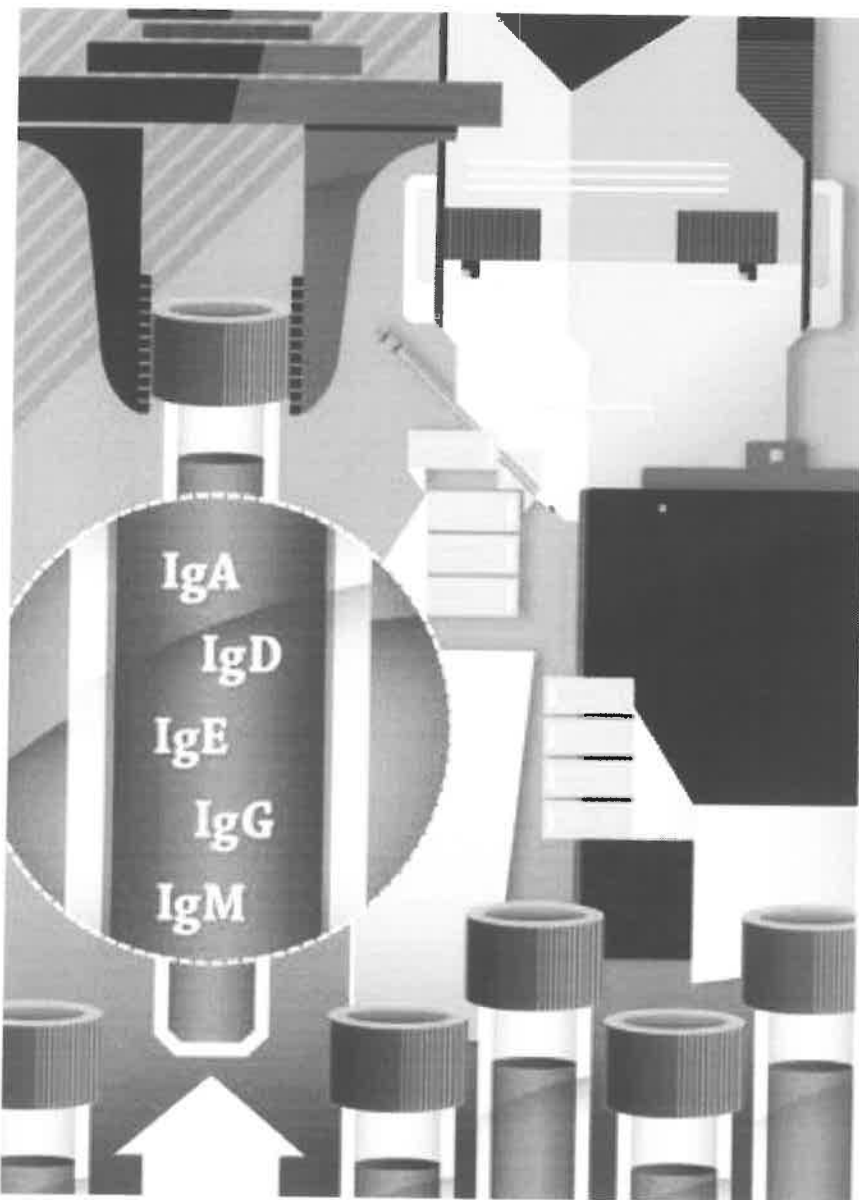


Primary Immunodeficiencies

Recognition and screening strategies

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Learning Objectives

1. Discuss the presentation of primary immunodeficiencies.
2. Explain when to screen for a primary immunodeficiency.
3. Specify which laboratory values indicate a possible primary immunodeficiency.
4. Discuss when it is appropriate to refer a patient to an allergy and immunology specialist.

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➤➤ **PRIMARY** immunodeficiencies are inherited disorders. About 60% of cases are detected in childhood, and the remaining 40% are detected in adults.¹ Immunodeficiencies were long considered uncommon, but that perception is changing. More than 200 primary immunodeficiencies have been classified.²

Overview of Screening

Whether an NP or PA is working in an emergency department, inpatient medicine, pediatrics or family medicine, at some point patients present with findings that should trigger screening for a primary immunodeficiency.

The Jeffrey Modell Foundation has identified 10 warning signs of primary immunodeficiency (Table 1). If a patient has two or more of the warning signs, he or she should be screened for an immune

Table 1

10 Warning Signs of Primary Immunodeficiency

| |
|--|
| 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 of antibiotic therapy with little 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 |
| 8. Need for intravenous antibiotics to clear infections |
| 9. Two or more deep-seated infections, including septicemia |
| 10. A family history of primary immunodeficiency |

Source: Jeffrey Modell Foundation Medical Advisory Board

deficiency. Table 2 lists laboratory tests that are part of the initial work-up for a primary immunodeficiency.³⁻⁵

Interpretation of lab results is fairly straightforward. Look for a significantly low immunoglobulin G (IgG), immunoglobulin M (IgM) or immunoglobulin A (IgA) level. Low vaccine titers in diphtheria, tetanus or strep pneumonia can also be an early sign of an immunodeficiency. A Tdap or pneumonia vaccine can be administered and then titers rechecked in 4 to 6 weeks. If testing still shows no response to the vaccine and the titers remain low, the patient may have a primary immunodeficiency. In any case, referral to an immunologist is indicated. If IgE is high, the patient may have significant allergies and should be referred to an allergist.

Antibody Overview

The five human antibodies are IgA, immunoglobulin D (IgD), immunoglobulin E (IgE), IgG and IgM. In a patient with recurring infections, IgA, IgM and IgG are most important when considering the possibility of a primary immunodeficiency.

IgA is produced in the mucous membranes to initiate the fight against infection as soon as the body comes in contact with a pathogen.⁶ If a patient's IgA level is extremely low (< 10 mg/dL), selective IgA deficiency is present. The most common infections associated with IgA deficiency are recurrent infections in the respiratory, gastrointestinal and genitourinary tracts.⁷

A deficiency in IgM is rare. When it is present, recurrent infections can occur and cause bacteremia. Common pathogens found with selective IgM disorder are *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Haemophilus influenzae*

and viral infections. IgM deficiency is sometimes associated with malignancy and autoimmune disorders.⁸

IgG is produced by the body to protect the immune system. Treatment options are available to replace IgG, such as intravenous IgG (IVIG) or subcutaneous IgG (SCIG).⁹ A patient with IgG deficiency should be referred to an immunologist.

When total IgE is high, the patient may be acquiring infections due to severe allergies.¹⁰ Referral to an allergist is indicated so that allergy skin testing can be performed and the severity of the allergies can be assessed. Vaccine titers should be drawn for tetanus, diphtheria and *Streptococcus pneumoniae*. A functional response should be noted, even with a normal titer. If the patient has low vaccine titers, a repeat vaccine should be given.¹¹

Four to 6 weeks after delivery of vaccine, a two- to fourfold type-specific increase in the vaccine titer should be documented in repeat testing.¹¹ A patient who does not respond this way to the vaccine should be referred to an immunologist.

If a patient has recurring sinus and pulmonary infections and the immune workup is normal, he or she may have cystic fibrosis, gastroesophageal reflux disease (GERD) or a sinus or lung abnormality.^{12,13} To screen for cystic fibrosis, order a sweat chloride test.¹⁴ For anatomical variants, a CT of the sinuses or chest may be helpful.¹³ For severe GERD, a gastroenterologist may be needed.

The following case studies are examples of possible immunodeficiency scenarios.

Rash and Pneumonia

Case #1: The parents of a 13-month-old girl bring her to the emergency depart-

ment for evaluation of a rash that had developed 4 days earlier (see photo below). She has a fever of 103° F and her parents said she had been lethargic when she awoke that morning. The child has been hospitalized three times for pneumonia. She is lymphopenic with an absolute lymphocyte count of 300 (normal absolute lymphocyte count 1,000–3,500). She has had recurrent thrush and has been diagnosed with failure to thrive.

The patient was admitted to the pediatric intensive care unit. Flow cytometry revealed a complete lack of CD4, CD8, CD19 and CD56 cells. The patient was diagnosed as having a severe combined immunodeficiency disease (SCID), later specified as adenosine deaminase deficiency. This immunodeficiency causes profound deficiencies in the functioning of both T and B cells.⁶ Unfortunately, the patient had received live-virus vaccines for MMR and varicella 2 days prior to her presentation to the hospital, and she died from overwhelming sepsis.

Case discussion: Two components of the immune system respond to infections. The first is the rapid, nonspecific response, called the innate immune response. This component consists of neutrophils, macrophages, natural killer cells and complement cells. The second component is the adaptive immune response; it involves T cells and B cells.

The T cells and B cells are dependent on each other. T cells occur in three forms: killer, helper and regulatory T cells. The B cells are responsible for producing antibodies (IgA, IgM and IgG). Helper T cells inform the B cells to make more antibodies and regulatory T cells tell the B cells when to stop making antibodies. Therefore, they maintain con-



courtesy the author

Table 2

Initial Laboratory Work-Up to Screen for Immunodeficiency Disorder*

| | | |
|--------------------------|---|--|
| Complete blood count | Total immunoglobulins IgA, IgM, IgG and IgE | Tetanus antitoxoid antibody |
| Complete metabolic panel | Diphtheria antitoxoid antibody | <i>Streptococcus pneumoniae</i> IgG (14 Serotype) antibodies |

*For pediatric values please refer to the Harriet Lane Handbook from the Johns Hopkins University

Specific Immunology Screening Laboratory Tests

| Lab Test | Abnormal Value | Normal Value |
|---|--|----------------------------|
| IgA | < 10 mg/dL suggests selective IgA deficiency | 41–368 mg/dL |
| IgM | < 30 mg/dL suggests selective IgM deficiency | 47–311 mg/dL |
| IgG | < 580 mg/dL suggests IgG deficiency | 673–1734 mg/dL |
| IgE | > 100 IU/mL suggests significant allergies | < 91 IU/mL |
| Diphtheria antitoxoid antibody | < 0.01 IU/mL | > 0.01 IU/mL |
| Tetanus antitoxoid antibody | < 0.01 IU/mL | > 0.01 IU/mL |
| <i>Streptococcus pneumoniae</i> IgG (14 Serotype) | Each Serotype < 0.3 mcg/mL | Each serotype > 0.3 mcg/mL |

stant communication with each other.²

This patient had a complete lack of CD4, CD8, CD19 and CD56 cells. CD4 and CD8 are T cell markers. CD19 is a B cell marker, and CD56 is a T cell natural killer cell marker. Due to severe deficiencies in both T cells and B cells, the infant did not have the ability to respond appropriately to infection and she should never have received a live vaccine. She already had displayed three of the 10 warning signs of a primary immunodeficiency: three hospitalizations for pneumonia, recurrent thrush and failure to thrive.

Approximately 80% of immune deficiencies are defects in either the B cells or T cells or both.¹⁵ Typically these defects are identified between ages 4 and 6 months, since this is when maternal antibodies wear off.¹⁶ Symptoms in an infant with an adaptive immune system problem (B, T or B and T cell defect combined) can include recurrent sinus and pulmonary infections; poor growth or failure to thrive; malabsorption syndromes; or chronic diarrhea.⁷

Infections in these patients are severe, and if bacteria are the cause, it is usually an encapsulated bacterium.⁷ Viral and fungal infections may include pneumocystis or mycobacterium. When screening for one of these defects, order flow cytometry, which breaks down the lymphocyte count and provides an absolute count of natural killer cells, T cells and B cells.

The other 20% of immune deficiencies are identified when the innate immune system is affected. These deficiencies involve defects in the neutrophils, macrophages, natural killer cells and complement cells. Complement defects are rare and can occur at any age. They are usually associated with an autoimmune disorder such as systemic lupus erythematosus or scleroderma. Neutrophil, macrophage and natural killer cell defects occur in infancy or childhood and present with severe infections. When a severe infection appears worse than would be expected, screening for a primary immune deficiency and referral to an immunologist are essential. Once a primary immunodeficiency has been diagnosed (or suspected), remember these points:

- Don't give live virus vaccines to patients or close contacts.
- Don't give varicella vaccine to siblings of patients who may have immunodeficiency.
- Administer only non-live vaccines.
- Patients should receive only CMV-negative, irradiated, leukopoor blood.
- Keep contacts with any illness away from the patient's room.
- Do not assess temperature rectally.
- Take caution when breastfeeding a newborn or infant with immunodeficiency due to risk of transmission of infection.
- Use only boiled or sterilized water in infant formula.

Recurring Sinusitis & Diarrhea

Case #2: A 15-year-old girl presents to a family practice office for evaluation of recurrent sinusitis and diarrhea. She has a past medical history of four myringotomies, three sinus surgeries and intermittent diarrhea for the past 2 months. Laboratory studies for ova and parasites on a stool sample were obtained, and the stool sample was positive for giardia. This patient was screened for a primary immunodeficiency and her IgA level was determined to be < 10 mg/dL. She was diagnosed with selective IgA deficiency.

Case discussion: Selective IgA deficiency is thought to be the most common immunodeficiency; it may occur in 1 of every 333 people.⁷ Affected patients have recurrent sinus, respiratory, gastrointestinal and genitourinary infections. They are generally unhealthy. These symptoms are commonly associated with collagen vascular and autoimmune disorders and can develop into common variable immunodeficiency (CVID). Patients with selective IgA deficiency should be referred to an immunologist. Both selective IgA deficiency and CVID are associated with an increased risk for malignancy.⁷ Selective IgA deficiency usually occurs with infections that affect the gastrointestinal, genitourinary or respiratory system.⁷ IgA protects humans from infections in the mucous membranes. IgA deficiency should be evaluated and treated by an immunologist. ➤

IgM deficiency is rare. An affected patient requires immunologist care.

Recurring Thrush

Case #3: An 8-year-old boy presents to the office with multiple sinus infections, two bouts of pneumonia in the past year, poor growth and recurrent candidiasis in the mouth. Because the patient had a history of asthma, his clinician believed the recurrent thrush was a result of inhaled corticosteroid medications. The inhaled corticosteroid was changed from a powder form to the HFA form.

To deliver the HFA formulation of the medication, the boy used an aerochamber and a mask. The patient and parent reported that he had been washing his mouth out after medication dosing. The child continued to have recurring thrush, so he was screened for a possible primary immunodeficiency.

Laboratory testing showed the following: complete blood count normal, complete metabolic panel normal, IgG 429 mg/dL (normal range 673 to 1,734), normal IgA, normal IgM and normal IgE. His vaccine titers to diphtheria, tetanus and *S pneumoniae* were low. He received vaccines but displayed no response in IgG levels to diphtheria, tetanus or strep pneumonia. He was referred to an immunologist and now receives intravenous immunoglobulin.

Repeat Sinus Infections

Case #4: A 58-year-old woman seeks evaluation for recurring sinus infections. Her most recent infection has lasted 6 months. The patient had been on four different courses of antibiotics, but after stopping an antibiotic for less than a week, the sinus infection recurred. She underwent two sinus surgeries and was referred to the allergy office for skin testing to determine whether she would benefit from immunotherapy. She reports no family history of a primary immune deficiency.

Skin testing determines that the patient did not have sensitivity to grass, weeds, trees, dust mites, cat, dog and mold.

The specialists determine she should be screened for a possible immune deficiency. Laboratory testing results reveal a total IgG of 350 mg/dL (normal range 673 to 1,734), IgA of 13 mg/dL, and normal IgM and IgE. Vaccine titers show no response to the pneumonia vaccine because her titers were low and she had received a pneumonia vaccine 1 year prior.

The patient had a history of rheumatoid arthritis. She was diagnosed with CVID and treated with subcutaneous IgG. Since starting the infusions, she has not had a sinus infection.

CVID is usually diagnosed in adulthood and it is the most common primary immunodeficiency in this age group.⁷ CVID occurs as a result of defects in the B cell leading to low antibody levels (primarily IgG and sometimes IgA).⁷ An enlarged spleen, enlarged lymph nodes and enlarged tonsils may be evident on physical exam.⁹ CVID occurs equally in men and women and the infections are not as severe as with some of the other x-linked primary immune deficiencies.⁷

Autoimmune disorders and collagen vascular disorders are associated with CVID.⁷ Autoimmune hemolytic anemia and autoimmune thrombocytopenia associated with CVID can predispose to malignancy.⁷ Research has documented a 438-fold increase in lymphomas in women who develop CVID in their 50s and 60s. As long as a patient does not develop a malignancy, the clinical outlook is good.⁷

Early Diagnosis Needed

Early diagnosis of a primary immune deficiency can produce many benefits. The required diagnostic tests are inexpensive and widely available. Early interventions include IgG replacement, bone marrow transplant, gene therapy, enzyme replacement therapy and early treatment of infections with antibiotic, antifungal or antiviral medications. Early diagnosis also improves survival rates, especially among patients with severe combined immunodeficiency syndrome and patients

who require bone marrow transplant.⁷

Many primary immune defects are genetically based, so early diagnosis can provide parents with an opportunity to obtain prenatal counseling and genetic counseling.

The genetic predisposition is predominantly autosomal recessive, autosomal dominant and X-linked. In children, immune deficiencies present more often in boys than girls (5:1), however, the incidence is nearly equal in adults.⁷

Due to better intensive care practices and increased antibiotic usage, many immune disorders can be masked. Consider the possibility of a primary immunodeficiency when a patient presents with two or more of the 10 warning signs. Increased awareness will improve early diagnosis and intervention and ultimately save lives. ■

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