

CONTAGIOUS COMMENTS

Department of Epidemiology

Series on the Top 5 Questions Regarding Pediatric Infectious Diseases

Topic # 4: Screening for Immunodeficiency

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When should I start worrying that a child might have underlying immunodeficiency?

When a patient has “too many” infections, recurrent invasive infections, infections that don’t respond to the usual treatment, infections with unusual organisms, or recurrent infections associated with significant growth and/or developmental delay, an underlying immunodeficiency is worth thinking about.

How many infections are “Too many”?

Remember, 8 to 10 episodes of upper respiratory infection is NOT unusual in children less than 5 years of age, particularly if the child is in out-of-home childcare with other children. However, some general rules of thumb for “too many” are:

- 10 or more episodes of otitis media/year (infants/children).
- 2 or more episodes of otitis media/year (adolescent/adult).
- 2 or more episodes of bacterial pneumonia/year.
- 2 or more episodes of severe sinusitis/year.
- 2 or more episodes of severe gastroenteritis/year.
- 2 or more life-threatening infections per lifetime.

Which types of infections should raise the question of underlying immunodeficiency?

Invasive infections such as sepsis, bacterial meningitis, and recurrent soft tissue abscesses should prompt a consideration of underlying immunodeficiency. Infections that are particularly difficult to treat are also a red flag. Examples include those requiring prolonged courses of antimicrobials, parenteral therapy (when oral therapy usually suffices), surgical debridement, or those that recur despite an adequate course of usual therapy.

What microbes should immediately raise the red flag for a possible underlying immunodeficiency?

Although not a complete list, infections with *Pneumocystis*, invasive fungi, herpesviruses (T-cell defects, HIV); *Pseudomonas*, *Burkholderia*, *Serratia*, *Aspergillus*, recurrent Staphylococcal (phagocyte defect); *Neisseria* (even single episode), recurrent encapsulated organisms- pneumococcus or haemophilus (complement) all warrant consideration of immunodeficiency.

How common is immunodeficiency?

Acquired immunodeficiency due to HIV infection, chronic steroid use, nephrotic syndrome (loss of immunoglobulin), and asplenia (trauma or sickle cell) are all more common than all other inherited immunodeficiencies combined. The overall incidence of inherited immunodeficiency is 1:5000. The most

common type is a B Cell defect (50%), followed by combined B and T cell defects (30%), T cell defects (10%), phagocyte defects (10%) and complement deficiencies (rare). However, it should be remembered that up to 10% of all individuals with a single episode of invasive meningococcal disease have an underlying complement deficiency. See table below for summary of inherited immunodeficiencies.

What are some other reasons (other than an underlying immunodeficiency) for recurrent infections?

Increased exposure is the most common reason for recurrent minor upper respiratory infection, as occurs with attendance in out-of-home childcare: Up to 2/3 children have more than 60 days respiratory illness/year. Other higher risk groups include children with atopy (asthma, allergic rhinitis), children exposed to passive smoke, children with anatomic abnormalities of the upper respiratory system (including immotile cilia syndrome), children with malnutrition, or children with cystic fibrosis.

Munchausen Syndrome is rarely a cause of recurrent infection.

What are specific questions I should ask when taking a history if I am worried about the possibility of an underlying immunodeficiency?

- **What age did the recurrent infections start?** Infections due to immunoglobulin deficiencies tend to start in children more than 6 months age due to waning maternal antibody, whereas those due to phagocyte and cell mediated immunity deficiencies start earlier
- **What is the frequency and type of infections?** Too many “routine” infections or more than one unusual / severe / invasive infections.
- **What is the severity of infections?** Did treatment require hospitalization, prolonged course of oral antibiotics, intravenous antibiotics or surgical excision/drainage?
- **When did the umbilical stump separate?** More than 3 weeks may indicate neutrophil defect such as lazy leukocyte syndrome
- **Get a complete vaccination history.** Were there any unusual reactions to live vaccines?
- **What infectious pathogens have caused prior infections?** Certain pathogens raise red flags for underlying immunodeficiency, even if they only occur once: *Examples: Pneumocystis, Pseudomonas, Aspergillus, Nocardia.*

- **Were there any unexplained childhood deaths in the extended family?** Also ask specifically if any known family history of immunodeficiency.
- **Is there a history of chronic intractable diarrhea or chronic severe eczema?** Often seen in conjunction with cell mediated immunity defects.

What specific findings on physical exam are clues to an underlying immunodeficiency?

Low weight for height and failure to thrive in conjunction with recurrent infections might be a clue. Hepatomegaly and/or splenomegaly can be seen in children with HIV infection, as well as other immunodeficiencies. Severe periodontal disease (gingivitis, apthous ulcers, toothlessness) may be seen in children with phagocytic defects. An abundance of lymph nodes (particularly if outside the cervical region), or NO palpable lymph nodes are also red flags. Cutaneous findings such as severe eczema (T cell defects, Job Syndrome, Wiscott Aldrich), or recurrent/severe candidal infections of the oropharynx (thrush) or nails are also concerning (T cell defect).

What laboratory tests should I send as an initial basic screening for immunodeficiency?

To screen the major arms of the immune system, the following is recommended:

1. **A basic CBC** including manual differential and peripheral smear. Abnormalities worth pursuing include lymphopenia, neutropenia, neutrophilia, eosinophilia, thrombocytopenia, platelets with giant granules, or Howell-Jolly bodies.
2. **Quantitative T and B Cell subsets** (which gives absolute numbers and percentages. As a rough guide, normal total lymphocyte counts are as follows: 7000 infancy, 4000 childhood, 2000 adolescent (50% T Cells, 25% NK Cells, 25% B cells).
3. **HIV testing:** Antibody testing and/or PCR depending on age.
4. **Quantitative Immunoglobulins (IgG, IgA, IgM, IgE, IgD).** IgG subsets are not recommended. Remember that Ig Levels are AGE SPECIFIC, high levels may also be abnormal (HIV, Hyper IGM syndrome), and normal levels do not always indicate normal function.
5. Complement testing: **CH50 / AH50.**
6. Phagocyte function: **NBT** (Oxidative burst and killing).
7. **CXR:** (Bronchiectasis, pneumatoceles, absence of thymic tissue, cardiac defects).

When should I refer to Infectious Diseases or Immunology?

Anytime history or physical suggests immunodeficiency, referral may be indicated. Basic screening laboratory tests (above) can be done in your office, but if tests are not available, referral can be arranged for this purpose. Abnormalities on basic screening should prompt referral for advanced laboratory testing.

Summary of Types of Inherited Immunodeficiencies

Type of Defect	Examples	Key Points
T Cells	SCID	T cell and antibody production, often have lymphopenia and low immunoglobulin levels.
	DiGeorges' Syndrome	Facies: Hypertelorism, short philtrum, Cardiac anomaly, thyroid/parathyroid.
	Wiscott Aldrich Syndrome	Thrombocytopenia, Eczema, Low IgM, High IgA, Opportunistic infections.
B Cells	X linked agammaglobulinemia	All Ig's very low or absent. Brutons: Pure B cell defect.
	X-linked Hyper IgM	Low IgG and IgA, High IgM.
	X-linked LPD – Duncans	EBV response.
	CVID	Low IgA and IgG.
	Transient Hypogammaglobulinemic of Infancy	
	IgA Deficiency	Low IgA.
Phagocytosis	SCID	See above (combined B and T cell).
	CGD	Absent NBT reduction, superoxide generation, 60% x-linked, 40% AR.
	Cyclic Neutropenia	Every 21 days.
	Chediak-Higashi	Giant granules neutrophils, albinism, decreased neutrophil number and chemotaxis, AR.
	Leukocyte Adhesion Deficiency (Lazy Leukocyte Syndrome)	CD18 deficiency, selectin/integrins missing, increased WBC number, short, MR.
	Myeloperoxidase Deficiency	
	Hyper IgE (Job Syndrome)	Poor chemotaxis, facies: hypertelorism, triangular chin, sinopulmonary infections, eczema, staph pneumatoceles.

Abnormalities on basic screening should prompt referral for advanced laboratory testing.

Topic # 5: I have a Child with a Positive Tuberculin Test

John Ogle, MD

Does the child have risk factors for tuberculosis?

The most common risk factors are birth in a country where tuberculosis is common, living with a foreign born adult, or travel to a country at high risk for tuberculosis. 15mm of induration is considered a positive skin test in a healthy child over 4 years with no risk factors for Tb.

Is the child ill with symptoms of tuberculosis or is the child immune compromised?

If the answer to either question is yes, then 5mm of induration is considered a positive test and evaluation for active tuberculosis including careful history, physical examination and chest radiographs should be done. Tuberculosis is a slowly progressive disease but evaluation should not be delayed in symptomatic children.

What are the symptoms of tuberculosis in children?

Most children with active Tb are not acutely or severely ill. Fever, persistent cough, weight loss (failure to thrive), pneumonia not improving on antibiotics are some of the most common presentations.

Was the child recently exposed to a family, household or other close contact with known or suspected tuberculosis?

If the answer is yes, 5mm of induration is considered a positive test and the child needs further evaluation.

Was the tuberculin test properly placed and read?

A Mantoux test consists of 5TU (0.1ml) of PPD injected intradermally, creating a wheal without bleeding. Induration is measured 48-72 hours later in mm using a ball point pen and ruler perpendicular to the long axis of the arm. Improperly placed Mantoux tests are not interpretable and should be repeated. Tine or other multiple puncture tests are not recommended.

Is the physical examination abnormal?

Many physical findings are described in tuberculosis. However many children with active tuberculosis have a normal physical examination. An abnormality on examination usually indicates more advanced or severe disease.

Do all children with a positive tuberculin test need a chest xray?

Yes. PA and lateral chest radiographs should be examined by someone familiar with tuberculosis in children. We ignore any prior history of receiving BCG in the decision to place and interpret a tuberculin test and in the decision to obtain a chest x-ray. A child with a positive tuberculin test, no symptoms of tuberculosis with a normal chest x-ray is considered to have latent tuberculosis infection (LTBI).

How should LTBI be treated?

Isoniazid 10 -15mg/kg/day (maximum 300mg) once daily for 9 months is standard. 100 and 300 mg scored tablets are used as INH suspension causes diarrhea. Routine liver function or other laboratory tests are not needed except in teens (ETOH should be avoided), children with liver disease or taking hepato-toxic medicines. Toxicity is monitored clinically. LFTs are measured in children who develop anorexia, vomiting, or abdominal pain on INH. Children treated for LTBI do not need follow-up chest xrays nor should skin tests be repeated.

The parents believe the BCG vaccine caused the positive skin?

BCG is given as a routine neonatal or childhood vaccine throughout much of the developing world. BCG is used in countries where tuberculosis is common and exposure of young children to tuberculosis is frequent. BCG reduces the incidence of disseminated Tb but does not prevent infection. Although BCG may cause a positive skin test, the reactions are usually small, less than 10mm and decrease with time since the BCG. It is not possible in an individual child to prove that a positive skin test is due to BCG, so usually for the safety of the child we ignore the previous BCG history.

Who can I call for help?

Cases of active tuberculosis are reportable and are given directly observed therapy (DOT). Denver Metro Tuberculosis Clinic (303-436-7286), the county health department, or the Tuberculosis Control Program of the Colorado Department of Public Health and Environment (303-692-2638) should be notified of active cases and can assist with evaluation and treatment. Dr. John Ogle (303-436-6690) provides the Pediatric staffing for Denver Metro Tb Clinic and can also help with questions.





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New *Chlamydia trachomatis* and *Neisseria gonorrhoeae* DNA Amplification Assay

Christine Robinson Ph.D. and Elaine Dowell SM (ASCP)
Microbiology-Virology

Microbiology has changed testing for *Chlamydia trachomatis* (CT) and *Neisseria gonorrhoeae* (GC) in urine and genital specimens from PCR to a DNA Amplification Assay. The new assay has similar sensitivity to PCR and several additional advantages, including the ability to detect CT and GC in urines from both females and males and in asymptomatic as well as symptomatic persons. There is no change in urine collection, but special collection kits must now be used for swabs. There are two swab kits - one for endocervical swabs and one for male urethral swabs (although urine is typically sent due to discomfort associated with male urethral swab collection.). A final change is that swabs collected using the new kits cannot be used for CT culture, which is also required if CT DNA amplification is ordered for a victim of sexual assault. The new collection kits, instructions for use, and materials for culture can be obtained from Microbiology (303-861-6703). See the [Laboratory's Test Directory](#) on the TCH Home Page or call Microbiology for more information.



Other topics in the Series on the Top 5 Questions Regarding Pediatric Infectious Diseases can be found in previous issues of Contagious Comments:

- Topic # 1: Chronic Fatigue Syndrome (February 2006 issue)
- Topic # 2: Approach to the Child with Prolonged Fever (February 2006 issue)
- Topic # 3: Pertussis (May 2006 issue)