

Identification of Immunodeficiency in the Primary Care Setting

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In the fight between you and the world, back the world.

—Frank Zappa

Learning Objectives:

1. Ascertain the prevalence of immunodeficiencies presenting in childhood.
2. Identify clinical features that suggest an immunodeficiency
3. Initiate and interpret laboratory testing for immunodeficiency
4. Debate the utility of newborn screening for the most common and treatable of the primary immunodeficiencies

Primary Reference:

1. Reust CE. Evaluation of primary immunodeficiency disease in children. *American Family Physician*. 2013;87(11): 773-778. <http://www.aafp.org/afp/2013/0601/p773.pdf>

CASE ONE:

Ayma Sicagin, a three-year-old comes to your office accompanied by her mother for evaluation of “frequent infections.” The mother tells you that she is worried because in the past year, her daughter has received four courses of antibiotics for ear infections, a single course of antibiotics for sinusitis, and two courses of antibiotics for pneumonia (one of which required hospitalization for IV administration). A thorough history and review of systems reveals chronic mucopurulent nasal drainage and abdominal pain with frequent, loose stools. There is no family history of similar symptoms. The physical exam is unremarkable except for height and weight in the 5th percentile and visible bilateral purulent nasal drainage.

1. How many respiratory infections do healthy children typically get per year?

Healthy children have on average four to eight respiratory infections per year. This number may be lower (one or two per year) in infants and children who are kept away from strangers, or higher (10 to 12 per year) in those who have older siblings, attend daycare or preschool, or who are exposed to secondhand smoke. Most of these infections are caused by viral pathogens. While the average duration of symptoms is eight days, the normal range may extend beyond two weeks. Healthy infants and children also generally do not have more than one episode of pneumonia or more than two episodes of otitis media in the first three years of life.

2. At what point might one consider an underlying immunodeficiency? What is the difference between primary and secondary immunodeficiency?

While recurrent infections with typical pathogens occurring in a single site are more indicative of an anatomic abnormality, immunodeficiency should be considered when a child has a multiplicity of sinopulmonary, gastrointestinal, and cutaneous infections, meningitis, and sepsis. Unusual organisms should also trigger concern for immunodeficiency, e.g., atypical mycobacteria and *Pneumocystis jiroveci*. A third scenario of concern is recurrent spontaneous infections in body sites that are normally protected, such as the peritoneum, bones, eyes, or central nervous system. Healthcare providers should consider an immunodeficiency and a referral to an immunologist in any child who has infections on a more frequent basis or in more sites than expected, poor growth and development attributable to infections, inadequate response to appropriate treatments, or incomplete recovery between infections. It is worth noting that a family history of immunodeficiency is the most predictive factor.

Approximately 30% of children with concern for recurrent infections have atopic disease without underlying immunodeficiency. Parents may mistake allergic symptoms for signs of infection. For example, they may confuse allergic rhinitis with chronic or recurrent upper respiratory infections, and

virally-associated cough or wheeze for pneumonia or bronchitis. However, atopic children often have characteristic physical examination findings such as “allergic shiners” or a transverse nasal crease. They also respond well to antihistamines but not to antibiotics.

Primary immunodeficiency disorders (PIDDs) are a group of more than 150 diseases that are caused by gene defects in various divisions of the immune system. The overall incidence of overtly symptomatic PIDDs is estimated at 1 in 2,000 individuals (or an estimated 2000 infants per year in the US). The clinical manifestation of each disease is based on the genetic defect, with some more common but less symptomatic variants such as IgA deficiency causing only sporadic increases in susceptibility to infections. In addition to increased risk of infections, immunodeficiencies can also increase the risk for autoimmune diseases, malignancy (most commonly leukemia and lymphoma), and hypersensitivity to both environmental and food allergens.

On the whole, secondary (acquired) immunodeficiencies are far more common than PIDDs. Over 50 disorders have been identified, and treatment for each is aimed at the underlying cause(s), which tend to fall into one of four categories. The first of these includes conditions affecting the health of the bone marrow and its ability to produce white blood cells. Examples include oncologic malignancies (via overcrowding) and malnutrition (because of depletion of nutrients necessary for white blood cell proliferation). The next category includes conditions that affect the ability of the immune system to function despite normal production of white blood cells, such as splenectomy (which affects phagocytosis and antibody production), immunosuppressive therapy, and diabetes mellitus. A third category involves infections that kill off white blood cells, such as HIV, measles, and human T-lymphotropic virus (HTLV). Other illnesses in this category can cause wasting of proteins (including antibodies) or loss of white blood cells, such as protein losing enteropathy, thoracic duct leakage, and nephrotic syndrome. A final category predisposes persons to infections by providing bacteria and fungi with additional resources that allow the infections to rapidly proliferate and outcompete the immune system’s killing ability; a prime example is diabetes, where the additional glucose is utilized by infections.

3. What information in this case is concerning? What further information would be important to know?

A detailed history and physical exam may reveal findings that suggest a specific underlying disease and/or an infection that requires treatment. Information gathered may reveal a pathognomonic finding for a specific PIDD, or suggest risk factors for a secondary immunodeficiency. It is also important to gather a detailed history of infections, including the source of infection, organism(s) responsible, and response to treatment. The types of infections that occur in a child with a PIDD can help to narrow the differential diagnosis. In this case, there are several pieces of information that are concerning, including her infection history and her chronic sinopulmonary and gastrointestinal symptoms that would make antibody deficiency or B-cell deficiency a possibility. Further history should be aimed at understanding how the infections were diagnosed, what antibiotics were used to treat the infections and for how long, response to therapy, and if the patient demonstrated complete recovery between infections. Questions about other allergic symptoms would be useful to identify whether her sinopulmonary symptoms are due to a primary infectious or allergic etiology. Questions about the quality and pattern of abdominal pain, in addition to the appearance of stools, and any history of recent travel would be useful to rule out underlying primary bowel disorders and infectious colitis.

Useful history findings:

- Failure to thrive - concerning but nonspecific
- Malaise and fatigue - concerning but nonspecific
- Fever without identifiable cause - concerning but nonspecific
- Intractable viral infections due to RSV, parainfluenza, CMV, EBV, or adenovirus - concerning for T-cell deficiencies
- Recurrent pneumococcal disease (e.g., otitis media, sinusitis, pneumonia, or bacteremia) - concerning for B-cell and antibody deficiencies
- Systemic Neisserial infections (especially in adolescents) - concerning for complement deficiencies or splenectomy

- Adverse reactions after live vaccines - concerning for T-cell deficiencies
- Chronic intractable diarrhea - concerning for both B- and T-cell deficiencies
- Delayed shedding of the umbilical cord (>30 days) - concerning for impaired neutrophil function or migration.
- Neurological findings such as ataxia or tetany of the newborn - ataxia telangiectasia has an associated T-cell immunodeficiency, and other T-cell disorders (e.g., adenosine deaminase deficiency) have major neurological components like seizures and ataxia.

The physical examination of a child with a suspected PIDD provides information regarding their general health and may reveal findings suggestive of atopic disease, chronic disease, or immunodeficiency. Useful physical examination findings include:

- Facial dysmorphism
- Mouth ulcers, gingivitis, mucosal candidiasis, poor dentition
- Absent, reduced or enlarged size of tonsils and lymph nodes; splenomegaly
- Perforated or scarred tympanic membranes
- Congenital heart disease (murmur)
- Pulmonary rales and rhonchi, digital clubbing
- Unusual skin changes, including absence of hair and eyebrows, eczema, abscesses, candidal skin infections that are disseminated or resistant to treatment, telangiectasia, petechiae, albinism, vitiligo, severe warts and/or molluscum contagiosum

4. What is the differential diagnosis for primary immunodeficiencies? Categorize these according to their main defects.

In this case, the differential diagnosis includes many diseases unrelated to PIDD, including anatomic abnormalities of the upper airways leading to obstruction, allergic rhinitis with secondary infections, recurrent aspiration with gastrointestinal reflux, cystic fibrosis, primary ciliary dyskinesia, and other secondary immunodeficiencies. **For the purposes of advancing the discussion related to immunodeficiency, moderators should focus the conversation on the diagnoses most germane to the learning objectives.**

Primary immunodeficiencies include many rare disorders, and for the primary care provider, developing comfort with general categorization of PIDDs as well as the pathognomonic findings of certain disorders is more important than the specifics of each disorder. The general categories to consider are defects in: B cells (over half of PIDDs are due to humoral immunity defects); B and T cells combined (15-20%); phagocytes (10%); complement factors (5%); and innate immunity (rare).

Patients with B-cell defects become ill due to quantitative or qualitative deficits in antibody production. They typically present with recurrent otitis media, sinopulmonary infections, enteroviral infections, giardiasis, and autoimmune diseases. The most common PIDDs in this category are X-linked agammaglobulinemia (Bruton's), common variable immunodeficiency (CVID), X-linked or autosomal hyper IgM syndrome, and selective IgA deficiency.

Patients with cellular defects have abnormal T-cell function, and as a result, also have problems with antibody production. Affected individuals can present with both common and unusual infections. Severe combined immunodeficiencies are a group of diseases with a spectrum of severity that are all characterized by T-cell lymphopenia. The most common form, Severe Combined Immunodeficiency (SCID) is inherited in an X-linked fashion, and when suspected, represents a true pediatric emergency. **Moderators can defer additional discussion about SCID at this juncture since it is the focus of the next case.** Other diseases in this category include DiGeorge syndrome (22q11 deletion syndrome), ataxia telangiectasia, and Wiskott-Aldrich syndrome.

Patients with phagocytic cell defects often present with frequent skin and soft tissue, oral, bone, and lung infections. The hallmark of these infections includes either copious production of pus containing non-functioning phagocytes (e.g., chronic granulomatous disease), or the absence of pus when it should have been present (e.g., leukocyte adhesion deficiencies). Defective phagocyte function can cause delayed umbilical cord separation and delayed or failed tooth eruption, which are typical findings of

diseases in this category. Other representative diseases of phagocyte function include Chediak-Higashi syndrome and cyclic neutropenia (Kostmann disease).

Patients with complement defects often present with recurrent infections, including those involving encapsulated organisms (e.g., *Streptococcus pneumoniae*, *Haemophilus influenzae type B*, *Neisseria* species) and autoimmune diseases. A variety of complement component deficiencies have been described (e.g., C2, C4, C1q). Patients with a deficiency of C1 esterase inhibitor also develop angioedema. Increased infections with *Neisseria* species are a hallmark of complement deficiencies, and can be a useful differentiating feature from antibody deficiencies. Complement deficiencies also do not usually affect the sinuses and airways to the same degree as antibody deficiency; infections are more often found in the bloodstream or in protected sites like the meninges. While vaccination may be less effective in patients with complement deficiencies due to the synergy between complement and antibody function, it still often provides a crucial edge to preventing infections.

Defects in innate immune signaling and function can predispose patients to various types of infections depending on the problem, as the innate immune system triggers various alert cascades that determine the flavor of the subsequent adaptive immune response. For example, defects in TLR3 or NK cells can cause susceptibility to herpesviruses, while deficits in other innate immune system molecules can predispose to bacterial and fungal infections, or predispose to immunodeficiency combined with autoimmunity and lymphoproliferation. Because these are the least common immunodeficiencies, a typical workup excludes more common causes of immunodeficiency prior to a workup for one of these conditions, unless the presentation is pathognomonic for a certain specific mutation.

5. What tests should be ordered to further evaluate this patient's condition?

Laboratory evaluation of children with recurrent infections depends upon history and physical examination findings. Initial testing can be performed by the primary care provider, with guidance by an immunologist as needed. Referral to an immunologist for a more in-depth evaluation is recommended for those children with abnormal or inconclusive results on initial testing or with normal tests but a strong clinical suspicion for immunodeficiency.

For this patient, whose history is most consistent with a possible antibody deficiency (due to the recurrent sinopulmonary infections), initial testing should include CBC with manual differential, quantitative serum immunoglobulin levels, and measurement of specific antibodies to vaccines. A reliable listing of age-adjusted values can be found in the Harriet Lane Handbook chapter on Immunity.

- CBC with manual differential: Abnormal lymphocyte, neutrophil, or platelet counts for age may be signs of an underlying immunodeficiency.
- Quantitative serum immunoglobulin (IgG, IgA, IgM, and IgE) levels: Results of immunoglobulin measurements must be compared with age-adjusted normal values to evaluate their significance. In general, antibody deficiency is suggested by an IgG less than 200 mg/dL and a total Ig (IgG plus IgM plus IgA) less than 400 mg/dL, or the complete absence of IgM or IgA after infancy. An elevated IgE (>100 IU/mL) suggests allergy, eczema, or may occur in PIDDs such as hyperimmunoglobulin E syndrome (levels are generally >2000 IU/mL), Omenn syndrome, or phagocytic disorders. Low or absent IgE levels suggest the absence of IgE-mediated allergic disease. Of note, most assays for IgA are not sensitive enough to distinguish between very low and absent levels.
- Measurement of specific antibodies to vaccines: These tests can provide insight into the status of an individual's immune function. It is important to test for antibodies to both protein (e.g., tetanus or diphtheria) and polysaccharide (e.g., pneumococcal polysaccharides) antigens.
- Testing for specific secondary immunodeficiencies should be guided by the patient's history and physical.

CASE TWO:

As you are reviewing lab reports at the end of the day, your nurse hands you an abnormal newborn screen result for Noah D'Aminase, a 7-day-old boy. He was born at 38 weeks and looked perfect when you saw him in the office three days ago. His newborn screen report

reveals abnormally low TRECs (24 copies/ μ L) and RNaseP (20; reference range >28), raising concern for severe combined immunodeficiency.

6. How should the newborn screen be interpreted? How would you manage this infant?

The newborn screen (NBS) is a critical part of evaluating infants as it detects potentially life-threatening conditions before they manifest themselves, leading to a reduced morbidity and mortality. For example, the mortality rate by age 5 of undiagnosed SCID is 95%, plummeting to a 5-25% rate when diagnosed and treated early. The T-cell receptor excision circle (TREC) level used in NBS is a biomarker for normal T-cell development and has been implemented for SCID screening in most states. Any condition that disrupts T-cell development, maturation, or induces T-cell apoptosis can result in a low TRECs level, so it has screening value for other T-cell lymphopenias as well (e.g., complete and partial DiGeorge syndrome, CHARGE syndrome, trisomy 21, Rac2 and dedicator of cytokinesis 8 [DOCK8] deficiencies such as hyper-IgE syndrome, ataxia-telangiectasia, acquired T-cell deficiencies). However, it is most useful for SCID given the importance of early diagnosis.

Infants with SCID are generally healthy at birth as they are protected by maternal IgG for their first few months of life. As protection declines, they begin to develop overwhelming infections, and most die by one year of age without treatment. Outside of NBS programs, there are many potential barriers to early diagnosis of SCID: it is rare, >80% of cases are sporadic, and presentations differ due to various gene defects and environmental exposures.

States have adopted various NBS strategies but the SCID screen is considered abnormal if the TREC level is low compared to the laboratory's designed range (the lower limit varies between states and laboratories). As with any screening test, false positives are common. The PCR technique employed for TREC testing may be falsely low due to an inadequate blood sample, the presence of PCR inhibitors (e.g., heparin), or failure to obtain an adequate amount of DNA from the NBS sample.

Many NBS programs measure a control gene, such as beta-actin or ribonuclease P (RNaseP) in parallel during the initial test. The control gene is used to determine whether the TREC result is artificially low; if both TREC and control levels are low, the findings may be a false-positive due to one of the reasons noted above and repeat testing is needed.

In this case, a repeat NBS sample must be collected and retested for both TREC and control gene levels. A true positive screen would be suggested by a low TREC level with a normal control gene level. If repeat levels remain abnormal or indeterminate, follow up testing is necessary to further evaluate these results. This follow up testing should be done in conjunction with an immunology referral. The American College of Medical Genetics suggests an initial approach of obtaining a CBC with differential and flow cytometry immunophenotyping lymphocyte subsets.

While the diagnosis is still uncertain, families should take special care to avoid exposing the baby to contagious illness, and no live virus vaccines should be administered (e.g., rotavirus). The importance of further evaluation by an immunologist must be stressed.

It is important to note that a normal NBS does not exclude PIDDs completely. Sensitivity for T cell disorders is high but imperfect, and there are many other primary immunodeficiencies that TRECs screening will not detect, including disorders of B cell and phagocytic function.

Some state NBS programs provide "fact sheets" to aid primary care providers in these steps. Moderators may wish to have learners download the American College of Medical Genetics ACTION sheet for SCID to assist with the discussion (see Resources), and can refer to the separate chapter on Newborn Screening for additional information on NBS.

Additional References:

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4. Esposito S, et al. Immunization of children with secondary immunodeficiency. Hum Vaccin Immunother. 2015;11(11): 2564-2570.
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6. Mayo Clinic. The Mayo Medical Laboratories Test Catalog. Test ID: IMMIG. Retrieved April 19, 2017, from <http://www.mayomedicallaboratories.com/test-catalog/Overview/8156>
7. Orange JS, et al. Use and interpretation of diagnostic vaccination in primary immunodeficiency: A working group report of the Basic and Clinical Immunology Interest Section of the American Academy of Allergy, Asthma & Immunology. J Allergy Clin Immunology. 2012;130(3): S1-S24.
8. Stiehm ER. Approach to the child with recurrent infections. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA. Retrieved April 19, 2017, from <http://www.uptodate.com/contents/approach-to-the-child-with-recurrent-infections>

Resources:

1. Mayo Clinic Medical Laboratories test catalog, clinical resource for ordering and interpreting laboratory tests. <http://www.mayomedicallaboratories.com/test-catalog/index.html>
2. Jeffrey Modell Foundation, information on primary immunodeficiencies for families and providers. <http://www.info4pi.org/>
3. Immune Deficiency Foundation handout for families about SCID. <http://primaryimmune.org/wp-content/uploads/2014/08/questions-about-SCID.pdf>
4. American College of Medical Genetics information sheets and confirmatory algorithms. https://www.acmg.net/ACMG/Publications/ACT_Sheets_and_Confirmatory_Algorithms/NBS_ACT_Sheets_and_Algorithm_Table/ACMG/Publications/ACT_Sheets_and_Confirmatory_Algorithms/NBS_ACT_Sheets_and_Algorithms_Table.aspx?hkey=e2c16055-8cdc-4b22-a53b-b863622007c0