

6. Secondary immunodeficiencies, including HIV infection

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The immune system can be adversely affected by a variety of extrinsic factors, including immunosuppressive drugs, exposure to harsh environmental conditions, hereditary disorders other than primary immunodeficiencies, and acquired metabolic disorders such as diabetic mellitus, with all of these resulting in conditions known as *secondary immunodeficiencies*. Perhaps the most well known secondary immunodeficiency is caused by HIV infection; however, the most prevalent cause of immunodeficiency worldwide is severe malnutrition, which affects as much as 50% of the population in some impoverished communities. The abnormalities of the immune system induced by secondary immunodeficiencies affect both the innate and the adaptive immunity, may be subtle, and are usually heterogeneous in their clinical manifestations. Treatment of the primary condition often results in the improvement of the compromised immune components of the disease complex. This article updates the concepts of some of the major categories of conditions that can potentially suppress the immune response, including HIV disease, to provide a conceptual frame to assess patients with suspected secondary deficiencies of the immune system. (*J Allergy Clin Immunol* 2008;121:S388-92.)

Key words: Secondary immunodeficiency, AIDS, immunosuppression, lymphopenia

When a patient presents with an increased susceptibility to infections or with a severe clinical course of an otherwise benign infection, physicians should include a deficiency of the immune system in their differential diagnosis, along with the more common choice of an infection caused by an unusually virulent pathogen. Immunodeficiencies are being increasingly recognized and characterized, possibly because of improved access to clinical immunology expertise and to immunodiagnostic tools.

Immunodeficiencies can be primary or secondary, according to their etiology. Secondary immunodeficiencies result from the adverse consequences of exposure to a variety of factors including

Abbreviations used

HAART: Highly active antiretroviral therapy
IRIS: Immune reconstitution inflammatory syndrome
SIV: Simian immunodeficiency virus

infectious agents, drugs, metabolic diseases, and environmental conditions (Fig 1). These conditions may affect the immune function in a manner that varies in presentation and severity, and the restoration of complete immunity is achieved with the improvement of the primary disease or the removal of the offending agent. Secondary immunodeficiencies are far more common than primary immunodeficiencies, which are caused by genetic defects.¹

AIDS, caused by infection by HIV, is the best known secondary immunodeficiency, largely because of its prevalence and its high mortality rate if untreated. However, the most common immunodeficiency worldwide is a result of severe malnutrition, affecting both innate and adaptive immunity. The number of new discoveries in AIDS research far exceeds that for other secondary immunodeficiencies, presumably reflecting the distribution of available funding. This chapter of the Mini-Primer summarizes the current concepts of selected secondary immunodeficiencies, with special emphasis on AIDS. Immunosuppressive drugs and immune adverse effects of drugs²⁻⁴ are considered beyond the scope of this article and are not discussed here.

AGE EXTREMES: THE YOUNG AND THE OLD

Premature newborns are known to have a high susceptibility to infections and sepsis, even though they can develop humoral responses to some antigens. Well documented explanations for the impaired immunity in these infants include the lack of maturity of secondary lymphoid organs and the absence of maternal IgG transfer before 32 weeks of gestational age. Other significant observations described at this early age are decreased memory responses after vaccination, decreased neutrophil function (phagocytosis, oxidative burst, chemotaxis, and adhesion), decreased *neutrophil storage pool* as defined as the ability to develop neutrophilia in response to an infection, decreased natural killer cell activity, decreased Toll-like receptor signaling, decreased production of cytokines, and complement components.

Poor cellular immunity in the elderly has been linked to the development of T-cell oligoclonality with advanced age, together with a restricted capacity to generate naive T cells able to respond to novel antigens. The loss of T-cell function may be evident by decreased cutaneous delayed-type hypersensitivity reactions and decreased lymphocyte proliferative response to mitogens. In addition, advanced age is associated with a restricted B-cell

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diversity repertoire, a limited response to vaccines, and a diminished capacity to secrete hematopoietic growth factors, which results in poor ability to upregulate the production of neutrophils.⁵

MALNUTRITION

Protein-calorie malnutrition is the most common cause of immunodeficiency worldwide. Poor nutritional status may occur not only because of depressed economical situation and limited access to food products but also as a result of diseases that induce cachexia, such as neoplastic diseases. T-cell production and function decline in proportion to the severity of nutrient depletion; however, specific antibody titers and immune response to vaccines can be detected in a malnourished individual for a relatively prolonged period, although eventually these immune responses decrease if malnutrition persists. Similar immune dysfunction occurs with kidney and intestinal conditions that result in protein losses and hypoproteinemia. The deficiency of micronutrients (eg, zinc, ascorbic acid) contributes to the weakening of barrier mucosa and facilitates penetration of pathogens.⁶ Nutritional repletion and recovery results in resolution of the immunologic defects.

METABOLIC DISEASES: DIABETES MELLITUS AND UREMIA

Two common metabolic disorders with deleterious effect on immunity are diabetes mellitus and uremia resulting from kidney or liver disease. The control of the metabolic abnormality usually leads to improved immune function. Defective immune functions described in diabetes mellitus include defective phagocytosis and cell chemotaxis, delayed hypersensitivity skin test demonstrating anergy, and poor lymphoproliferative response to mitogens. Impaired glucose metabolism, insufficient blood supply, and denervation are other factors that contribute to explain the increased susceptibility to infections in patients with diabetes.

Patients with uremia present with a 6-fold to 16-fold increased incidence of tuberculosis compared with nonuremic controls. The need for dialysis procedures and use of vascular devices are independent risk factors for invasive infections. In addition to an elevated chronic state of immunologic activation, uremic patients consistently show defective phagocyte chemotaxis and microbicidal activity. Antibody responses do not persist for more than 6 months in uremic patients, regardless of repeated vaccination.

INHERITED DEFECTS OTHER THAN PRIMARY IMMUNODEFICIENCIES

Many genetic diseases are associated with impaired immunity to infections, resulting from metabolic and cellular dysfunction, such as poor expression of adhesion molecules and defects in the DNA repair machinery. For example, patients with Down syndrome, or trisomy of chromosome 21, present with increased incidence of infections; however, they are usually not severe, such as periodontitis and upper respiratory tract infections. Neutrophils isolated from patients with Down syndrome have shown defects in chemotaxis and phagocytosis. Most recent studies have focused on the overexpression of the gene Down syndrome critical region 1 and its role in phagocyte function.⁷ Patients with Turner syndrome also have an increased number of infections, and hypogammaglobulinemia may be diagnosed, although

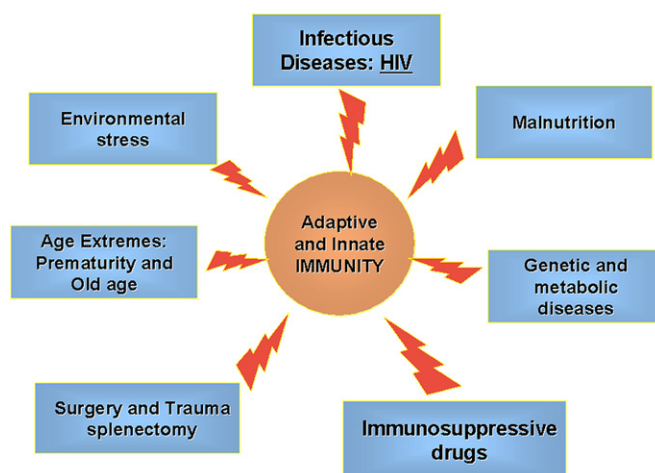


FIG 1. Secondary immunodeficiencies affecting the immune system.

the immune defect is not consistently demonstrated in these patients. In other diseases such as cystic fibrosis, the increased susceptibility to infections is explained by defective mechanisms of innate immunity. Patients with cystic fibrosis have an impaired airway mucous clearance that favors the development of respiratory infections caused by *Pseudomonas* spp. It is recommended that patients receive prompt antibiotic therapy when infection is suspected, and antibiotic prophylaxis should be given to those patients with recurrent infections.

SURGERY AND TRAUMA

The disruption of epithelial barriers and the cell destruction produced by surgery or trauma trigger an inflammatory response that promotes healing and local microbicidal activity. In this scenario, inflammatory cytokines are released and the patient may develop, if the reaction is severe, the adult inflammatory respiratory syndrome in the lung, or the systemic inflammatory response syndrome, when there is multiorgan failure. The inflammatory response to trauma develops gradually: loss of epithelial barriers, vasodilatation and increased vascular permeability, cellular activation and adhesion, and a neuroendocrine stress response. Loss of epithelial barriers, nonspecific cell activation concomitant with an anergic immune state, and elevated levels of cortisol induced by stress may contribute to the immunosuppression of an injured patient.

Splenectomized patients deserve special consideration because they are particularly susceptible to infections by encapsulated bacteria such as *Streptococcus pneumoniae*. The mortality for sepsis in splenectomized patients is between 50% and 70%, emphasizing the need to avoid splenectomy when possible. Patients who are scheduled for elective splenectomy should receive anti-pneumococcal, anti-*Haemophilus influenzae*, and antimeningococcal immunizations at least 2 weeks before surgery.

ENVIRONMENTAL CONDITIONS: ULTRAVIOLET LIGHT, IONIZING RADIATION, HIGH ALTITUDE, CHRONIC HYPOXIA, AND SPACE FLIGHTS

The immune system may be affected by chronic exposure to adverse environmental conditions, such as extreme cold or high



FIG 2. The 2007 HIV pandemic. Adapted from UNAIDS. AIDS pandemic update: special report on HIV/AIDS: December 2006. Geneva, Switzerland: Joint United Nations Programme on HIV/AIDS (UNAIDS) and World Health Organization (WHO); 2006.¹⁰

altitude. Ultraviolet light induces T-cell apoptosis and nonspecific release of tolerogenic cytokines from antigen-presenting cells in the epidermis; hence, ultraviolet light has been used in the treatment of eczema and the skin manifestations of autoimmune disorders. The immunosuppressive effect of ionizing radiation affects all blood cell lineages by depleting the bone marrow and inducing cytopenias, whereas the humoral response and phagocytosis are considered radio-resistant. However, continuous exposure to radiation eventually weakens all immune functions. Animal experiments of space radiation similar to that human beings would experience in long-duration space flights have demonstrated a weakness of T-cell-mediated immunity and reactivation of latent viral infections.⁸

Conditions such as chronic hypoxia at high altitude locations and long-duration space flights may affect immunity by causing physical and mental stress. Confinement, isolation, and sleep cycle alterations induce chronic stress, which disturbs the cortico-adrenal regulation and increases cortisol levels. In human beings, space flight-equivalent models including acute sleep deprivation have shown to increase blood levels of inflammatory cytokines and suppression of IL-10 secretion.⁸

INFECTIOUS DISEASES

HIV infection is the best known example of secondary immunodeficiency caused by pathogens. However, other microbial infections may also disturb the host immune system directly or indirectly. Transient periods of immunosuppression have been associated with viral infections since the 1900s, when it was observed that the tuberculin skin test became negative in patients with measles during the acute phase of the infection. Some infectious agents or their products may overstimulate the immune system, leading to a nonresponsive state, such as T-cell anergy observed after toxic shock syndrome induced by staphylococcal superantigen. Tissue destruction caused by microbial-induced damage or inflammatory reaction to a particular infection facilitates access for other microbes to develop secondary infections. Measles virus, cytomegalovirus, and influenza virus infections may induce lymphopenia and T-cell anergy; however, these are

transient and usually less severe than the immunodeficiency seen in AIDS.

AIDS Background

AIDS is the advanced stage of the disease caused by HIV infection, characterized by profound lymphopenia and susceptibility to infections with opportunistic pathogens. HIV is transmitted sexually for the most part, but it is also transmitted parenterally among intravenous drug users and vertically from mothers to their infants. Initially recognized during the early 1980s in a handful of cases,⁹ it is currently estimated that over 40 million people are infected with HIV worldwide. Two thirds of these individuals are living in the sub-Saharan region of Africa, with approximately half of them women and children (Fig 2). The HIV epidemics in North America and Europe have shown decreasing trends in the last decade, thanks to massive education campaigns and the use of potent anti-HIV drugs.¹⁰ However, more than 40,000 new cases of HIV infection are reported annually in the United States, and approximately half of these are individuals under 25 years of age.¹¹ There is an increasing number of reports of viral multidrug resistance and clinical complications secondary to the chronic use of antiretroviral drugs.

Virology

HIV is a double-stranded, enveloped RNA retrovirus from the group lentiviruses, with a tropism for human CD4⁺-expressing cells, including T cells and macrophages.¹² Two HIV types have been identified, HIV-1 and HIV-2, and both cause human disease. HIV-2 is more prevalent in West Africa and may take more time from infection to the development of immunodeficiency than HIV-1. The HIV genome contains 3 structural genes—*gag*, *pol* and *env*—and 6 regulatory genes—*tat*, *rev*, *nef*, *vif*, *vpr*, and *vpu*. Gag protein is split by the HIV protease into the proteins named capsid (p24), matrix, nucleocapsid, p6, and p2, all of which form the viral particle and stabilize the viral genome. Pol protein is also split to produce 3 enzymes: integrase, reverse transcriptase, and the protease that cleaves the viral proteins. After the viral genomic RNA is converted into DNA by the reverse transcriptase, the integrase facilitates the incorporation of the viral DNA into the host genome and uses the host cell replication mechanisms to produce more virions. The Env protein is also cleaved to produce 2 envelope proteins named gp120 and gp41, involved in the binding to CD4 and to the chemokine receptors CXCR4 and CCR5. Tat protein increases the transcription of HIV genes by 100-fold, whereas Rev protein allows the expression of the different HIV genes by regulating mRNA splicing. The roles of the other regulatory genes have only been clarified in the last few years. Nef protein downregulates CD4 and MHC class I surface expression on the membrane of infected cells, probably facilitating escape from immune surveillance. Vif is a protein that induces the degradation of APO-BEC3G, a cytosine deaminase that causes mutations during viral transcription.¹³ Interestingly, HIV Vif does not affect the simian APOBEC3G, and similarly, the simian immunodeficiency virus (SIV) Vif does not interact with the human APOBEC3G, which may account for the species specificity of these retroviruses. Vpr and Vpu proteins seem to facilitate the intracellular transport of viral proteins for viral particle formation.

Immunopathogenesis

HIV infects CD4⁺ T cells by the binding of the gp120 protein to the CD4 molecule and the chemokine receptor CCR5. Infected cells migrate to the lymph nodes, where initial replication occurs and there is an opportunity to infect other CD4⁺ T cells. During acute HIV infection, the gut-associated lymphoid tissue is severely depleted, with predominant loss of memory CD4⁺ T cells, and with high viremia and immune activation.^{14,15} HIV induces T-cell lymphopenia by several mechanisms: HIV-induced apoptosis, viral cytopathic effect, apoptosis secondary to nonspecific immune activation, and cytotoxicity to HIV-infected cells.⁹ A recently described form of cell death named *autophagy*, in which organelles are sequestered and directed toward lysosomal pathways, has been shown to be induced by HIV Env protein in uninfected T cells.¹⁶

The acute phase of HIV infection occurs 1 week to 6 weeks after infection with nonspecific symptoms such as fever, fatigue, myalgia, and headaches. Few acutely infected patients with HIV are diagnosed despite these symptoms. The period of clinical latency that follows is characterized by a virtual absence of signs or symptoms until symptomatic disease occurs and may last as long as 10 years. Higher viral loads predict shorter clinical latency.¹⁷ Without anti-HIV drug treatment, CD4⁺ T-cell counts progressively decrease, and the host usually succumbs to infections with opportunistic organisms, such as *Pneumocystis jiroveci* pneumonia. Investigators have been able to demonstrate the production of specific anti-HIV CD4⁺ T cells and CD8⁺ T cells as well as neutralizing anti-HIV antibodies; however, these immune responses are eventually overcome by viral escape strategies. At this stage, patients present with fever, weight loss, diarrhea, lymphadenopathy, and fungal and viral skin infections, indicating compromise of the immune system. When the peripheral CD4⁺ T-cell count is less than 200 cells/ μ L, the patient may present with any of a number of infections that define AIDS, such as *P jiroveci* pneumonia, histoplasmosis, toxoplasmosis, and coccidioidomycosis. If the patient does not receive antiretroviral treatment, repeated infections that are difficult to manage lead to the patient's death. A small proportion of HIV-infected patients remains asymptomatic and does not develop AIDS. These patients are called *long-term nonprogressors* and have been the focus of multiple studies to understand the basis of their protection. This immunity appears to be explained by different viral and host factors. The best known of these factors is the inherited defect in the gene encoding the CCR5 receptor, a T-cell surface molecule that is necessary for HIV cell entry. CCR5 gene mutations have been found with significant prevalence in people from Northern European ancestry.⁹ Other factors identified in long-term nonprogressors include a low number of activated CD8⁺ T cells,¹⁸ the presence of particular HLA haplotypes, and viral mutations that result in low virulence.

Diagnosis

HIV infection is tested by using a sensitive ELISA to detect antibodies against the HIV protein p24. A positive HIV ELISA is confirmed by using the more specific Western blot, which detects antibodies to several HIV proteins, or the detection of HIV DNA sequences by PCR. Rapid diagnostic tests to rule out HIV infection use serum, saliva, or urine with similar sensitivity and specificity to the ELISA and may be performed in the office or at home. In infants and children as old as 18 months born to HIV-

infected mothers, diagnosis of HIV infection should be performed with an HIV DNA PCR test, because the presence of passively acquired maternal antibodies in the serum of the child may result in a positive HIV ELISA test, even if the child is not infected with HIV. Other useful laboratory tests are genotyping and phenotyping assays. Genotyping identifies HIV mutations that confer viral resistance to antiretroviral drugs. Phenotyping measures the inhibitory action of anti-HIV drugs on the isolated HIV strain, similar to a bacterial susceptibility assay. These assays define anti-HIV drug susceptibility profiles of viral strains isolated from infected patients and help design the combination of drugs with the most probability to have a therapeutic effect in a particular patient.

Treatment and prevention

Specific anti-HIV therapy is recommended when the patient develops an AIDS-defining illness, the CD4⁺ T-cell count is less than 350 cells/mm³, or the HIV viral load is higher than 100,000 copies/mL. Caution should be exercised in other clinical situations because of the development of viral resistance to the antiretroviral agents and significant drug adverse effects, including allergic and metabolic syndromes. In children, treatment is considered for any HIV-infected infant because disease progresses faster than in older children. For children older than 12 months, the criteria are similar to those in adults: presence of an AIDS-defining illness, CD4⁺ T-cell count less than 15% of PBMCs, or viral load higher than 100,000 copies/mL.¹⁹ Anti-HIV drug classes are defined according to their mechanism of action: Nucleoside reverse transcriptase inhibitor, nonnucleoside reverse transcriptase inhibitor, protease inhibitor, and cell fusion inhibitor. There is active research for new agents that can inhibit other mechanisms of the viral replication cycle, which include viral integrase inhibitors and viral particle maturation inhibitors.¹⁹ Combinations of 3 synergistic anti-HIV drugs from 2 different classes are known as highly active antiretroviral therapy (HAART). HAART protocols have been effective on reducing viremia and restoring normal T-cell counts, with drastic reduction of mortality and number of infections; however, they do not eradicate HIV and need to be administered continuously for life.

The immune reconstitution inflammatory syndrome (IRIS) is a severe inflammatory response to existing opportunistic infections that may be observed in 15% to 25% of patients with AIDS 2 to 3 weeks after starting HAART treatment.²⁰ The management of IRIS consists of corticosteroid therapy and simultaneous treatment of the opportunistic infections; however, IRIS may not occur if these infections are recognized and treated before starting the HAART therapy. Drug-allergic reactions have an increased prevalence in this patient population. Urticarial or maculopapular rashes, which occasionally present as the Steven-Johnson syndrome, occur in as many as 60% of patients with HIV receiving trimethoprim-sulfamethoxazole and in 17% of those receiving the antiretroviral nevirapine.²¹ Abacavir is a nucleoside reverse transcriptase inhibitor that causes a multiorgan hypersensitivity syndrome characterized by fever, rash, diarrhea, myalgia, and arthralgia in as many as 14% of patients who take this drug. This has a strong association with the presence of HLA B5701. This syndrome presents within the first weeks of treatment and can be fatal; however, it usually resolves after 72 hours of discontinuing the drug.²¹

The incomplete elimination of the HIV virus by current antiretroviral therapy emphasizes the need of preventive measures to control the HIV pandemic. The research for an anti-HIV vaccine has yielded several lessons; perhaps the most important is the need to demonstrate the development of specific cellular immunity as well as humoral responses.²² The first vaccine candidates were based on strategies that had worked for other infectious diseases, such as inactivated virus and HIV proteins conjugated to adjuvants. These were able to induce only weak neutralizing antibody activity and did not provide significant protection against HIV infection in clinical trials. Live-attenuated SIV strains have been demonstrated to protect macaques from SIV challenge; however, there are safety concerns related to the extraordinary capacity of HIV for recombination, which may lead to wild-type revertant strains. Novel approaches such as DNA vaccines and viruslike particles are currently being tested in phase I/II clinical trials. Topical anti-HIV microbicides may become an alternative to the use of condoms.²³

Considerable resources have been placed on educational campaigns to control the HIV epidemics. Preventive interventions that have been useful are using condoms, providing intravenous drug users with free sterile needles, screening blood products, and administering antiretroviral agents to HIV-infected pregnant women and their infants. Avoiding breast-feeding has been recommended on the basis of the increased risk of transmitting the virus through breast milk; however this may be revised because this policy had an unexpected outcome in Botswana, evidenced by epidemiologic studies showing that feeding milk formula increased 50-fold the mortality rate of children because of an outbreak of diarrheal disease linked to the use of contaminated water.²⁴ Three recent studies in Africa showed that male circumcision reduces the risk of HIV infection in heterosexual males by 50% to 60%.²⁵ The control of this deadly disease will only result from a combined effort of researchers and physicians developing and using anti-HIV drugs effectively and educators working in the promotion of safe behavioral practices in communities at risk.

Conclusion

Practitioners in the specialty of allergy and immunology should be aware of the diverse conditions that may affect the immune response and cause a state of immunodeficiency. Secondary immunodeficiencies are far more prevalent than primary immunodeficiencies; however, with the exception of HIV infection, the specific immune defects in secondary immunodeficiencies have not been well defined. The clinical presentation is usually heterogeneous, affecting both innate and adaptive immunities, and resolves with the improvement of the primary condition. When considering a diagnosis of immunodeficiency in adults and children, physicians should not ignore the diverse factors affecting the immune system, such as infection, malnutrition, age extremes, concomitant metabolic or neoplastic diseases, use of

immunosuppressive drugs, surgery and trauma, and exposure to harsh environmental conditions.

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Learning objectives: "Secondary immunodeficiencies, including HIV infection"

1. To define the concept of secondary immunodeficiency as a condition in which nonimmunologic factors suppress immune functions.
 2. To study the immunopathogenesis of HIV infection as one the most challenging examples of a secondary immunodeficiency.
 3. To enumerate the different factors and conditions that produce secondary immunodeficiency and appreciate that the number of patients with secondary immunodeficiencies far exceeds those with primary (genetic) immunodeficiencies.
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CME items

Question 1. Which of the following is the most common cause of secondary immunodeficiency?

- A. radiotherapy
- B. severe malnutrition
- C. iron deficiency
- D. diabetes mellitus

Question 2. Acute HIV infection in adults is characterized by which of the following clinical conditions?

- A. fever, fatigue, and myalgias
- B. focal seizures
- C. *Pneumocystis jiroveci* pneumonia
- D. metabolic syndrome

Question 3. The highest incidence of urticarial or maculopapular rash in HIV infections has been associated with the use of which of the following medications?

- A. azidothymidine
- B. penicillin
- C. trimethoprim-sulfamethoxazol
- D. insulin

Question 4. Increased susceptibility to respiratory infections in cystic fibrosis patients is mainly secondary to which of the following?

- A. complement deficiency
- B. poor humoral response to polysaccharides
- C. impaired mucous airway clearance
- D. colonization by unusually virulent bacterial strains