# APPROACH TO THE CHILD WITH RECURRENT INFECTIONS

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إن الأطفال الذين لديهم تاريخ عدوى متكررة أو حادة أو غير عادية يمثلون تحدياً تشخيصياً , بسبب صعوبه التفريق بين حالات العدوى الناشئة عن عوامل الخطر العامة أو الاختلال الوظيفي في الجهاز المناعي . التفريق بين هذه الأسباب ينبغي أن يكون على أساس تاريخ مرضي مفصل للطفل وكذلك فحص جسدي, تليها الدراسات المختبرية إذا لزم الأمر. وتهدف ورقة البحث هذه إلى تقديم الإرشادات لتقييم الأطفال أصحاب الإصابة بالعدوى المتكررة وتوضح متى تكون عملية الفحص الإضافي مطلوبة ومبررة.
**الكلمات المرجعية :** نقص الأجسام المضادة ، نقص المناعة الابتدائي ، العدوى المتكررة ، نقص المناعة الحاد.

*Children with a history of recurrent, severe, or unusual infections present a diagnostic challenge. It is important to maintain a high index of suspicion for the diagnosis of immunodeficiency, for early diagnosis and treatment can improve outcome. Differentiation between infections caused by common risk factors, or immune dysfunction should be based on a detailed history and physical examination and, if indicated, followed by appropriate laboratory studies. This paper aims at providing guidelines for the evaluation of children with recurrent infections. It provides an overview of the diagnostic approach including important details required from the history, physical examination, and an appropriate choice of screening test to be ordered.*

***Key Words:** Antibody deficiency, Primary immunodeficiency,Recurrent infection,Severe combined immunodeficiency.*

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## INTRODUCTION

Recurrent or persistent infection is the major manifestation of primary immunodeficiency. While most children with recurrent infections have a normal immunity, it is important to recognize the child with an underlying immunodeficiency in order to investigate and treat appropriately. Early diagnosis and treatment of immunodeficiency will improve the quality of life. It may also be life-saving in patients with primary immunodeficiency (PID).[1] A pattern of recurrent or persistent infection is the major manifestation of PID. Possible effective treatment includes early and judicious use of prophylactic antibiotics and replacement immunoglobulin.[2] This modality of treatment can prevent significant end-organ damage. Hematopoetic stem cell transplantation is used for an increasing number of severe immunodeficiencies. The survival of such patients can reach up to 95%, depending on the time of the transplantation and the availability of donors.[3] To distinguish normal children from children with immunodeficiencies, it is important to have some basic knowledge of the immune system and recognize some specific warning signs of a possible underlying immune defect. This paper will review the approach to the child with recurrent infections as well as the important presenting features of PID.

### The Normal Child

The average child has four to eight respiratory infections per year.[4] This number varies depending on the presence or absence of risk factors that predispose to an increase in infectious agent exposure. Risk factors include day-care attendance, school-aged siblings, and second-hand smoke.[5] Children with atopic disease seem more likely to develop recurrent and persistent upper respiratory infections. This may be due to enhanced adherence of pathogens to inflamed respiratory epithelium.[6]

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In children with normal underlying immune system, growth and development is unaffected. They respond quickly to appropriate treatment, recover completely, and appear healthy between infections. The physical examination and laboratory tests are normal.

**The Child with an Underlying Immunodeficiency**

Immunodeficiency may be secondary or primary. Secondary immunodeficiency usually occurs well after infancy while most primary immunodeficiencies are inherited and present during the first few years of life. The two commonest causes of secondary immunodeficiencies are malnutrition and HIV infection.[6] Other causes include malignancy such as lymphoma and leukemia, immunosuppressive medications and protein loss, including protein-losing enteropathy. Secondary immunodeficiency also occurs in patients with asplenia, sickle cell disease, diabetes mellitus, severe liver disease, and renal failure.[7]

Primary immunodeficiencies are inherited disorders of immune system function that predispose affected individuals to increased rate and severity of infection, immune dysregulation with autoimmune disease, and malignancy. Primary immunodeficiencies occur in as many as 1 in 2,000 live births.[8] Abnormalities leading to immunodeficiency can be broadly classified as defects of the (1) humoral, or B-cell, system; (2) cellular, or T-cell, system; (3) complement system; and (4) phagocytic system. Defects involving humoral immunity are the commonest immune abnormalities, accounting for more than 50% of the recognized causes of primary immunodeficiency.[6]

Table I shows features that should arouse suspicion of an immunodeficiency whether primary or secondary.[8-10] A patient with a history suggestive or arousing suspicion of an underlying immune deficiency should be referred to an immunologist as a matter of urgency.

**MEDICAL HISTORY & PHYSICAL EXAMINATION**

The approach to a child with recurrent infections should begin with the taking of a thorough medical history and an extensive physical examination. The frequency, duration, severity, complications of infection, and the response to antimicrobial treatment are important. It is also important to note the type of organism isolated. In general, the pattern of infection gives a clue to the component of the immune system that is most likely affected. Infections with gram-negative organisms, viruses, protozoa, or mycobacterium are more common in patients with cell-mediated immunodeficiency.[11] *Mycobacteriurn avium-intracellulare* and *Pneumocystis carinii* represent typical opportunistic infections seen in patients with severe T cell defects.[10] Patients with humoral immunodeficiency are prone to infections with gram-positive encapsulated organisms such as *Streptococcus pneumoniae* or *Haemophilus infuenzae,*[6] and to mycoplasma species.[2] Phagocytic defects such as in Chronic Granulomatous disease (CGD) predispose to staphylococcal and gram negative infections, particularly *Klebsiella* and *Serratia,*[12] while recurrent neisserial infections are the hallmark of deficiencies in the membrane attacking complex of the complement system (C5-9).[13,14] In contrast, autoimmune disease with increased susceptibility to infection occurs in patients with deficiencies of the early complement components (Cl, C4, and C2).[14]

The organ system affected can provide valuable clues to the nature of the underlying immune defect. B-cell abnormalities most commonly lead to recurrent sinopulmonary infections. Chronic gastrointestinal symptoms caused by *Giardia lamblia* are likely to be related to impaired mucosal immunity and lack of secretory IgA. This commonly occurs in patients with Common Variable immunodeficiency (CVID) and IgA deficiency.[15-17] Table 2 shows general guidelines to determine whether a patient may be experiencing too many or unusual infections.

Family history is a very important part of the history. The presence of family members with a similar disease, recurrent infections, unexplained death, malignancy, or autoimmune disease suggests the possibility of a genetic illness. A history of consanguinity is important when considering autosomal recessive disease.

The physical examination of a child with suspected immune deficiency should be thorough. The presence or absence of the lymphoid tissue should be evaluated in the head and neck examination. Absence of tonsils and lymph nodes suggests a severe immunodeficiency, as seen in patients with X-linked Agammaglobulinemia (XLA), also called Bruton's disease, or in severe combined immunodeficiency (SCID).[7,11] On the

other hand, cervical adenopathy and enlarged liver or spleen can be seen in patients with a T-cell

***Table 1:*** *Features suspicious of an underlying primary or secondary immunodeficiency*[8-10]

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|---|
| Six or more new infections within 12 months. |
| Two or more serious sinus infections or pneumonias within one year. |
| Two or more episodes of sepsis or meningitis. |
| Two or more months of antibiotics with little effect. |
| Need for intravenous antibiotics and/or hospitalization to clear infections. |
| Failure to gain weight or grow normally. |
| Resistant superficial or oral candidiasis. |
| Recurrent tissue or organ abscesses. |
| Infection with opportunistic organism such as Pneumocystis jiroveci (carinii) pneumonia. |
| Complications from a live vaccine such as oral polio, measles, varicella, or BCG. |
| Family history of immunodeficiency or unexplained early death. |
| Unexplained autoimmunity. |
| Lymphopenia in infancy* |

*See text for definition of Lymphopenia

***Table 2:*** *General guidelines for determining if a patient may be experiencing too many infections*

| | |
|---|---|
| 1. | The need for more than four courses of antibiotic treatment per year in children or more than two times per year in adults. |
| 2. | The occurrence of more than four new ear infections in one year after four years of age. |
| 3. | The development of pneumonia twice over any time. |
| 4. | The occurrence of more than three episodes of bacterial sinusitis in one year or the occurrence of chronic sinusitis. |
| 5. | The need for preventive antibiotics to decrease the number of infections. |
| 6. | Any unusually severe infection or infections caused by bacteria that do not usually cause problems in most people at the patient's age.* |

*See text for the patterns of infection that may correspond to the underlying immune defect.

deficiency, CVID, IgA deficiency, or with HIV infection.[15]

The recognition of a number of symptom complexes aids laboratory investigation and diagnosis. For example, infants younger than 6 months, with hypocalcaemia, mandibular hypoplasia, and congenital cardiac abnormalities, particularly truncus arteriosus, suggest a diagnosis of DiGeorge syndrome (thymic aplasia).[16] The presence of Eczema and petechiae in a young boy may indicate the diagnosis of Wiskott-Aldrich syndrome (WAS).[16,18] Generalized molluscum contagiosum, extensive warts, and Candidiasis indicate a T cell dysfunction.[16] The presence of telangiectasia, along with ataxia is highly suggestive of Ataxia-telangiectasia syndrome.[16,19] Oculocutaneous albinism is characteristic of Chediak-Higashi syndrome.[20] In addition, chronic dermatitis accompanied by folliculitis and recurrent sinopulmonary disease may indicate the presence of Hyper-IgE syndrome.[16,21]

If a child is experiencing too many infections, or is suspected to have any of the previously mentioned features, it is important to consider evaluating him or her for immunodeficiency. Very often, this evaluation may give reassuring results. However; if an immunodeficiency is detected, early treatment prevents complication of infection, and therefore, improves outcome and survival.

## LABORATORY INVESTIGATIONS OF CHILDREN WITH IMMUNODEFICIENCY

In patients with suspected immunodeficiency, it is wise to start investigation using some initial screening tests. Abnormalities of the initial tests may support the presence of immunodeficiency and serve as a guide for subsequent investigations. Further laboratory evaluation would be unnecessary if these tests are normal, and the patient's family can be reassured. Further monitoring may be indicated in some patients depending on the severity of their presentation.

### Initial laboratory evaluation

The initial screening test should include a complete blood count including a differential white blood cell count with platelet determination. The total leukocyte count and the absolute numbers of lymphocytes, neutrophils, and eosinophils should be noted and interpreted according to age-appropriate normal values. The finding of lymphopenia in a child with recurrent or persistent infection should prompt further investigation. Lymphopenia is defined as a lymphocytic count of less than 3000 cells/$mm^3$ in infants; whereas in older children or adults, a total lymphocyte count of less than 1500 cells/$mm^3$ is abnormal.[6] The presence of lymphopenia on two or more occasions, particularly in an infant, is

highly suggestive of SCID and warrants further investigation. However, a normal lymphocyte count does not preclude the diagnosis of SCID.[11,23] Persistent or cyclical neutropenia can predispose the patient to abscesses. On the other hand, persistent neutrophilia occurs in patients with Leukocyte Adhesion Defect (LAD).[22] LAD is a defect in the expression of the adhesion molecules on the neutrophil surface, resulting in a defective chemotaxis. The condition is characterized by delayed separation of the umbilical cord, neutrophilia, and predisposition to staphylococcal infection.[1,22]

A peripheral blood smear can be very informative. The presence of giant cytoplasmic granules in leukocytes in the peripheral smear may suggest Chediak-Higashi syndrome,[20] whereas Howell-Jolly bodies in erythrocytes occur in patients with asplenia. Thrombocytopenia and small platelet size is characteristic of WAS.[18]

It is important to include electrolytes, glucose, urine analysis, renal, and liver function tests in the initial assessment of every patient. HIV testing is indicated in every patient with suspected T cell defect. Testing is either done by determining the antibody titers or by PCR.

To exclude anatomical factors, a chest x-ray is indicated if the child has frequent respiratory symptoms or infections. Thymic size should be noted in chest radiographs of newborns with recurrent infections, as its absence may suggest a diagnosis of DiGeorge syndrome.[16] In addition, if sinopulmonary disease is the major presenting feature, cystic fibrosis and immotile cilia must be excluded by Sweat Chloride test and nasal ciliary biopsy, respectively.

**Specific Immunological Assessment**

A wide variety of tests is available for the evaluation of immune response. For ease of discussion, the laboratory approach to immunodeficiency is subdivided into investigation of defects primarily affecting humoral immunity, cellular immunity, the complement system, and the phagocytic system. Within each system, screening tests are considered first, followed by more sophisticated assays.

**Evaluation of Humoral Immunity**

Serum immunoglobulin level including IgM, IgA, IgG, and IgE is considered a screening test for the evaluation of the humoral or B-cell immunity. Low level of immunoglobulin is called Hypogammaglobulinemia. This can be secondary to gastrointestinal or renal loss. Therefore, it is important to include urine albumin level to the panel of investigations in order to exclude renal losses as a cause for low immunoglobulin.

There are various patterns of immunoglobulin deficiency. Selective IgA deficiency occurs in approximately 1 in 500 individuals in the general population.[17] Most of those people are clinically well. A low level of IgG could occur in infants between six to eight months of age, a condition termed Transient Hypogammaglobulinemia of Infancy (THI).[24] These patients may present with recurrent otitis media, pneumonia, and occasionally septic arthritis or osteomyelitis. The majority of these patients will eventually develop normal immunoglobulin levels and normal immunity. Persistence of low immunoglobulin beyond infancy could point to the diagnosis of XLA.[2]

In order to further distinguish these conditions from each other; in vitro evaluation of lymphocytes is important, and involves identification of B lymphocyte with the use of flow cytometry. B cells can be identified by using monoclonal antibodies against the cell surface markers, termed clusters of differentiation (CD nomenclature). CD19 or CD20 are considered the cell surface markers of B cells.[25] B cells are usually normal in patients with THI, distinguishing them from patients with XLA.[24]

Specific antibodies to vaccines (tetanus, *Haemophilus influenzae* B, and pneumococcus), should be taken whenever possible, four weeks after vaccination. This is considered a qualitative assessment of immunoglobulin and helps in the diagnosis of Dysgammaglobulinemia, a condition in which patients cannot produce specific antibody response to antigens, predisposing them to recurrent infections.

**Evaluation of Cellular Immunity**

Cellular immunodeficiency testing includes the measurement of T cell surface markers by flow cytometry.[25] The CD3 marker serves as identification of T cells in general, CD4 marker serves as identification for T helper cells; and CD8 marker identifies cytotoxic T cells.[25] Cellular immune function can also be assessed by the delayed hypersensitivity skin tests to microbial antigen to which the patient has been exposed such as *Candida albicans,*[26] and by the lymphocyte proliferation assays to mitogens, antigens, and allogeneic cells.[27]

Evaluation of cellular immune deficiency requires specialized laboratory facilities and expertise not available in most clinical testing laboratories. The advice of an immunologist is extremely important for the interpretation of the results, even during the diagnostic process.

## Evaluation of the Complement System

The total hemolytic complement (CH50) assay evaluates the functional integrity of the classic complement pathway.[14] It is a useful screening test for detecting functional deficiencies of the components of the classical and alternate pathways of the complement system. The CH50 is a measure of the lowest dilution of test serum that is able to lyse 50% of a standard sheep erythrocyte suspension. Thus, normal activity of all complement system components is required for a normal CH50. An immeasurable or low value suggests a complement deficiency and may need to be followed by more specific tests to delineate the abnormal complement component since it is possible to assay each individual complement component in order to identify the abnormal protein.

## Evaluation of the Phagocytic System

Evaluation of phagocytic function can be done by microscopy through enumeration and characterization of neutrophils and monocytes. Assessment of patients for CGD is done by nitroblue tetrazolium (NBT) test or flow cytometry to evaluate oxidative burst.[12] Assays for neutrophil phagocytic and chemotactic function is only performed in specialized immunodiagnostic laboratories and requires expert interpretation.

## CONCLUSION

Recurrent or persistent infection is a major manifestation of primary immunodeficiency. While most children with recurrent infection have a normal immunity, it is important to be vigilant in this population for unusually frequent or severe infections. The early involvement of a clinical immunologist in cases of suspected immunodeficiency is crucial since early investigation and treatment of a child with an underlying primary immunodeficiency can prevent significant end-organ damage and improve survival and long-term outlook.

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