

INFECTIONS THAT SUGGEST AN IMMUNODEFICIENCY

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1. INTRODUCTION

Normal children have infections that can be considered an integral part of growing up. However, when these infections are recurrent or their severity is disproportionate to the virulence of the offending infectious agent, an immunodeficiency or other predisposing factor must be suspected and sought.

In the process of deciding if recurrent or single infections are suggestive of predisposing factors, it is helpful to follow a stepwise method of evaluation:

1. Is the infection “normal” or “pathologic”?
2. If the infection is “pathologic”, it is important to ask the question of why the patient may have these infections: can it be explained by the presence of known risk factors or is an immunologic evaluation indicated?

Once it is determined that the infection(s) are “pathologic”, the next step is to decide what component of the immune system needs to be evaluated. This can be done in general by determining if the infections are caused by extracellular or intracellular pathogens and by knowing about special associations between infection phenotypes and immunodeficiency groups or specific immunodeficiencies. The age of the patient and the presence of associated abnormalities, e.g. failure to thrive, also determine the type of immunological evaluation to be performed.

A brief review of host defense mechanisms and of the main groups of immunodeficiencies is essential to understand the relative importance of different host defense components in keeping individuals free of recurrent, severe or unusual infections.

The aim of this review is to define risk factors for severe and/or recurrent infections and to offer a list of infections that require immunologic evaluation.

General indications to evaluate for immunodeficiency, the evaluation itself and the criteria for normality or abnormality will be described elsewhere, under **38_00_Evaluation of Immunity**.

2. OVERVIEW OF HOST DEFENSES

Host-defenses include non-specific and specific mechanisms.

Non-specific mechanisms

- Skin and mucosal integrity
- Complement
- Phagocytic systems.

Specific mechanisms

- antibody-mediated
- cell-mediated immunity.

The first mechanism to clear microorganisms breaking epithelial surface-integrity is phagocytosis by polymorphonuclear (PMN) and mononuclear phagocytes (monocytes and macrophages) (M ϕ). In the absence of antibodies, bacterial surface polysaccharides activate the alternative pathway of complement, resulting in the attachment of C3b to the bacterial surface, which in turn activates the membrane-attack components of complement (C5 to C9), which lyse susceptible bacteria. For resistant, encapsulated bacteria, C3b provides opsonization for phagocytosis by PMNs and M ϕ s. Minor bacterial infections are terminated by these mechanisms without the manifestation of disease, but such subclinical infections may be sufficient to trigger the development of protective antibodies and/or cell-mediated immunity.

Specific immunity develops after presentation of microbial components by antigen-presenting cells to T- and B-lymphocytes. In response to stimulation by microbial antigens, T helper cells (CD4⁺ cells) proliferate and secrete lymphokines, e.g., interferon- γ (IFN- γ), which activates M ϕ . This M ϕ activation is an essential step in clearing intracellular pathogens not eliminated after ingestion by non-activated M ϕ . Upon interaction with antigens, T suppressor cells (CD8⁺ cells) develop into cytotoxic cells capable of killing virally infected cells and terminating a viral infection.

The binding of an antigen to B cell surface immunoglobulins leads to the production of specific antibodies to many microbial antigens in the presence of antigen-specific CD4⁺ T helper cells. Secreted antibodies attach to surviving bacteria, producing further opsonization for phagocytosis by PMNs and M ϕ s. Furthermore, immunoglobulins (Ig) M and G activate complement through the classic pathway, which also leads to lysis of susceptible bacteria and opsonization by C3b. Three-

to-six days after the initial infection, the combination of specific antibodies that direct and amplify the non-specific host defense mechanisms usually terminate an infection in a normal host.

3. HOST DEFENSES AND INFECTION GROUPS

Two large groups of pathogens, each one including viruses, bacteria, mycobacteria and protozoa, involve two different host defense mechanisms: extracellular pathogens and intracellular pathogens.

Extracellular pathogens

Extracellular pathogens include many common bacteria and viruses before intracellular infection occurs. These pathogens have in common that they are rapidly killed by phagocytic cells once ingested. The pathogens include *Streptococcus pneumoniae*, *Moraxella catarrhalis*, *Haemophilus influenzae* and also *Staphylococcus aureus*, and *Neisseria meningitidis*.

The host defense mechanisms involved are:

- Phagocytosis,
- Complement, alternate and classic pathway,
- Antibody mediated immunity

Extracellular pathogens that cause infections in defects of intracellular killing by phagocytes are frequent and some infrequent pathogens that are all catalase positive. Complement deficiencies lead to infections with common extracellular pathogens and also with neisseria species. Further details will be given in each specific section.

Intracellular pathogens

Intracellular pathogens are more resistant to intraphagocytic action and frequently survive within monocytes and macrophages. Cellular immunity with activation of monocytes and macrophages by T lymphocyte secreted lymphokines is the main mechanism of defense against these microorganisms. Intracellular infections can be divided in two groups:

- Intracytosolic: viruses, chlamydia, listeria.

The main host defense mechanisms are cytotoxic T cells (class I mediated cell lysis), NK cells, antibodies and antibody-mediated cell cytotoxicity

- Intravesicular infections: mycobacteria, salmonella, fungi such as *Pneumocystis carinii*, and protozoa like *Toxoplasma gondii*.

The main mechanisms of defense are CD4 T cells and IFN-g secretion leading to M ϕ activation.

4. CLASSIFICATION OF IMMUNODEFICIENCIES

Immunodeficiencies are classified according to their immunologic phenotypes, e.g., deficiencies of cell mediated immunity, deficiencies of antibody mediated immunity, abnormalities of phagocytosis and complement deficiencies. Since T lymphocytes are essential for an adequate function of antibody-mediated immunity, some primary immunodeficiencies are considered combined abnormalities of T and B cells. Furthermore, in many instances the molecular defect leading to an abnormal function of host defenses also affect other cells and organs, leading to syndromes where immunological abnormalities are associated with platelet abnormalities (Wiskott-Aldrich syndrome), facial, parathyroid and conotruncal abnormalities (Di George syndrome), neurological abnormalities (ataxia telangiectasia), etc. A comprehensive phenotypic classification of primary immunodeficiencies is presented elsewhere.

- T and B cell combined immunodeficiencies and cellular immunodeficiencies
- Deficiencies of antibody mediated immunity
- Defects of phagocytosis (polymorphonuclear cells)
- Defects of complement

This classification is not perfect and new knowledge about molecular defects and gene mutations causing the majority of primary immunodeficiency syndromes has led to constant revisions of the classifications of immunodeficiencies.

The virtue of the phenotypic classification presented above is that it functionally defines which components of host defenses need to be evaluated.

5. WARNING SIGNS FOR IMMUNODEFICIENCIES

The Jeffrey Modell Foundation has widely publicized 10 warning signs for immunodeficiencies. These include infections, general conditions such as failure to thrive, and a family history positive for immunodeficiency.

“10 warning signs of immunodeficiency”, Jeffrey Modell Foundation

- 1 - Eight or more new ear infections within 1 year
- 2 - Two or more serious sinus infections within 1 year
- 3 - Two or more months on antibiotics with little effect"
- 4 - Two or more pneumonias within 1 year
- 5 - Recurrent, deep skin or organ abscesses

- 6 - Failure of an infant to gain weight or grow normally
- 7 - Persistent thrush in mouth or elsewhere on skin, after age 1
- 8 - Need for intravenous antibiotics to clear infections
- 9 - Two or more deep-seated infections such as meningitis, osteomyelitis, cellulitis, or sepsis
- 10 - A family history of primary immune deficiency

While these warning signs have contributed to awareness of immunodeficiency diseases, they do not list many specific situations that do require evaluation and they do not assist practitioners performing an initial evaluation of their patients in deciding which elements of host defenses need to be evaluated.

6. INFECTIONS THAT SUGGEST AN IMMUNODEFICIENCY

General characteristics of infections in immunodeficient patients

The infections that suggest an immune abnormality can be divided in two general groups: recurrent infections with diverse pathogens and single infections caused by one pathogen.

For **recurrent infections**, it is important to define what pathologic recurrent infections are as opposed to the normal infections that are part of growing up for any normal child. Some general characteristics are helpful in defining pathologic infections: recurrence after 3 - 5 years of age, when most children have developed immunity to the most frequent childhood pathogens; rapid recurrence after completing antibiotic treatments; and lack of known systemic or local predisposing factors.

For **single pathogen infections** the need for an immunologic evaluation is defined by an infection disproportionate to the virulence of the offending infectious agent. This can be identified by an unusual age of onset, an unexpected site of infection, or a severity and failure to respond to treatment uncharacteristic for a given pathogen.

In general, recurrent infections with extracellular pathogens are typical for antibody deficiency syndromes, while unusual infections with single extracellular pathogens are the hallmark of complement and phagocytic deficiencies, and single infections with intracellular pathogens are characteristic for deficiencies in cell-mediated immunity.

Detailed lists of infections suggestive of deficiencies of phagocytosis, complement deficiencies, antibody deficiencies, and of infections in deficiencies of cell mediated immunity are presented in tables 2-5 [Lekstrom-Himes, 2000 #61; Sorensen, 2000 #59].

Infections suggestive of specific immune defects

In recent years, it has become clear that specific components of host-defense mechanisms appear essential for immunity against specific microorganisms (PAMPS = Pathogen Associated Molecular Pathways). Therefore, recurrent or severe infections with some pathogens can point the way toward specific areas of possible immune deficiencies. The infections and immune defects listed in Table 6 are examples of these associations.

Most infections can occur in association with several different types of immunodeficiency. Thus, for each type of infection one has to consider a differential diagnosis of possible underlying immunodeficiencies in addition to other predisposing causes. Examples of the different immune abnormalities that may be associated with a given infection are listed in Table 8.

For practical purposes, we will discuss first recurrent infections and then single pathogen infections, listing the type of abnormality that need to be ruled out for each of these infection phenotypes.

Recurrent infection

The main clinical assessment is to differentiate “normal” recurrent from “pathologic” infections. Among the latter, it is important to differentiate recurrent infections that suggest an immunodeficiency from those that have another accepted explanation.

Pathologic recurrent infections with a possible immunologic cause are defined by:

- Need for antibiotic treatment
- Recurrence after discontinuing antibiotics
- Severity and sequelae
- Age < 6 months and > 3-5 years
- Different infection sites and pathogens
- Absence of sick contacts

Recurrent infections caused by non-immunological diseases

In general, no immunologic evaluation is required in the following conditions that by themselves are sufficient to explain recurrent or some unusual infections:

Systemic or generalized diseases

- Cystic fibrosis (P aeruginosa sinusitis, lung infections)
- Alfa 1 antitripsin deficiency
- Immotile cilia syndrome/ situs inversus
- Diabetes (mucosal candidiasis)

Local factors (anatomical causes – infections tend to occur at the same site):

- Sinus outflow obstruction: primary – secondary
- Lungs: congenital cysts, etc
- bronchiectasis: primary vs secondary

- Right middle lobe syndrome
- Aspiration pneumonias (left upper lobe)
- Urinary tract infections

7. INFECTIONS RARELY CAUSED BY AN IMMUNODEFICIENCY

Recurrent infections rarely associated with an immune defect:

- Recurrent strep throat
- Staph aureus and other bacterial skin infections in atopic dermatitis
(Note: SCID, XLA, hyper-IgE, Wiskott Aldrich patients may present with dermatitis)
- Arthritis and osteomyelitis except if caused by atypical mycobacteria (or Staph aureus in patients with lymphadenopathy and or splenomegaly)
- Recurrent boils (specially due to MRSA)

“Normal” recurrent infections (opposite of “pathological” infections).

- Siblings/ other household exposure
- Day care/ Kindergarten/School

These infections may be frequent but they do not have the characteristics of pathologic infections defined above.

Single, virulent pathogen infections that are usually not associated with an immunodeficiency are numerous. Some examples are listed below:

Mononucleosis

Line infections in patients with indwelling catheters

Meningococcal meningitis in close contact outbreaks

Pulmonary tuberculosis

Malaria

Most parasitic infections

8. CONDITIONS THAT MAY COEXIST WITH AN IMMUNODEFICIENCY

Several known immunodeficiency syndromes have associated non-immunological abnormalities, e.g., hypoparathyroidism and heart disease in the Di George syndrome, eczema and thrombocytopenia in the Wiskott Aldrich syndrome, ataxia and telangiectasia in the syndrome named after these abnormalities, etc.

In addition to these well known immunodeficiencies, some patients with diseases that are not constitutively associated with immune defects may have associated immune abnormalities as the source of their recurrent or unusual infections. For instance, if a patient with Down syndrome has recurrent respiratory infections, these should not be attributed to this chromosomal abnormality, as most patients with this condition do not have recurrent infections.

- Smoke exposure / pollution
- Allergy
- Multiple diseases not usually associated with an immune defect:
 - Down syndrome
 - Cerebral palsy
 - Mental retardation
 - Muscular dystrophy
 - Dysmorphic syndromes, etc.

9. HOW TO TARGET AN IMMUNE EVALUATION

The decision of which component(s) of the immune system require evaluation can be done by determining if the infections are caused by extra-cellular or intracellular pathogens, and by recognizing the special associations between infection phenotypes and immunodeficiency groups or specific immunodeficiencies. The age of the patient and the presence of associated abnormalities, e.g. failure to thrive, also determine the type of immunological evaluation to be performed.

The frequency of different immunodeficiencies is another important consideration. Deficiencies of antibody-mediated immunity are by far the most frequently reported, usually 50-60% of large series of immunodeficiency patients, while complement deficiencies are the less frequent, with only 1 to 2% of patients reported.

For practical purposes, it is possible to identify infections requiring evaluation of antibody-mediated immunity, and other infections which, in addition, require evaluation of cellular immunity and /or phagocytosis, or complement. In each case, recurrent infections with diverse pathogens or single pathogen infections need to be considered.

10.1. INFECTIONS THAT SUGGEST ANTIBODY DEFICIENCY ONLY

Infections with extracellular pathogens that respond to antibiotics but recur promptly after discontinuation of treatment usually require only the evaluation of antibody-mediated immunity.

Because of the frequency with which otitis media and sinusitis are caused by *Streptococcus pneumoniae* strains, patients having only these infections should be evaluated only after they are fully immunized according to ACIP recommendations. Notable exceptions are boys who do not have detectable tonsils or patients that present with infections and neutropenia. The absence of tonsils and neutropenia are hallmarks of X linked agammaglobulinemia and these boys need to be evaluated at any time if they have recurrent infections.

The frequent use of antibiotics may alter the natural history of immunodeficiency diseases. Therefore we recommend an immunological evaluation of patients that require frequent antibiotic use even if this treatment is effective and keeps the patient from having serious infections.

Table 1. Infections that warrant an evaluation of antibody-mediated immunity*

Indications	Allergy/Immunology Clinics LSUHSC, New Orleans		Jeffrey Model Foundation ^a
	2-5 years	> 5 years	Any age
	Number of episodes		
UPPER RESPIRATORY INFECTIONS			
URI treated with antibiotics (per year)	≥ 4	≥ 2	
Otitis treated with antibiotics (per year)	≥ 4	≥ 2	≥ 8
Sinusitis episodes (per year)	≥ 2	≥ 1	≥ 2
Chronic sinusitis (> 1 mo)	≥ 1	≥ 1	
SEVERE AND INVASIVE INFECTION			
Pneumonias (per year)	≥ 2	≥ 2	≥ 2
Pneumonias (lifetime)	≥ 3	≥ 2	
Uncomplicated Invasive infections (sepsis, meningitis, osteomyelitis)	≥ 2	≥ 2	≥ 2
Severe invasive infections	≥ 1	≥ 1	
GASTROINTESTINAL INFECTIONS			
Chronic diarrhea due to rotavirus/other	≥ 1	≥ 1	
Chronic/recurrent <i>Giardia lamblia</i> infection	≥ 1	≥ 1	
ANTIBIOTIC USE			
Chronic antibiotic use without effect (>2 years)			≥ 1
Need for IV antibiotics to clear infection			≥ 1
Need for preventive antibiotic use**	≥ 1	≥ 1	
Antibiotic use for respiratory infections	≥ 4	≥ 2	
Allergy to antibiotics	≥ 1	≥ 1	
CLINICAL VACCINE FAILURES***			
Hib, Strep pneumo infections	≥ 1	≥ 1	

*Adapted from Sorensen RU, Moore C. Antibody deficiency syndromes. *Peds Clin N A* 42: 1225-1232, 2000

** This excludes patients needing chronic antibiotic use for functional or anatomical asplenia, urinary tract infections, or other known risk factors for infection.

***Clinical vaccine failures are defined by an invasive or severe infection with a bacteria included in the Hib or pneumococcal vaccines

10.2. INFECTIONS THAT SUGGEST COMBINED IMMUNODEFICIENCIES

Since combined immunodeficiencies have both T cell and antibody deficiencies, affected patients may have **recurrent infections** with both extracellular and intracellular pathogens. Infections with intracellular pathogens start in the first 6 months of life, while infections with extracellular pathogens may start after 6 months, when maternal IgG concentrations are no longer protective against the majority of pathogens. However, recurrent infections with extracellular pathogens may also start early in life.

Patients with any kind of recurrent infection severe enough to warrant an immunological evaluation under 6 months of life, especially if accompanied with **failure to thrive**, (even if this failure starts only after 3 or 4 months of age) **always** need an evaluation of **cellular immunity** in addition to antibody-mediated immunity.

Single pathogen infections that suggest mild or severe deficiencies of cellular immunity are listed in the following table:

Table 2. Infections with single pathogens suggestive of T cell deficiencies

INFECTIONS	T Cell deficiencies	
	<i>Mild to Moderate</i>	<i>Severe</i>
VIRAL		
Cytomegalovirus (CMV)	Onset < 1 month of age	Onset > 1 month of age, disseminated beyond liver, spleen, or lymph nodes
Herpes simplex (HSV)	Stomatitis >2 episodes/year Bronchitis, pneumonitis, or esophagitis <1 month of age	Disseminated infection
Herpes zoster	2 distinct episodes or > 1 dermatome	
Varicella	Disseminated, complicated	Disseminated, severe
Adenovirus		Severe pneumonitis, Disseminated infection
Influenza & parainfluenza viruses		Severe pneumonitis Disseminated infection
Vaccine Virus Infection		Disseminated infection
Papilloma virus	Disseminated, persistent warts	

<p>BACTERIAL Mycobacterium tuberculosis</p> <p><i>Mycobacterium avium intracellulare</i> (MAC)</p> <p>Other atypical mycobacteria</p>	<p>Local Infection</p> <p>Local Infection</p>	<p>Disseminated or extrapulmonary</p> <p>Disseminated infection</p> <p>Disseminated infection</p>
<p>FUNGAL Candidiasis</p> <p>Nocardiosis</p> <p>Cryptococcosis</p> <p><i>Pneumocystis carinii</i></p> <p>Histoplasmosis</p> <p>Coccidioidomycosis</p>	<p>Oropharyngeal lasting >2 months in children >6 months old</p> <p>Soft tissue infection</p> <p>Pneumonia</p>	<p>Esophageal or lower airways</p> <p>Meningitis</p> <p>Extrapulmonary</p> <p>Pneumonia</p> <p>Disseminated infection</p> <p>Disseminated infection</p>
<p>PROTOZOAL Toxoplasmosis</p> <p>Cryptosporidiosis</p> <p>Isosporiasis</p>	<p>Onset <1 month of age</p>	<p>Cerebral, onset >1 month of age</p> <p>Chronic diarrhea</p> <p>Chronic diarrhea</p>
<p>PARASITIC Strongiloidosis</p>	<p>Overwhelming gut infection</p>	<p>Severe intestinal and lung infection</p>

Clinical vaccine failures of viral vaccines, e.g. paralytic polio in an immunized child (due to wild or vaccine polio strains), measles or severe varicella in fully immunized patients suggest the need to evaluate antibody and cell-mediated immunity.

10.3. INFECTIONS THAT SUGGEST PHAGOCYTTIC DEFICIENCIES ONLY

Some infections are highly characteristic of defects of phagocytosis and rarely associated with any other defects. They differ from defects of chemotaxis and from intracellular killing defects.

Defects of chemotaxis

- Skin infections (cold abscesses), periodontal infections and deep-seated abscesses due to *Staphylococcus aureus* or mixed flora.
- Omphalitis with delayed separation of the umbilical cord
- Severe periodontitis

Intracellular killing defects

Some infections with rarely encountered pathogens are found almost exclusively in chronic granulomatous disease, an intracellular killing defect. Many other pathogens that cause infection in patients with phagocytic defects, including CGD, may also infect patients with deficient cellular immunity. Pathogens seen almost exclusively in CGD are:

- *Chromobacterium violaceum*
- *Candida lipolytica*
- *Burkholderia cepacia*
- *Torulopsis glabrata*
- *Francisella philomiragia*
- *Xanthomonas maltophilia*
- *Serratia marcescens*

The sites of infection are chronic skin abscesses, lymphadenitis, osteomyelitis (*Serratia marcescens*), liver abscesses (*Staph*), and lung infections (*aspergillus*).

10.4. INFECTIONS THAT SUGGEST PHAGOCYTTIC OR CELLULAR IMMUNODEFICIENCIES

Some pathogens can cause infection both in chronic granulomatous disease and in various deficiencies of cellular immunity. These include:

- Skin, lymphoid, pulmonary, or liver infections caused by *Staphylococcus aureus* (liver abscesses)
- *Aspergillus fumigatus*,
- *enterobacteriaceae*
- *salmonella*, *proteus*
- bacillus Calmette – Guerin
- non-tuberculous, atypical mycobacteria
- *Nocardia* spp

10.5. INFECTIONS THAT SUGGEST COMPLEMENT OR ANTIBODY DEFICIENCIES

Classic pathway deficiencies: C1q, C1r, C1s, C4, C2 deficiency

- Streptococcal infections
- Neisserial infections (rare in classic pathway deficiencies)

C3 and C3b deficiency

- Recurrent pyogenic infections*

Membrane attack complex: C5 to C9 deficiencies

- Meningococcal sepsis or meningitis**
- Disseminated gonococcal infection, gonococcal arthritis

Alternate pathway: factor B, properdin deficiency

- Recurrent pyogenic infections*
- Meningococcal sepsis and meningitis

*Recurrent pyogenic infections are most likely caused by antibody deficiencies. It is not recommended to add the evaluation of complement deficiencies to the initial workup of these patients. Complement evaluation is justified only if no other predisposing cause can be identified.

**Complement should be evaluated in all patients with a second episode of meningococcal infection. Evaluation in patients with a single infection is recommended in patients > 12 years of age with sporadic infections, in African Americans (the prevalence of complement deficiencies is 10% vs 1 in Caucasians that have meningococcal infections) and in family members of patients that had meningococcal infections.

Table 3. Summary of infections that suggest a Complement Deficiency

Recurrent Strep infections	Classic pathway	C1q, C1r, C1s
Strep pneumoni, Hib infections	Classic pathway	C4B
Recurrent pyogenic infections	C3 Alternate pathway	C3, Factor I, Factor H, Factor B, Properdin
Neisserial meningitis Neisserial sepsis Disseminated gonococcal infections	Classic pathway & Alternate pathway	C5-C9 C1q, r, s, C4, C2 (rare) Factor B, Properdin

10.6. CONGENITAL OR SECONDARY ASPLENIA OR ANTIBODY DEFICIENCY

Recurrent sepsis with Streptococcus pneumoniae or other capsulated bacteria or salmonella in infants and children are highly suggestive of asplenia, but they may also be caused by antibody deficiencies.

Asplenia also needs to be considered in unexplained sepsis with encapsulated bacteria in older children, adolescents and adults. It should be noted that congenital asplenia usually does not lead to recurrent infections, but severe infections may occur at any age.