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NARRATIVE REVIEW

Evaluation of the child with frequent respiratory tract infections

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ABBREVIATIONS

A-T: ataxia-telangiectasia

CBC: complete blood count

CGD: chronic granulomatous disease

CVID: common variable immunodeficiency

HSCT: hematopoietic stem cell transplantation

HIES: hyper-IgE syndrome

HIMS: hyper-IgM syndrome

ID: immunodeficiency

IEI: inborn errors of immunity

IUIS: International Union of Immunological Socities

LAD: leucocyte adhesion deficiency

NBS: newborn screening

NGS: next-generation genetic sequencing

PID: primary immunodeficiency

RTIs: respiratory tract infections

VUS: variants of uncertain significance

WAS: Wiskott-Aldrich syndrome

WES: whole exome sequencing

WGS: whole genome sequencing

ABSTRACT

Frequent respiratory tract infections (RTIs) in children represent a significant clinical challenge. While the majority of these children have identifiable benign explanations, such as maturing immune system or increased environmental exposure (e.g., attending daycare or having school-age siblings), a small subset suffers from serious immune deficiency (ID). Inborn errors of immunity (IEI) - historically referred to as primary immunodeficiencies (PID) - comprise a growing list of > 550 monogenic disorders. Delayed diagnosis of IEI remains a major problem, leading to significant morbidity and mortality. This review provides a practical approach for clinical evaluation and screening laboratory tests of children with frequent or unusual RTIs. A skillful medical history-taking and a comprehensive physical examination are of utmost importance in identifying valuable clues for suspicion of ID and sometimes a definite recognition of the disorder. Laboratory evaluation is essential to delineate the specific immune defect. The

value of a routine complete blood count (CBC) with differential cannot be over-emphasized in discovering any cytopenia. Evaluation of the main components of the immune system should be in a systematic way, starting with screening tests and proceeding for detailed testing of the most suspected immunity compartment. Molecular genetic testing greatly enhanced the arrival to a precise diagnosis. Early involvement of a clinical immunologist would markedly expedite the diagnostic process and the planning of appropriate management, including family counselling. Until the specific treatment is initiated, the child should be protected from exposure to infections, live vaccines, and transfusion of non-irradiated blood cells. Advances in diagnostic tests and therapeutic modalities led to marked improvement in early diagnosis and targeted therapies ranging from immunoglobulin replacement to hematopoietic stem cell transplantation (HSCT) and gene therapy.

IMPACT STATEMENT

This article provides a systematic approach to identification of immunodeficiencies in children with frequent or unusual RTIs. The impact of early diagnosis and instatement of targeted therapy would be marked reductions in morbidity and mortality in immunodeficient children.

Key words

Respiratory infections; pulmonary infections; evaluation of immunity; immunodeficiency; inborn errors of immunity; primary immune deficiencies.

INTRODUCTION

In addition to the immune system, human host defenses comprise physical, chemical, enzymatic, and microbial barriers provided by the skin, mucous membranes, and secretions. The immune system has two main arms: non-specific innate immunity and specific acquired (adaptive) immunity. RTIs are among the most prevalent illnesses in pediatric practice -- they are mostly self-limited or easily treatable. However, when they occur with unusually high frequency, severity, or duration, or fail to respond to standard treatment, an underlying immunodeficiency should be suspected and systematically evaluated. Although individually rare, inborn errors of immunity (IEI) as a group represent a significant health burden. Most IEI disorders manifest during early childhood, though the diagnosis is usually delayed for some years.

Collectively, the estimated prevalence of IEI in the United States' general population is approximately 6 per 10,000 individuals and true prevalence may be as high as 1 in 500 when milder or late-presenting phenotypes are included (1). The 2024 International Union of Immunological Societies update catalogs 555 distinct disorders caused by pathogenic variants in 508 genes (2, 3). This number is expected to grow as next-generation genetic sequencing (NGS) continues to uncover novel defects.

IEIs, formerly called primary immunodeficiencies (PID), are associated with substantial morbidity and mortality; a recent systematic review and meta-analysis encompassing 12,581 IEI fatalities reported an overall mortality rate of 24% representing an approximately 27-fold higher than in the general population (4). The most common causes of death were infections, complications related to hematopoietic stem cell transplantation (HSCT), and non-infectious pulmonary comorbidities. Pulmonary

disease is the most common form of end-organ damage in some large studies. Chronic lung disease, including interstitial lung disease and bronchiectasis, eventually develop in about one-third of patients with common variable immunodeficiency (CVID) (5, 6).

IEIs are typically diagnosed after a significant delay ranging between 2.2 years to longer than 9 years (7, 8). In fact, many children die before a diagnosis is made. The 2017 Immune Deficiency Foundation (IDF) National Patient Survey, which obtained data from more than 1,100 individuals with IEI, revealed that prolonged delay in diagnosis translates directly into increased morbidity and mortality (9).

Problematic infections are not the only clinical manifestations of IEI. Patients may also present with autoimmunity, autoinflammation, severe atopy, lymphoproliferation, and malignancy (10). This has practical implications as it raises the probability of suspecting IEI in children seen by various medical specialists, including pulmonologists, allergists, dermatologists, rheumatologists, and gastroenterologists. This also underscores the need for increased awareness among clinicians who may not routinely include IEI in the differential diagnosis.

The objective of this article is to facilitate the recognition and diagnosis of immunodeficiency (ID) in children with frequent RTIs. Valuable clues from the medical history, physical findings, and screening laboratory tests will be presented to reach an early diagnosis and achieve better prognosis. The terms ID, IEI and PID are used interchangeably throughout this review.

MEDICAL HISTORY

A thorough medical history, particularly regarding problematic infections, is the first and most important procedure in suspecting ID (**Table 1**). Immunocompetent children can have 6–8 viral upper RTIs per year during early childhood, and even more if the child has siblings or attending daycare. The Jeffrey Modell Foundation Medical Advisory Board has developed ten warning signs that should prompt an immunologic evaluation (**Table 2**) (11, 12). However, these warning signs focus on infection history. A systematic review in 2023 highlighted that the classic infection-based warning signs do not adequately capture the large spectrum of IEI, particularly those presenting with immune dysregulation (13). Another study demonstrated that among 16,486 patients in the European Society for Immunodeficiencies registry, 9% presented with immune dysregulation alone and a further 9% with immune dysregulation combined with infection, so that an exclusively infection-based warning-sign approach would have missed approximately one quarter of patients (14). Noninfectious events also carry prognostic weight: in a national cohort followed for 10 years, malignancy and autoimmunity were independent risk factors for death (15). There is an emerging consensus that specialty-specific warning signs should be developed; for example, a study in two tertiary pediatric respiratory units in the United Kingdom found that 36% of children with non-cystic fibrosis bronchiectasis had an underlying IEI -- underscoring the value of routine immunological screening in this population (16). Infectious and non-infections manifestations of IEIs are listed in **Table 3.**

The earlier the age at onset of infections, the more likely IEI exists. During early infancy (< 6 months), the onset of severe infections especially with opportunistic pathogens like

Pneumocystis jirovecii, *Candida* or viruses, suggests T-cell or combined T- and B-cells ID. Late-infancy-onset (6–9 months) infection is usually recurrent sinopulmonary infections with encapsulated bacteria (*S. pneumoniae*, *H. influenzae*) typically emerge as maternal IgG antibodies wane, suggesting B-cell defects. Complement and phagocytic defects may present at any age, often as *Neisseria* infection, skin abscesses, or mucosal ulceration.

Patients with T-cell or phagocytic defects are at a catastrophic risk from the administration of live-attenuated vaccines: MMR, oral polio, nasal influenza, oral typhoid, BCG, yellow fever, cholera. Cases of poliomyelitis have been reported following oral attenuated live polio vaccine in children who turned to be immunodeficient. Approximately one-third of children with severe combined immunodeficincy (SCID) who received BCG vaccine during the neonatal period developed localized BCGitis (**Figure 1**) or systemic BCGosis which can be life-threatening and require specialized therapy (17-19).

FAMILY HISTORY

Inquiry should be made about parental consanguinity, history of similar illnesses or early childhood deaths in the family, and the age and sex of affected members. Family history is the best predictor of IEI. Consanguinity increases the risk of autosomal recessive disorders, and unexplained childhood deaths, especially in maternal male relatives suggest X-linked ID. Many IEIs are inherited (**Table 4**), with a particularly high frequency in regions with high rates of consanguinity (20). A family history of IEI or cystic fibrosis should prompt specific testing for that disease.

PHYSICAL EXAMINATION

The physical examination should be comprehensive, with particular attention to findings that characterize specific IEI syndromes (**Table 5).** Children with ID, particularly with T-cell defects, often suffer from failure to thrive. However, normal growth and development should not deter from suspecting ID. The lymphoid tissue, including tonsils, is an integral part of the immune system and it should be specifically documented in the physical examination by location – whether normal, hypoplastic, or hypertrophic. Prominent conjunctival vasculature should suggest ataxia-telangiectasia syndrome (**Figure 2**), though is usually delayed until after the discovery of ataxia. Skin manifestations were observed in 48% of children with PID (21). Chronic fungal infections of the nails or *Candida* infection of skin or mucous membranes suggest chronic mucocutaneous candidiasis or other T cell defects. Granulomatous skin disease may be seen in several combined immunodeficiencies, CVID, chronic granulomatous disease (CGD), Omenn syndrome, and DNA-repair defects such as Ataxia-Telangiectasia (A-T) (22). Scoliosis is a feature in of hyper-IgE (Job's) syndrome though the deformity may not be as obvious on physical examination as on a radiographic film (**Figure 3**). Congenital dysmorphic syndromes are associated with a higher frequency of various clinical or subclinical immunologic disorders, particularly Trisomy 21 (Down syndrome) and defects in the X-chromosome (Turner syndrome) (23, 24).

LABORATORY EVALUATION

The immune system comprises very complex components that work in concert and intricate coordination in protecting the human body against infections. Defects can be quantitative or functional. A dysfunction in a particular component can be secondary to

a defect in another component. It is broadly divided into two main branches; innate and acquired or adaptive. The innate immunity has a general protective function (phagocytes and complement system). The acquired immunity reflects the B- and T-cells' specific experience with exposure to infections or immunizations. It is estimated that approximately 50% of PID involve the humoral immunity (B- cell), 10% cell-mediated (T-cell), 20% combined humoral and cell-mediated defects, 15-18% phagocytic dysfunction, and 2-5% complement system defects. The 2024 update of IUIS classified PIDs into 10 distinct categories based on their clinical and molecular phenotypes (**Table 6**) (25).

For laboratory assessment of the immune system, testing goes through stages; general basic tests, screening tests for the humoral immunity, cell-mediated immunity, the phagocytic function, and the complement system (26). Depending on the results of screening tests and clinical findings, further specialized selected tests would be needed for a definitive identification of the basic defect and for planning the specific treatment. Whenever the result of a test is equivocal or does not fit with the clinical or other laboratory findings, the test should be repeated, preferably by another laboratory. Identification of the genetic defect in IEI is now the standard of care, as it guides precise therapy and family counseling. A summary of screening and advanced tests by immune component is presented in **Table 7.**

General Basic Tests

CBC with differential may reveal lymphopenia, anemia, thrombocytopenia, or neutropenia. It is worth noting that the normal lymphocyte count is much higher in infants than in older children; lymphopenia should be considered serious if the count <

3000/mm^3 in children < 2 years and < 1500/mm^3 in older children. Leukocytosis without evidence of infection may suggest leukocyte adhesion defect whereas increased blast cells warrant investigation for leukemia. Thrombocytopenia is particularly present in Wiskott-Aldrich syndrome (WAS) (with small platelets) and neutropenia is often seen in X-linked hyper-IgM syndrome and in X-linked hypogammaglobulinemia particularly during infections.

A high erythrocyte sedimentation rate may indicate active infection, but it may not be elevated in cases of hypogammaglobulinemia. A decreased serum globulin suggests hypogammaglobulinemia, malnutrition, or protein loss in urine or gut. However, elevated globulin level is a common finding in chronic infections, and even some PIDs such as CGD. Hypocalcemia is a classic early finding in DiGeorge syndrome.

Radiologic evaluation may start with a chest radiograph to look for lung lesions, thymic shadow, mediastinal lymphnodes, and the cardiac configuration. In patients with chronic lung disease, a baseline high-resolution computerized tomography (HRCT) may detect bronchiectasis or other lesions that may not be revealed in chest radiograph.

Microbiologic and/or serologic tests may identify the infecting organism and its antimicrobial sensitivity. It is worth noting that in immunodeficient patients, infection may be present despite negative serologic tests, low sedimentation rate, and absent leucocytosis.

Sweat electrolyte test or, more reliable, molecular genetic testing is indicated in children with chronic pulmonary illness and/or malabsorption, or a family history of cystic fibrosis.

Electron microscopic examination of the respiratory tract cilia is indicated in patients with *situs inversus* or chronic sinopulmonary disease.

Assessing Humoral Immunity (B-Cell Function)

In B-cell dysfunction, the onset of infection is usually delayed until 6-9 months of age though can be earlier in premature infants. It is mostly sinopulmonary bacterial infections and less commonly sepsis, abscess, osteomyelitis, or meningitis. Patients with just B-cell defects, rarely suffer major fungal or viral infections except for enteroviral meningoencephalitis.

Serum immunoglobulin levels

B-cells constitute 15-35% of circulating lymphocytes and can be enumerated by flow cytometry as CD19 or CD20. Evaluation of humoral immunity function begins with measuring serum IgG, IgA, IgM, and IgE levels. The result should always be compared with normal values for age at that laboratory. Transplacental transfer of maternal IgG occurs mostly during the last trimester; premature infants would have low levels depending on the degree of prematurity. Maternally-transmitted IgG concentration in the infant slowly decreases to negligible levels around 6 months of age while the infant's own production is gradually increasing. In full-term infants, IgG concentration reaches a nadir of 300 to 400 mg/dL at 3-6 months of age, reaches 60% of adult level by 12 months and attains adult levels by 6 years of age. In some infants, IgG production can be slow and may not reach age-appropriate levels for up to 2-3 years – a state called transient hypogammaglobulinemia of infancy which pass uneventfully in most cases. IgM production rises rapidly from the first month of life and reaches about 60% of the adult level around 1 year of age. It is the first immunoglobulin secreted by B-cells which then undergo class switch recombination to produce IgG, IgA, and IgE. If the switching

does not happen, IgM level remains normal or reaches high levels whereas other immunoglobulins levels remain low - the hallmark of hyper-IgM syndrome.

IgA has the highest rate of production but its serum level is much lower than IgG because of its shorter half-life (6 days versus 21 days). It is the slowest to develop and approaches adult level by preadolescence. Hence, a normal IgA level for age may exclude major B-cell defects. Selective IgA deficiency is generally considered at a serum IgA level below 10 mg/dL in subjects older than 4 years. It is worth noting that IgA production can be suppressed by certain drugs such as phenytoin, carbamazepine, valproic acid, zonisamide, sulfasalazine, gold, penicillamine, hydroxychloroquine, and nonsteroidal anti-inflammatory drugs (27).

An elevated IgE level may indicate allergy as the underlying cause of symptoms but an extremely elevated IgE level (> 1000 IU/mL) together with eczema and skin carbuncles would suggest hyper-IgE (Job's) syndrome.

Specific antibody levels

In some subjects with normal immunoglobulin levels, the specificity of antibodies can be deficient as detected by measuring the antibody levels to diphtheria, tetanus and pneumococcus. If the level is non-protective, a vaccine booster dose is administered and the titer is measured 4-6 weeks later. Regarding pneumococcal antibodies, if the response was inadequate to a booster with the polysaccharide vaccine *Pneumovax-23* (T-cell independent antigen), some subjects may respond to the conjugate vaccine *Prevnar-13 or 20*) (T-cell dependent antigen) (28). An adequate response would be an antibody level of at least 1.3 mcg/mL or a 2-4-fold rise compared with pre-vaccination

level. The ability to produce antibodies to polysaccharide antigens may not fully develop until two years of age. For younger children, measurement of antibodies to the ABO red blood cell antigens (isohemagglutinins of the IgM class) would be a helpful substitute.

Assessing Cell-Mediated Immunity (T-cell Function)

T-cells constitute 55-80% of circulating lymphocytes, hence T-cell defect can be suspected early if CBC shows lymphopenia. In addition to the total number, the role of T-cell depends on the balance between its subsets. Flow-cytometry can quantitate the total T-cells (CD3+), the helper T-cells (CD4+) and cytotoxic T-cells (CD8+). In addition to the numbers, the ratio of CD4:CD8 cells (normal 1.5 – 2) should be considered; a reversed ratio can result from various causes and warrant further evaluation.

In T-cell dysfunction, infections start during early infancy, usually by three months of age, in the form of oral or cutaneous candidiasis, *Pneumocystis jirovecii, or* viral infections (cytomegalovirus, adenovirus, varicella). Chronic diarrhea and failure to thrive are common.

Two important advances have reshaped the laboratory landscape in diagnosing IEI. First, newborn screening (NBS) for SCID using T-cell receptor excision circles (TRECs) from dried blood spots has been implemented in more than 35 countries (29, 30). In the United States, universal TREC-based NBS has dramatically improved outcomes; newborns in California identified by NBS achieved a post-hematopoietic stem cell transplantation (HSCT) survival rate of 94%, compared to 66-90% in European centers without routine NBS (31). Although the sensitivity of TREC-based screening for typical SCID is excellent, false-positive results occur and are more common. Most false-positive screens are attributable to transient T-cell lymphopenia in premature infants,

critically-ill neonates, newborns with certain congenital anomalies (e.g., trisomy 21 or DiGeorge syndrome), or perinatal corticosteroid exposure. On the other hand, false-negative results are uncommon but may occur in disorders with adequate T-cell production but impaired function (e.g., some forms of ZAP70 deficiency or MHC class II deficiency), in delayed-onset SCID, or rarely because of specimen-related or laboratory technical issues (32). Therefore, a normal TREC result does not completely exclude all forms of clinically significant T-cell immunodeficiency, and infants with a strong clinical suspicion still require diagnostic immunologic evaluation. A global survey conducted by the Clinical Immunology Society and the Association of Public Health Laboratories through the SCID Harmonization Initiative analyzed 80 unique program responses and found that among 39 non-US countries, only 15 (38%) had national universal screening, while 24 (62%) operated regional, pilot, or other limited programs (33). Programs differ in TREC cutoffs, second-tier strategies, gestational-age–specific protocols, referral thresholds, and how urgency is communicated to clinicians.

Combined TREC/KREC (kappa-deleting recombination excision circles), NBS benefit by simultaneously detecting B-cell lymphopenia enabling early identification of congenital agammaglobulinemia in addition to SCID (34). Second, NGS has transformed the diagnostic approach to IEI. An integrated NBS-plus-NGS strategy, in which targeted gene panels are automatically applied to newborns with abnormal TREC/KREC results, has proven feasible and efficient (35).

In clinical practice, a simple screening test for cell-mediated immunity function can be done by the delayed hypersensitivity intradermal skin testing using selected T-cell-dependent antigens that the patient had most likely been exposed to. Commonly

available testing antigens include *Candida albicans* 1:100, tetanus toxoid 1:100, and trichophyton 1:30 (26). The test result is read at 48 hours; a good response is ≥ 5 mm induration. A more sensitive test would be *in vitro* stimulation assays such as lymphocyte proliferation to mitogens and selected specific antigens. It is worth noting that cell-mediated immunity may be suppressed for several weeks after viral illnesses, severe infections, immunization with viral vaccines, and immunosuppressants.

Assessing the Phagocytic Function

Phagocytosis is a function of neutrophils, monocytes, and macrophages. It is a sequence of multiple steps by the cell in dealing with a microorganism: rolling, adhesion, diapedesis, recognition, chemotaxis, ingestion, phagosome formation, enzyme production, generation of oxygen radicals, killing, and exocytosis. A defect at any of these critical steps may affect the phagocytic process. Assays for most of these functions are of very limited availability – primarily in highly specialized research laboratories.

Phagocytic defects should be suspected in children with delayed separation of the umbilical cord, abscesses, poor wound healing, osteomyelitis, gingivitis, or infection in multiple sites. Phagocytic dysfunction may also exist in patients with glucose-6-phosphate-dehydrogenase deficiency. The organisms are commonly *Staphylococcus*, *Klebsiella*, *Serratia*, *Salmonella*, and fungi.

An initial CBC with differential may reveal neutropenia (< 1500/mm^3), with risk of infection below 1000/mm^3. Hematologic and immunologic evaluation would be necessary in identifying the underlying cause (**Table 7**). Neutropenia can be due to poor mobilization from the marginal pool or poor production by the bone marrow. In cyclic

neutropenia, the neutrophil count drops at 2-3 weeks intervals, and can be identified by checking the neutrophil count 2-3 times a week for at least 6 weeks or by molecular genetic testing for elastase mutation. A bone marrow biopsy is often needed. Detailed functional evaluation of phagocytosis requires complex assays that may be available at certain specialty or academic laboratories.

Assessing The Complement System

Defects in the complement system seem to be very rare (2-5% of all IEIs) but should be particularly suspected in patients with recurrent *Neisseria* infections. The complement function is screened with the complement hemolytic assays CH50 (classic pathway) and AH50 (alternative pathway), along with quantitative levels of C3 and C4 components. Abnormal screening assays prompt measurement of individual components and their functions -- most of which require specialty or reference laboratories. Complement components are heat-labile and undergo rapid degradation at room temperature, hence the specimen tube must be immediately put and transported on ice, separated promptly, and stored frozen at -70^{o}C if not tested immediately. Improper specimen handling is the most common cause of falsely low complement level results.

Molecular Genetic Testing

Genetic confirmation is now considered the standard of care for IEI, as it guides the timing and choice of treatment, enables family screening and is essential for accurate genetic counseling. Three approaches are in common use. First, targeted gene panels that simultaneously sequence a curated set of IEI-associated genes. They are relatively inexpensive, provide deep and uniform coverage, generate few incidental findings, and are most efficient when the clinical and laboratory phenotype points to a recognized

disease category. Second, whole exome sequencing (WES) analyzes the protein-coding regions of virtually all genes and is preferable when the presentation is atypical, when more than one compartment is involved, or when a targeted panel has been uninformative (36). Third, whole genome sequencing (WGS) that additionally analyses non-coding, regulatory and structural variations. However, it is more expensive and its incremental yield in IEI remains to be defined (37). Results should be interpreted with caution. Sequence variants are classified as pathogenic, likely pathogenic, of uncertain significance, likely benign, or benign.(38) Variants of uncertain significance (VUS) are common. VUS is not a diagnosis and should not by itself justify a change in treatment. (39) Conversely, a negative result does not exclude an IEI. When the phenotype is compelling but the genotype is equivocal, functional confirmation and segregation studies in relatives may be needed.

The value of a precise molecular diagnosis is practical rather than academic. Among 1,000 families evaluated by exome sequencing at one referral center, 32.7% received a molecular diagnosis, and approximately 70% of those diagnoses carried at least one management implication (40). The genotype guides the timing and the conditioning regimen of hematopoietic stem cell transplantation, identifies candidates for gene therapy, and increasingly directs mechanism-based treatment. (41, 42) Finally, a confirmed molecular diagnosis permits accurate genetic counseling. (7, 20).

DIFFERENTIAL DIAGNOSIS

When evaluating children with recurrent RTIs, a broad differential diagnosis of non-immunologic causes of the patient's illness and of diseases that cause secondary imunodeficiency (**Table 8).** A frequently misdiagnosed disease is milk-induced

hypersensitivity pulmonary disease (Heiner syndrome) that can be associated with pulmonary hemosiderosis (43, 44). Ruling out such conditions should precede an elaborate laboratory evaluation for immunodeficiency.

MANAGEMENT PRINCIPLES

Though the primary focus of this article is evaluation for IEI, until the definitive diagnosis and specific treatment is settled, the patient should be protected against infection. Prophylactic antimicrobials, such as trimethoprim-sulfamethoxazole for *Pneumocystis*) and antifungals are necessary in cases of SCID or phagocytic defects. Immunoglobulin replacement therapy is the mainstay for B-cell defects and is essential in patients with SCID while waiting for immune recnstitution. Blood *transfusion, if needed, should be CMV-seronegative or leuco-reduced and irradiated to inactivate donor T-cells to prevent transfusion-associated graft-versus-host disease. With the rapid advances in diagnostic and therapeutic modalities of IEI, all patients with suspected ID should be managed in consultation with a clinical immunologist for establishing the definitive specific diagnosis, planning personalized management, and providing periodical assessment (41, 42).

CONCLUSIONS

Immunodeficiency is a major, yet markedly underdiagnosed, underlying cause of frequent or chronic respiratory infections in children. Early diagnosis depends on systematic evaluation, starting with a detailed history-taking guided by the ten warning signs of IEI, followed by a thorough physical examination, and screening laboratory tests (**Figure 5**). The selection of more laboratory tests should be guided by the medical

history, clinical findings, and initial screening tests results. Genetic and other advanced immunologic tests can lead to a precise specific diagnosis of the immune defect and targeted therapy that can be in the form of replacement immunoglobulin therapy, stem cell/bone marrow transplant, gene therapy, or targeted small-molecule therapies. While immunodeficiency is being considered, the patient should be guarded against infections, live vaccines and transfusion of non-irradiated blood cells. Advances in this field led to markedly improved quality of life and a complete cure of several immunodeficiency diseases that once were fatal.

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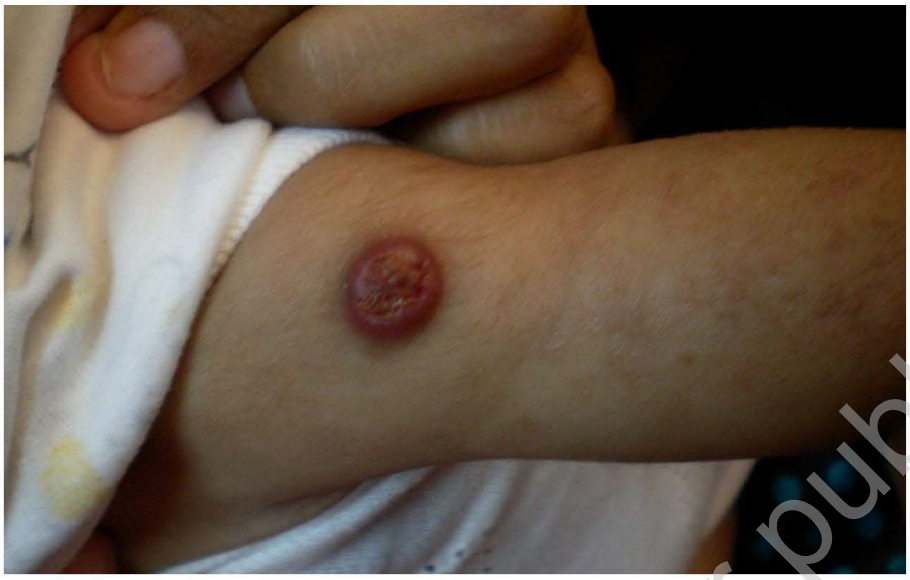

Figure 1. *Localized BCGitis in an 8-months-old infant with SCID who received BCG vaccine at 3 months (Courtesy of Dr. Waleed Al-Herz). It is usually self-limited unlike systemic BCGosis that can be life-threatening.*

Figure 2. *Conjunctival telangiectasia in a 6-year-old child with ataxia-telangiectasia. It may take up to a few years for mucous membrane or cutaneous telangiectasia to appear after ataxia is manifested.*

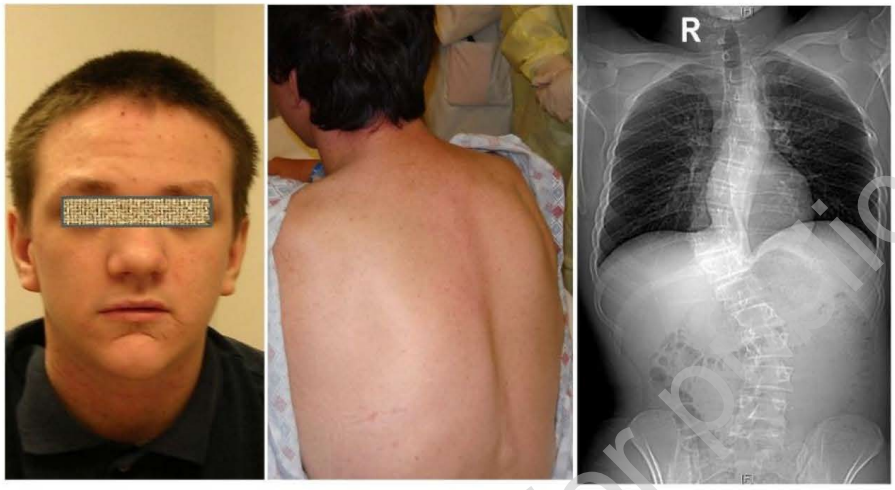

Figure 3. An adolescent with hyper-IgE syndrome showing eczematous coarse facial features and scoliosis that seemed mild on physical examination but was very prominent radiologically. He also had bronchiectasis and left upper lobe scarring post-resection of an aspergillus abscess.

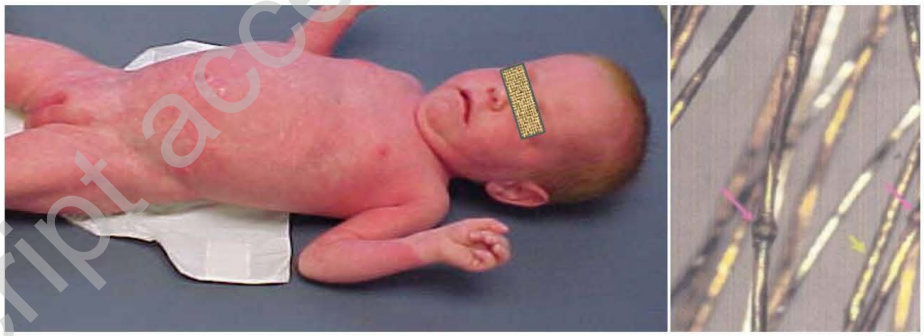

Figure 4. *An infantwith Comel-Netherton syndrome showing failure to thrive, generalized ichthyotic erythroderma, and thin sparse hair with abnormal microscopic morphology such as twisting, bamboo (trichorrhexis invaginata), or fractured (trichorrhexis nodosa)*

Figure 5. Evaluation algorithm of the child with frequent, severe, persistent or unusual respiratory tract infections

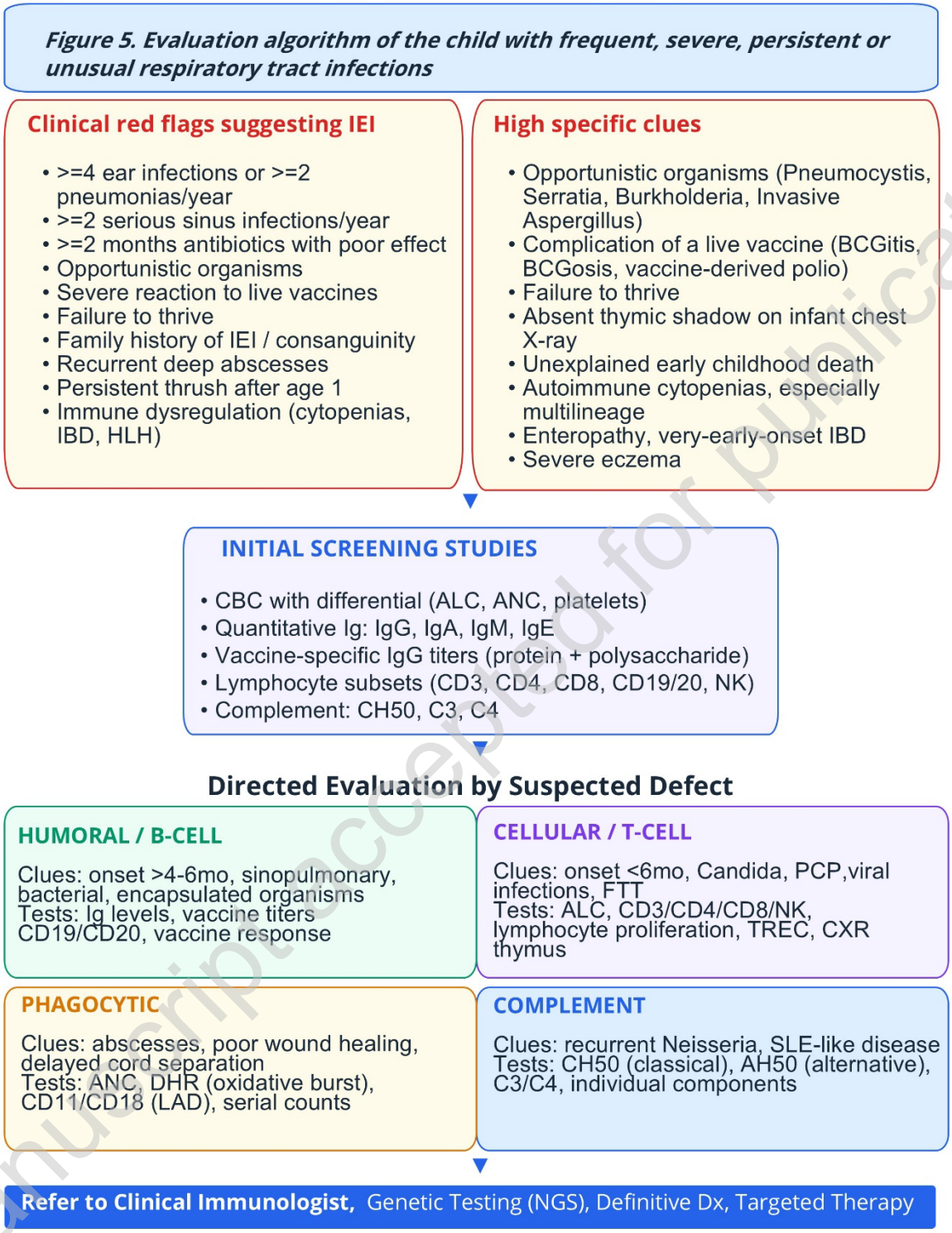

Table 1. Clues from the Medical History that Alert to Immunodeficiency

-Infection:

Frequent, chronic, severe, or in multiple sites.

Poor response to standard treatment.

Opportunistic organisms.

Following live vaccines.

-Early childhood deaths in the family.

-Blood transfusion reaction: anaphylaxis *(anti-IgA antibodies*) or rash of graft-versus-host disease *(T cell defect*).

-Failure to thrive: mal- or under-nutrition may be a cause or a consequence to immunodeficiency.

-Tetany in newborn *(DiGeorge syndrome).*

- Delayed umbilical cord separation (> 3-4 weeks) or poor wound healing *(leucocyte adhesion defect*).

- Bleeding tendency *(Wiskott-Aldrich syndrome, hyper-IgM syndrome*).

- Eczema with immune deficiency syndromes (Wiskott-Aldrich, Omenn, Comel-Netherton)

- Conditions causing secondary immunodeficiency (**Table 7)**

Table 2. The Ten Warning Signs of Inborn Errors of Immunity in Children < 18 years (11, 12)

(Developed by the Jeffrey Modell Foundation Medical Advisory Board)

#	Warning sign
1	Four or more new ear infections within 1 year.
2	Two or more serious sinus infections within 1 year.
3	Two or more months within a year on antibiotics with little or no effect.
4	Two or more pneumonias within 1 year.
5	Failure of an infant to gain weight or grow normally.
6	Recurrent deep skin or organ abscesses.
7	Persistent thrush in mouth or fungal infection on skin after age 1 year.
8	Need for intravenous antibiotics to clear infections.
9	Two or more deep-seated infections including septicemia.
10	A family history of an inborn error of immunity.

(Modified from Jeffrey Modell Foundation https://www.info4pi.org/information-booth/10-warning-signs)

Table 3. *Infectious and noninfectious manifestations of inborn errors of immunity by immune compartment's defect*

Immune defect	**Characteristic infections and organisms**	**Noninfectious manifestations**	**Examples**
Predominantly antibody (B-cell) deficiency	• Encapsulated bacteria: *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, *Staphylococcus aureus* • *Mycoplasma* and *Ureaplasma* (septic arthritis) • *Campylobacter*, *Giardia lamblia* (chronic diarrhe*a) • Enteroviruses (chronic meningoencephalitis) Pattern: recurrent otitis, sinusitis and pneumonia beginning after 4-6 months of age	• Bronchiectasis • Granulomatous-lymphocytic interstitial lung disease • Autoimmune cytopenia • Noncaseating granulomas • Enteropathy Lymphoproliferation, splenomegaly, lymphoma	CVID, X-linked agammaglobulinemia, hyper-IgM syndromes, selective IgA deficiency, specific antibody deficiency, tra*nsient hypogammaglobulinemia of infancy
Cellular (T-cell) alone or combined with humoral deficiency	• *Pneumocystis jirovecii* • CMV, EBV, adenovirus, RSV, parainfluenza, rotavirus • *Candida* (persistent thrush), *Cryptosporidium* • Disseminated BCG and nontuberculous mycobacteria • Disease from live vaccines (rotavirus, varicella, oral polio) Pattern: onset before 3–6 months with interstitial pneumonitis, chronic diarrhea and failure to thrive	• Failure to thrive • Erythroderma (Omenn syndrome) • Maternal T-cell engraftment with graft-versus-host disease • Absent thymic shadow Autoimmunity and lymphoproliferation	SCID (IL2RG, ADA, RAG1/2, JAK3), Omenn syndrome, 22q11.2 deletion, Wiskott-Aldrich syndrome, ataxia-telangiectasia

Phagocyte number or function	• Catalase-positive organisms: *Staphylococcus aureus*, *Serratia marcescens*, *Burkholderia cepacia* complex, *Nocardia*, *Aspergillus* species • *Salmonella*, *Klebsiella*, *Candida* Pattern: deep skin, liver and lung abscesses; osteomyelitis; suppurative lymphadenitis, severe gingivitis and periodontitis	• Delayed umbilical cord separation • Poor wound healing • Obstructing granulomas of the gastrointestinal or urinary tract Inflammatory bowel disease	Chronic granulomatous disease, leukocyte adhesion deficiency, cyclic and congenital neutropenia, Chediak-Higashi syndrome
Complement deficiency	• *Neisseria meningitidis* (recurrent, often uncommon serogroups) and *Neisseria gonorrhoeae* (terminal component defects) • *Streptococcus pneumoniae*, *Haemophilus influenzae* (early classical component and mannose-binding lectin defects) Pattern: recurrent meningitis or sepsis	• Lupus-like disease (C1q, C1r/s, C4, C2) • Glomerulonephritis • Angioedema without urticaria (C1-inhibitor defect) Atypical hemolytic uremic syndrome (regulatory defects)	Terminal component (C5–C9) deficiency, properdin and factor D deficiency, C1q/C2/C4 deficiency, hereditary angioedema
Intrinsic and innate immunity defects	• *Mycobacteria* (BCG, environmental nontuberculous species) and *Salmonella* (MSMD) • Pyogenic bacteria without fever or acute-phase response (IRAK4 and MyD88 deficiency) • Herpes simplex virus encephalitis (TLR3 pathway defects) • Chronic mucocutaneous *Candida* (IL-17 pathway defects, STAT1 gain-of-function)	• Nail dystrophy and enamel defects with chronic candidiasis • Autoimmune thyroiditis Aneurysms and vasculopathy in some interferonopathies	MSMD (IFNGR1/2, IL12RB1, STAT1 loss-of-function), IRAK4 and MyD88 deficiency, TLR3/UNC93B1 defects, STAT1 gain-of-function, epidermodysplasia verruciformis

	• Severe influenza or COVID-19 (type I interferon defects) Widespread human papillomavirus warts		
Immune dysregulation	• EBV - fulminant or recurrent infection, often triggering hemophagocytic lymphohistiocytosis • CMV Pattern: infection burden may be unremarkable; the presentation is dominated by inflammation rather than infection	• Hemophagocytic lymphohistiocytosis • Autoimmune cytopenia • Lymphoproliferation and lymphoma • Enteropathy and very-early-onset IBD • Autoimmune endocrinopathy • Severe eczema Oculocutaneous albinism with silvery hair	Familial HLH (PRF1, UNC13D), XLP1 and XIAP deficiency, ALPS, IPEX, APECED, CTLA-4 and LRBA defects, Griscelli syndrome
Autoinflammatory disorders	• None - inflammation is sterile Cultures are repeatedly negative and there is no response to antimicrobials; this is the key discriminator from infection	• Recurrent unexplained fever • Serositis and arthritis • Urticarial or neutrophilic rash • Aphthous ulceration • Acute-phase reactants elevated between attacks AA amyloidosis	Familial Mediterranean fever, TRAPS, cryopyrin-associated periodic syndromes, mevalonate kinase deficiency, haploinsufficiency of A20, DADA2

ALPS: autoimmune lymphoproliferative syndrome; APECED: autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy; BCG: bacille Calmette-Guérin; CMV: cytomegalovirus; CVID: common variable immunodeficiency; DADA2: deficiency of adenosine deaminase 2; EBV: Epstein-Barr virus; HLH: hemophagocytic lymphohistiocytosis; IBD: inflammatory bowel disease; IEI: inborn errors of immunity; IPEX: immune dysregulation, polyendocrinopathy, enteropathy, X-linked; MSMD:

Mendelian susceptibility to mycobacterial diseases; RSV: respiratory syncytial virus; SCID: severe combined immunodeficiency; TRAPS: tumor necrosis factor receptor-associated periodic syndrome; XLP: X-linked lymphoproliferative disease.

Table 4. Inheritance of Common Primary Immunodeficiency Disorders

X-linked

- Wiskott-Aldrich syndrome
- G-6-P-D deficiency
- X-linked congenital hypogammaglobulinemia
- Certain forms of SCID, CGD, hyper-IgM syndrome

Autosomal recessive

- Ataxia-telangiectasia syndrome
- Chediak-Higashi syndrome
- Complement defects, except C1-inhibitor deficiency and properdin deficiency
- Certain forms of congenital hypogammaglobulinemia, SCID, CGD

Autosomal dominant

- DiGeorge syndrome
- Certain other PID
- C1 inhibitor deficiency (angioedema)

G-6-P-D: glucose-6-phosphate-dehydrogenase; SCID: severe combined immune deficiency; CGD: chronic granulomatous disease.; PID: primary immunedeficiencies

Table 5. Findings on Physical Examination that Alert to Specific Immunodeficiency Disorders

Growth and development

- Malnutrition and failure to thrive (T-cell defects).

- Disproportionate growth (short-limbed dwarfism with hypogammaglobulinemia).

- Short stature (hypogammaglobulinemia with growth hormone deficiency).

- Ataxia (ataxia-telangiectasia).

Abnormal features

- Coarse facies (hyper-IgE syndrome).

- Abnormal facies (Down syndrome, DiGeorge syndrome).

- Partial albinism and photophobia (Chediak-Higashi syndrome).

- Hair or nail dystrophy (cartilage-hair hypoplasia).

Lymphoid tissue

- Hypoplastic tonsils and lymph nodes (B-cell defect).

- Lymphadenopathy, hepatosplenomegaly (AIDS, CGD, CVID, mononucleosis, lymphoma).

Congenital heart anomalies

- Endocardial cushion defects (Down syndrome).

- Cono-truncal cardiac anomalies (DiGeorge syndrome).

Skin and mucous membranes

-Persistent monilia infection (T-cell defect).

- Eczema (hyper-IgE syndrome, Wiskott-Aldrich syndrome).

- Bleeding tendency (Wiskott-Aldrich syndrome; X-linked hyper-IgM syndrome).

- Pyoderma, abscesses, oral ulcers, gingivitis (phagocytic defect).

- Telangiectasis (ataxia-telangiectasia).

- SLE-like rash (complement defect).

- Generalized seborrhea (Omenn syndrome).

- Generalized maculopapular rash (graft-versus-host reaction; Omenn syndrome).

- Generalized erythroderma and sparse abnormal hair (Comel-Netherton syndrome)

Extremities

- Arthropathy (infection, autoimmune).

- Finger clubbing (chronic infection, cystic fibrosis, cardiopulmonary disease).

Diseases with secondary immunodeficiency (Table 7)

AIDS: acquired immunodeficiency disease; CGD: chronic granulomatous disease; CVID: common variable immunodeficiency.

Table 6. Phenotypic Classification of Inborn Errors of Immunity (International Union of Immunological Societies) (3,23)

Category	Description	Examples
1	Immunodeficiencies affecting cellular and humoral immunity	SCID, Omenn syndrome
2	Combined immunodeficiencies with syndromic features	Wiskott-Aldrich, Ataxia-telangiectasia
3	Predominantly antibody deficiencies	CVID, X-linked hypogammaglobulinemia
4	Diseases of immune dysregulation	ALPS, HLH, IPEX syndrome
5	Congenital defects of phagocyte number or function	CGD, Leukocyte adhesion deficiency
6	Defects in intrinsic and innate immunity	MSMD, TLR signaling defects
7	Autoinflammatory disorders	FMF, TRAPS, CAPS
8	Complement deficiencies	C1-C9 deficiencies, C1-inhibitor defect
9	Bone marrow failure	Fanconi anemia, Diamond-Blackfan
10	Phenocopies of IEI	Somatic mutations, Autoantibodies

ALPS: Autoimmune lymphoproliferative syndrome; CAPS: Cryopyrin-associated periodic syndromes; CGD: Chronic granulomatous disease; CVID: Common variable immunodeficiency; FMF: Familial Mediterranean Fever; HLH: Hemophagocytic

lymphohistiocytosis; IPEX: Immune dysregulation, polyendocrinopathy, enteropathy, X-linked; MSMD: Mendelian susceptibility to mycobacterial diseases; SCID: Severe combined immunodeficiency; TLR: Toll-like receptor; TRAPS: Tumor necrosis factor receptor-associated periodic syndrome.

Table 7. Laboratory Screening for Immunodeficiency

Complete blood count

Absolute counts of lymphocytes, neutrophils,, platelets, eosinophils, and red blood cells

Humoral immunity (B-cell) evaluation

- Serum IgG, IgA, IgM, IgE.

- IgG subclasses

- Specific antibodies (IgG): and response to vaccines:

  Proteins: diphtheria, tetanus, polio, measles, rubella.

  Polysaccharides: pneumococcus (Pneumovax), meningococcus, isohemagglutinins (IgM)

  Conjugate: pneumococcus *(Prevnar*), H. influenzae, meningococcus

-Flowcytometry for B-cell number (CD19, CD20).

Cell-mediated immunity (T-cell) evaluation

- Chest radiograph for thymic shadow in infants.

- Delayed hypersensitivity skin testing: candida, trichophyton, mumps, tetanus, tuberculin PPD.

- Flow cytometry for T-cell numbers: total (CD3), helper (CD4), suppressor (CD8), CD4:CD8 ratio, and natural killer T-cells ($CD16^+$ or $CD56^+/CD3^-$)

Phagocytic function evaluation

- Peripheral neutrophil count.

- Neutrophil morphology.

- Flow cytometry dihydrorhodamine assay for the oxidative mechanism

- Flow cytometry for leukocyte adhesion molecules (CD11/CD18, CD15)

- Anti-neutrophil autoantibodies.

- For cyclic neutropenia, genetic panel for neutropenia

Complement system evaluation

- Hemolytic activity CH50 for classic pathway

- C3, C4

Advanced tests

- AH50 for alternate pathway

- Mannan-binding lectin assay

- Selected individual complement components or fractions

Table 8. Differential Diagnoses of Inborn Errors of Immunity

Secondary immunodeficiencies	Other causes
• Prematurity • Malnutrition • Hematologic: malignancy, sickle cell disease • Metabolic: diabetes, uremia • Dysmorphic syndromes • Immunosuppressants • Radiation therapy • Post-splenectomy • Post-viral or severe bacterial infections • Loss of plasma or blood cells: – Enteropathies – Nephropathies – Extensive burns	• Allergic rhinitis, asthma w recurrent viral infections **<u>Non immunologic causes</u>** • Foreign body aspiration • Chronic aspiration syndromes • Airway malacia syndromes • Environmental tobacco smoke exposure • Bronchopulmonary dysplasia • Cystic fibrosis • Primary ciliary dyskinesis • Anatomic malformation – Bronchopulmonary – Sinuses – Tracheo-esophageal fistula – Gastroesophageal reflux • Household members colonized with microorganisms • Hypersensitivity – Allergic chronic rhinosinusitis – Allergic bronchopulmonary aspergillosis – Hypersensitivity pneumonitis – Heiner syndrome