Diagnostic Approach to the Adult with Suspected Immune Deficiency

Posted: December 2008

Sasawan Chinratanapisit, M.D.
Research Fellow
Division of Allergy, Immunology, and Rheumatology
University of South Florida, Dept. of Pediatrics
Saint Petersburg, FL, USA

Panida Sriaroon, M.D.
Clinical Fellow
Division of Allergy, Immunology, and Rheumatology
University of South Florida, Dept. of Pediatrics
Saint Petersburg, FL, USA

John W. Sleasman, M.D.
Robert A. Good Professor and Chief
Division of Allergy, Immunology, and Rheumatology
University of South Florida, Dept. of Pediatrics
Saint Petersburg, FL, USA

Select One

1.0 Disease Definition

Primary and secondary immunodeficiency disorders are a diverse group of illnesses resulting from one or more abnormalities of the immune system. The clinical manifestations include increased susceptibility to infection and an increased risk for autoimmune disease and malignancy. Primary immune deficiency (PID) diseases are a group of serious disorders arising from an intrinsic defect in the immune system, generally the result of a genetic disease that can be traced directly to a particular immune pathway. In contrast, secondary immune deficiencies stem from impairment of the immune response through another mechanism, such as an infection, metabolic derangement, malignancy or toxins, with the immune defect being a secondary manifestation. Although the possibility of immunodeficiency should be considered in any individual with recurrent infections, it is also important to consider nonimmune conditions as a cause. Such disorders include circulatory abnormalities leading to stasis or cellular ischemia, as can occur in sickle cell disease, diabetes or heart failure; obstructive lung conditions such as chronic obstructive pulmonary disease, ciliary dyskinesia, and cystic fibrosis; or ureteral stenosis, resulting in defective pathogen clearance; and breaches in the integument and mucosal surfaces, as is seen in erythema multiforme or burns, allowing entry to opportunistic organisms and infection. Each of these is associated with infection by specific pathogens and results in characteristic clinical manifestations.

Secondary immune dysfunctions are far more common in adults than PID. Common causes include malnutrition, HIV/AIDS, malignancy, immune suppressive drugs, and toxin exposure. Malignancy can directly suppress B-cell function, as is seen in chronic lymphocytic leukemia and lymphomas. Malignancy can also directly cause bone marrow failure, resulting in neutropenia and impaired T-cell function.

Metabolic disorders such as diabetes, uremia and liver failure are often associated with severe, life threatening infections due to impairment of the cellular functions of lymphoid and myeloid cells. Protein-losing enteropathies, burns and nephrosis lead to loss of soluble factors, such as immunoglobulin and complement, thereby increasing the risk for sepsis and peritonitis. Autoimmune diseases, especially those associated with immune complexes such as systemic lupus erythematosis (SLE), often result in secondary complement deficiency due to chronic consumption that exceeds hepatic synthesis. Transient activation and depletion of complement can also occur with sepsis, viremia, burns and trauma. In the diagnostic approach to an adult with recurrent infections and suspected immune deficiency, these nonimmune and secondary causes need to be considered.

2.0 Classification and Clinical Presentation

Although less frequent than secondary immune disorders, PID can be quite common. For example, in some ethnic populations, such as Scandinavians, mannose-binding lectin deficiency has a prevalence of 5%-7%. Selective immunoglobulin (Ig)A deficiency occurs in as many as 1 in 300 individuals. These common PIDs are usually of low clinical relevance, whereas other PIDs can result in life-threatening infections. The American Academy of Allergy Asthma and Immunology (AAAAI) and the American College of Allergy Asthma and Immunology (ACAAI), as well as other groups, have developed classification systems for the different categories of immune disorders. The characteristics and clinical features of the categories of primary and secondary immune disorders in adults are listed in Table 1.

2.1 Antibody Deficiencies are the most common cause of PID, accounting for over half of all cases. Clinical manifestations are primarily recurrent bacterial sinopulmonary infections, including pneumonia and sinusitis, although bacterial sepsis and meningitis have been frequently reported. Infections with *Haemophilus influenzae*, Streptococcus pneumoniae and other encapsulated bacterial organisms are most common. Manifestations are not limited to sinopulmonary infections, as chronic Giardia enteritis, gastrointestinal lymphoid hyperplasia, polymyositis, autoimmune cytopenias, and chronic arthritis also occur. The most common clinically significant antibody deficiency disorder in adults is common variable immune deficiency (CVID). CVID is often associated with recurrent bacterial

pneumonia, often with bronchiectasis; persistent gastrointestinal symptoms, suggestive of inflammatory bowel disease or celiac disease; and autoimmunity. As many as 20% of patients with CVID develop granulomas in the lungs, liver and spleen that can be confused with sarcoidosis. Other antibody deficiencies seen in adults that have similar clinical presentations to CVID include IgG subclass deficiency, selective IgA deficiency, fuctional antibody deficiency, B - cell chronic lymphocytic leukemia, and protein-losing enteropathies.

2.2. Cellular Immune Deficiency. Clinical symptoms resulting from a primary defect in cellular immunity or combined cellular and antibody immunity are more rare in adults than in children; instead, secondary immune deficiencies associated with HIV infection or drugs targeting T-cell function predominate. Commonly encountered infections consist of chronic mucocutaneous candidiasis, persistent infections with cytomegalovirus and other herpes viruses such as simplex or zoster, *Pneumocystis jiroveci* pneumonia and infections with atypical mycobacteria species. Defective cellular immunity increases the risk for malignancy, particularly B-cell lymphomas or lymphoproliferative diseases, driven by Epstein-Barr virus.

2.3. Phagocytic Cell Deficiency. Defective phagocytic cell function and neutropenia syndromes are commonly associated with recurrent infections of the soft tissues, including cellulitis, lymphadenitis and osteomyelitis. Abscesses and granulomas caused by fungal pathogens within the liver, lung and spleen are also manifested. Many times, the clinical presentation will consist solely of fever of unknown origin due to occult deep-seated infection. Oral and periodontal disease is common, including chronic necrotizing gingivitis, oral ulcers and dental abscesses. Poor or delayed wound healing is often observed. Systemic infections with catalase-positive organisms such as *Staphylococcus aureus, Serratia, Aspergillus, Burkholderia cepacia* and *Nocardia* are the hallmark of chronic granulomatous disease which is defective in oxidative burst capacity. Rare late presenting forms of phagocytic disorders include Hyper IgE syndrome, autosomal recessive (p47phox) chronic granulomatous disease, IL-12 and interferon gamma receptor (IFNγR) pathway defects. Defects in the IL-12 and interferon gamma receptor (IFNγR) pathway result in chronic infections with atypical mycobacteria species. Hyper-IgE syndrome is due to a mutation in STAT3 resulting in severe eczema, soft tissue infections, and staphylococcal pneumonia. Secondary causes of neutrophil disorders include myelodysplastic syndromes, malignancy, myeloablative chemotherapy, and autoimmune neutropenia.

2.4. Complement Deficiency. Hereditary deficiencies in the complement system have highly variable clinical manifestations depending on the particular component of the complement cascade affected. Impairment of the regulatory proteins involved in C1 inhibitor produces clinical symptoms that include episodic nonpruritic angioedema of the airway, soft tissues and gastrointestinal tract. Individuals with defects in the early or classical complement components have an increased risk for bacterial infection and commonly develop autoimmune diseases such as SLE, rheumatoid arthritis and glomerulonephritis. Patients with defects in the terminal components of the complement cascade often develop chronic or recurrent infections, especially meningitis, with *Neisseria* species and also have increased risk for autoimmunity. Most complement disorders are inherited in an autosomal-dominant or co-dominant pattern, making a family history helpful in the diagnosis.

3.0 Evaluation for Suspected Immunodeficiency

Evaluation of suspected PID in the adult patient should be based on the clinical findings associated with the categories of immune deficiency diseases. The diagnosis should be directed toward primary and secondary etiologies that are consistent with the clinical presentation and pattern of infections. Therefore, the nature of the infecting organism, the history and clinical presentation, and systematic use of the laboratory and diagnostic procedures can be utilized to identify the nature of the immune defect. The results will assist in identifying which patients need to be referred to tertiary centers for definitive diagnosis and treatment or can be managed by the primary practicing allergist and immunologist.

3.1 History is an important initial step in the evaluation process. Unusual or severe complications of common infections are often seen in patients with immune deficiency. For example, empyema associated with bacterial pneumonia suggests antibody deficiency. Hepatic or splenic granuloma caused by *S. aureus* suggests chronic granulomatous disease. The need to treat infection with prolonged or repeated use of antibiotics is common in patients with immune deficiency. The medical history should include a complete family history to determine if there is a pattern of inheritance consistent with known PID, such as autosomal dominant, X-linked, or autosomal recessive patterns. When taking the family history, the physician should inquire about consanguinity and recurrent or severe infections among family members. Associated noninfectious features of immune deficiency, such as premature loss of dentition or poor or delayed wound healing, should be investigated. Recurrent herpes zoster infections or persistent cutaneous warts are common in patients with cellular immune deficiencies, whereas a history of recurrent aphthous ulcers may be the only clue that phagocyte function is defective.

3.2 Physical examination also provides clues to the nature of immune deficiency. For example, wasting and unexplained weight loss is common in both antibody and cellular immune deficiencies, although any chronic inflammatory condition can be associated with abnormal catabolic states. Scarred tympanic membranes or chronic perforation due to recurrent otitis media is commonly seen in patients with antibody deficiencies. Coarse facial features and severe eczema suggest a hyper-IgE syndrome, whereas vitiligo or alopecia areata are associated with mucocutaneous candidiasis with autoimmune polyglandular disease. Hepatosplenomegaly and lymphadenopathy are frequently found in patients with CVID and cellular immune deficiency. Cutaneous fungal infections suggest defects in cellular immunity. Furuncles and soft tissue abscesses are seen in phagocytic disorders. Ocular telangiectasia in association with cerebellar ataxia is the hallmark of ataxia telangiectasia, which leads to progressive combined immunodeficiency. Chronic inflammatory arthritis is seen in antibody and complement deficiencies.

3.3 Diagnostic testing should focus on distinguishing between non-immune, secondary, and PID diseases. Evaluation of recurrent sinopulmonary infections should include, where necessary, a detailed radiographic assessment of the sinuses and high resolution imaging of the lungs to detect occult bronchiectasis, hilar adenopathy, and granulomas. Interpretations of the findings should be in the context of other laboratory and clinical findings. For example, granulomas in the lungs, liver or spleen can be seen in chronic granulamatous disease, CVID or sarcoidosis.

In patients with recurrent pneumonia, ciliary biopsy and sweat testing for late-presentation cystic fibrosis should be considered. Neutrophil counts and splenic function should be assessed in patients with bacterial sepsis. All forms of neutropenia should be further evaluated with a bone marrow aspirate to assess for occult malignancy or myelodysplasia. The complete metabolic profile of all patients with severe or recurrent infections should be evaluated to assess hepatic, renal and endocrine function; a urinalysis should also be performed to detect occult proteinuria.

3.4 Laboratory assessment of immunity consists of step-by-step analysis that correlates the clinical manifestations with the specific suspected immune disorder. In order to optimize the use of the clinical laboratory, testing should first focus on quantitative and qualitative screening evaluations, with more costly and complex testing used to pinpoint the precise nature of the disorder and confirm the suspected diagnosis. A summary of the screening tests and studies to confirm the diagnosis is provided in Table 2. Screening tests for defects in **antibody production** include quantitative serum immunoglobulins, in which total IgG, IgA, and IgM can be precisely measured. The predominant immune globulin in the blood is IgG, normally ranging from 800 to 1500 mg/dL with a slight decline after the age 60. Selective IgA deficiency is defined as serum levels < 10 mg/dL. Typical IgM levels in adults range from 70 to 130 mg/dL. Isolated selective IgM deficiency (< 10 mg/dL) is extremely rare whereas elevated IgM is indicative of infection or autoimmunity. Elevations in multiple isotypes may reflect polyclonal B cell activation as in HIV or other viral infections such as EBV or CMV, sarcoidosis, or SLE. Elevations in a single isotype should be evaluated by serum protein electrophoresis in order to exclude multiple myeloma, Waldenstrom's macroglobulinemia, or primary systemic amyloidosis. As many as 1% of normal adults of age 50 develop benign monoclonal gammopathy. Specific antibody titers measured prior to and 30 days after immunization is an accepted means to measure functional immunity to T-dependent (tetanus and diphtheria) and T-independent (different serotypes of pneumococcal polysaccharide) antigens. In more than 90% of healthy individuals usual postimmunization protective response to T-dependent antigens such as tetanus and diphtheria exceeds 1.0 IU/ml. The response to T-independent antigens is generally measured by pre and post titers to different serotypes within the pneumococcal polysaccharide vaccine. The protective level of antibody following the pneumococcal polysaccharide vaccine is poorly defined, however, the ACAAI and AAAAI practice parameters define a normal response in adults to be titers >e; 1.3 µg/ml or a four-fold rise in at least 70% of the immunizing serotypes. However, many experts believe this definition is too broad as many healthy individuals do not achieve this level of response following immunization.

Elevation in total serum IgE can be helpful in suspected patients who have IgE mediated allergic rhinosinusitis, allergic asthma, and other allergic diseases from those who have antibody defects. In patients with low total IgG or defective functional immunity, measurement of IgG subclasses is helpful in pinpointing the diagnosis. However, the significance of IgG subclass deficiency in the presence of normal antibody responses to protein and polysaccharide antigen is not known. Low or absent IgG4 is present in up to 5% of healthy adults and its deficiency is not considered to be clinically relevant. Enumeration of B cells using flow cytometry can differentiate late-onset congenital agammaglobulinemia where CD20+ or CD19+ B cells are low or absent from CVID where total B cell numbers are generally normal.

Screening laboratory tests to evaluate **cellular immunity** include total lymphocyte count, T- and B-cell enumeration using flow cytometry and HIV antibody testing. HIV is the most common secondary immune deficiency among adults. In healthy individuals, CD3-positive T cells make up 60%-70% of the total lymphocyte count. These cells are sub-divided into CD4 T cells or CD8 T cells in a typical ratio that is greater than 1.0. Inverted CD4 to CD8 T ratios with low total CD4 T cell numbers are seen in AIDS, severe CVID, and idiopathic CD4 T-cell lymphopenia. Functional assessment of cellular immunity includes delayed type hypersensitivity (DTH) skin testing to recall antigens and mitogens and antigen-induced lymphocyte proliferation, which are in vitro measurements of lymphocyte function computed as a stimulation index. For example, the antigen-specific proliferation response and DTH to *Candida* is low in mucocutaneous candidiasis. Genetically characterized, combined immune deficiency diseases due to defects in purine salvage pathways or T-cell signaling rarely have their initial clinical presentation in adolescents and adults. Clinical manifestations of these disorders usually occur in infancy and are fatal if untreated.

A complete blood count to enumerate neutrophils, other granulocytes and monocytes can be used as an initial test for **phagocyte deficiencies**. Persistent leukocytosis over 25,000 cells/µl suggests a possible leukocyte adhesion deficiency that can be confirmed on the basis of low expression of adhesion molecules such as CD11b and CD18. Detection of rare variants of chronic granulomatous disease reported in adults and adolescents can be done by flow cytometry analysis using dihydrorhodamine dye or oxidative respiratory burst assays which have largely replaced the nitroblue tetrazolium assay as the best assessment of phagocyte function. The different genetic variants of chronic granulomatous disease, 91phox, p22 and p47, have recognizable patterns of fluorescence that can help confirm the diagnosis.

Screening tests for the **complement system** include total C3, total C4, total serum hemolytic complement (CH50) and alternative pathway (AH50). Together, these four tests can be used to differentiate defects in the classical, alternative or terminal complement components. The C3 and C4 levels are helpful in determining if there is ongoing complement consumption, as is seen in immune complex or autoimmune diseases. In these conditions, multiple complement components are depressed, whereas in isolated inherited deficiencies, the absence of a single component results in abnormal function of the entire pathway. A low or totally depressed CH50 with normal AH50 is characteristic of defects in the classical pathway (examples are C1, C2 and C4 deficiency). A low or absent AH50 with normal CH50 is typical of a defect in the alternative pathway (such as properdin deficiency). Low or absent AH50 and CH50 (C5 through C9) is characteristic of defects in the terminal complement components that make up the membrane attack complex. Abnormal results should be followed with factor-specific assays to identify the specific deficient component. In mannose-binding lectin deficiency, the AH50, CH50, C3, and C4 are normal, but the mannose-binding lectin level is low. The diagnosis can be confirmed and further characterized by genotyping for the various alleles associated with these disorders.

4.0 Management

The management of PID depends on which component of the immune system is impaired and whether function can be restored. In cases involving severe defects in cellular immunity bone marrow transplantation may be the only

treatment available to reverse the condition. In older patients, this procedure generally requires pre-ablation with chemotherapy and immune suppression, carrying an inherent risk for poor outcome. Gene therapy may become an alternative for the treatment of single gene defects in the near future. In contrast, patients with antibody deficiency IgG can be replaced with monthly intravenous gammaglobulin or weekly infusions of subcutaneous IgG. This therapy is effective in controlling sinopulmonary infections and their complications. The use of gammaglobulin replacement therapy should be reserved for those individuals who show laboratory evidence of a defect in humoral immunity, have recurrent infections, fail conservative therapy with antibiotics, and have no other causes for their recurrent infections.

Cellular immune deficiency, particularly those associated with low CD4 T cell counts, should receive prophylaxis for opportunistic infections. Current recommendations are that patients with CD4 T cell counts of less than 200 cells/µl should have prophylaxis with trimethoprim/sulfamethoxazole for *Pneumocystis jiroveci* pneumonia, and those with CD4 T cell counts of less than 50 cells/µl should have prophylaxis for atypical mycobacterium infections. Patients with defective phagocytic cell function should receive prophylaxis for *Aspergillus*. Patients with chronic granulomatous disease benefit from gamma interferon replacement therapy. All PIDs are chronic and life-long conditions that require close clinical monitoring and aggressive interventions to optimize health and quality of life.

Table 1: Characteristics of Immunodeficiency Disorders in Adults

Clinical Pattern	**PID**	**Secondary Immunodeficiency**
Bacterial Infections		
• Sinopulmonary, Sepsis,	• CVID	• Ciliary Dyskinesia
Meningitis	• XLA (late onset)	• Cystic Fibrosis (late onset)
	• Autosomal recessive hyper-IgM syndrome	• Splenectomy • B cell CLL
	• Selective IgA deficiency	• Protein loss
	• IgG subclass deficiency	- Nephrotic syndrome
	• Functional antibody deficiency	- Protein-losing enteropathy
		- Burns
Opportunistic Infections		
• *Mucocutaneous Candida*	• Idiopathic CD4+ T lymphocytopenia	• Chemotherapy/Radiation
Cryptococcus	• Natural killer cell deficiency	• HIV/AIDS
• Chronic *Herpes simplex* and	• Combined immunodeficiency	• Malignancy
• Pneumocystis	- Adenosine deaminase (ADA) deficiency	• Immunosuppressive drugs
	- Purine nucleoside phosphorylase (PNP)	- Steroids
	deficiency	- Cyclosporin, tacrolimus
Soft Tissue Infections		
• Osteomyelitis	• CGD (late onset such as gp47phox deficiency)	• Myeloablative chemotherapy
• Lymphadenitis	• Neutropenia Syndromes	• Severe eczema
• Splenic/hepatic abscesses	• Hyper IgE Syndrome	• Myelodysplastic syndromes
• Atypical mycobacterial infection	• Leukocyte adhesion deficiency (LAD-1)	• Autoimmune neutropenia
• Staphylococcal pneumonia	• IL-12/ IFNγR pathway defects	
• Aphthous ulcers		
Chronic/Recurrent Infection		
• *Neisseria meningitidis/*	• C2 or C4 deficiency	• SLE

gonorrhoeae	• Properdin deficiency	• Serum sickness
• Pyogenic infection	• Terminal complement deficiencies (C5-C9)	• Complement depletion
• Arthritis / Autoimmunity	• Mannose-binding lectin deficiency	- Sepsis, burn, trauma
	- Systemic ischemic injury	
		- Nephrosis

Table 2: Laboratory Values for Evaluation of T Cell or B Cell Immune Deficiency

Defects in Antibody and Cellular Immunity

IgG	IgA	IgM	IgE	Specific Ab Response	CD4	CD8	CD19	Diagnostic Assays	Diagnosis
Low	Low	Low	Low	Low	Low/Nl	Nl	Nl	Quantitative Immunoglobulins	CVID
Abs / low	Abs / low	Abs / low	Abs	Abs/low	Nl	Nl	Abs/low	BTK mutation analysis	XLA (late onset)
Low	Low	Ele/Nl	Low	Low	Nl	Nl	Nl	AID mutation analysis	AR-Hyper-IgM
Nl	Abs	Nl	Nl	Low/Nl	Nl	Nl	Nl	Quantitative Immunoglobulins	Selective IgA deficiency
Nl	Nl	Nl	Ele	Low/Nl	Nl	Nl	Nl	STAT3 mutation	Hyper-IgE syndrome
Low/Nl	Low/Nl	Nl	Nl	Low/Nl	Nl	Nl	Nl	IgG subclasses	IgG subclass deficiency
Low	Low	Low	Low	Low	Low	Low	Low	ADA level	ADA deficiency
Low/Nl	Low/Nl	Low/Nl	Low/Nl	Low	Low	Low	Nl	PNP level	PNP deficiency
Ele	Ele	Ele	Ele/Nl	Low	Low	Ele	Nl	HIV antibody or antigen	HIV infection
Low	Low/Nl	Low/Nl	Nl	Low/Nl	Nl	Nl	Nl	Endoscopy, stool analysis	Protein-loss enteropathy Intestinal lymphangiectasia
Low/Nl	Low	Nl	Nl	Low/Nl	Nl	Nl	Nl	Urinalysis	Mephrosis

Defects in Neutrophils and Phagocytes

CBC			Bone Marrow Exam	Specific Assays	Diagnosis
Neut	Mono	Lymph			
Low*	Ele/Nl*	Nl	Abnormal	Serial CBC	Cyclic neutropenia
Ele/Nl	Nl	Nl	Nl	DHR (flow cytometry)	Chronic granulomatous disease (CGD)
Ele	Nl	Nl	Nl	Low / absent CD18 / CD11a / CD11b / CD11c	Leukocyte adhesion deficiency type 1 (LAD-1)
Low	Low	Low	Abnormal	Abnormal histology	Myelodysplastic syndrome
Low	Nl	Nl	Nl	Autoantibody	Autoimmune neutropenia

*Cycle at an average of 21 days

Defects in the Complement System

C3	C4	CH50	AH50	Specific assays	Diagnosis
Nl	Low	Low	Nl	C1, C2, or C4	Complement C1, C2, or C4 deficiency
Nl	Nl	Nl	Low	Factor B, Factor D, or Properdin	Factor B, factor D, or Properdin deficiency
Nl	Nl	Low	Low	C3, C5-C9	Membrane attack complex (MAC) - C3, C5-C9 deficiency
Low	Nl	Low	Low	Factor H or Factor I	Factor H deficiency or Factor I deficiency
Nl	Nl	Nl	Nl	Mannose-binding lectin (MBL) level, mutation analysis	MBL deficiency
Low	Low	Low	Low	ANAs, Immune Complex	Autoimmune disease (SLE)

Abs: Absent Nl: Normal, Ele: Elevated, CVID: common variable immune deficiency, BTK: Bruton tyrosine kinase, XLA: X-linked agammaglobulinemia, CLL; Chronic Lymphocytic Leukemia, AID: Activation-induced cytidine deaminase, ADA: Adenosine deaminase, PNP: Purine nucleoside phosphorylase, IL-12: Interleukin-12, IFNγR; Interferon gamma receptor, CBC: Complete blood cell count, DHR: Dihydrorhodamine dye, SLE: Systemic lupus erythematosus, AR-Hyper-IgM: Autosomal Recessive Hyper-IgM, STAT 3: Signal transducer and activator of transcription 3, ANAs: Antinuclear antibodies

Bibliography

1. Sleasman JW, Virella G. Diagnosis of immunodeficiency diseases. In: Virella G. *Medical Immunology*. 6th ed. New York, NY:Informa Healthcare; 2007: 397-407
2. Orange JS, Hossny EM, et al. Use of intravenous immunoglobulin in human disease: A review of evidence by members of the Primary Immunodeficiency Committee of the American Academy of Allergy, Asthma and Immunology: *J Allergy Clin Immunol*. 2006 April;117(4):525-553
3. Bonilla FA, Bernstein IL, Khan DA, et al. Practice parameter for the diagnosis and management of primary immunodeficiency: *Ann Allergy Asthma Immunol* 2005; 94(5 Suppl 1):S1-S63
4. Ballow M, O'Neil KM. Approach to the patient with recurrent infections. In: Adkinson NF, Yunginger JW, Busse WW, Bochner BS, Holgate ST, Simons FE, eds. *Middleton's Allergy Principles and Practice*. 6th ed. Philadelphia, PA: Mosby; 2003:1043-1072
5. Wen L, Atkinson JP, Giclas PC. Clinical and laboratory evaluation of complement deficiency: *J Allergy Clin Immunol*. 2004 April;113(4):585-593
6. Rosenzweig SD, Holland SM. Phagocyte immunodeficiencies and their infections: *J Allergy Clin Immunol*. 2004 April;113(4):620-626