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CME Review

Secondary immunodeficiencies
An overview

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Karen S. Tuano, MD*,†; Neha Seth, MD*,†; Javier Chinen, MD, PhD*,†

* Section of Allergy, Immunology and Retrovirology, Department of Pediatrics, Baylor College of Medicine, Houston, Texas
† Texas Children's Hospital, The Woodlands, Texas

Key Messages

- Secondary immunodeficiencies may be defined as an impairment of the immune response resulting from conditions or factors extrinsic to the immune system.

- Secondary immunodeficiencies are more frequently diagnosed than primary immunodeficiencies.

- The immune response depends on the integrity of other systems, such as the skin and the gastrointestinal system.

- Immunodeficiency can occur as a consequence of malnutrition, metabolic disorders, use of immunosuppressive medications, chronic infections, malignancies, and severe trauma.

- The neonate and the elderly may have decreased immune responses relative to healthy adults.

- Optimal management of the secondary immunodeficiencies focuses on the improvement of the primary condition and their manifestations and provides recommendations to reduce the risk of infections.

ARTICLE INFO

ABSTRACT

Objective: To review the different causes of secondary immunodeficiencies and provide clinicians with an updated overview of potential factors that contribute to immunodeficiency.

Data Sources: Recent published literature obtained through PubMed database searches, including research articles, review articles, and case reports.

Study Selections: PubMed database searches were conducted using the following keywords: immunodeficiency, antibody deficiency, immunosuppressive drugs, genetic syndrome, malignancy, HIV infection, viral infection, secondary immunodeficiency, nutrition, prematurity, aging, protein-losing enteropathy, nephropathy, trauma, space travel, high altitude, and ultraviolet light. Studies published in the last decade and relevant to the pathogenesis, epidemiology, and clinical characteristics of secondary immunodeficiencies were selected and reviewed.

Results: Researchers continue to investigate and report abnormal immune parameters in the different entities collectively known as secondary immunodeficiencies. Immunodeficiency might occur as a consequence of malnutrition, metabolic disorders, use of immunosuppressive medications, chronic infections, malignancies, severe injuries, and exposure to adverse environmental conditions. The neonate and the elderly may have decreased immune responses relative to healthy adults. Each of these conditions may present with different immune defects of variable severity. The acquired immunodeficiency syndrome results from infections by the human immunodeficiency virus, which targets CD4 T cells leading to defective immune responses. Rituximab is a monoclonal antibody that targets CD20 B cells, and its use might result in persistent hypogammaglobulinemia.

Conclusion: Clinicians should consider secondary immunodeficiencies in the differential diagnosis of a patient with recurrent infections and abnormal immunologic evaluation. The use of biological agents for the treatment of inflammatory conditions and malignancies is an increasingly important cause of secondary immunodeficiency.

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Overall Purpose

Participants will be able to demonstrate increased knowledge of the clinical treatment of allergy/asthma/immunology and how new information can be applied to their own practices.

Learning Objectives

At the conclusion of this activity, participants should be able to:

- Discuss the concept and definition of secondary immunodeficiencies.
- Describe the pathogenic mechanisms of secondary immunodeficiencies.

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Target Audience

Physicians involved in providing patient care in the field of allergy/asthma/immunology

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All identified conflicts of interest have been resolved. Any unapproved/investigative uses of therapeutic agents/devices discussed are appropriately noted.

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<u>**Authors**</u>

- Karen S. Tuano, MD has no relevant financial relationships to disclose.
- Neha Seth, MD has no relevant financial relationships to disclose
- Javier Chinen, MD, PhD, has no relevant financial relationships to disclose.

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Introduction

Allergy and immunology specialists are increasingly consulted to assist in the management of patients with an altered immune response. One current example is the concern for the severity of disease in patients with either primary or secondary immunodeficiencies who develop coronavirus disease 2019 (COVID-19).[1] Primary immunodeficiencies are now included under the term inborn errors of immunity (IEI), representing a group of more than 450 genetically defined diseases.[2] Secondary immunodeficiency might be defined as a transient or persistent impairment of the function of cells or tissues of the immune system, caused by factors that are not intrinsic to the immune system. These groups of factors include environmental agents, medications, and a variety of heterogeneous conditions (Fig 1). In the last 5 decades, the most studied secondary immunodeficiency has been the acquired immunodeficiency syndrome (AIDS), caused by the HIV infection. HIV-infected individuals who receive antiretroviral therapy retain their immune function and do not develop AIDS, although chronic inflammation is most often present and contributes to the development of the following comorbidities: non-AIDS malignancies, cardiovascular events, renal and hepatic diseases, bone disorders, and neurocognitive impairment.[3] In addition, the routine use of biological agents to treat autoimmune and inflammatory diseases has become a cause of concern because of the increased risk of infections and secondary immunodeficiency.[4] Because of global food insecurity, malnutrition is the most prevalent cause of immunodeficiency worldwide. Its association with frequent infections is observed in low-income communities,[5] including in patients with chronic diseases.[6] In this review, our objective is to discuss the diversity of factors and `conditions that can affect the immune response. These conditions are grouped in categories, and a few examples are selected based on frequency or representativeness.

Evaluation and Management of Secondary Immunodeficiencies

Immunodeficiency should be considered in a patient with infections characterized by increased frequency, need of parenteral antibiotics, unusual severity, difficult recovery, or uncommon etiologic pathogens. Of note, there are conditions affecting the immune system that may also suggest the presence of an underlying IEI. For example, malnutrition impairs the immune response but also is one of the hallmark signs of a patient with severe combined immunodeficiency.[7] The recommended initial approach for secondary immunodeficiency
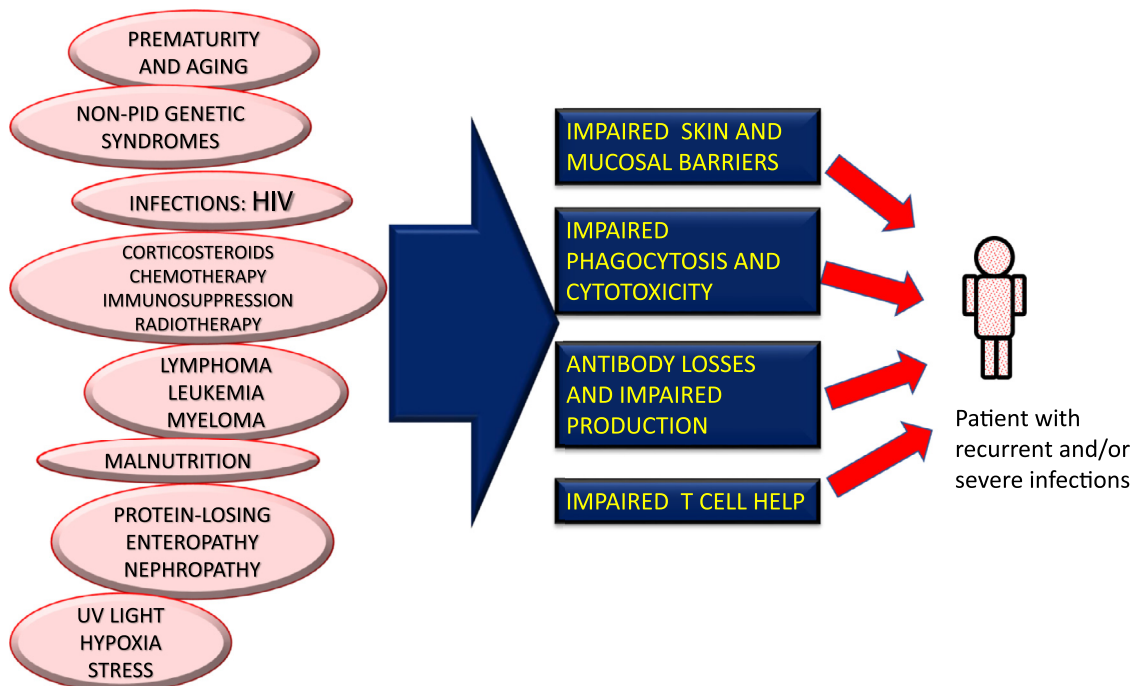

Figure 1. Secondary immunodeficiencies. Several factors and conditions may impair different components of the immune system, alone or in combination, to induce an increased susceptibility to infections. PID, primary immunodeficiency; UV, ultraviolet.
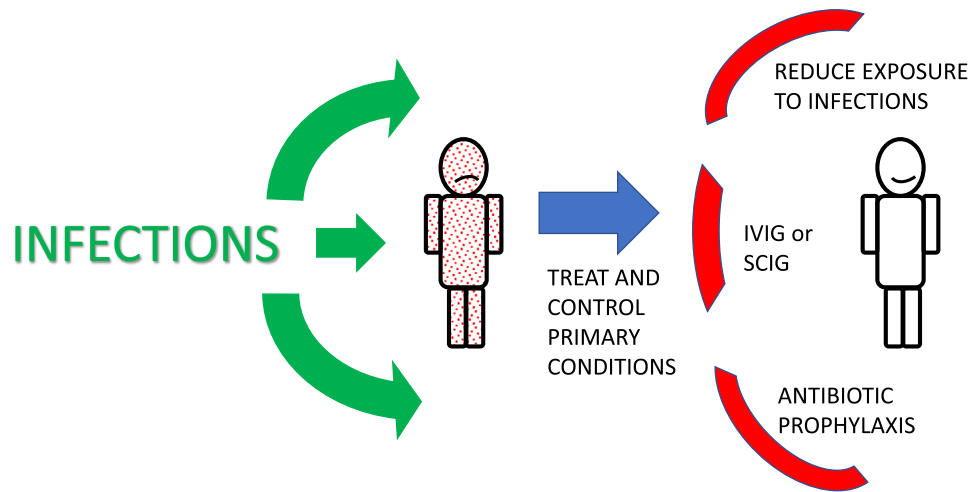
Figure 2. Basic principles of the management of secondary immunodeficiencies: treat and control primary condition or factor, implement measures to reduce risk of infections, and use immunoglobulin supplementation and antibiotic (antibacterial, antiviral, and antifungal) prophylaxis if indicated by low serum IgG levels and frequent infections. Ig, immunoglobulin; IVIG, intravenous immunoglobulin; SCIG, subcutaneous immunoglobulin.

follows guidelines for the evaluation of the immune response.[8] Findings of the clinical history, in particular patterns of infections, and physical examination abnormalities are essential to guide the assessment of the immune system. Secondary causes of immunodeficiency should be sought, because the diversity and frequency of factors or conditions (eg, immunosuppressive medications, chronic diseases, prematurity) that affect the immune response are greater than the frequency of IEI. Laboratory testing indicated in the assessment of immunodeficiency includes blood cell counts and lymphocyte phenotyping to measure neutrophils, monocytes, T cells, B cells, and natural killer (NK) cells. Measurement of levels of serum immunoglobulins (Igs) G, A, M, and E and antibody responses to previous immunizations are helpful to evaluate humoral immunity. Serum albumin and total protein levels are useful to identify hypoproteinemia, which raises the suspicion of either malnutrition or protein-losing diseases.

The management of a patient with secondary immunodeficiency should be focused on the improvement of the primary condition, and when possible, the removal of the offending environmental factor (Fig 2). For example, when protein-losing enteropathy (PLE) leads to hypogammaglobulinemia, successful treatment of the enteropathy restores normal serum immunoglobulin levels.

General measures to consider for the patient with a secondary immunodeficiency (Table 1) include measures to reduce exposure to infections, antibiotic prophylaxis, and immunoglobulin replacement and immunizations.

Immunosuppressive Medications

Iatrogenic secondary immunodeficiency may be caused by medications used to treat various inflammatory conditions, autoimmune disorders, allergic diseases, malignancies, transplant rejection, and graft-vs-host disease. These medications target cytokines and cells of the immune system and might be grouped under anti-inflammatory and immunosuppressive small molecule agents (eg, corticosteroids, methotrexate, cyclosporin), protein kinase inhibitors, and biological agents (eg, anti-CD20 antibodies)[9,10] (Table 2). Owing to space limitations, only an overview of the vast available information can be discussed. We will briefly discuss glucocorticoids and rituximab, which are representatives of immunosuppressive medications.

Glucocorticoids are widely used because of their potent anti-inflammatory action that results in reduction of symptoms in autoimmune and allergic diseases.[11] Prednisone and dexamethasone are 2 of the most used medications in this group. Their immunosuppressive action is mediated by multiple molecular mechanisms, such as the inhibition of NF-κb pathways, followed by the suppression of the proinflammatory cytokines interleukin (IL)-1, IL-2, IL-6, tumor necrosis factor (TNF)-α, and interferon gamma and prostaglandins. In addition, glucocorticoids induce anergy and apoptosis of lymphocytes, increased neutrophil detachment from the endothelium into the peripheral blood, and release of immature neutrophils from the bone marrow, which is translated into lymphopenia and neutrophilia. Glucocorticoids reduce histamine secretion, IgE, IL-4, IL-5, and other mediators of allergic disease. The anti-inflammatory and anti-allergic benefits are linked with increased risk of infection owing to the immunosuppression, which is proportional to the duration of treatment and to the dose. Viral, bacterial, and fungal infections are common with prolonged glucocorticoid treatment. Other adverse effects associated with the use of glucocorticoids are cataracts, osteoporosis, adrenal axis suppression, hypertension, Cushing syndrome, and diabetes mellitus. The use of topical forms of glucocorticoids, such as ointments and nasal sprays, substantially reduces the risk of these adverse effects because of their minimal systemic bioavailability; however, misuse of topical treatments can lead to the adverse events mentioned.[12]

Table 1
Management of the Patient With Immunodeficiency

1. Reduce risk of contact with potentially infectious individuals and with environmental pathogens. Avoid crowded places.
2. Periodic clinical follow-up for prompt diagnosis of systemic and invasive infections.
3. Consider antibiotic prophylaxis to reduce risk of infections.
4. Consider immunoglobulin G replacement for patients with significantly low serum IgG levels (<2 SDs below the mean) or absent antibody response to pneumococcal immunization.
5. Immunizations for infections by encapsulated bacteria, for example, *Streptococcus pneumoniae* and *Haemophilus influenzae*, are indicated in patients with deficit of specific antibacterial immunity, or when a high risk of invasive infection has been observed, as has been found for patients receiving cochlear implants.
6. Complete scheduled immunizations, with exception of live vaccines for patients with severe immunodeficiency. Live vaccines might induce vaccine-associated disease in these patients.

Abbreviation: IgG, immunoglobulin G.

Table 2
Selected Agents Targeting the Immune Response

Drug	Effect on immune function
Small molecules	
1. Glucocorticoids (prednisone)	Decreased cellular response and anergy
	Decreased proinflammatory cytokines
	Decreased phagocytosis
	Decreased chemotaxis
2. Cytotoxic agents (methotrexate)	Cytopenias
	Decreased T and B cell proliferation
	Decreased cellular and antibody responses
3. Calcineurin inhibitors (cyclosporin)	Decreased T cell proliferation
	Decreased proinflammatory cytokines
	Decreased activation of innate immune cells
JAK inhibitors	
Baricitinib, tofacitinib, upadacitinib, ruxolitinib	Reduced inflammatory response
	Impaired T and B cell activation
Biological agents	
TNF-α inhibitors (certolizumab, adalimumab, infliximab, golimumab, etarnecept)	Neutralization of soluble or bound TNF-α
	Down-regulation of cytokine expression
	Cell apoptosis
Monoclonal antibodies targeting B cells	Antibody deficiency
Anti-CD20 (rituximab, veltuzumab, ocrelizumab, ofatumumab, binutuzumab, ublituximab)	B cell lymphopenia
Anti-CD22 (epratuzumab)	
Anti-C19 (blinatumumab)	
Anti-CD52 (alemtuzumab)	
Anti-CD38 (daratumumab, isatuximab)	
Anti-BAFF (belimumab)	
IL-1 inhibitor (anakinra, canakinumab)	Reduced inflammatory response
	Decreased lymphokine synthesis
	Decreased T and B cell stimulation and proliferation
IL-6 inhibitor (sarlimumab, tocilizumab)	Reduced inflammatory response
	Neutropenia
	Decreased innate and adaptive immunity

Abbreviations: IL, interleukin; JAK, Janus kinase; TNF, tumor necrosis factor.

According to the type of molecule and function, biological agents might be classified in monoclonal antibodies and competitive inhibitors of receptor binding. Anti-CD20 antibodies and TNF-α inhibitors are some of the most prescribed biological agents. The following are the 6 anti-CD20 monoclonal antibodies that have been developed: rituximab, veltuzumab, ocrelizumab, ofatumumab, binutuzumab, and ublituximab. Rituximab was the first agent of this group to be developed for clinical use. It is indicated to treat autoimmune diseases and lymphoid malignancies. Several studies have reported hypogammaglobulinemia and increased risk of infections associated with the use of rituximab.[13] McAtee et al[10] reported that 224 of 468 (47.9%) patients in a tertiary care center receiving at least 1 dose of rituximab developed infections. Of 117 patients, 16 (13.7%) had low serum IgG levels and 48 of 95 patients (51%) had persistently low B cell counts 1 year after stopping rituximab. The presence of malignancy and the use of other anticancer treatments might contribute to the increased frequency of infections. Of note, a clinical indication for the use of rituximab, such as refractory autoimmune cytopenia, might represent a manifestation of an IEI.[14] Therefore, the assessment of humoral immunity before rituximab treatment has been suggested to rule-out a preexisting antibody deficiency. In addition, scheduled immunizations should be complete and antibiotic prophylaxis and immunoglobulin supplementation should be considered in patients with recurrent infections or a severe depression of the humoral immune function.

Four monoclonal antibodies binding TNF-α and one fusion protein TNF-α receptor antagonist have been approved for the treatment of inflammatory bowel disease, rheumatoid arthritis, ankylosing spondylitis, and psoriasis (Table 2) A major concern with the use of these biological agents is the central role of TNF-α in antimycobacterial immunity.[15] To reduce their risk of tuberculosis reactivation and severe disease, patients receiving TNF-α inhibitors are recommended to undergo tuberculosis screening before treatment and receive antibiotic prophylaxis if the screening is positive.[16]

Other drugs are associated with deleterious effects in the immune system that are not clearly related to the pharmacologic activity of the molecule (eg, antiepileptic medications—phenytoin, carbamazepine, levetiracetam—may cause antibody deficiency).[17]

Infections

HIV infection is a well-known cause of secondary immunodeficiency, termed AIDS. Other microbial infections, mainly viral and mycobacterial, are associated with transient periods of immunosuppression. Cell death and excess of toxic metabolites may lead to a nonresponsive immunologic state, and the break of skin and mucosal barriers facilitates access for other pathogens to develop secondary infections.[18]

Other viruses have coevolved with their hosts and use multitude of strategies to modulate the host immune response.[19] In several chronic infections, persistent antigen stimulation induces decreased T cell effector functions, a condition known as T cell exhaustion.[20]

HIV

HIV infection targets CD4 T cells and induces T cell lymphopenia through several mechanisms, such as follows: HIV-induced apoptosis, apoptosis caused by nonspecific immune activation, viral cytopathic effect, T cell cytotoxicity to HIV-infected cells, and autophagy.[21] Without treatment, CD4 T cell counts and immune responses progressively decrease rendering the host susceptible to infections with opportunistic organisms. Because of advances in antiretroviral

therapy, HIV infection can now be controlled but not eradicated. HIV infects other cells expressing CD4, such as microglial cells, liver Kupffer cells, and renal tubular epithelial cells, which become viral reservoirs. Incomplete immune reconstitution of CD4 T cells with a predominant proportion of activated cells is often found in patients with HIV receiving antiretroviral therapy. In most treated patients with HIV, excess of infections is controlled; however, chronic inflammation is common, leading to early development of malignancies, metabolic syndrome, and cardiovascular disease.[3]

Measles Virus

Measles is a highly infectious virus found to result in immunosuppression that can persist for months to years after initial infection in immunocompetent hosts.[22] The immunosuppressive effect of measles was initially found more than a hundred years ago, when loss of the tuberculin skin test positive response during the acute phase of measles infection was noted. Proposed mechanisms of immunosuppression include T and B cell lymphopenia, inhibition of lymphocyte proliferation, skewing toward T_H2 cytokine responses, and decreased B cell and Tcell memory cells, all of which contribute to an increased risk of infections by other microbes.

Mycobacteria

Mycobacterium tuberculosis infection affects one-third of world's population and is the leading cause of mortality by an infectious disease.[23] Apoptosis and necrosis of antigen-presenting cells are accelerated owing to mycobacteria replication. Patients with mycobacterial infection have decreased lymphoproliferative responses, increased production of interferon gamma, and suppression of IL-17$^+$ CD4 T cells. Fungal and atypical mycobacteria infections occur. Furthermore, damaging inflammatory reactions induce significant regulatory T cell activity, which attenuates the ability of monocyte-derived and alveolar macrophages to restrict mycobacterial growth.[24]

Coronavirus Disease 2019

The COVID-19 pandemic, caused by severe acute respiratory syndrome coronavirus 2, has become one of the top causes of mortality worldwide. Concomitant community and hospital-acquired bacterial pneumonias occur with increased severity of disease and hospitalization.[25] Several changes in the immune system have been reported in patients with severe infection of severe acute respiratory syndrome coronavirus 2 which play a role in the occurrence of secondary infections, such as follows: impaired interferon alfa signaling, reduced number and function of NK cells, and peripheral CD4 and CD8 T cell lymphopenia.[26] In severe COVID-19 cases, a massive inflammatory response develops in the lungs with serum cytokines at increased levels, similar to the "cytokine storm" reported in patients receiving tumor T cell immunotherapy. This event is followed by T cell exhaustion, lung tissue destruction, and hypoxia, which are predisposing factors to secondary bacterial infections.

Age Extremes

Neonate and Prematurity

The infant mortality owing to sepsis is 16.1 per 100,000 live births in the United States.[27] The increased susceptibility to infections of neonates has been attributed to immature innate and adaptive immune responses. Except for lymphocyte and neutrophil cell counts, almost all immune parameters are lower at birth than in adulthood. Neonatal adaptive immunity is biased toward the T_H2 immune phenotype rather than T_H1 phenotype. Peripheral blood mononuclear cells from newborns have reduced Toll-like receptor

(TLR) responses with decreased production of proinflammatory cytokines.[28] Cord blood cell response to TLR ligands produces less T_H1 cytokines (IL-12, interferon alfa, and interferon gamma) and more IL-10 and T_H17 polarizing cytokines (IL-6, IL-23, and IL-1β) than adult peripheral blood mononuclear cells. Neutrophils from neonates have decreased expression of surface adhesion molecules leading to impaired tissue migration, which is most pronounced in premature infants.[29] NK cell cytotoxicity is lower at birth and in young children than in adults. The major components of the complement cascade (C1q, C3, C4, properdin, and factor B) are also decreased in newborns.[30] Impaired production of IL-12p70 in neonates results in nonproductive activation and failure to differentiate into effector cytotoxic T cells.[31] However, neonatal B cells are abundant at birth but most are naive and have a partially developed cell surface immunoglobulin repertoire.[32] The protective maternal IgG that is mostly transferred during the third trimester is limited in the premature owing to gestational age. The development of IgG repertoire in preterm neonates is slower than that in term neonates and remains low until the newborn reaches the expected day of delivery; however, responses to scheduled immunizations are adequate, with exception of the hepatitis B vaccine for newborns under 2000 g, which may require an additional dose.[33] The development of the gut microbiome and its interaction with the adaptive immune response play an important role in the development of a normal immune system.[34] Breastmilk feeding is another participant in these interactions, as evidenced by its protective effect against the development of necrotizing enterocolitis.[35]

Aging/Immunosenescence

The elderly population has an increased risk of acquiring infections and high severity of disease, which is consistent with the increased mortality of patients with advanced age with COVID-19.[36] Immune system changes owing to aging, or immunosenescence, might explain the increased burden of disease in these populations and include decreases in the TLR function, chemotaxis, phagocytosis, and cytokine production.[37] NK cells from elderly population are predominantly the mature CD14$^+$CD56$^{+bright}$ subset with reduced cytotoxicity function, cytokine function, and migration capacity. Aging of the adaptive immune system is often described as a shift from naive to memory T and B cells owing to chronic exposure to foreign antigens during a lifetime. Thymic involution contributes to quantitative changes to decrease naive T cells and effector memory T cell subsets. In the B cell compartment, switched memory B cells, plasma cells, and antibody responses to antigens including vaccines decrease with age.[38]

Malnutrition and Metabolic Disorders

Malnutrition

Malnutrition negatively affects immune responses leading to increased frequency and severity of infections; conversely, infections lead to malnutrition as a result of limited food intake and absorption and increased metabolic needs.[39] Direct effects of malnutrition in lymphoid organs have been observed in malnourished mice and include thymic atrophy, thymocyte apoptosis, decreased levels of secretory IgA, and reduced cellularity in the spleen and lymph nodes. Children with protein energy malnutrition have reduced serum levels of IL-1, IL-6, TNF-α, and the complement system components and impaired neutrophil chemotaxis and function, NK cell cytotoxicity, and dendritic cell maturation. In addition, malnourished individuals have reduced numbers of memory and effector T cells, reduced delayed-type hypersensitivity, impaired T cell responses, and fewer circulating B cells. Malnutrition affects embryonic and fetal development; hence, a mother's nutritional state during pregnancy might

Table 3
Micronutrients and Their Effects on the Immune System

Micronutrient	Effect on immune function	Micronutrient deficiency
Zinc	Thymic hormone that regulates T cell maturation	Thymic apoptosis
	Promotes T_H1 cell differentiation	Lymphopenia
	Regulates release of proinflammatory cytokines and neutrophil function	Reduced T_H1 cytokines
		Impaired phagocytosis
		Impaired mucosal immunity
Selenium	Anti-inflammatory effects	Reduced CD4 T cell proliferation and function
	Antioxidant activity	Reduced T cell activation
		Decrease IL-2, IL-2R expression
		Impaired calcium mobilization
Vitamin A	Differentiation of epithelial cells	Impaired epithelial barrier function
	Regulation of dendritic cells and T cell differentiation	Reduced CD4 and CD8 T cell numbers
Vitamin C	Regulates apoptosis in monocytes, macrophages, neutrophils, and B cells	Exaggerated inflammation in murine models
Vitamin D	Anti-inflammatory effects	Associated with increased risk of respiratory infections in children
	Activation of antimicrobial host defense	
	Regulation of innate and adaptive immunity	
	Promotes T regulatory cells	
Vitamin E	Epithelial barrier	Associated with reduced infections in the elderly
	T cell activation	
	NK cell activity	

Abbreviations: IL, interleukin; NK, natural killer.

have long-term effects on immune responses from birth to adulthood.[40] Table 3 summarizes the known effects of micronutrient deficits on immunity. Adequate nutrition restores normal immune responses.

Protein-Losing Enteropathy

PLE occurs secondary to gastrointestinal loss of protein owing to erosive and nonerosive gastrointestinal disorders. In addition, increased central venous pressure or mesenteric lymphatic obstruction might result in PLE.[41] This process is observed in patients with univentricular hearts who underwent cardiovascular surgery to divert systemic venous blood to the lungs (the Fontan procedure). The patients have hypogammaglobulinemia, severe lymphopenia with decreased CD4 T cell counts, and altered T cell differentiation toward memory and terminally differentiated T cells.[42] Hypogammaglobulinemia is a common finding in patients with PLE, as a result of gut protein losses. Patients with PLE might have conserved antibody responses and normal rate of infections, which depends on the severity of lymphopenia and hypogammaglobulinemia.[43] Immunoglobulin supplementation is not usually required; however, it might be considered for patients with recurrent infections and severe hypoproteinemia. Owing to rapid protein loss, achieving optimal trough serum IgG level is often challenging and might require modifications of the frequency and dose of IgG infusions. The subcutaneous route of infusion might be of advantage than the intravenous route for maintaining serum IgG levels.

Diabetes Mellitus

People with diabetes have a high risk of infections related to disturbances in glucose metabolism, particularly affecting neutrophil functions.[44] They are hospitalized for infections 2 to 10 times more than people without diabetes.[45] The evidence of immune dysfunction is focused on the innate immune response. Hyperglycemia markedly decreases neutrophil function and the formation of neutrophil extracellular traps.[46] Other abnormalities reported in patients with diabetes include low cytokine production in response to mitogens and antigens. Large studies of patients with diabetes analyzing immunologic markers suggest that chronic inflammation and immune senescence are present, depending on the degree of glycemia control.[47] These findings might play a role in the increased severity of infections

and contribute to the pathogenesis of noninfectious comorbidities, such as cardiovascular disease.

Chronic Kidney Disease

Immune dysfunction in chronic renal disease is due to proteinuria and uremia, which result in chronic immune activation and chronic immune suppression.[48] Nephropathies associated with proteinuria typically induce hypogammaglobulinemia, and immunoglobulin supplementation may be considered to reduce risk of infections. Both innate and adaptive arms of the immune system are affected (Table 4).

Genetic Defects Other Than Primary Immunodeficiencies

Many genetic syndromes that are not considered primary immunodeficiencies are also associated with recurrent infections. Factors that favor the development of infections fall into the following categories: impairment of secretion clearance, anatomic abnormalities, and metabolic deficiencies that indirectly affect the function of the cells of the immune system. Abnormalities of immune parameters might be observed, although the molecular mechanisms are not always clear. We selected a few of these conditions to illustrate the association of these genetic conditions with immunodeficiency. Inborn errors of metabolism associated with immune abnormalities are presented in Table 5.

Table 4
Effects of Uremia in the Immune System

Cell type	Immune dysfunction
Dendritic cells	Decreased antigen presentation
	Decreased costimulation
Monocytes	Decreased phagocytosis
Natural killer cells	Decreased activation
Neutrophils	Increased apoptosis
	Increased TLR2 and TLR4 expression
B cells	Decreased naive B cell population
	Decreased B cell activation
	Increased apoptosis
T cells	Decreased naive T cell population
	Decreased function of effector T cells
	Decreased IL-2 production
	Increase in CD4+CD28− T cell population

Abbreviation: IL, interleukin.

Table 5
Inborn Errors of Metabolism Associated With Immune Abnormalities

Name	Inheritance	Associated features	Immune defect
Congenital disorders of glycosylation	Various	Hypotonia Failure to thrive Microcephaly	B cell defect Phagocyte defect
Branched chain amino acidurias	Autosomal recessive	Metabolic acidosis Failure to thrive	Low B cell counts Hypogammaglobulinemia
Lysinuric protein intolerance	Autosomal recessive	Hyperammonemia, Failure to thrive Protein intolerance Hepatomegaly	Low CD4$^+$ T cell counts IgG subclass deficiency Impaired humoral response to vaccines

Abbreviation: IgG, immunoglobulin G.

Down Syndrome (Trisomy 21)

Down syndrome (DS) is the most common genetic diagnosis. A subset of individuals with DS reports an increased frequency of infections, autoimmunity, autoinflammatory disorders, and hematologic malignancies.[49] Immune defects in these patients are thought to occur as a result of dysregulation of expression from genes located in chromosome 21, in particular, interferon-related genes. The most common infectious disease is frequent otitis media in childhood, which usually improves with placement of ear tubes and resolves by adolescence.[50,51] Determinants of the wide variability of susceptibility to infections include abnormal immune response, midline face architecture, allergic inflammation, and genetic interactions. Anatomic findings in the upper airway anatomy, such as macroglossia, enlarged tonsils and adenoids, facial phenotype with small passages and small hypopharynx that may lead to eustachian tube dysfunction, contribute to the increased risk of respiratory infections. Children with DS can present with a smaller thymus and undergo premature thymic involution with reduced thymic output and function.[52] Many patients with DS present with hypogammaglobulinemia and decreased number of naive and memory B cells owing to a high rate of B cell apoptosis.[49] Low serum IgG levels in DS have been associated to PLE secondary to inflammatory bowel disease (K. S. Tuano et al, unpublished data, 2021).

Turner Syndrome (Monosomy XO)

Turner syndrome (TS) is a genetic disorder characterized by absence of whole or part of an X-chromosome. Low T and B cell population can be found in individuals with TS, but these changes have not been associated with increased risk of frequent infections except for ear infections.[53] Lymphedema of extremities is associated with lymphopenia and hypogammaglobulinemia, usually mild to moderate. The risk factor for recurrent ear infections in TS is likely related to the structural abnormalities of the skull and facial bones (low-set ears, cupped auricles, narrow external ear canals, high-arched palate, and micrognathia) and eustachian tube dysfunction.[54]

Cystic Fibrosis

Cystic fibrosis (CF) is an autosomal recessive disorder associated with mutations in the *CFTR* gene resulting in altered mucociliary transport in both the lung and gut mucosa. CF is an example of defective mucosal barriers as a risk factor for infections. Dehydration of the surface mucosa leads to a dense mucus retention and impaired mucociliary clearance, which favors trapping of bacteria and growth of opportunistic microorganisms and impaired function of airway macrophages.[55] The function of neutrophils, macrophages, lymphocytes, and dendritic cells has been reported abnormal in patients with CF. Hypergammaglobulinemia has been described in CF as a marker of lung disease severity and prognosis.[56]

Trauma, Burns, and Major Surgery

Severe and extensive trauma, burns, and surgeries are major injuries associated with marked immunosuppression and might be followed by postoperative sepsis, with a mortality of almost one-third of patients.[57] Disruption of epithelial barriers and significant cell destruction after injuries induces a complex immune response triggered by tissue damage, leading to a release of endogenous damage-associated patterns (DAMPs).[58] DAMPs, or alarmins, are intracellular molecules, such as DNA, RNA, IL-1, histones, heat-shock proteins, and defensins. DAMPs activate inflammasomes and complement systems, followed by a noninfectious systemic inflammatory response syndrome owing to a rapid increase of inflammatory cytokines. To prevent tissue damage from overwhelming inflammatory reactions, compensatory mechanisms (eg, IL-10 and other anti-inflammatory cytokines) are activated simultaneously.[59] An inadequate balance of pro- and anti-inflammatory regulatory mechanisms may result in a long-term state of immunosuppression and anergy. The consideration of this challenging mechanism of pathogenesis supports increased infection surveillance and prompt treatment and the use of immunomodulators to reduce the abnormal inflammatory responses.

Thymectomy and Splenectomy

Surgical removal of the thymus or the spleen is immunologically significant because of their role as organs of the immune system. Partial or complete thymectomy is typically performed during heart surgery for congenital cardiac malformations, to improve surgical access to the heart. Thymectomy in infants results in T cell lymphopenia, with CD4 T cells typically affected more than CD8 T cells.[60] Young adults after thymectomy in infancy have lymphocyte populations skewed toward effector T cells and a reduced diversity of the T cell repertoire, suggesting premature aging.[61] The long-term risks of infection or autoimmunity induced by the observed immune abnormalities are being investigated.[62]

The spleen is important in regulating immune homeostasis through its ability to link innate immunity and adaptive immunity. Splenectomy is considered in certain cases of abdominal trauma, autoimmune cytopenias, and malignancies. Functional asplenia occurs owing to repeated ischemia or infarcts in the spleen, which is common in sickle cell disease. The adaptive immune response is affected in splenectomized individuals, who have an increased susceptibility to invasive and severe infections with encapsulated bacteria, mainly *Streptococcus pneumoniae*.[63] Vaccinations against *S pneumoniae, Neisseria meningitidis*, and *Haemophilus influenzae* type b and antibiotic prophylaxis are typically recommended. Children under 5 years of age seem to be at high risk of infections because they might not have yet developed protective specific antibody titers to childhood immunizations. Owing to its essential role in innate immunity mechanisms, the absence of the spleen results in an impairment of the opsonizing filter function and pathogen clearance, reduced removal of immune complexes, delayed and impaired immunoglobulin production, and reduced phagocytic function.[64]

Hematological Neoplasias

The treatment of patients with malignant neoplasia involves different protocols of chemotherapy, biological agents, and radiotherapy, which often deplete cells of the immune system and produce secondary immunodeficiency. Bone marrow failure conditions and malignancies of B cells and plasma cells can present with recurrent infections and hypogammaglobulinemia at diagnosis, before treatment is started.[65] This group of lymphoproliferative diseases includes chronic lymphocytic leukemia, multiple myeloma, non-Hodgkin lymphoma, and thymoma with immunodeficiency (Good's syndrome). Patients diagnosed as having these diseases benefit from immunoglobulin supplementation therapy to reduce their risk of infections.[66] Chronic lymphocytic leukemia is associated with hypogammaglobulinemia in 85% of cases and is an indication for immunoglobulin supplementation.

Environmental Conditions

People living under extreme environmental conditions might present with a degree of immunodeficiency. With increased space exploration and venturing into places with harsh environments, there is interest on the effects of these conditions on the immune response. The secondary immune deficiency owing to the environment is a hazard for certain occupations, such as astronauts, high-altitude air pilots, and miners. We discuss examples of environmental conditions affecting the immune system, such as follows: ultraviolet radiation, high altitude, and space travel.

Ultraviolet Radiation Exposure

Ultraviolet radiation (UVR) is immunosuppressive and clinically used to treat skin inflammatory conditions. The natural source of UVR is the sun, and according to its wavelength, it can be divided in the following 3 subtypes: UVA (320-400 nm wavelength), UVB (280-320 nm wavelength), and UVC (< 280 nm wavelength). The atmosphere blocks UVC radiation and approximately 90% of UVB radiation (UVBR). UVA radiation (UVAR) and UVBR are both immunosuppressive, but UVBR is more potent than UVAR and can damage DNA. Exposure to UVR increases the risk of malignant transformation of skin cells. Signaling events leading to UVR-induced immunosuppression are triggered by DNA and RNA damage in skin cells, promoting IL-10 secretion, inhibition of Langerhans cells, and differentiation of T regulatory cells.[67,68]

High Altitude

People living in high altitude and mountain climbers are constantly exposed to hypoxic environment, cold, and UVR. The effect of this environment in the immune response was revealed by studies conducted in the 1970s to early 2000s. Changes include increased serum IgA and IgG levels, decreased CD4 T cell counts, and impaired T cell function and phagocytosis.[69] The clinical consequences of these changes are difficult to assess, considering the relatively low presence of pathogens and that most communities living at high altitude might not have adequate access to health services. One study addressed the capacity to develop immune memory in humans ascending to high altitude, compared with controls staying at sea level, using diphenylcyclopropenone, a compound known to induce contact dermatitis. Skin reactions to this compound at high altitude were significantly reduced by 50%, indicating high altitude impairs the cellular immunity.[70]

Space Travel

Exposure to extraterrestrial conditions, such as cosmic radiation and absent or extreme gravitational forces, is a potent stressor that can affect the immune system. Spaceships are designed to attenuate the effect of these elements to the human body. Nevertheless, it has been found that spaceflights result in persistent immune abnormalities. These changes include CD4 and CD8 T cell lymphopenia and impaired CD4 T cell function.[71] Moreover, an increase in proinflammatory cytokines (TNF-α and IL-8) and chemokines (CXCL5 and CCL2) was noted during spaceflight but returned to baseline after landing. In a recent twin study, gene expression analysis revealed changes during the spaceflight of immune-related pathways involved in the differentiation and activation of T cells.[72] Astronauts have been reported to have reactivation and shedding of latent herpes viruses (herpes simplex virus 1, Epstein-Barr virus, cytomegalovirus, and varicella-zoster virus) during spaceflight.[73] It is unclear whether these findings are the result of the influence of one condition, for example, cosmic radiation, or a combination of all unique factors present during spaceflights.

Conclusion

Secondary immunodeficiencies are the result of a diverse group of factors and conditions that affect the immune response. These include the use of immunosuppressive and anti-inflammatory medications, diseases affecting anatomic barriers, HIV infection, and environmental factors. The impairment of immune function owing to any of these heterogeneous factors is variable in severity and the type of immune component affected. Knowledge of these conditions is helpful to provide the most adequate management of the patient, which would address the primary factor or condition, while providing recommendations to reduce the risk of frequent or severe infections. In addition, secondary immune dysfunction might have a role in the immunopathogenesis of autoimmunity, autoinflammation, and susceptibility to malignancy.

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