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Understanding Primary and Secondary Immunodeficiency: Mechanisms, Diagnosis, and Management

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Abstract

Immunodeficiencies are a group of disorders characterized by an impaired immune response, leading to increased susceptibility to infections. These conditions are categorized into two main types: primary and secondary immunodeficiency. Primary immunodeficiencies (PIDs) are typically genetic in origin and result from defects in the immune system's development or function, manifesting from infancy. These disorders are diverse, affecting components such as B-cells, T-cells, phagocytes, and the complement system, often requiring lifelong management through therapies like immunoglobulin replacement and stem cell transplantation. Secondary immunodeficiencies (SIDs) arise as a consequence of external factors, such as infections, malnutrition, or immunosuppressive treatments. The most notable example of secondary immunodeficiency is acquired immunodeficiency syndrome (AIDS), caused by HIV infection, which specifically targets CD4⁺ T-cells, leading to immune suppression. Other causes of SID include cancer treatments and chronic conditions like diabetes. Management of SIDs involves addressing the underlying cause, such as antiretroviral therapy for HIV or nutritional support for malnutrition-induced immunodeficiency.

Keywords: Primary Immunodeficiency, Secondary Immunodeficiency, Immune Dysfunction, Diagnosis, Treatment Strategies

Introduction

Immunodeficiency disorders represent a critical aspect of immunology, as they involve conditions where the immune system is either underactive or dysfunctional, leading to increased susceptibility to infections and certain malignancies. These disorders can be broadly categorized into two main groups: primary immunodeficiencies (PIDs) and secondary immunodeficiencies (SIDs). Primary immunodeficiencies are usually inherited genetic disorders that result in intrinsic immune system defects. In contrast, secondary immunodeficiencies occur as a consequence of external factors, such as infections, medications, or malnutrition, which impair the immune system's ability to respond to pathogens effectively. The understanding of both categories has advanced significantly in recent years, providing clinicians with improved diagnostic tools and therapeutic strategies.¹⁻² Primary immunodeficiencies (PIDs), also known as inborn errors of immunity, are a group of disorders caused by genetic mutations that affect various components of the immune system, including B-cells, T-cells, phagocytes, and the complement system. These defects often lead to an inadequate immune response, leaving individuals vulnerable to recurrent and severe infections. The majority of PIDs are inherited in an autosomal recessive or X-linked pattern, and their clinical presentation can range from mild to life-threatening. As these disorders often present in infancy or early childhood, early diagnosis and intervention are critical to prevent complications and

improve the quality of life for affected individuals.³⁻⁴

Secondary immunodeficiencies (SIDs), on the other hand, arise from external factors that cause immune dysfunction. Unlike PIDs, SIDs are not genetic in origin and are typically acquired later in life. The most well-known example of secondary immunodeficiency is acquired immunodeficiency syndrome (AIDS), caused by the human immunodeficiency virus (HIV). HIV targets CD4⁺ T-cells, leading to a gradual decline in immune function and increased susceptibility to opportunistic infections and cancers. Other common causes of SIDs include chemotherapy, which suppresses bone marrow function, as well as malnutrition, which can lead to deficiencies in key immune components. The ability to diagnose and manage SIDs relies on identifying the underlying cause and providing appropriate interventions to restore immune function.⁵ The pathophysiology of primary immunodeficiencies varies depending on the specific genetic defect. For example, defects in B-cells result in impaired antibody production, leading to recurrent bacterial infections, while T-cell deficiencies, such as in severe combined immunodeficiency (SCID), compromise both humoral and cellular immunity, leading to a broad range of infections. Additionally, phagocytic defects, such as in chronic granulomatous disease, result in impaired clearance of certain pathogens, particularly those that require phagocytic activity. Complement deficiencies, on the other hand, can lead to increased

susceptibility to infections by impairing the ability of the immune system to recognize and clear pathogens.⁶⁻⁷ In secondary immunodeficiencies, the immune system is typically functional but is impaired by external factors. HIV infection is a prime example, where the virus selectively infects and destroys CD4+ T-cells, leading to progressive immune suppression. Malnutrition-induced immunodeficiency, commonly observed in developing countries, leads to deficiencies in key nutrients such as proteins, vitamins, and minerals, all of which are essential for normal immune function. Immunosuppressive drugs, such as corticosteroids and chemotherapy agents, also cause immune suppression by inhibiting the function of immune cells or by directly affecting the production of immune cells in the bone marrow. Identifying and managing the underlying cause of SID is essential to preventing further immune dysfunction and improving patient outcomes.⁸⁻⁹

Diagnosis of both primary and secondary immunodeficiencies requires a comprehensive approach, including clinical evaluation, family history, and laboratory tests. In PIDs, molecular genetic testing plays a crucial role in identifying specific mutations that cause immune dysfunction. Flow cytometry and immunoglobulin levels are commonly used to assess immune function, and targeted testing for specific defects in T-cell, B-cell, or phagocytic function helps confirm the diagnosis. In cases of secondary immunodeficiencies, the diagnosis focuses on identifying the underlying cause, such

as HIV testing, imaging studies for malignancies, or nutritional assessments for malnutrition-related immunodeficiency.¹⁰ The treatment of primary immunodeficiencies varies depending on the specific condition and the immune system components affected. For instance, individuals with B-cell deficiencies often benefit from immunoglobulin replacement therapy to restore their ability to fight infections. In cases of T-cell deficiencies, hematopoietic stem cell transplantation may offer the possibility of a cure, particularly when performed early in life. Gene therapy, though still experimental, holds promise for treating certain genetic defects by correcting the underlying mutations. Long-term management strategies for PIDs typically involve prophylactic antibiotics, immunoglobulin therapy, and vaccinations to reduce the risk of infections.¹¹ Secondary immunodeficiencies are managed by addressing the underlying cause of the immune dysfunction. For example, in HIV/AIDS, the primary treatment involves antiretroviral therapy (ART), which works to suppress the virus and restore immune function. In cases of drug-induced immunodeficiency, adjusting or discontinuing the offending medications may help restore immune activity. Malnutrition-induced immunodeficiency is treated through nutritional support, including the administration of vitamins, minerals, and proteins, to enhance immune function. Treatment of secondary immunodeficiencies often involves a combination of therapies aimed at both managing the immune deficiency and treating the underlying condition.¹²

Both primary and secondary immunodeficiencies present unique challenges for healthcare providers. Primary immunodeficiencies are often diagnosed in infancy or early childhood, requiring long-term management and vigilance to prevent infections and complications.

Secondary immunodeficiencies, while often acquired later in life, can also result in significant morbidity and mortality if not properly managed. The rapid advances in diagnostic technologies, such as next-generation sequencing and immunophenotyping, have improved the early detection of both types of immunodeficiency, allowing for more timely interventions. Furthermore, ongoing research into immunotherapy, gene therapy, and stem cell transplantation offers hope for improved treatment options in the future.¹³ The global burden of immunodeficiencies, both primary and secondary, continues to be significant, particularly in low- and middle-income countries where access to healthcare and resources may be limited. In resource-limited settings, secondary immunodeficiencies due to malnutrition, HIV, and infections pose a considerable challenge to public health systems. Early detection, proper diagnosis, and appropriate treatment are essential to improving patient outcomes and reducing the global burden of immune dysfunction. Strengthening healthcare infrastructure, increasing awareness, and improving access to diagnostic and therapeutic interventions are key to addressing the growing impact of immunodeficiencies worldwide.¹⁴ Ultimately, the management

of immunodeficiencies requires a multidisciplinary approach, involving immunologists, geneticists, infectious disease specialists, and other healthcare professionals. As research continues to uncover the genetic and molecular underpinnings of these disorders, the potential for personalized medicine and targeted therapies offers new hope for individuals living with immunodeficiencies. Continued collaboration between researchers, clinicians, and healthcare providers will be essential in improving the lives of those affected by these challenging and often life-threatening conditions.¹⁴

Aim

The aim of this review is to provide a comprehensive comparison between primary and secondary immunodeficiencies, highlighting the distinct causes, clinical manifestations, diagnostic approaches, treatment options, and management strategies for each.

Review Methods

Literature Search Strategy

A comprehensive search of electronic databases was conducted to gather relevant articles on primary and secondary immunodeficiencies. Databases such as PubMed, Google Scholar, Scopus, and Web of Science were used to ensure a broad and inclusive selection of articles. The search terms included "primary immunodeficiencies," "secondary immunodeficiencies," "immune system

dysfunction," "diagnosis," "treatment strategies," and "management." The search was limited to English-language articles published in peer-reviewed journals, with no restrictions on publication date to ensure an up-to-date and wide-ranging understanding of the topic.

Inclusion and Exclusion Criteria

Articles were selected based on the following inclusion criteria:

- Original research, systematic reviews, meta-analyses, and clinical guidelines.
- Studies focused on the pathophysiology, diagnosis, treatment, and management of primary and secondary immunodeficiencies.
- Clinical and epidemiological studies from diverse populations to capture global perspectives.

Articles were excluded if they:

- Focused on unrelated immune disorders or did not specifically discuss immunodeficiencies.
- Were not available in full text or lacked sufficient methodological rigor.
- Were published in languages other than English.

Primary Immunodeficiency Disorders (PIDs)

Primary Immunodeficiency Disorders (PIDs) refer to a group of rare, genetically

inherited disorders that result from defects in one or more components of the immune system, leading to an increased susceptibility to infections, autoimmune diseases, and certain cancers. These disorders are typically congenital and manifest early in life, though some may remain undiagnosed until adulthood. PIDs are caused by mutations in genes that control immune system function, and their severity can range from mild, with recurrent infections, to severe, potentially life-threatening conditions that require aggressive treatments.¹⁵ The World Health Organization (WHO) estimates that over 400 types of PIDs exist, with different genetic causes, clinical manifestations, and treatment options.¹⁶

Classification of Primary Immunodeficiencies

PIDs are classified based on the immune system components that are affected. The major categories include:

1. B-Cell Deficiencies (Humoral Immunodeficiencies):

B-cells are responsible for producing antibodies that neutralize pathogens. When B-cell function is impaired, individuals are vulnerable to recurrent bacterial infections, particularly those caused by encapsulated organisms (e.g., *Streptococcus pneumoniae*, *Haemophilus influenzae*). The most common example of B-cell deficiency is **X-linked agammaglobulinemia (XLA)**, caused by mutations in the Bruton's tyrosine

kinase (BTK) gene, leading to an absence of mature B-cells and low antibody levels. Treatment typically involves regular immunoglobulin replacement therapy to provide antibodies and prevent infections.¹⁷

2. **T-Cell Deficiencies (Cellular Immunodeficiencies):**

T-cells play a critical role in controlling viral infections and coordinating immune responses. When T-cell function is impaired, individuals may experience a broad range of infections, including viral, fungal, and opportunistic infections. Severe Combined Immunodeficiency (SCID) is one of the most severe T-cell disorders, characterized by both T-cell and B-cell dysfunction. SCID is often caused by mutations in genes like **IL2RG**, leading to a lack of functional T-cells and defective antibody production. Bone marrow or stem cell transplantation is typically the treatment of choice for SCID, aiming to restore immune function.¹⁸

3. **Phagocytic Cell Deficiencies:**

Phagocytes, such as neutrophils and macrophages, are responsible for engulfing and killing microorganisms. Defects in phagocytes impair the body's ability to clear certain pathogens, leading to chronic infections. Chronic Granulomatous Disease (CGD) is a notable example, caused by mutations in genes encoding components of the NADPH oxidase complex, leading to impaired bacterial killing by neutrophils. Individuals with CGD are

at risk of infections from fungi and catalase-positive bacteria, and management typically involves prophylactic antibiotics and interferon-gamma therapy to boost immune function.¹⁹

4. **Complement System Deficiencies:**

The complement system is a group of proteins that work together to enhance immune responses by marking pathogens for destruction, promoting inflammation, and enhancing phagocytosis. Defects in any of the complement proteins can lead to increased susceptibility to infections, particularly those caused by bacteria. C3 deficiency, for instance, can result in a higher incidence of infections caused by *Streptococcus pneumoniae* and *Neisseria meningitidis*. Complement deficiencies may also predispose individuals to autoimmune diseases due to the failure to remove immune complexes. Treatment may include antibiotics and, in some cases, complement protein replacement.²⁰

5. **Combined Immunodeficiencies:**

Some PIDs involve defects in both humoral and cellular immunity, leading to more complex immunodeficiencies. Wiskott-Aldrich Syndrome (WAS), for example, is a combined immunodeficiency characterized by eczema, thrombocytopenia, and increased susceptibility to infections. WAS is caused by mutations in the **WAS** gene, leading to dysfunctional T-cells and impaired B-cell activation. Affected individuals often require

hematopoietic stem cell transplantation as a definitive treatment.²¹

Clinical Manifestations of Primary Immunodeficiencies

The clinical manifestations of PIDs are diverse and depend on the specific immune components affected. The hallmark feature of PIDs is an increased susceptibility to infections, which may be recurrent, unusual, or severe. These infections can involve the respiratory tract, gastrointestinal system, skin, and other body organs.²²

- **Recurrent Bacterial Infections:** Common in patients with B-cell deficiencies, such as XLA. Infections are often seen in the sinuses, ears, and lungs.²³
- **Fungal Infections:** More frequent in individuals with T-cell deficiencies like SCID, as T-cells are responsible for controlling fungal pathogens.²⁴
- **Opportunistic Infections:** Individuals with severe PIDs, such as SCID or combined immunodeficiencies, are vulnerable to infections caused by organisms that do not usually pose a threat to healthy individuals, such as *Pneumocystis jirovecii* (a fungal infection) and cytomegalovirus (CMV).²⁵
- **Autoimmune Disorders:** Some individuals with PIDs, especially those with complement deficiencies, may develop autoimmune diseases such as systemic lupus erythematosus

(SLE), due to the failure of immune regulation.

Diagnosis of Primary Immunodeficiencies

Early diagnosis of PIDs is essential for managing and treating the disorders effectively. Diagnostic approaches for PIDs typically include:

1. **Clinical Assessment:** A detailed medical history and family history are crucial in identifying possible signs of immune dysfunction, such as frequent infections, poor growth, or a family history of similar conditions.
2. **Laboratory Tests:** Immunoglobulin levels, complete blood count (CBC), and flow cytometry are used to assess immune cell populations. Genetic testing and sequencing can confirm the presence of mutations associated with specific PIDs.²⁶
3. **Functional Assays:** Tests that assess the functionality of immune cells, such as delayed hypersensitivity skin testing or tests for phagocytic function, can aid in the diagnosis of specific defects in immune response.

Treatment and Management

The treatment of PIDs is primarily focused on preventing infections and managing the specific immunodeficiency. For most B-cell deficiencies, immunoglobulin replacement therapy (IVIG or subcutaneous immunoglobulin) is the cornerstone of treatment, providing passive immunity to prevent recurrent infections. In cases of T-cell deficiencies like

SCID, hematopoietic stem cell transplantation (HSCT) is often the only curative option, with gene therapy being explored as a potential treatment. Prophylactic antibiotics, antifungal agents, and vaccinations are used to prevent infections, while newer approaches like enzyme replacement therapy and gene editing offer promising alternatives for certain disorders.²⁷

Secondary Immunodeficiency Disorders

Secondary Immunodeficiency Disorders (SIDs) are acquired conditions where the immune system is impaired due to external factors or underlying diseases, unlike primary immunodeficiencies, which are congenital. These disorders result from various factors such as infections, malnutrition, immunosuppressive therapies, and certain chronic diseases that compromise the immune response. Secondary immunodeficiencies are more common than primary immunodeficiencies and are often reversible once the underlying cause is addressed. However, the impact on the immune system can vary, and the severity of secondary immunodeficiencies can range from mild to life-threatening.²⁸

Causes of Secondary Immunodeficiencies

The most common causes of secondary immunodeficiency include:

1. **Human Immunodeficiency Virus (HIV) Infection:** HIV is one of the most well-known causes of secondary immunodeficiency. The virus attacks

CD4+ T-cells, leading to a gradual depletion of these critical immune cells and impairing both humoral and cellular immune responses. As HIV progresses to acquired immunodeficiency syndrome (AIDS), patients become highly susceptible to opportunistic infections, malignancies, and other complications due to a weakened immune system. Antiretroviral therapy (ART) has revolutionized the treatment of HIV/AIDS, allowing individuals to live longer and manage infections more effectively.²⁹⁻³¹

2. **Malnutrition:** Malnutrition, particularly deficiencies in protein, vitamins, and minerals, can lead to a weakened immune system. Protein-calorie malnutrition and deficiencies in vitamins like A, C, D, and E, as well as zinc, are known to impair immune function. The lack of adequate nutrients affects the production and function of immune cells such as T-cells, B-cells, and phagocytes. Malnourished individuals are more vulnerable to infections and often experience more severe outcomes from illnesses. Addressing nutritional deficiencies through dietary interventions can restore immune function over time.³²
3. **Immunosuppressive Therapy:** Immunosuppressive drugs, which are commonly used to treat autoimmune diseases, organ transplant recipients, and some cancers, can lead to secondary immunodeficiency. These

medications, such as corticosteroids, calcineurin inhibitors (e.g., cyclosporine), and biologic agents, suppress various aspects of the immune response to prevent rejection or manage chronic inflammation. While effective for their intended purposes, these therapies increase susceptibility to infections, especially bacterial, fungal, and viral infections. Long-term immunosuppressive therapy requires careful monitoring and may necessitate the use of prophylactic antibiotics or antifungal treatments.³³

4. **Cancer and Chemotherapy:** Certain cancers, particularly hematologic malignancies (e.g., leukemia, lymphoma), can lead to secondary immunodeficiency by affecting the bone marrow and lymphoid tissues, where immune cells are produced. Moreover, chemotherapy and radiation therapies used to treat cancer can damage the bone marrow, resulting in reduced production of immune cells and an increased risk of infections. The immunosuppressive effects of these therapies are often temporary, with immune function typically recovering after treatment, although this can vary depending on the type and intensity of the therapy.³⁴

5. **Chronic Diseases:** Chronic diseases such as diabetes, chronic kidney disease, and liver cirrhosis can lead to secondary immunodeficiency by disrupting the normal functioning of the immune system. In diabetes, for instance, high blood sugar levels

impair the function of neutrophils and other immune cells, making individuals more susceptible to infections. In kidney and liver diseases, impaired organ function can lead to an altered immune response and an increased risk of infection. Managing these underlying diseases and optimizing control of conditions like diabetes can help mitigate their impact on immune function.³⁵

6. **Autoimmune Disorders:** Autoimmune diseases, in which the body's immune system attacks its own tissues, can also lead to secondary immunodeficiencies. In conditions like systemic lupus erythematosus (SLE) or rheumatoid arthritis (RA), the immune system is dysregulated, and the chronic inflammation associated with these diseases can impair normal immune responses. Additionally, medications used to manage autoimmune diseases, such as immunosuppressive drugs, can contribute to immunodeficiency. Treatment of autoimmune diseases typically involves a balance between controlling disease activity and minimizing the impact of immunosuppressive therapy on the immune system.³⁶

7. **Splenectomy:** The spleen plays a vital role in filtering blood and managing immune responses, particularly against bacterial infections. Removal of the spleen (splenectomy), either due to trauma, disease, or as part of medical treatment, can lead to a significant

increase in susceptibility to certain infections, especially those caused by encapsulated bacteria like *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Neisseria meningitidis*. After splenectomy, individuals may need vaccinations and prophylactic antibiotics to prevent infection.³⁷

Clinical Manifestations of Secondary Immunodeficiency

Secondary immunodeficiencies present a wide range of clinical manifestations, primarily dependent on the underlying cause and the severity of the immune impairment.³⁸ Common features include:

1. **Increased Susceptibility to Infections:** Individuals with secondary immunodeficiencies are at increased risk of recurrent or prolonged infections, including respiratory tract infections, urinary tract infections, skin infections, and gastrointestinal infections. Opportunistic infections are common in severe cases, such as those associated with HIV/AIDS, cancer treatments, or organ transplantation.³⁹
2. **Delayed Recovery from Infections:** In some cases, individuals with secondary immunodeficiencies may experience prolonged or delayed recovery from infections due to impaired immune function. This can result in more severe infections and increased morbidity.⁴⁰

3. **Autoimmune Complications:** In some cases, secondary immunodeficiency may exacerbate underlying autoimmune diseases or lead to the development of new autoimmune symptoms due to the dysregulation of the immune response.⁴¹

4. **Cancer Risk:** Chronic immunosuppression, such as that caused by HIV or immunosuppressive therapies, can increase the risk of certain types of cancer, particularly lymphomas, Kaposi's sarcoma, and other malignancies. These cancers are more common in individuals with a weakened immune system.⁴²

Diagnosis of Secondary Immunodeficiency

Diagnosing secondary immunodeficiency involves a comprehensive assessment of the patient's medical history, underlying conditions, medications, and clinical symptoms. The following approaches are commonly used:

1. **Clinical Evaluation:** A thorough history and physical examination can help identify potential causes of secondary immunodeficiency, such as chronic diseases, infections, or immunosuppressive therapies.⁴³
2. **Laboratory Tests:** Blood tests can evaluate immune cell counts (e.g., T-cells, B-cells, neutrophils) and assess the function of the immune system. Tests for HIV, hepatitis, and other infectious agents may also be conducted.
3. **Genetic Testing:** In some cases, genetic testing may be useful to

assess susceptibility to certain conditions that can lead to immunodeficiency, such as autoimmune diseases or inherited immunodeficiencies.⁴³

4. **Immunoglobulin Levels:** Measurement of immunoglobulin levels can help assess humoral immunity, particularly in cases of suspected immunosuppressive therapy or chronic disease-induced immune impairment.

Treatment and Management

The management of secondary immunodeficiency largely depends on addressing the underlying cause and restoring immune function as much as possible. Approaches include:

1. **Antiretroviral Therapy (ART):** For individuals with HIV/AIDS, ART is critical in suppressing the virus and preventing further damage to the immune system. Successful ART can lead to a significant improvement in immune function and a reduction in opportunistic infections.
2. **Nutritional Support:** In cases of malnutrition, appropriate dietary interventions and supplementation of essential vitamins and minerals can help restore immune function and reduce susceptibility to infections.
3. **Immunosuppressive Adjustment:** For patients receiving immunosuppressive therapies, adjustments to medication regimens or the addition of prophylactic

treatments may be necessary to reduce the risk of infections without compromising the effectiveness of treatment for underlying conditions.

4. **Vaccination and Prophylactic Antibiotics:** Individuals with secondary immunodeficiencies may benefit from vaccinations to prevent infections and the use of prophylactic antibiotics, especially in cases like splenectomy or post-transplantation.
5. **Cancer Treatment:** For patients with cancer, appropriate cancer therapies (e.g., chemotherapy, radiotherapy, stem cell transplantation) are essential for treating the underlying malignancy. Post-treatment recovery often involves supporting the immune system to restore its function.⁴⁴

Comparison between Primary and Secondary Immunodeficiencies

Immunodeficiency disorders, both primary and secondary, impair the immune system's ability to defend the body against infections, malignancies, and other diseases. While they share some common clinical outcomes, the underlying causes, presentation, and management strategies differ significantly. The comparison between primary and secondary immunodeficiencies can be structured across various dimensions such as etiology, age of onset, clinical presentation, diagnosis, and treatment approaches.

1. Etiology and Cause

- **Primary Immunodeficiencies (PIDs):**

Primary immunodeficiencies are typically inherited disorders caused by genetic mutations that affect the development or function of the immune system. These genetic mutations can be present at birth, affecting various components of the immune system, including T-cells, B-cells, phagocytes, and complement proteins. PIDs are often classified based on the specific immune component affected. Examples include severe combined immunodeficiency (SCID), X-linked agammaglobulinemia (XLA), and chronic granulomatous disease (CGD).⁴⁵

- **Secondary Immunodeficiencies (SIDs):**

Secondary immunodeficiencies are acquired conditions resulting from external factors or underlying diseases that impair immune function. These factors can include infections (e.g., HIV), malnutrition, certain chronic diseases (e.g., diabetes), cancer treatments (e.g., chemotherapy), immunosuppressive medications, and trauma (e.g., splenectomy). SIDs are not inherited and develop as a consequence of environmental or pathological causes.⁴⁶

2. Age of Onset

- **Primary Immunodeficiencies (PIDs):**

PIDs are often diagnosed in childhood because they are

congenital. Some PIDs may manifest in the first few months of life, while others might not present until later in childhood or even adulthood. However, the majority are recognized during infancy and early childhood due to recurrent infections or failure to thrive.⁴⁵

- **Secondary Immunodeficiencies (SIDs):**

SIDs can develop at any age and typically arise later in life. These disorders are not congenital, so their onset is linked to the development of underlying conditions or external factors, such as infections (e.g., HIV), chemotherapy, or organ transplantation. The onset of secondary immunodeficiency often occurs after significant immune system disruption.⁴⁶

3. Clinical Presentation

- **Primary Immunodeficiencies (PIDs):**

The clinical features of PIDs often include recurrent infections, especially those caused by opportunistic pathogens that do not typically affect immunocompetent individuals. Common infections include respiratory tract infections, ear infections, gastrointestinal infections, and fungal or viral infections. In some PIDs, there is a higher susceptibility to certain cancers, autoimmune diseases, and chronic inflammation. Symptoms may also include failure to thrive, delayed development, or unexplained growth issues.⁴⁵

- **Secondary Immunodeficiencies (SIDs):** Individuals with secondary immunodeficiencies also experience increased susceptibility to infections. However, the types of infections may vary depending on the underlying cause. For example, HIV-infected individuals are particularly susceptible to opportunistic infections, while those undergoing chemotherapy may have a higher risk of bacterial infections due to neutropenia. Symptoms of secondary immunodeficiencies are closely related to the underlying condition, such as the presence of infections or complications related to organ transplant rejection, cancer treatment, or malnutrition.⁴⁶

4. Diagnosis

- **Primary Immunodeficiencies (PIDs):** Diagnosis of PIDs typically involves genetic testing, immune function tests, and clinical assessment. Blood tests to measure levels of immunoglobulins, T-cell counts, and specific enzyme activity are commonly used to identify the type of primary immunodeficiency. Genetic sequencing can confirm the presence of mutations known to cause these disorders. Early diagnosis is essential, as timely intervention can prevent severe infections and other complications.⁴⁵
- **Secondary Immunodeficiencies (SIDs):** Diagnosing secondary immunodeficiencies focuses on identifying the underlying cause of

immune dysfunction. This includes medical history assessment (e.g., HIV infection, immunosuppressive therapy), laboratory tests (e.g., CD4 counts in HIV, kidney function in chronic disease), and imaging or biopsy when needed (e.g., in cases of cancer). Diagnosis often requires understanding the patient's exposure to risk factors that may have triggered the secondary immunodeficiency.⁴⁶

5. Treatment

- **Primary Immunodeficiencies (PIDs):** Treatment of PIDs depends on the type and severity of the condition. In many cases, the goal is to restore immune function. This can involve regular immunoglobulin replacement therapy, stem cell or bone marrow transplantation, gene therapy (in specific disorders), or enzyme replacement therapy. Infections are treated with antibiotics, antivirals, and antifungals, with careful consideration given to the patient's specific immunodeficiency.⁴⁵
- **Secondary Immunodeficiencies (SIDs):** The management of secondary immunodeficiencies largely focuses on addressing the underlying cause. For example, in HIV-infected individuals, antiretroviral therapy (ART) is essential to control viral replication and restore immune function. In individuals with cancer-related immunodeficiency, chemotherapy adjustments,

prophylactic antibiotics, and stem cell transplants may be considered. Nutritional support is vital in cases of malnutrition, and immunosuppressive drugs may need to be adjusted in autoimmune disease treatments to balance immune function.⁴⁶

6. Prognosis

- **Primary Immunodeficiencies (PIDs):** The prognosis for individuals with PIDs can vary widely depending on the type and severity of the disorder. Early diagnosis and appropriate treatment significantly improve outcomes and quality of life. However, some severe forms, such as SCID, can be life-threatening without intervention, while milder forms allow for a near-normal life expectancy with proper management.⁴⁵
- **Secondary Immunodeficiencies (SIDs):** The prognosis of secondary immunodeficiencies is heavily dependent on the underlying cause. If the cause is reversible, such as correcting nutritional deficiencies or halting immunosuppressive therapy, immune function can recover over time. In cases where the cause is chronic or progressive (e.g., HIV or cancer treatment), the immune system may not fully recover, and ongoing management will be necessary to mitigate risks and complications.⁴⁶

7. Reversibility

- **Primary Immunodeficiencies (PIDs):** Primary immunodeficiencies are not reversible, as they are caused by genetic mutations. Treatment aims to manage symptoms, prevent infections, and restore immune function as much as possible. However, the genetic basis of the disorder persists throughout the individual's life.⁴⁵
- **Secondary Immunodeficiencies (SIDs):** Secondary immunodeficiencies can often be reversed or managed if the underlying cause is addressed. For instance, HIV-positive individuals can improve immune function with ART, and patients who receive adequate nutrition may experience a recovery of immune capacity. Reversal is typically possible if the cause is transient, such as following chemotherapy or immunosuppressive therapy adjustments.⁴⁶

8. Prevention

- **Primary Immunodeficiencies (PIDs):** Prevention of primary immunodeficiencies is not possible because they are genetic in nature. Early diagnosis and regular medical surveillance are critical to managing these conditions. Family screening and genetic counseling may also help identify potential risks for offspring.
- **Secondary Immunodeficiencies (SIDs):** Prevention of secondary immunodeficiencies involves

reducing exposure to risk factors. For example, preventing HIV transmission through safe sex practices, using prophylactic treatments for transplant patients, ensuring proper nutrition, and minimizing unnecessary immunosuppressive therapies can reduce the risk of developing secondary immunodeficiencies.⁴⁶

9. Epidemiology

- **Primary Immunodeficiencies (PIDs):** PIDs are relatively rare, with an estimated prevalence of 1 in 1,200 to 1 in 5,000 live births. However, these disorders are often underdiagnosed, and the true prevalence may be higher. Due to their genetic nature, they can affect individuals across all populations and geographical regions.⁴⁵
- **Secondary Immunodeficiencies (SIDs):** SIDs are far more common than primary immunodeficiencies due to the wide variety of external factors that can cause them. These disorders are seen globally and often correlate with prevalent conditions such as HIV/AIDS, malnutrition, cancer, and immunosuppressive drug use.

10. Impact on Public Health

- **Primary Immunodeficiencies (PIDs):** While PIDs are relatively rare, their impact on public health can be significant, particularly in terms of healthcare costs and the need for

long-term care. Effective management has led to improved survival rates, but challenges remain in terms of early diagnosis and access to specialized care.⁴⁵

- **Secondary Immunodeficiencies (SIDs):** Secondary immunodeficiencies pose a broader public health challenge due to their higher prevalence and association with common global health issues like HIV, malnutrition, and chronic diseases. Addressing these factors through preventive health measures and interventions can reduce the burden of secondary immunodeficiencies.⁴⁶

New Insights into Immunodeficiency

The field of immunodeficiency research is evolving rapidly, bringing forth new insights that challenge conventional understanding and open doors to innovative treatment strategies. Once viewed simply as conditions of heightened infection susceptibility, both primary and secondary immunodeficiencies are now recognized as complex disorders with far-reaching implications, including links to autoimmunity, cancer, inflammation, and even neurological dysfunction. One of the most groundbreaking discoveries in recent years is the realization that immune dysfunction in immunodeficiency disorders is not merely a failure of defense but often an imbalance in immune regulation. For example, patients with Common Variable Immunodeficiency (CVID), once thought to suffer only from defective antibody production, are now known to have

dysregulated T-cell responses and a predisposition to autoimmune diseases such as inflammatory bowel disease and rheumatoid arthritis. This insight has shifted treatment paradigms, leading to the increasing use of immunomodulatory therapies alongside traditional immunoglobulin replacement.⁴⁷ Similarly, the perception of HIV/AIDS has undergone a transformation. While antiretroviral therapy (ART) has been a game-changer in controlling viral replication, recent studies suggest that persistent immune activation and inflammation remain major obstacles to full immune recovery. Even in virally suppressed patients, immune exhaustion markers—such as PD-1 expression on T-cells and heightened levels of pro-inflammatory cytokines—indicate ongoing immune dysfunction. These findings have fueled research into immune checkpoint inhibitors and therapeutic vaccines, which may offer pathways toward functional HIV cures.⁴⁸

Beyond classical immune deficiencies, new insights are emerging into the role of the gut microbiome in shaping immune health. Evidence now suggests that dysbiosis (an imbalance in gut microbial composition) plays a crucial role in immunodeficiency-related complications, influencing everything from susceptibility to infections to chronic inflammation. This revelation has sparked interest in microbiome-targeted therapies, including probiotics, prebiotics, and fecal microbiota transplantation (FMT), as potential adjunctive treatments for immunodeficient individuals.⁴⁹ Another exciting development is the expansion of gene-

editing technologies in treating inherited immunodeficiencies. Traditional hematopoietic stem cell transplantation (HSCT) has long been the gold standard for conditions like Severe Combined Immunodeficiency (SCID), but risks such as graft-versus-host disease and donor availability issues have posed significant challenges. The advent of CRISPR/Cas9 and other gene-editing platforms is now paving the way for autologous stem cell correction, allowing patients to receive genetically repaired versions of their own cells. Early clinical trials in X-linked SCID and Chronic Granulomatous Disease (CGD) have shown promising results, hinting at a future where genetic immunodeficiencies are permanently cured rather than managed.⁵⁰ Additionally, the recognition of novel immunodeficiency syndromes has expanded significantly due to advancements in next-generation sequencing (NGS). Previously unclassified immune disorders are now being identified as distinct clinical entities, many of which are caused by single-gene mutations affecting immune signaling pathways. This molecular-level understanding has led to the development of precision medicine approaches, where targeted small-molecule inhibitors or monoclonal antibodies can be used to correct specific immune dysfunctions.⁵⁰ One of the most unexpected areas of recent insight has been the neurological implications of immunodeficiency. Increasing evidence suggests that immune dysregulation in conditions like CVID, HIV, and even congenital immunodeficiencies may contribute to neuroinflammation, cognitive decline, and psychiatric disorders. This has

led researchers to investigate immune-modulating therapies not just for infection control but also for protecting neurological function, potentially changing how immunodeficiency-related neurodegeneration is managed.

Clinical Relevance of Findings

The clinical implications of primary and secondary immunodeficiency disorders extend beyond susceptibility to infections. These conditions significantly impact patient morbidity, healthcare burden, and long-term management strategies. Understanding the underlying mechanisms of immune dysfunction has not only improved diagnostic precision but has also guided the development of targeted therapies aimed at restoring immune balance. In the case of Primary Immunodeficiency Disorders (PIDs), early diagnosis is critical. Conditions such as Severe Combined Immunodeficiency (SCID) require urgent intervention, as untreated infants often succumb to fatal infections within the first year of life. The introduction of newborn screening for SCID in several countries has led to earlier detection and increased survival rates following hematopoietic stem cell transplantation (HSCT). Similarly, for antibody deficiencies like Common Variable Immunodeficiency (CVID), lifelong immunoglobulin replacement therapy has transformed a previously life-threatening condition into a manageable chronic disease, reducing the frequency and severity of infections.¹ Moreover, research into genetic corrections has begun to reshape the management of

PIDs. The success of gene therapy in treating X-linked Severe Combined Immunodeficiency (X-SCID) demonstrates how cutting-edge biotechnology can provide curative treatment for a previously fatal disorder. As gene-editing tools like CRISPR/Cas9 continue to evolve, personalized genetic corrections may become a routine intervention in immunodeficiency management.²

On the other hand, Secondary Immunodeficiency Disorders (SIDs) pose an even greater challenge due to their acquired nature. The most well-known example is HIV/AIDS, where the depletion of CD4⁺ T cells leads to opportunistic infections and malignancies. The introduction of Antiretroviral Therapy (ART) has been a landmark achievement, transforming HIV/AIDS from a terminal illness into a manageable chronic condition. However, despite ART's effectiveness, immune reconstitution remains incomplete in many patients, necessitating ongoing research into adjunctive therapies that can restore immune function more comprehensively.⁵¹⁻⁵² Beyond infections, immunodeficiency conditions also predispose patients to autoimmune diseases, malignancies, and inflammatory disorders. CVID, for instance, has been linked to an increased risk of autoimmune diseases such as rheumatoid arthritis and inflammatory bowel disease, highlighting the complex interplay between immune deficiency and immune dysregulation. Understanding these associations has led to more individualized treatment plans that balance infection control with the risk of autoimmunity.⁵³ From

a public health perspective, the management of immunodeficiency disorders requires a multidisciplinary approach. The burden of recurrent infections in patients with undiagnosed immunodeficiencies leads to excessive antibiotic use, contributing to antimicrobial resistance—a growing global concern. Thus, timely diagnosis and appropriate prophylactic strategies are essential not only for patient care but also for broader public health implications.

Optimizing Treatment and Prognosis for Patients with Immunodeficiency Disorders

Managing immunodeficiency disorders is one marked by significant advancements in medical science, yet it remains fraught with challenges that demand continuous innovation. Both primary and secondary immunodeficiencies present unique obstacles, but a shared goal unites their management—restoring immune competence and improving patient outcomes. At the heart of optimizing treatment lies early diagnosis, a critical factor that determines the success of therapeutic interventions. For primary immunodeficiency disorders (PIDs), advancements in newborn screening programs have significantly altered disease trajectories. Conditions like Severe Combined Immunodeficiency (SCID), which once led to early mortality, are now diagnosed within weeks of birth, allowing for timely interventions such as hematopoietic stem cell transplantation (HSCT) or gene therapy. Similarly, genetic

sequencing has revolutionized PID management by enabling targeted therapies tailored to specific mutations, moving the field toward personalized medicine.⁵⁴ For secondary immunodeficiency disorders (SIDs), especially those caused by HIV/AIDS, malignancies, or immunosuppressive treatments, the focus shifts to immune restoration and infection control. The advent of combination antiretroviral therapy (ART) has been one of the most transformative medical breakthroughs, turning HIV from a fatal disease into a chronic, manageable condition. However, even with viral suppression, immune reconstitution remains incomplete in many patients, necessitating research into immune-boosting adjuncts such as cytokine therapies and latency-reversing agents. Similarly, in patients undergoing chemotherapy or receiving immunosuppressive drugs, immune monitoring has become an essential part of care, guiding decisions on prophylactic antimicrobials and vaccination strategies.⁵⁵

Despite these advances, infection prevention remains a cornerstone of treatment optimization. Patients with antibody deficiencies, such as Common Variable Immunodeficiency (CVID), benefit greatly from immunoglobulin replacement therapy (IVIG or SCIG), reducing the frequency of severe infections. For those at heightened risk of opportunistic infections, prophylactic antibiotics and antifungals serve as a critical safeguard, while evolving vaccine strategies ensure protection without triggering immune complications. In immunocompromised

populations, the traditional approach to vaccination has been carefully reevaluated, with a shift toward conjugate vaccines, higher-dose formulations, and booster schedules designed to elicit stronger immune responses.⁵² The role of nutritional and lifestyle interventions in immune function cannot be overstated. Malnutrition remains a significant contributor to SIDs, particularly in resource-limited settings, where protein-energy malnutrition and micronutrient deficiencies compound immune suppression. Zinc, vitamin A, and vitamin D supplementation have shown promising results in bolstering immune defenses, especially in children with recurrent infections. Meanwhile, gut microbiome restoration through probiotics and dietary modifications is gaining attention as a potential strategy to enhance immune recovery, particularly in individuals with HIV or post-chemotherapy immunosuppression.⁵³ Emerging technologies are further reshaping the long-term prognosis of immunodeficiency disorders. Gene therapy, once experimental, is now a reality for certain forms of SCID, with clinical trials demonstrating lasting immune reconstitution. Innovations in CRISPR-based gene editing hold promise for broader applications, potentially offering curative solutions for a range of genetic immunodeficiencies. In parallel, monoclonal antibody therapies and immune checkpoint inhibitors are being explored not only for cancer treatment but also for modulating immune dysfunction in conditions like CVID and HIV-associated immune exhaustion.⁵⁶ For many patients, the challenge is not just achieving immune

restoration but also managing the long-term complications of their condition. Chronic inflammation, autoimmunity, and malignancy risk are heightened in immunodeficient individuals, necessitating lifelong monitoring and tailored therapeutic adjustments. The integration of biomarkers, such as T-cell receptor diversity analysis, inflammatory cytokine profiling, and residual viral reservoir assessments, has improved the precision of prognosis estimation and treatment response monitoring.

Conclusion

Primary and secondary immunodeficiencies represent distinct categories of immune system dysfunction, with different underlying causes, clinical presentations, diagnostic approaches, and management strategies. Primary immunodeficiencies are congenital, resulting from genetic mutations that impair the immune system's development or function, while secondary immunodeficiencies are acquired due to external factors such as infections, medications, or chronic diseases. Despite their differences, both conditions lead to an increased susceptibility to infections, malignancies, and other health complications, requiring tailored therapeutic interventions. In terms of diagnosis, early identification of primary immunodeficiencies is crucial for initiating appropriate treatment, which often includes immunoglobulin replacement or stem cell therapy. Secondary immunodeficiencies, on the other hand, require identifying and addressing the root

cause, whether it be through antiviral therapy, nutritional support, or adjusting immunosuppressive treatments. The treatment of secondary immunodeficiencies often offers better chances for immune recovery if the underlying cause is controlled or reversed.

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