

# APPROACH TO THE CHILD WITH RECURRENT INFECTIONS – PRESENTATION AND INVESTIGATION OF PRIMARY IMMUNODEFICIENCY

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## ABSTRACT

Infants and children, as part of normal development of immune competence, experience and survive many infections – mostly subclinical – and a fair number of clinically apparent infectious illnesses. Mature immunity is generally achieved by the time a child reaches school age. An abnormal number and severity of infections are the hallmarks of deficient immunity.

The commonest causes of immunodeficiency worldwide are **malnutrition, HIV and immunosuppressive-iatrogenic** agents.

**Primary immunodeficiencies (PIDs)**, generally the result of genetic defects, are rare conditions. These are suspected when a child or adult suffers from **recurrent, prolonged, severe or unusual infections** which would not normally cause problems in otherwise healthy individuals.

Early diagnosis of PID improves quality of life as **many PIDs are treatable**. The related morbidity and mortality which inevitably accompanies a delayed diagnosis can often be prevented. Unfortunately delayed diagnosis and its consequences are frequently seen in practice in South Africa.

**Algorithms for detecting PIDs** exist for clinical and laboratory investigations. Guidelines for patient management are easily accessed via the Internet and antenatal diagnosis and genetic counselling are becoming a reality. Gene transfer may offer hope for cures eventually.

An overview of approach to history, clinical examination and appropriate laboratory investigation for suspected diagnosis of PID in children is presented.

## INTRODUCTION

With the advent of the African AIDS pandemic the term 'immunodeficiency' has gained new meaning. Some of the infection patterns seen as a result of HIV infection are similar to those seen in the patient with PID. Cluster Differentiation – CD4 counts have become common knowledge and **medical staff are aware of the need for HIV testing** in the patient with recurrent or unusual infections. But when HIV infection has been excluded, there is no evidence of malnutrition, allergies have been addressed as possible causes, the child has been taken out of the crèche, second-hand smoking

has been avoided and recurrent infections continue, the question of primary or inborn deficiencies as a cause should arise. The majority of these present in infancy with a 5:1 male over female predominance because of the X-linked inherited PIDs, but a large number are not recognised until adolescence or early adulthood.

They may occur as frequently as 1/2 000 live births for milder defects<sup>1</sup> and even as frequently as 1/400 in the case of IgA deficiencies which are asymptomatic in the majority of cases. There are currently more than 120 PIDs with known genetic causes – the recent increase in classifications has been facilitated by the completion of the Human Genome Project in April of 2003. Accurate figures for prevalence in South Africa are not available but probably approach those quoted internationally for the well-recognised syndromes. Unusually high incidences of late complement deficiencies have however been reported by Orren *et al.*<sup>2</sup> for the Cape region and other genetic immunodeficiencies particular to the Southern African region may yet be researched.

Despite awareness about immunodeficiency related to the HIV pandemic, **the investigation of the child with recurrent infections is still frequently delayed** in South Africa, and if diagnosed correctly, is managed suboptimally in many cases. Even in developed countries such as the UK diagnostic delays for antibody deficiencies of a median of 5.5 years in adults and 2.5 years in children have been shown.<sup>3</sup> Late diagnosis in this group of patients is tragic as effective intravenous preparations of gammaglobulin became available as early as 1980.<sup>4</sup> **Seamless monitoring is essential** but follow-up is frequently interrupted and suboptimal with transfer of the adolescent to the adult service – as happens to many youngsters with other chronic illnesses too.

## WHAT IS UNACCEPTABLE/ABNORMAL FOR A CHILD IN TERMS OF RECURRENT INFECTIONS?

Most doctors with some years of clinical experience develop a good investigative threshold for this question. It is surprising therefore that the **diagnosis of PID is often equally if not more delayed in more affluent communities in South Africa**. The easy access to broad-spectrum antibiotics, nutritional support – even hyperalimentation, antireflux procedures and the practice of **changing doctors if all else fails** often mark the trail of a late diagnosis in the face of good health care access. Neglect and lack of resources however may precipitate a more catastrophic course and paradoxically sometimes earlier investigation and diagnosis.

Healthy young children may experience up to 6 upper respiratory tract infections per year and even 10 or more if exposed to day care, schoolgoing sibs or smoking.<sup>5</sup> These infections should clear promptly and in the case of bacterial infections they should respond rapidly to antibiotics.

While respiratory and gastrointestinal infections are common in immunodeficiency, **skin infections** such as **ulcerating BCG marks** or with organisms such as

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*Burkholderia cepacia* may be serious warning signs of significant lack of cellular immunity or phagocyte dysfunction respectively.

**Recurrent pneumococcal** infections may signal lack of specific antibody or IRAK4 deficiency. **The recurrence of a pneumonia or pneumonia with an unusual/opportunistic organism such as *Pneumocystis carinii* or infections with *Giardia*** should be investigated.

Recurrence of **meningococcal meningitis** should precipitate investigation for **complement deficiencies**. **Deficient antibody responses** especially to polysaccharide antigens may persist after infancy and result in recurrent respiratory infections **despite normal levels of immunoglobulins**.

**Recurrence of infection at one site** obviously should alert to anatomical defects or obstructions.

**Recurrent fevers** in an otherwise healthy child where no pathogens can be documented and resolution is spontaneous may signify one of the periodic fever syndromes where maintenance treatment with colchicine in some variants may prevent onset of amyloidosis.

More recently described defects of the interferon gamma and interleukin 12, as well as the nuclear factor kappa B essential modulator (NEMO), pathways may present with disseminated **mycobacterial and *Salmonella*** infections. Patients with NEMO mutations also frequently have features of ectodermal dysplasia of varying degrees such as conical teeth, sparse hair and decreased or absent sweat production.

The Jeffrey Modell Foundation Medical Advisory Board<sup>6</sup> has also developed a useful list of 10 warning signs which include most of the above, as well as a relevant family history, and these should prompt immunological investigations.

**Contributing factors** for recurrent infections in childhood must be excluded early on to prevent unnecessary and costly investigation for PID:

- Increased exposure including overcrowded housing and day care
- Second-hand smoke
- Atopy/asthma
- Foreign body
- Cystic fibrosis – incidence of about 1/2 500 in some Caucasian populations
- Anatomical obstructions
- Gastro-oesophageal reflux
- Prematurity
- Not having been breastfed

**Medical causes/associations for secondary** or acquired immunodeficiency may mimic PID and must be investigated if appropriate:

- Malnutrition
- Infectious diseases – suspected HIV, Epstein Barr virus, *Mycobacterium tuberculosis*, *Cryptococcus*
- Malignancy
- Immune suppressant treatment
- Chronic inflammatory diseases such as systemic lupus erythematosus, rheumatoid arthritis
- Protein loss
- Chronic illness of organ systems
- Asplenia, sickle cell disease

## HISTORY

After review of the above factors and associations, specific questions are important which will guide the examination and further investigation for PID:

- **History of age of onset of infections.** These details are very important as severe combined deficiencies are likely to start in the first months of life, whereas antibody deficiencies may only become symptomatic in later childhood even in the virtual absence of serum IgG. Passively transferred maternal antibodies are detectable until 18 months of life in the infant's serum and prolonged breastfeeding may protect against common pathogens. Although most patients with PID will present in infancy or early childhood because of the combined effects of immaturity and inborn deficiency of the immune system, deficiencies other than severe combined forms may even be diagnosed as late as mid-adulthood despite significant morbidity.

- **Detailed perinatal history** and history of the pregnancy

- **Pathogen history** can point towards the broad group of defects in the immune defence.<sup>7</sup>

**T cells** – *Pneumocystis carinii*, mycobacteriae, *Cryptococcus neoformans*, herpes viruses

**B cells** – *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Giardia lamblia*, enteroviruses, staphylococci, *Campylobacter* spp

**Complement** – *Neisseria* spp

**Phagocytes** – staphylococci, *Aspergillus* spp, *Burkholderia cepacia*

Because of the close co-operation between different components of the immune defence system these categories and divisions are artificial and serve as guidelines only. Overlap of functions also termed immunological redundancy can further obscure a specific susceptibility. Comprehensive practice parameters, classifications and algorithms are available for these specific defects.<sup>8-10</sup>

- **History for hallmark special features**

- Severe eczema and petechiae of Wiskott-Aldrich syndrome
- Delayed umbilical stump separation of leukocyte adhesion defect (although rarely observed in clinical practice) or poor wound healing
- Postvaccination disseminated BCG or paralytic polio in T-cell or B-cell disorders
- Hypocalcaemic tetany of the neonate in DiGeorge anomaly
- Graft-versus-host disease caused by maternal engraftment or non-irradiated blood transfusion in T-cell defects
- Arthritis which does not fit the defined categories of juvenile idiopathic arthritis (JIA) in agammaglobulinaemia (but also in acquired immunodeficiency syndrome)
- Autoimmunity of B-cell-related disorders or early complement component deficiencies
- Generalised molluscum contagiosum or extensive warts of T-cell disorders
- Dysplastic features (Fig. 1)

- **History of the family**

- Unexplained death in infancy or recurrent infection history in maternal male relatives may be a clue to **X-linked immunodeficiency** where the mother is a carrier of the condition (Fig. 2).
- A history of autoimmunity in family members may be positive for the patient with common variable immunodeficiency or IgA deficiency.
- It is important to remember that a negative family



Fig. 1. Dysplasia and immunodeficiency – dysplastic teeth.

history does not exclude PID which can also be due to new mutations.

- In South African practice adequacy and accuracy of the history must be evaluated critically in the context of multiple caretakers of the extended family and language differences.

## EXAMINATION

A thorough physical examination of these children requires additional time and a normal exam does not exclude significant immune defects. Exposure to the pathogen to which the patient is unduly susceptible may not have occurred yet, a protected environment may have limited exposure to pathogens and breastfeeding may have aided in defence against infection early in life. The anxious and worried parents should never be ignored, as they see their child for much more time than the usual consultation and they are mostly justified in their concerns.

- **General appearance** gives many clues to the alert medical practitioner or nurse, especially with features of chronic illness such as pallor, wasting, clubbing and especially listlessness for which there is no other obvious explanation.
- **Detailed weight and height mapping** and longitudinal analysis give important information for onset of illness and response to intervention.
- **Skin and mucosal** features as mentioned above may be visible, and scarring from chronic infections or disseminated *Varicella* may alert to PID.
- **Dysmorphic** features of DiGeorge anomaly with micrognathia or those of trisomy 21 may be apparent.
- **Absence of lymphoid** including tonsillar tissue in

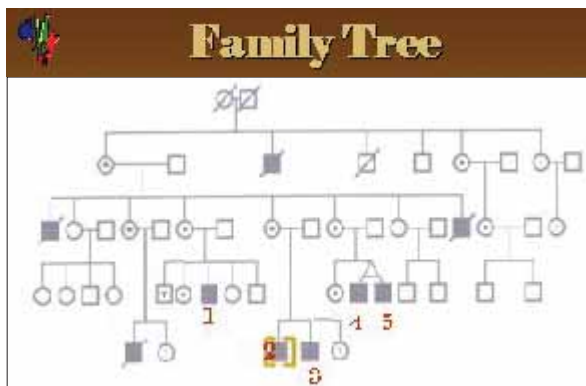


Fig. 2. X-linked agammaglobulinemia – family tree (S Pienaar).

the presence of chronic infections may alert to X-linked agammaglobulinemia with inability to form immunoglobulins due to absence of B cells.

- **Respiratory and ENT** exams frequently reveal evidence of scarred or perforated tympanic membranes with purulent discharge and bronchiectasis may already be established
- **GIT examination** may show hepatosplenomegaly due to chronic immune activation or hepatomegaly with or without jaundice as part of T-cell disorders and intrahepatic chronic infections.
- **Neurological exam** should be evaluated particularly in the presence of telangiectasia – although ataxia and immunodeficiency can also occur without the hallmark ocular findings (Fig. 3).



Fig. 3. Ocular telangiectasia.

## LABORATORY EXAMINATION

Selective laboratory investigations are available at referral centres of major hospitals in South Africa for assessment of a child who has been identified for further investigation after the above history and examination approach.

The investigations where possible should be discussed with the relevant immunology or general laboratories in consultation with a pathologist/immunologist/infectious disease specialist to arrive at a correct diagnosis for appropriate treatment.

A modified approach of the guidelines as proposed by the **Jeffrey Modell Foundation**<sup>6</sup> (© 2003 Jeffrey Modell Foundation) for PID investigation suitable for South Africa will result in sensible laboratory investigation.

The **adapted model of screening in bold** also allows for the high prevalence of HIV/AIDS, tuberculosis and malnutrition in South Africa.

### Stage 1

Initial laboratory screen

- Full blood count and differential count
- IgG, M, A including **IgE**
- **HIV screen**

Where indicated a **sweat test** for cystic fibrosis (Fig. 4), a **Mantoux test** and chest X-ray to exclude tuberculosis are performed. The Mantoux test and where available trychophyton and *Candida* skin tests can be used to document presence of delayed-type hypersensitivity.

### Stage 2

Where B-cell-related deficiencies are suspected a **specific antibody response** to universal vaccination with tetanus, diphtheria and pertussis protein antigens is performed.



Fig. 4. Sweat test.

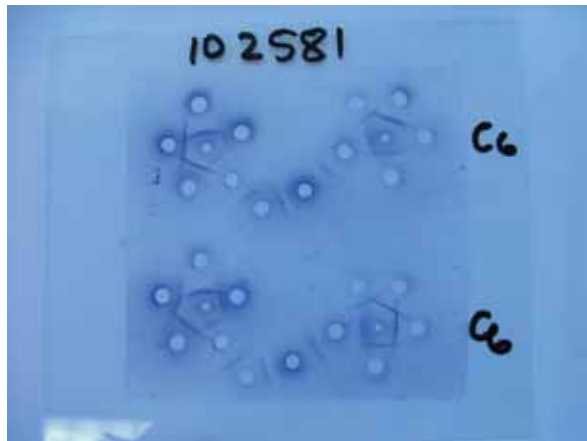


Fig 5. Complement C6 deficiency.

A response to conjugate pneumococcal vaccine or to polyvalent pneumococcal (pure polysaccharide response) vaccine in older children may also be used as a further screen of antibody production after vaccination.

Haemophilus influenzae to b (Hib) vaccine response can also be used as a screen for conjugate vaccine response.

Where appropriate, **lymphocyte phenotyping** is requested in stage 2.

- CD3 (total T cells)
- CD4 (helper T cells)
- CD8 (suppressor T cells)
- CD19 (B cell)
- CD16 + 56 (NK cell)

IgG subclass analysis can be used in selected patients to differentiate deficiencies and to delineate subclass deficiencies if antibody responses are defective. Practically these have been superseded by the antibody responses which yield better results for functional and treatment implications.

A **total complement screen** functional evaluation on ice is also included at an earlier stage where patients are from distant referral hospitals. More extensive investigations at the initial visit aim to contain costs of repeat visits.

Where certain indicator diseases are present (e.g. recurrent Neisserial infections, indicative of C6 deficiency (Fig. 5)) **complement fractions** are requested.

### Stage 3

Lymphocyte phenotyping is requested together with lymphocyte proliferation studies when not already tested in stage 2. Here one can further define lymphocyte functional problems.

The gold standard for lymphocyte proliferation measures radioactive thymidine uptake of actively dividing cells upon stimulation with mitogens (or new flow method) phylo haemagglutinin A (PHA), Con A, protein A and pokeweed and, where available, antigens (*Candida*).

The patient's clinical picture is taken into account when deciding which further investigations to request, such as neutrophil or other specialised lymphocyte investigations.

Where chronic granulomatous disease is suspected the neutrophil burst test (flow cytometry) (Fig. 6) is indicated.

### Stage 4

Access to highly specialised stage 4 investigations such as enzyme measurements, cytokine studies and genetic investigations is limited in South Africa.

Detailed complement fraction studies, Bruton's tyrosine kinase (Btk) assays, neutrophil chemotactic/phagocytic assays, leukocyte adhesion studies and CD40 ligand screening are available at specialised laboratories.

Following these steps of investigation the laboratory guides the clinician to the early diagnosis of PID.

Early screening in stages 1 and 2 is very cost-effective as it identifies most of the commoner antibody deficiencies.

An algorithm for suspected antibody deficit is presented in Figure 7.

## SUMMARY

The above guidelines for history, examination and a structured approach to laboratory investigations should be followed, including baseline:

- full blood count and differential count
- serum immunoglobulin isotypes
- specific antibody studies and T- and B-cell phenotypes

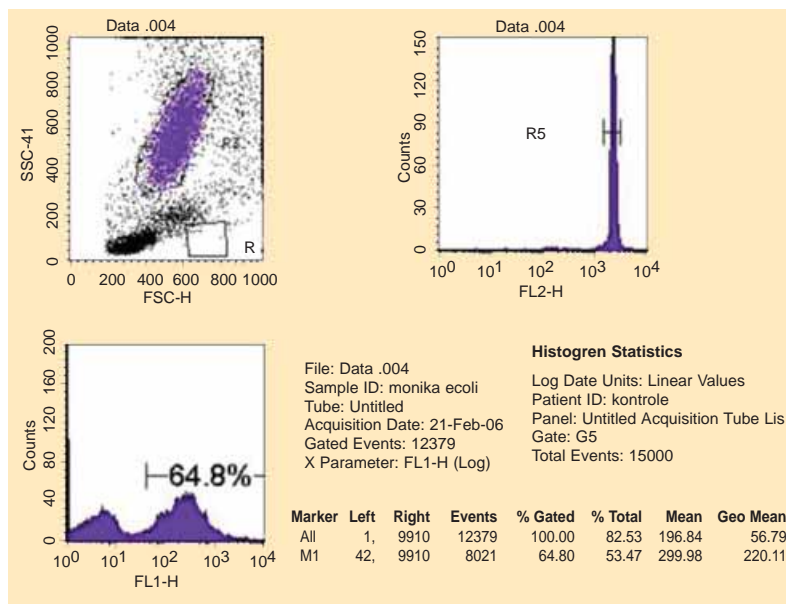


Fig. 6. Neutrophil burst response flow cytometer.

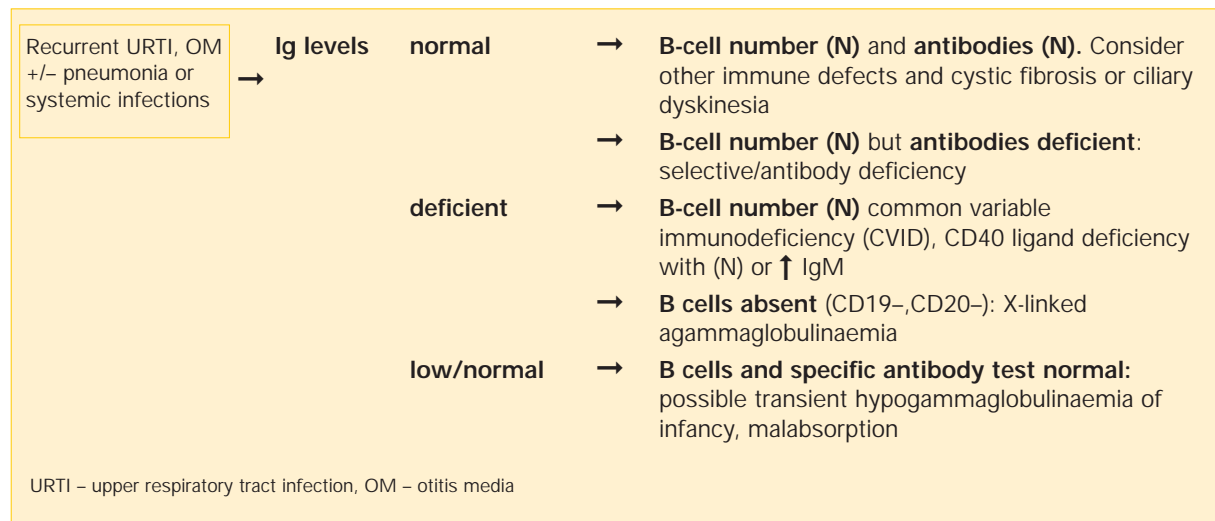


Fig. 7. Algorithm for recurrent infections with serum immunoglobulin (Selg) evaluation if antibody deficit is suspected.

- when indicated a total complement screen and
- neutrophil burst test will diagnose the majority of the commoner immunodeficiencies such as the antibody deficiencies, the complement disorders and chronic granulomatous disease

When this outline is followed, most children with PIDs should be diagnosed adequately enough to decide on a dysfunctional category and, very important, to decide on an appropriate treatment plan.

Because of the diversity of immune defects and the clinical overlap with the immune competent host, where conditions which occur in immunodeficient patients are also common in patients with normal immune systems some clinicians use scoring systems for diagnosis of PID.<sup>10</sup>

Accurate diagnosis is crucial as an incorrect diagnosis may lead to high-risk interventions such as bone marrow transplants or years of unnecessary and costly treatment.<sup>11</sup>

For the diagnosed child the **empowerment of the parent with information** regarding their child's immunodeficiency and follow-up is probably one of the most important predictors for better outcome in countries with low level of awareness for rare diseases. Support organisations such as PINSA (Primary Immunodeficiency Network South Africa) and national registries further assist in creating awareness and support strategies with statistics.

Other useful contacts include:

For immunoglobulin replacement – National Bioproducts Information Centre – [www.nbi-kzn.org.za](http://www.nbi-kzn.org.za)

For immunology case histories – Immunopaedia – [www.immunopaedia.org.za](http://www.immunopaedia.org.za)

#### Declaration of conflict of interest

The author declares no conflict of interest.

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