# Assessment of suspected immune deficiency in childhood

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## Abstract

Primary immune deficiencies in children are rare. However, delay in diagnosis can be associated with morbidity from end organ damage and increased mortality. Secondary immune deficiency especially in the context of immune suppressive therapy is increasingly recognised in children. However, the majority of children with infections do not have an underlying disorder. The pattern of infections, pathogens involved and other associated features can direct the clinician to the most likely immunological defect. First line laboratory investigations can be performed by most immunology laboratories. Simple history taking algorithms can be adopted to identify children requiring further investigation. Exciting developments in genetic testing such as whole exome sequencing and newborn screening programmes will help prompt identification of suspected immune deficiency, however the processes of clinical evaluation discussed here will remain of central importance for many years to come.

**Keywords** common variable immunodeficiency; immunoglobulins; lymphocyte subsets; primary immunodeficiency; severe combined immunodeficiency

## Introduction

Primary immune deficiencies (PIDs) are a heterogeneous group of inherited disorders of immune system function. They most commonly give rise to increased susceptibility to infection however immune dysregulation, autoimmunity, aberrant inflammatory responses and increased risk of malignancy are also recognised. To date more than 200 distinct genetic disorders have been identified. The precise incidence of PID is uncertain but has been suggested to affect approximately 1:2000 live births. This is likely to be an underestimate with minor defects such as selective IgA deficiency affecting as many as 1:500 individuals and many other children demonstrating evidence of an immune deficiency that has yet to be genetically determined. Secondary immune deficiencies (in particular those associated with immune suppressive therapy) are increasingly recognised in children. Although the focus of this review will be on the assessment of suspected primary immune deficiency, the principles discussed will also apply to these patients.

This genetic heterogeneity and diversity of clinical presentations means that children with primary immune deficiency may first present to any specialty or in the community, and at any age from the newborn to adolescent. Thorough history taking and examination is essential. Recurrent infections are common in childhood and most children do not have an underlying immune deficiency. When evaluating a child with recurrent infections, the following simple acronym can be used to help determine whether their pattern of infection warrants further investigation: Serious, Persistent, Unusual (pathogens or site), Recurrent (SPUR).

In this review, the most common clinical presentations of children with suspected immunodeficiency will be summarised alongside their initial assessment. Current aspects of management of PID will be considered in a separate review. The accompanying bibliography provides further detail on many of the specific conditions that will be discussed as well as several rare conditions that are outside the scope of this review.

## The infant presenting with recurrent (and opportunistic) infections and failure to thrive (Severe Combined Immune Deficiency – SCID)

Severe Combined Immune Deficiency (SCID) is a paediatric emergency. Delayed diagnosis is associated with significant morbidity and mortality. The underlying disorder is of T cell deficiency or dysfunction. B cell numbers are variably present but functionally impaired due to failure to receive T cell help. Presentation is usually in the neonatal period or early infancy. However, later presentations are recognised (see Pitfalls). These children are at high risk of experiencing overwhelming infections including from opportunistic pathogens, and death within the first 2 years of life is likely if left untreated. The mainstay of treatment remains bone marrow transplant. Several genotypes of SCID are recognised with distinct immunological findings seen on laboratory investigation. However, their clinical presentation is essentially the same.

### Presentation

The most common presenting picture is faltering growth with early onset of recurrent infections (bacterial, viral and fungal). These include opportunistic pathogens such as *Pneumocystis jirovecii*. Persistent candida is common. The child may have chronic diarrhoea (due to enterovirus or rotavirus). There is failure to clear live vaccines including BCG.

### Investigations

1. Full blood count: an absolute lymphopenia should lead to suspicion of SCID until proven otherwise.
2. Lymphocyte markers: evaluation of T, B and NK lymphocyte counts will help to confirm SCID as well as identifying the likely underlying genetic abnormality.

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3. Immunoglobulin levels: even in the presence of B cells, immunoglobulins are usually reduced. However, if presenting within the first 6 months of life, maternal IgG may still be detected. Levels should therefore be interpreted with caution.
4. Additional investigations: functional T cell studies (proliferation assays) and assessment of T cell receptor repertoire may also be required. However, these do not form part of the primary evaluation and initiation of emergency management should not be delayed for these. T cell receptor excision circles (TRECs) are produced as by-products of T cell development in the thymus and are reduced in most forms of SCID. Numbers may be evaluated from the Guthrie dried blood spot card. It is likely that newborn screening for SCID by this method should become available in the UK (as it already is in the US) in the near future. Currently, TRECs can be evaluated by specialist laboratories as a further confirmatory test. Acquisition of the Guthrie card of patient (and potentially siblings, especially if there are features suggestive of immune deficiency) can be helpful.

### Emergency management

We include a summary of early management of suspected SCID (Table 1).

### Pitfalls

1. HIV infection as an alternative cause of absolute lymphopenia must be excluded.
2. Reactive lymphopenia may be seen in children with acute infections. This should resolve in convalescence. A previous normal lymphocyte count makes SCID unlikely.
3. Atypical presentations of SCID: in Omen's Syndrome, CD4+ T cells are present. These are clonally restricted (demonstrate a reduced T cell receptor repertoire) and usually non-functional. A high CD8+ T cell count and evidence of increased T cell activation may be seen when there is materno-fetal engraftment. These may both be associated with a severe erythrodermic rash that may be mistaken for atopic eczema.
4. 'Leaky SCID' is a term given to patients who have SCID but with variably reduced but not absent T cells. Presentation may occur in later childhood. There is still commonly a history of recurrent infections suggestive of a combined T-cell and B cell deficiency although generally the pattern is less severe. Specialist advice with respect to immunological work-up of these complex patients is essential.

**Early management of a child with suspected SCID**

- Inform national specialist centre for paediatric bone marrow transplantation (for immune deficiency)
- Nurse in side room (HEPA filtered/laminar flow if available)
- Do not administer any live vaccines
- If required blood products should be irradiated and CMV negative
- Treat all suspected infections aggressively
- Commence prophylactic co-trimoxazole
- Commence prophylactic anti-fungal and anti-viral therapy
- If BCG has been given — seek specialist advice from microbiology
- Commence immunoglobulin replacement therapy as directed by immunology team

**Table 1**

## The child with recurrent chest and sinus infections caused by encapsulated bacteria (most commonly antibody deficiency)

Most children with antibody deficiencies present with recurrent or persistent bacterial respiratory tract infections, particularly otitis media, sinusitis and pneumonia. The most frequently encountered primary antibody deficiency is common variable immune deficiency (CVID). This affects approximately 1:30,000 individuals and has two main peak incidences of presentation — in early childhood and adolescence. The aetiology of this condition has not been definitively established and indeed, multiple genetic abnormalities are now recognised to exist under the umbrella term of CVID. This may explain the variability of infections and occurrence of other significant features such as autoimmune diseases and granulomatous lesions in the lungs or GI tract. Children with CVID may also struggle to clear enteroviruses (paralytic poliomyelitis with vaccine-strain polio from live oral vaccination has historically been reported). *Campylobacter*, persistent norovirus and *Giardia* infection are also reported.

X-linked agammaglobulinaemia (XLA) occurs due to mutation of the *BTK* gene that codes for the protein Bruton's tyrosine kinase (BTK), involved in the process of B cell maturation. Presentation is similar to that in CVID but usually manifests in infancy (after waning of maternal IgG). A family history of male relatives with recurrent infections is also suggestive although de novo mutations occur.

Selective IgA deficiency is common, affecting approximately 1:500 of the general population. Most individuals are asymptomatic (although an increased frequency of upper respiratory tract and GI infections is sometimes seen). There may also be an increased frequency of autoimmune conditions, including coeliac disease. Further investigations are rarely warranted. However, in a small number of cases, IgA deficiency may evolve to a more significant antibody deficiency. If severe or recurrent infections are observed, further investigations should be performed.

It is possible for some individuals to have normal total immunoglobulin levels but demonstrate a failure to respond to polysaccharide antigens. This is often referred to as specific antibody deficiency and may be associated with increased sinopulmonary infections. In children specific antibody deficiency is often transient and resolves with age.

### Investigations

1. Immunoglobulin levels: this is an essential part of the diagnosis of primary antibody deficiency. Although XLA is most likely to present with a profound panhypogammaglobulinaemia, the pattern of antibody deficiency cannot be used to reliably identify any specific PID.
2. Functional Antibody Levels: it is possible to measure specific antibody levels to some pathogens including the serotypes of Pneumococcus (including many contained within the Prevenar and Pneumovax vaccines), tetanus and *Haemophilus*