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Secondary Immunodeficiencies: Clinical Immunology for Infectious Disease Specialists

Russell M. Petrak, MD [1,*]

[1] Metro Infectious Disease Consultants, Burr Ridge, IL 60527, USA
* Corresponding author: rpetrak@midcusa.com

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Abstract: Secondary immunodeficiencies (SIDs) are acquired disorders of immune function arising from extrinsic insults to an otherwise intact immune system. Unlike primary immunodeficiencies, which are heritable, SIDs are far more prevalent, and encompass a broad spectrum of etiologies including infection, malignancy, malnutrition, metabolic disease, and iatrogenic causes. Among the latter, B cell depletion therapy has emerged as a clinically significant and increasingly utilized modality in the management of autoimmune disease, hematologic malignancy, and transplant medicine. This paper presents a structured review of secondary immunodeficiency states with particular attention to the mechanisms, clinical indications, immunological sequelae, infectious complications, and management strategies associated with B cell depletion therapy.

Keywords: immunodeficiency; infectious disease; B cell depletion

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1. Introduction

The immune system serves as the principal defense against microbial invasion and neoplastic transformation. When its functional integrity is compromised by extrinsic factors, a state of secondary immunodeficiency arises, exposing the host to heightened susceptibility to infection and other immune-related complications. Unlike congenital or primary immunodeficiencies, which result from heritable genetic defects affecting lymphocyte development or function, secondary immunodeficiencies (SIDs) develop in individuals with previously normal immune systems as a consequence of an identifiable external cause [1–3].

Secondary immunodeficiencies represent the most common form of immune impairment encountered in clinical medicine. They are encountered across virtually every medical subspecialty, from oncology and infectious disease to rheumatology, nephrology, and critical care. The range of precipitating causes is extensive, including human immunodeficiency virus (HIV) infection, protein–calorie malnutrition, hematologic malignancies, splenectomy, and a growing array of immunosuppressive therapies deployed in the treatment of autoimmune, neoplastic, and inflammatory conditions [2,4].

Of particular contemporary relevance is the class of agents that induce targeted B cell depletion. Drugs such as rituximab, ocrelizumab, and obinutuzumab have fundamentally altered the therapeutic landscape for conditions ranging from B cell lymphomas and chronic lymphocytic leukemia (CLL) to rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and multiple sclerosis (MS). While clinically effective, these agents impose a predictable and often prolonged state of humoral immunodeficiency, with implications for infectious risk, vaccine responsiveness, and long-term immune reconstitution [5,6].

This review aims to provide a systematic account of secondary immunodeficiency states, with comprehensive coverage of their major etiologic categories and a detailed examination of B cell depletion therapy as a clinically important iatrogenic cause.

2. Etiologic Categories and Pathophysiologic Mechanisms

2.1. Infection-Induced

HIV infection remains the paradigmatic infection-induced secondary immunodeficiency. The virus preferentially targets CD4+ T helper lymphocytes, the central coordinators of adaptive immune responses, by binding the CD4 receptor and co-receptors CCR5 or CXCR4. Progressive viral replication leads to depletion of the CD4+ T cell compartment, measured clinically as the absolute CD4+ count. When this count falls below 200 cells/μL, cell-mediated immunity is sufficiently compromised that the host becomes susceptible to opportunistic pathogens, organisms of low virulence that are normally controlled without difficulty by a competent immune system. This state defines the clinical syndrome of acquired immunodeficiency syndrome (AIDS) [1,2].

Beyond HIV, acute viral infections can cause transient but clinically meaningful immune suppression. Epstein–Barr virus, cytomegalovirus (CMV), and SARS-CoV2 induce lymphocyte dysfunction and can precipitate prolonged lymphopenia. Measles virus is well recognized for its capacity to impair T cell responses and induce immunological amnesia, a phenomenon in which prior antibody memory is partially erased, increasing vulnerability to secondary bacterial infections for months to years following acute illness [2].

2.2. Malnutrition

Nutritional status is intimately linked to immune competence. Protein-energy malnutrition, including kwashiorkor and marasmus, impairs lymphocyte proliferation, reduces cytokine synthesis, and diminishes complement activity. The thymus, critically dependent on adequate nutrition during development, undergoes pronounced atrophy in malnourished children, resulting in a depleted naïve T cell pool [2].

Micronutrient deficiencies compound these effects. Zinc deficiency disrupts T cell maturation and signaling, resulting in lymphopenia and impaired delayed-type hypersensitivity responses. Vitamin A is essential for the integrity of mucosal epithelial surfaces and the differentiation of T helper cell subsets. Vitamin D, functioning as a secosteroid hormone, modulates innate immune activation through effects on macrophage and dendritic cell function. Iron deficiency impairs lymphocyte proliferation and natural killer (NK) cell activity [2].

2.3. Metabolic and Endocrine Disorders

Several systemic metabolic diseases are associated with immune dysfunction. Poorly controlled diabetes mellitus impairs multiple aspects of innate immunity, including neutrophil chemotaxis, phagocytosis, and oxidative burst. Hyperglycemia also reduces complement activation and promotes glycosylation of immunoglobulins, reducing their functional efficacy. Diabetic patients are consequently at elevated risk for skin and soft tissue infections, urinary tract infections, and invasive fungal disease, particularly mucormycosis [2].

Uremia, arising from chronic kidney disease, suppresses T lymphocyte proliferation, reduces NK cell cytotoxicity, and impairs B cell antibody production. These defects contribute to the observed high infection-related mortality in dialysis populations and the suboptimal vaccine responses documented in this cohort. Hypothyroidism is associated with reduced lymphocyte proliferation and attenuated antibody responses, though immune effects are generally milder than those seen with uremia or diabetes [2].

2.4. Hematologic Malignancies

Malignancies of hematopoietic origin compromise immunity through multiple overlapping mechanisms. Multiple myeloma produces a clonal proliferation of plasma cells that suppresses the remaining normal B cell compartment, leading to hypogammaglobulinemia and impaired specific antibody synthesis. Chronic lymphocytic leukemia (CLL) is characterized by an expansion of dysfunctional, mature B cells that fail to mount adequate antibody responses, contributing to both quantitative and qualitative humoral deficiency. Hodgkin lymphoma is classically associated with impaired cell-mediated immunity, manifesting as cutaneous anergy and susceptibility to intracellular pathogens including Mycobacterium tuberculosis, fungi, and herpesviruses. Acute leukemias produce neutropenia through bone marrow infiltration and displacement of normal hematopoiesis, rendering patients acutely vulnerable to bacterial and fungal infections [4,7].

2.5. Protein and Lymphocyte Loss

Immunodeficiency may arise not only from impaired production of immune mediators but also from their accelerated loss. Nephrotic syndrome, characterized by massive proteinuria, results in urinary loss of immunoglobulins, particularly IgG, along with complement proteins and opsonins. Protein-losing enteropathy, which may accompany inflammatory bowel disease, intestinal lymphangiectasia, or cardiac disease with elevated venous pressure, leads to enteral loss of both immunoglobulins and lymphocytes, potentially producing combined humoral and cellular deficiency. Extensive burns and major trauma result in barrier disruption, massive protein catabolism, and functional lymphocyte depletion, creating a window of profound immune vulnerability in the acute post-injury period.

2.6. Splenectomy and Functional Asplenia

The spleen serves as a critical site for filtration of encapsulated bacteria from the bloodstream and for the rapid generation of T-independent antibody responses mediated by marginal zone B cells. Following splenectomy, whether surgical or functional, patients face lifelong elevated risk of overwhelming post-splenectomy infection (OPSI). OPSI is characteristically caused by encapsulated organisms including *Streptococcus pneumoniae, Haemophilus influenzae type b*, and *Neisseria meningitidis*. The risk is highest in the first two years following splenectomy but persists indefinitely, underscoring the importance of vaccination and penicillin prophylaxis [8,9].

3. Iatrogenic Immunodeficiency and B Cell Depletion Therapy

Iatrogenic immunosuppression has become one of the leading causes of secondary immunodeficiency in high-income countries. The therapeutic arsenal of immunosuppressive agents has expanded considerably over the past three decades, encompassing corticosteroids, cytotoxic chemotherapeutics, calcineurin inhibitors, mTOR inhibitors, biologic agents, and targeted B cell depletion therapies (BCDTs). While each class carries its own immunologic profile, B cell depletion therapy merits particular attention given its potent and durable effects on humoral immunity.

3.1. Overview and Rationale

B lymphocytes occupy a central role not only in antibody production but also in antigen presentation, cytokine secretion, and regulation of T cell responses. In conditions characterized by pathogenic autoantibodies or B cell clonal proliferation, targeted depletion of this lineage offers mechanistic precision unavailable with conventional broad-spectrum immunosuppression. The introduction of rituximab, a chimeric monoclonal antibody targeting the CD20 surface antigen expressed on pre-B cells, mature B cells, and certain plasma cell precursors, inaugurated this therapeutic era in the late 1990s [5,6].

CD20 was selected as the target antigen because it is expressed throughout most of B cell ontogeny but is absent on hematopoietic stem cells and terminally differentiated plasma cells. These characteristics theoretically preserve long-lived antibody-secreting cells and allow for eventual B cell reconstitution from the stem cell pool. However, in clinical practice, deep and prolonged depletion of B cell precursors and memory B cells often leads to significant, sustained humoral immunodeficiency [5].

3.2. Mechanisms of B Cell Depletion

Anti-CD20 monoclonal antibodies eliminate B cells through three principal mechanisms: antibody-dependent cellular cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC), and direct induction of apoptosis. ADCC involves engagement of Fc receptors on natural killer cells and macrophages, recruiting cytolytic effector function against antibody-coated target cells. CDC activates the classical complement cascade, leading to membrane attack complex formation and direct cell lysis. The relative contributions of these pathways differ between agents; for example, glycoengineered antibodies such as obinutuzumab demonstrate enhanced ADCC relative to rituximab, while also inducing greater direct cell death [5].

Newer agents in this class, such as ofatumumab, a fully human anti-CD20 antibody, bind a distinct epitope on the CD20 extracellular loop and demonstrate enhanced CDC relative to rituximab, potentially improving efficacy in rituximab-refractory settings. Ocrelizumab, a humanized anti-CD20 antibody, has been developed specifically for neuroimmunological indications and shares mechanistic similarity with rituximab but with reduced immunogenicity. Belimumab, targeting the B lymphocyte stimulator (BLyS/BAFF), operates through a distinct mechanism. Instead of directly depleting B cells, it deprives them of a critical survival signal, selectively reducing transitional and naïve B cell populations as well as autoreactive B cells.

3.3. Clinical Indications

B cell depletion therapy has secured regulatory approval across a wide spectrum of clinical indications. In oncology, rituximab has become the standard of care in the treatment of CD20-positive B cell non-Hodgkin lymphomas, including diffuse large B cell lymphoma and follicular lymphoma, as well as CLL and Waldenström's macroglobulinemia, both as monotherapy and in combination with cytotoxic chemotherapy regimens such as R-CHOP [5].

In rheumatology, rituximab is approved for the treatment of rheumatoid arthritis refractory to anti-TNF therapy and has demonstrated efficacy in ANCA-associated vasculitis, SLE, inflammatory myopathies, and pemphigus vulgaris, conditions in which B cells and autoantibodies drive pathogenesis. Ocrelizumab has transformed the treatment of multiple sclerosis, demonstrating superior efficacy over interferon-beta in both relapsing–remitting and primary progressive forms of the disease. In nephrology, rituximab is used in the management of membranous nephropathy, minimal change disease, and antibody-mediated rejection following renal transplantation [5].

3.4. Key Therapeutic Agents

Table 1 summarizes the major B cell depletion agents currently in clinical use.

Table 1: Major B cell-depleting agents.

Agent	Target	Mechanism	Primary Indications
Rituximab	CD20	Chimeric anti-CD20; ADCC, CDC, apoptosis	NHL, CLL, RA, ANCA vasculitis, pemphigus
Obinutuzumab	CD20	Glycoengineered; enhanced ADCC	CLL, follicular lymphoma
Ofatumumab	CD20	Fully human; enhanced CDC	CLL, relapsing MS
Ocrelizumab	CD20	Humanized; reduced immunogenicity	Relapsing & progressive MS
Belimumab	BLyS/BAFF	Reduces B cell survival signal	SLE, lupus nephritis
Blinatumomab	CD19/CD3	BiTE antibody; T cell-mediated killing	B-ALL, B cell NHL

3.5. Immunological Consequences

The immunological consequences of B cell depletion are predictable but variable in severity and duration. Following a standard course of rituximab, peripheral blood B cells are depleted to nearly undetectable levels within days to weeks. B cell reconstitution is typically slow, beginning with transitional B cells approximately six months after treatment, with naïve B cells recovering over 9–12 months. Memory B cells and marginal zone B cell equivalents recover even more slowly, often lagging by 18–24 months or longer following repeated courses [5,6].

Hypogammaglobulinemia constitutes the principal humoral sequela of BCDT. Because rituximab does not target terminally differentiated plasma cells, which lack CD20 expression, pre-existing serum immunoglobulin levels may be initially maintained by long-lived plasma cells. However, as these cells senesce without replacement from the depleted B cell pool, IgG levels progressively decline. The nadir of IgG typically occurs 4–8 months post-treatment and may persist for considerably longer, particularly in patients receiving repeated cycles or concomitant immunosuppressive therapy [5,6,10].

Secondary antibody deficiency (SAD), clinically defined as a reduction in IgG below 4 g/L in association with recurrent or severe infections, develops in an estimated 25–40% of patients receiving long-term rituximab-based regimens. Risk factors include pre-existing low IgG levels, multiple prior rituximab cycles, concomitant use of corticosteroids or other immunosuppressants, and underlying diagnoses associated with intrinsic B cell dysfunction such as CLL. An important consideration is that T cell immunity is largely preserved following anti-CD20 therapy, since T lymphocytes do not express CD20. This preservation provides partial protection against intracellular pathogens, though it does not mitigate the humoral deficiency [6,10].

3.6. Infectious Complications

The infectious risk associated with BCDT reflects the specific immunologic defect imposed. Respiratory tract infections caused by encapsulated bacteria, particularly *Streptococcus pneumoniae* and *Haemophilus influenzae*, are the most common and account for a substantial proportion of morbidity in this population. Sinopulmonary infections may become recurrent and chronic in patients with persistent SAD, mimicking the phenotype of common variable immunodeficiency [5].

Reactivation of latent viral infections represents a specific and serious concern. Hepatitis B virus (HBV) reactivation may occur in patients who are HBsAg-positive or have resolved prior HBV infection (anti-HBc-positive), potentially causing fulminant hepatitis, liver failure, and death. This risk necessitates universal serological screening prior to initiating BCDT and prophylactic antiviral therapy with entecavir or tenofovir in at-risk patients throughout and for at least 12 months following treatment [11–13].

Progressive multifocal leukoencephalopathy (PML), caused by reactivation of JC polyomavirus in the CNS, has been reported in association with rituximab. This has been noted particularly in hematology patients also receiving cytotoxic chemotherapy or corticosteroids. While rare, PML carries high morbidity and mortality, and its occurrence has reinforced the importance of careful patient selection and ongoing pharmacovigilance. The COVID-19 pandemic further highlighted the vulnerability of patients receiving anti-CD20 therapy, with multiple studies demonstrating attenuated or absent serological responses to SARS-CoV-2 vaccination in patients on ocrelizumab for MS, prompting specific guidance on vaccine timing relative to therapy cycles [14–18].

3.7. Monitoring and Clinical Management

Systematic monitoring is essential for the safe administration of BCDT. Baseline assessment should include quantitative serum immunoglobulins (IgG, IgA, IgM), lymphocyte subset enumeration by flow cytometry, hepatitis B surface antigen, hepatitis B core antibody, and HIV serology. Patients should ideally receive age-appropriate vaccinations, including pneumococcal, meningococcal, and influenza vaccines, at least four weeks prior to initiating therapy, as vaccine responses are substantially impaired during active B cell depletion [5,19].

Serial monitoring of immunoglobulin levels should be performed every three to six months during and following therapy. When IgG levels fall below 4–5 g/L in the context of recurrent infections, immunoglobulin replacement therapy is indicated. Both intravenous immunoglobulin (IVIg) and subcutaneous immunoglobulin preparations are effective. Dosing targets an IgG trough of at least 6–8 g/L in patients with active or recurrent infections [19,20].

In patients receiving concomitant corticosteroids or other immunosuppressants, prophylaxis against *Pneumocystis jirovecii* pneumonia (PCP) with trimethoprim–sulfamethoxazole (TMP-SMX) should be considered, given the additive immunosuppressive burden. For patients who are intolerant of TMP-SMX, alternatives include dapsone, atovaquone, or inhaled pentamidine. The duration of all prophylactic measures should be guided by ongoing immune reconstitution assessments rather than fixed timelines.

4. Clinical Approach to Secondary Immunodeficiency

4.1. Diagnostic Evaluation

Evaluation of a patient with suspected secondary immunodeficiency should be guided by the clinical pattern of infections, their severity, causative organisms, and the presence of an identifiable precipitating condition. Recurrent sinopulmonary infections with encapsulated bacteria suggest humoral deficiency; opportunistic infections with Pneumocystis, Toxoplasma, or Cryptococcus

implicate T cell or combined immunodeficiency; invasive fungal infections and Gram-negative bacteremia raise the possibility of neutropenia or phagocyte dysfunction.

The laboratory evaluation should be comprehensive. A complete blood count with differential quantifies circulating leukocyte populations and identifies lymphopenia or neutropenia. Quantitative serum immunoglobulins assess the humoral compartment, while functional antibody titers to pneumococcal polysaccharide antigens and tetanus toxoid distinguish quantitative from functional antibody deficiency. Flow cytometric immunophenotyping characterizes the relative abundance of T cell subsets, B cells, and NK cells. HIV serology should be obtained in any patient with unexplained cellular immunodeficiency. Complement activity and complement levels (C3, C4) are indicated when recurrent Neisseria infections or membranoproliferative nephropathy are present.

4.2. Management Principles

The cornerstone of management in secondary immunodeficiency is identification and correction of the underlying cause wherever feasible. In HIV infection, this is achieved through suppression of viral replication with antiretroviral therapy, enabling CD4+ T cell recovery and progressive immune reconstitution. In malnutrition, restoration of adequate protein and micronutrient intake reverses most immune deficits. In iatrogenic immunosuppression, dose reduction or discontinuation of the offending agent, when clinically permissible, may allow for immune recovery [2,19].

Where the underlying cause cannot be corrected, management focuses on reducing infectious risk through antimicrobial prophylaxis, immunoglobulin replacement, and immunization. The specific prophylactic regimen is dictated by the predominant immune defect: antibiotics targeting encapsulated bacteria for hypogammaglobulinemia, antifungal prophylaxis for prolonged neutropenia, antiviral agents for high-risk cellular immunodeficiency, and PCP prophylaxis when the CD4 count falls below 200 cells/μL or in the setting of significant combined immunosuppression. Live-attenuated vaccines are generally contraindicated during active immunosuppression due to the risk of vaccine-strain infection; inactivated vaccines are safe but may elicit suboptimal responses [19].

5. Summary of Immune Defects by Etiology

Table 2 summarizes the principal immune defects and associated pathogen vulnerabilities across the major categories of secondary immunodeficiency.

Table 2: Principal immune defects and associated pathogen vulnerabilities.

Category	Primary Immune Defect	Key Susceptible Pathogens
HIV/AIDS	CD4+ T cell depletion	PCP, Toxoplasma, MAC, CMV, Cryptococcus, TB
B cell depletion therapy	B cell loss, hypogammaglobulinemia	Encapsulated bacteria, HBV, JC virus, COVID-19
Chemotherapy-induced neutropenia	Phagocyte deficiency	Gram-negatives, Staphylococcus, Candida, Aspergillus
Splenectomy/functional asplenia	Marginal zone B cells, filtration	*S. pneumoniae*, *H. influenzae*, *N. meningitidis*

Table 2: *Cont.*

Category	Primary Immune Defect	Key Susceptible Pathogens
Protein–energy malnutrition	Global (T cells predominantly)	TB, measles complications, gastrointestinal pathogens
Myeloma/CLL	Antibody quantity and quality	Encapsulated bacteria, enteroviruses
Nephrotic syndrome	Immunoglobulin and complement loss	Encapsulated bacteria, Gram-negatives
Uremia (CKD)	T cell signaling, antibody production	Staphylococcus, Gram-negatives, HBV

6. Conclusion

Secondary immunodeficiencies represent a clinically diverse and highly prevalent group of acquired immune disorders with significant implications for morbidity, mortality, and quality of life. Their increasing recognition in clinical medicine reflects both the growing sophistication of immune assessment and the expanding use of immunomodulatory therapies that constitute an important iatrogenic cause.

B cell depletion therapy exemplifies the double-edged nature of immunologically targeted treatment: delivering meaningful clinical benefit in malignancy and autoimmunity while imposing predictable and often prolonged humoral immunodeficiency. A thorough understanding of the mechanisms, consequences, and management of B cell depletion-associated immunodeficiency is essential for clinicians across oncology, rheumatology, neurology, and infectious disease.

As the therapeutic landscape continues to evolve, with novel agents targeting additional B cell antigens, survival signals, and migratory pathways entering clinical use, the need for structured immune monitoring protocols, evidence-based prophylactic strategies, and individualized risk assessment will only grow. Proactive identification of patients at risk for secondary immunodeficiency, coupled with timely intervention, represents a critical opportunity to reduce preventable infectious morbidity in this vulnerable population.

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