tonsils, spleen). Absence of lymphoid tissue suggests SCID or combined immune deficiency. Lymphadenopathy and hepatosplenomegaly can be seen in antibody deficiencies (eg, common variable immune deficiency, CVID), apoptosis defects (eg, Fas ligand deficiency) and HIV. Suppurative adenitis is usually seen in chronic granulomatous disease.

Physical examination findings that could point to PID are summarised in table 3.

## SECONDARY IMMUNE DEFICIENCIES

Children may present with an immune deficiency secondary to an underlying disorder. Secondary

**Table 3** Physical examination findings that could point to primary immune deficiencies (PIDs)<sup>17</sup>

|                      |                                                                                                                                                       |
|----------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------|
| General appearance   | Poor weight gain<br>Short stature<br>Dysmorphism (eg, DiGeorge facies)                                                                                |
| Ear, nose and throat | Chronically discharging ears<br>Perforated tympanic membranes                                                                                         |
| Mouth                | Severe gingivostomatitis<br>Ulcers<br>Recurrent or severe candidiasis<br>Poor dentition                                                               |
| Lymphoid tissue      | Excessive lymphadenopathy<br>Absence of lymph nodes or tonsils<br>Organomegaly                                                                        |
| Skin                 | Severe eczema<br>Neonatal erythroderma<br>Severe BCG reaction<br>Extensive warts or molluscum<br>Albinism<br>Telangiectasia<br>Incontinentia pigmenti |
| Eyes                 | Retinal lesions<br>Telangiectasia                                                                                                                     |
| Respiratory          | Clubbing<br>Signs respiratory infection                                                                                                               |

BCG, Bacillus Calmette-Guerin.

immunodeficiencies are more common in children than PID, and clinicians should be aware of this possibility, especially in hospitalised children or intensive care units. Careful history and examination can help distinguish between primary and secondary immune deficiency. Some common and serious causes of secondary immune deficiencies are considered in table 4.

## WHAT SHOULD I DO IF I SUSPECT PID?

Investigations are tailored to identifying the likely underlying pathology given the pattern of presentation (see investigations). The full ESID guidelines are available via the UK Primary Immune deficiency Network (UKPIN) website, where detailed investigations required for each category can be found<sup>22</sup> There are also explanations of what to do whether results are abnormal or normal but there is still a clinical concern. In the majority of patients, common investigations such as full blood count/differential and immunoglobulins are the first-line investigations. In patients with unusual infections or failure to thrive, a T-cell- or combined immune deficiency needs to be investigated; therefore, lymphocyte subsets and a HIV test should be included. If a PID is suspected, then early discussion with a paediatric immunologist is recommended. SCID should be treated as a medical emergency.

A recommended approach to investigating children with PID is outlined in figure 3.

## COMMON INVESTIGATIONS AND THEIR INTERPRETATION

### Neutropenia

Neutropenia is defined as a decrease in circulating or absolute neutrophil count to  $<1.5 \times 10^9/L$ . It is

**Table 4** Causes of secondary immune deficiencies in children, with associated immune system defect (defect in innate or physiological barriers, predominantly T-cell defect, predominantly antibody defect) and presenting features

|                                                     | Cause                                                        | Defect                                                                                                                                                                                                                                                                                                                                                | Presentation                                                                                                                                                                                                                                                                                                          |
|-----------------------------------------------------|--------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Defect in Innate immunity or physiological barriers | Breach of anatomical and physiological barriers <sup>7</sup> | For example, central lines, burns, eczema, mechanical ventilation                                                                                                                                                                                                                                                                                     | Increased risk bacterial infections especially staphylococcus and pseudomonas                                                                                                                                                                                                                                         |
|                                                     | Splenectomy/congenital asplenia or polysplenia               | Defect in splenic function including role of phagocytes in clearing encapsulated bacteria <sup>8</sup>                                                                                                                                                                                                                                                | Post surgery or part of congenital abnormality – increased risk infections with encapsulated bacteria, particularly strep pneumonia                                                                                                                                                                                   |
| Predominantly T cell defect                         | HIV                                                          | CD4 T-cell depletion                                                                                                                                                                                                                                                                                                                                  | Multiple but commonly pneumococcal bacteraemia (at all levels of CD4 counts) as well as respiratory and skin manifestations and opportunistic organisms (with significant immune depression) for example, tuberculosis, pneumocystis carinii pneumonia, cytomegalovirus                                               |
|                                                     | Malnutrition                                                 | Complex probably T cell mediated immunity <sup>8</sup>                                                                                                                                                                                                                                                                                                | Particularly increased risk pneumonia, measles and tuberculosis                                                                                                                                                                                                                                                       |
|                                                     | Leukaemia/Lymphoma                                           | Marrow and lymphoid infiltration affecting number and function of immune cells                                                                                                                                                                                                                                                                        | Multiple presentations depending on underlying cause – can present with infection particularly bacterial infections as functionally neutropenic as well as opportunistic infections                                                                                                                                   |
|                                                     | Immunosuppressive and Immune mediating drugs                 | Corticosteroids—wide ranging effects by inducing or suppressing gene transcription<br>Biologics e.g. anti- TNF $\alpha$ agents (Infliximab, etanercept)<br>Cytotoxic—inhibit DNA synthesis and suppress dividing cells for example, tumour, lymphocytes<br>Cyclosporine, tacrolimus interfere with T cell signalling, inhibiting T cell proliferation | Increased risk multiple organisms including viral and fungal<br>Intracellular bacteria particularly TB and salmonella<br><br>Toxic effects on other organs<br>Multiple risk for infection<br>Impaired function against intracellular bacteria, for example, mycobacterium and salmonellae and opportunistic infection |
| Predominantly antibody defect                       | Prematurity                                                  | Reduced maternal IgG transfer during the third trimester, reduced neutrophil bone marrow pool and complement function                                                                                                                                                                                                                                 | Increased risk intracellular bacteria (Salmonella, Listeria monocytogenes) and polysaccharide encapsulated organisms                                                                                                                                                                                                  |
|                                                     | Nephrotic syndrome                                           | Multiple—decreased perfusion of the spleen, urinary loss of complement factor and immunoglobulin, immunosuppressive drugs <sup>8</sup>                                                                                                                                                                                                                | Increased risk encapsulated bacteria particularly pneumococcal spontaneous bacterial peritonitis                                                                                                                                                                                                                      |

further classified as mild ( $1.0\text{--}1.5\times 10^9/\text{L}$ ), moderate ( $0.5\text{--}1.0\times 10^9/\text{L}$ ) or severe ( $<0.5\times 10^9/\text{L}$ ).<sup>23</sup> It is important to remember that there is a variation with age and ethnic origin. Healthy infants of Afro Caribbean origin have been shown to have a neutrophil count  $<1.0\times 10^9/\text{L}$ .<sup>24</sup>

The most common cause of transient neutropenia is postviral infection in normal children. Neutropenia is often picked up incidentally when a full blood count is ordered for reasons other than possible immune deficiency. It does not usually need to be repeated unless there are concerns about underlying immune deficiency, for example, severe or recurrent bacterial infections. More severe forms of neutropenia associated with clinical immune dysfunction can be classified into congenital, cyclical, idiopathic and acquired due to medication, infection, immune mediated, haematological or malignancy.<sup>25</sup>

### Lymphopaenia

Immune deficiency should always be considered in a child with a low lymphocyte count ( $<2\times 10^9/\text{L}$ ), especially in children aged less than 6 months, although the majority will be secondary to viral illness.

However, it is worth remembering that 80% of children with SCID will be lymphopaenic and a persistently low lymphocyte count should not be ignored. Age-matched lymphocyte counts should be used as infants less than 3 months may have a higher total lymphocyte count than older infants. Lymphopaenia is often seen in children presenting to general paediatricians. A retrospective audit identified lymphopaenia in 3% of all infants with a full blood count (performed for a variety of reasons) in a district general hospital over 2 years.<sup>26</sup> There was no evidence that SCID was considered in any of these despite nine patients having clinical features consistent with possible SCID (although none were retrospectively diagnosed with SCID). Persistent lymphopaenia in children  $<2$  years should have initial screening for SCID and discussed with a paediatric immunologist as recommended by UKPIN.<sup>22</sup>

### Lymphocyte subpopulations

Discussion of these is beyond the scope of this document except that normal subpopulations do not always rule out a T-cell immune deficiency. They should be compared to age-matched reference ranges

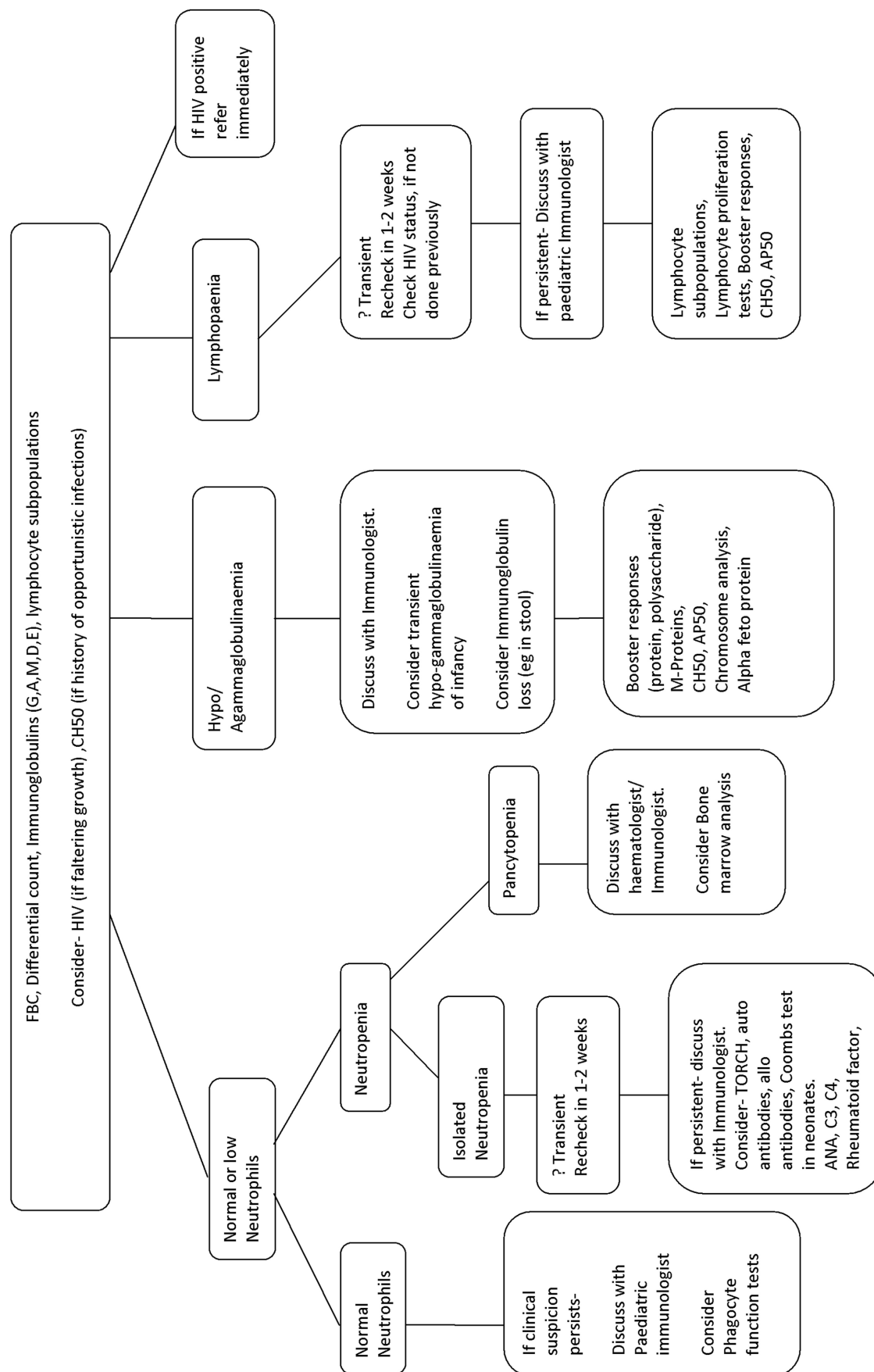


**Figure 3** Investigations in children with possible immune deficiency.

but as with neutrophils often vary with infections, especially if these are severe. These should be discussed with an immunologist should there be any concerns.

#### Immunoglobulins and vaccine responses

Produced by B lymphocytes and plasma cells, immunoglobulins play a central role in the adaptive immune system and are classed into IgA, IgG, IgM, IgD and IgE. IgG constitutes 75% of all immunoglobulins and is the only type that can cross the placenta and hence is largely responsible for the protection of infants in the first few months of life. Immunoglobulin values should always be interpreted with age-specific ranges and in the clinical context. If immunoglobulins are absent, protein loss should also be considered, for example, congenital lymphangiectasia, nephrotic syndrome, chylothorax, which are often associated with low albumin and lymphocyte populations.

It is not uncommon to find that a child's absolute immunoglobulin results are lower (sometimes only slightly lower) than the normal values. If the child is having recurrent infections, then the significance of these results is questioned. It is often not clear whether the low immunoglobulins are responsible for the clinical presentation. It is then useful to look at the function of the immunoglobulin to see whether the child has responded to their primary vaccines. A patient's response to a protein (tetanus) or conjugate (Hib or Prevenar) vaccines are often assessed. A 'low' result does not mean 'no' response but often is due to waning antibody titres after vaccination, which if no antibody deficiency will usually respond rapidly to a booster vaccine dose (measured 4–6 weeks postvaccination). In patients older than 5 years, their response to primary pneumovax was previously assessed to see whether they had a specific deficiency dealing with polysaccharide vaccines. However, Prevenar 13 (a conjugate vaccine) is now used to boost the response and until new serotypes not in Prevenar 13 can be assessed this assay is no longer helpful.

Between 1 in 300 and 2000 people have selective IgA deficiency (sIgA). The majority of people with sIgA have no or minimal symptoms. However some have significantly more upper respiratory or gastrointestinal infections. sIgA can be associated with other antibody or complement deficiencies and needs to be considered in these patients. We do not understand why the majority of patients with this condition remain well.<sup>27</sup>

#### Complement function

Complement deficiencies are rare but increase a child's susceptibility to encapsulated organisms, for example, recurrent pneumococcal, meningococcal or Hib infections. They can present as vaccine failures. If a complement deficiency is suspected, serum urgently centrifuged and frozen should be analysed for C3 levels

as well as markers of complement function, classical and alternative pathway, for example, CH50 and AP50.

#### TREATMENT AND PROGNOSIS

PIDs are a heterogeneous group of disorders, and treatment depends upon underlying diagnosis. Early recognition/identification of the child with PID is the key to treatment. Many PIDs are relatively insidious and cause illness occasionally while others may be rapidly fatal. For the most severe forms of PID (SCID), immune reconstitution can be achieved by bone marrow transplantation, gene therapy or enzyme replacement. Unrecognised SCID carries a mortality of nearly 100% within the first year of life, and prognosis is dependent on rapid diagnosis and definitive treatment.<sup>4</sup> Patients diagnosed with SCID at birth due to a positive family history have a significantly improved outcome compared to the first presenting family member (90% vs 40%).<sup>28</sup> Prior to definitive treatment, children with SCID, combined T- and B-cell deficiencies and other forms of immunodeficiencies should be given prophylactic antibiotics, antivirals, for example, aciclovir (and antifungals if severe) and intercurrent infections need to be treated aggressively. It is important to note that live vaccines, including Bacillus Calmette-Guerin (BCG), mumps, measles, rubella (MMR) and rotavirus vaccines are contra-indicated in children with SCID/suspected SCID or T-lymphocyte defects. Not all types of live bacterial and viral vaccines are contraindicated in all types of immune deficiency, so once a diagnosis is established then specific vaccination programmes can be recommended.

Screening for SCID and other T-cell immune deficiencies by T-cell receptor excision circles (TRECs) analysis on the newborn dried blood spot card, as a surrogate marker of lymphopaenia, is being assessed for probable introduction in the UK. This is already implemented in several US states with encouraging results.<sup>29 30</sup>

Children with less severe PIDs or those who are being investigated for possible PID are often given antibiotic prophylaxis, especially over the winter with aggressive treatment of acute infections. Children with antibody deficiencies often require immunoglobulin replacement therapy. In children, IV access is often problematic and stressful for the patient, family and staff. Subcutaneously administered immunoglobulin (SCIg) is routinely offered to stable children; parents can administer this at home after training with outcomes comparable to IV immunoglobulin (IVIg) and have significant improvement in family quality of life (personal observation).

#### Cases (examples of cases based on authors clinical experience)

**Case 1:** A 2-year-old Caucasian boy presents to his general practitioner (GP) with his third episode of

suppurative otitis media in 6 months. He responded to amoxicillin each time and an ear swab grew *Haemophilus influenzae*. He is fully immunised. He was hospitalised with respiratory syncytial virus positive bronchiolitis when he was 6 weeks old and has also received a further two courses of antibiotics in the last year for a 'chest infections'. He regularly coughs in the winter, and his mother is worried that he may have something wrong. He attends nursery 3 days a week and has been sent home twice in the last month with a fever and cough. There is no family history of atopy and his growth is normal. His older brother had 'low white cells' when he was recently admitted with pneumonia. The GP is concerned about a possible immune deficiency and sends him to general paediatrics for further investigations. Although the examination was normal, the paediatrician is concerned enough to do first-line investigations for a primary immune deficiency—a full blood count, immunoglobulins and an HIV test, which are normal. The mother is reassured and plan agreed for the child to be reviewed in 3 months. In the next review at 3 months, the child is discharged as his symptoms resolved.

**Comment:** Recurrent ear and respiratory infections are common in children with PID but they are very common in normal children, especially under 2 years. This child had no 'SPUR' features; he did not require IV antibiotics and had no family history of PID. His brother's low 'white cell count' is probably secondary to infection, although should be investigated further. A watch-and-wait approach is appropriate here as initial investigations were normal.

**Case 2:** A 12-week-old baby is referred due to failure to thrive (weight 2nd centile; born 50th centile) and a severe nappy rash. Parents are not consanguineous, and this is their only child. She breast feeds well, has loose stools without blood and has a widespread eczematous rash and small palpable lymph nodes in the axillary regions. Her nappy area is oozing and swabs reveal *S. aureus* and *candida spp*. The paediatric registrar is concerned about immune deficiency and orders a full blood count and differential, immunoglobulins and an HIV test. In addition, due to the age and the presenting symptoms, he also orders lymphocyte subpopulations. The full blood count revealed a mild lymphopaenia. The registrar discusses with a paediatric immunologist who advises prompt referral. The lymphocyte subpopulations reveal T cell negative, B cell negative, natural killer (NK) cell positive forms of SCID. The baby is urgently referred for a stem cell transplant.

**Comment:** This is a classic presentation for SCID with failure to thrive, skin involvement and lymphadenopathy. Omenn's syndrome is the most likely diagnosis. This is SCID with low B and T cells, classically due to autosomal recessive mutation in RAG1 or

RAG2 genes, although other recessive mutations are known to be associated. Immune deficiency is the most urgent diagnosis to be ruled out but other diagnoses should be considered. SCID should be treated as a paediatric emergency. Live vaccines are contraindicated in SCID or suspected SCID.

**Case 3:** A 15-year-old Afro-Caribbean boy presents to the paediatric ward with a deep-seated abscess in his buttock region that requires surgical drainage. Oral Co-amoxiclav for 7 days had no effect. He had been admitted a year ago with recurrent abscesses in his axilla requiring IV antibiotics and has received two courses of antibiotics from his GP for sinusitis with upper respiratory tract infections. He was well in early childhood and is fully immunised. There is no family history of recurrent infections. He had lost 7 kg in the past month with increasingly loose mucous bloody stools. Full blood count revealed a borderline neutropenia, anaemia, red cell fragments on film and a positive direct antiglobulin test (Coombs test).

**Comment:** The combination of autoimmunity and recurrent infections prompted a discussion with a paediatric immunologist. Further investigations suggested include full blood count, immunoglobulin levels and a HIV test. Results show normal neutrophils, a low IgA, markedly low IgG 1.2 g/L (normal 5–16) and very low IgM. His lymphocyte subsets were normal. He made no response to tetanus vaccine and was diagnosed with common variable immune deficiency (CVID). His HIV viral load was negative (the antibody test is not useful in antibody deficiency). He was also diagnosed with inflammatory bowel disease. CVID is a mixed group of conditions characterised by low immunoglobulin production in response to infection. This patient has several key features, including hypogammaglobulinaemia, recurrent deep-seated infections, inflammatory bowel disease and probable has autoimmune anaemia.

**Case 4:** A 5-year-old Caucasian boy was referred by GP with poor weight gain and recurrent wheezy episodes despite beclomethasone and salbutamol inhalers and recurrent courses of antibiotics. His parents were non-consanguineous, although had been separated and no longer in contact. He had newborn blood spot screening which looks for phenylketonuria, congenital hypothyroidism, sickle cell disease, cystic fibrosis and medium-chain-acyl-CoA dehydrogenase deficiency (MCADD), all negative. He was fully immunised. Examination revealed a pale, thin child whose weight and height were on the 9th centile. He had scattered crepitations in his chest and was clubbed. He had a productive cough. CXR revealed persistent right lower and left lingular changes possibly bronchiectasis. He had some planar warts over his face but no other skin findings.

Comment: The paediatrician considered PID and sent a full blood count, immunoglobulins, HIV test and a sweat test. His FBC, immunoglobulins and sweat test were normal. He was HIV positive on antibody test, confirmed by PCR. He was promptly referred along with his mother and brother to HIV clinic. His mother had refused antenatal HIV screening but was negative for syphilis, hepatitis B and was rubella immune. He was commenced on antiretroviral medication, his bronchiectasis (confirmed by CT scan) was aggressively managed with physiotherapy and antibiotics, he gained weight and his respiratory symptoms improved. Secondary immune deficiency is more common than PID and should not be forgotten in initial screening. The British HIV association (BHIVA) recommends targeting HIV screening in children who are at high risk, or present with features suggesting HIV, even if they are not thought to be high risk due to ethnicity or family history. Other differentials including PID and cystic fibrosis still should be considered in this case.

## CONCLUSION

Immune deficiencies are important to recognise, and although differentiating children with PID is challenging, there are a number of features in the history and examination that can help. Early identification is important, especially in severe forms of immune deficiency and can result in reduced morbidity and mortality. Although there are numerous types of PID with complex underlying genetic diagnoses the approach to investigating a child with suspected PID can be broadly divided based on clinical patterns of presentation. In the majority of patients' full blood count/differential and immunoglobulins are recommended initial investigations. Causes of secondary immune deficiency

should also be considered. Any case of suspected PID should be discussed with a paediatric immunologist at the earliest available opportunity. Consideration of the diagnosis is the most important step!

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## REFERENCES

- 1 Al-Herz W, Bousfiha A, Casanova JL, *et al.* Primary immunodeficiency diseases: an update on the classification from the international union of immunological societies expert committee for primary immunodeficiency. *Front Immunol* 2011;2:54.
- 2 Casanova J-L, Abel L. Primary immunodeficiencies: a field in its infancy. *Science* 2007;317:617–19.
- 3 Boyle JM, Buckley RH. Population prevalence of diagnosed primary immunodeficiency diseases in the United States. *J Clin Immunol* 2007;27:497–502.
- 4 Yee A, De Ravin SS, Elliott E, *et al.* Contributors to the Australian Paediatric Surveillance Unit. Severe combined immunodeficiency: a national surveillance study. *Pediatr Allergy Immunol* 2008;19:298–302.
- 5 de Vries E, Driessen G. Educational paper: primary immunodeficiencies in children: a diagnostic challenge. *Eur J Pediatr* 2011;170:169–77.
- 6 Primary Immune deficiency Association (PIA) survey. <http://www.oysterhc.co.uk/market-research.cfm> (accessed Dec 2012).
- 7 Turvey SE, Bonilla FA, Junker AK. Primary immunodeficiency diseases: a practical guide for physicians. *Postgrad Med J* 2009;85:660–6.
- 8 Janeway C, Travers P, Walport M, *et al.* *Immunobiology—the immune system in health and disease*. 6th edn. New York: Garland Science Publishing, 2005. Chapter 11, Failures of Host Defence Mechanisms, 470–490.
- 9 de Vries E, de Groot R, de Bruin-Versteeg S, *et al.* Analysing the developing lymphocyte system of neonates and infants. *Eur J Pediatr* 1999;158:611–17.
- 10 Chapel H, Haeney M, Misbah S, *et al.* *Essentials of clinical immunology*. 5th edn. Blackwell Publishing, 2006. p53.
- 11 Grüber C, Keil T, Kulig M, *et al.* MAS-90 Study Group. History of respiratory infections in the first 12 yr among children from a birth cohort. *Pediatr Allergy Immunol* 2008;19:505–12.
- 12 Bush A. Recurrent Respiratory Infections. *Pediatr Clin North Am* 2009;56:67–100.
- 13 Slatter MA, Gennery AR. Clinical immunology review series: an approach to the patient with recurrent infections in childhood. *Clin Exp Immunol* 2008;152:389–96.
- 14 MacGinnitie A, Aloï F, Mishra S. Clinical characteristics of paediatric patients evaluated for primary immunodeficiency. *Pediatr Allergy Immunol* 2011;22:671–5.
- 15 Jeffrey Modell Foundation. *10 Warning Signs of Primary Immunodeficiency*. <http://www.info4pi.org/aboutPI/pdf/General10WarningSignsFINAL> (accessed Dec 2012).
- 16 Subbarayan A, Colarusso G, Hughes SM, *et al.* Clinical features that identify children with primary immunodeficiency diseases. *Pediatrics* 2011;127:810–16.

## Key points

- ▶ Children with primary immune deficiencies (PIDs) are difficult to differentiate from normal children, especially in those less than 2 years of age. However, PIDs need to be considered, especially by neonatologists and general paediatricians to prevent morbidity and mortality.
- ▶ There are a number of screening models for children with PID but they have low sensitivities and specificities.
- ▶ The majority of children will be identified if failure to thrive, requirement for IV antibiotics to treat an infection and or a family history of a PID is used.
- ▶ Initial investigation in suspected child with PID is a small set of widely available laboratory examinations.
- ▶ Early discussion with a paediatric immunologist is advised if PID is considered
- ▶ Early diagnosis and treatment of PIDs save life, prevent morbidity and improve quality of life

- 17 de Vries E, European Society for Immunodeficiencies (ESID) members. Patient-centred screening for primary immunodeficiency, a multi-stage diagnostic protocol designed for non-immunologists: 2011 update. *Clin Exp Immunol* 2011;167:108–19.
- 18 Pasteur MC, Bilton D, Hill AT. British Thoracic Society Bronchiectasis non-CF Guideline Group British Thoracic Society guideline for non-CF bronchiectasis. *Thorax* 2010;65 (Suppl 1):i1–i58.
- 19 Desrosiers M, Evans GA, Keith PK, *et al.* Canadian clinical practice guidelines for acute and chronic rhinosinusitis. *Allergy Asthma Clin Immunol* 2011;7:1–38.
- 20 Sancho-Shimizu V, Pérez de Diego R, Lorenzo L, *et al.* Herpes simplex encephalitis in children with autosomal recessive and dominant TRIF deficiency. *J Clin Invest* 2011;121:4889–902.
- 21 O'Sullivan MD, Cant AJ. The 10 Warning signs: a time for change? *Curr Opin Allergy Clin Immunol* 2012;12:588–94.
- 22 UK PIN and E de Vries. ESID Protocols. *Patient-centred screening for primary immunodeficiency: a multi-stage diagnostic protocol designed for non-immunologists*. <http://www.ukpin.org.uk/home/ESID/index.htm> (accessed Dec 2012).
- 23 James RM, Kinsey SE. The investigation and management of chronic neutropenia in children. *Arch Dis Child* 2006;91:852–8.
- 24 Sadowitz PO, Oski FA. Differences in polymorphonuclear cell counts between healthy white and black infants: response to meningitis. *Pediatrics* 1983;72:405.
- 25 Dale DC, Williams WJ. *Haematology*. 6th edn. New York: McGraw-Hill, 2001. Neutropenia and neutrophilia, 823–34.
- 26 Krishna MT, Tarrant JL, Cheadle EA, *et al.* An audit of lymphopenia in infants under 3 months of age. *Arch Dis Child* 2008;93:90–1.
- 27 Yel L. Selective IgA deficiency. *J Clin Immunol* 2010;30:10–16.
- 28 Brown L, Xu-Bayford J, Allwood , *et al.* Neonatal diagnosis of severe combined immunodeficiency leads to significantly improved survival outcome: the case for newborn screening. *Blood* 2011;117:3243–6.
- 29 Routes JM, Grossman WJ, Verbsky J, *et al.* Statewide newborn screening for severe T-cell lymphopenia. *JAMA* 2009;302:2465–70.
- 30 Chan K, Puck JM. Development of population-based newborn screening for severe combined immunodeficiency. *J All Clin Immunol* 2005;2:391–8.



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