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REVIEW

Immunodeficiencies in Adults: Key Considerations for Diagnosis and Management

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Abstract
Immunodeficiencies in adults are increasingly recognized yet often remain underdiagnosed, leading to significant morbidity from recurrent infections, autoimmunity, and malignancy. Both primary immunodeficiencies (PIDs), now known as inborn errors of immunity (IEI), and secondary immunodeficiencies (SIDs) contribute to immune dysfunction in adults. Although SIDs are more common in adults due to factors like medications, malignancies, metabolic disorders, chronic conditions, and protein-losing conditions, IEI—particularly common variable immunodeficiency (CVID)—can also manifest in adulthood with diverse clinical features. Early recognition is crucial, with key warning signs including recurrent sinopulmonary infections, unexplained autoimmunity, poor vaccine responses, chronic diarrhea, bronchiectasis, and persistent lymphadenopathy. The diagnostic approach should be systematic. It begins with a detailed patient history and status followed by the evaluation of immunoglobulin levels, lymphocyte subsets, vaccine-specific antibody responses, and exclusion of secondary causes. Genetic testing, increasingly accessible, plays an important role in confirming the diagnosis of IEI and guiding prognosis and treatment. Management strategies focus on treating the underlying condition in SIDs. Preventive measures, including antimicrobial prophylaxis, vaccination, and immunoglobulin replacement therapy (IGRT) in patients with significant antibody deficiencies, are essential for reducing infections and complications in high-risk patients. Given the growing recognition of adult-onset immunodeficiency, clinicians should maintain a high index of suspicion and adopt a structured diagnostic and management approach to improve patient outcomes and quality of life.

Keywords Primary immunodeficiencies · Secondary immunodeficiencies · Inborn errors of immunity · Common variable immunodeficiency

Introduction

Immunodeficiency, defined as a weakened or dysfunctional immune system that increases susceptibility to infections and cancer, is common in adults. Recent estimates suggest that more than 6% of US adults may be affected [1], with most cases resulting from secondary immunodeficiencies (SID). These deficiencies arise due to external factors such as human immunodeficiency virus (HIV) infection, medications, intrinsic factors including systemic diseases, malignancies, and metabolic disorders, or a combination of both. Primary immunodeficiencies, traditionally referred to as "primary immune deficiencies (PID)," are now classified as inborn errors of immunity (IEI). These conditions can also be diagnosed in adult patients, often with delayed diagnoses due to their heterogeneous manifestations. Importantly, this terminology can be misleading, as not all IEI initially

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present with immunodeficiency, and some may manifest only in adulthood [2–5]. Moreover, IEI encompasses not only classical primary immunodeficiencies with recurrent or severe infections, but also conditions of immune dysregulation, including autoimmunity, autoinflammation, allergy, and malignancy.

This review aims to provide clinicians with a practical framework for recognizing immunodeficiency in adults, with a focus on SID, which accounts for most cases. We will outline key warning signs, initial diagnostic steps, and indications for specialist referral and management. Additionally, we will discuss common variable immunodeficiency (CVID), the most frequently diagnosed symptomatic IEI in adults. These considerations are based on a narrative review of literature, expert consensus, and the authors' clinical experience to guide decision making in practice.

Methods

This narrative review searched PubMed and Scopus from database inception to May 1, 2025, without language or date restrictions. The search terms included *immunodeficiency*, *common variable immunodeficiency*, *primary immunodeficiency*, *inborn errors of immunity*, *recurrent infections*, *opportunistic infections*, *and antibiotic prophylaxis*. We also reviewed key American and European guidelines on immunodeficiency, infectious risk stratification, treatment, and vaccination.

Clinical Presentation and Warning Signs

The clinical presentation of immunodeficiencies is highly variable, but most patients present with recurrent and/or severe infections. While no universally accepted definition exists for recurrent or severe infections in the context of immunodeficiency, certain patterns of infections should raise suspicion of an underlying immune defect. These include opportunistic infections (i.e., infections due to pathogens that would not cause disease in individuals with healthy immune systems), recurrent sinopulmonary infections, and severe infections requiring intravenous antibiotics, hospitalization, invasive interventions or that are life-threatening [6]. In the context of IEI, the European Society for Immunodeficiency (ESID) and the Jeffrey Modell Foundation (JMF) have proposed warning signs [7, 8] which should raise the suspicion of an underlying IEI in adults and children (Table 1). The JMF criteria have been clinically validated to evaluate IEI and SID patients [9], and may serve as a useful tool for the early detection of SID. Other warning signs for immunodeficiency in adults that should not be overlooked include chronic diarrhea, bronchiectasis, poor vaccine responses, autoimmune disorders, persistent lymphadenopathy or splenomegaly, and granulomatous lesions [10, 11]. Additional scoring systems for early identification of patients affected by IEI based on expert opinions are in development, aiming to improve diagnostic accuracy in primary care settings [12]. Data-driven model systems using machine learning can also help screen individuals at high risk of IEI [13].

Adapted from references (2,3)

Types of Immunodeficiency

Primary Immunodeficiency

Distinguishing between IEI and SID in adult patients can be challenging, as autoimmune and hematologic or oncologic conditions can be both the causes and the manifestations of immune dysfunction. IEI is usually diagnosed during childhood, but some entities, particularly CVID, may manifest in adulthood. In addition, hypomorphic variants of classically severe IEI (e.g., mutations in RAG1/2, ADA2, or NF-κB1 genes) can present with attenuated phenotypes and

Table 1 European Society for Immunodeficiency (ESID) and the Jeffrey Modell Foundation (JMF) warning signs for primary immunodeficiency in adults

The 6 ESID warning signs (≥ 1 criterion)	The Jeffrey Model Foundation warning signs (≥ 2 criteria)
1. Four or more infections requiring antibiotics within one year (otitis, bronchitis, sinusitis, pneumonia)	1. Two or more new ear infections within one year
2. Recurring infections or infections requiring prolonged antibiotic therapy	2. Two or more new sinus infections within one year, in the absence of allergy
3. Two or more severe bacterial infections (osteomyelitis, meningitis, septicemia, cellulitis)	3. One pneumonia per year for > 1 year
4. Two or more radiologically proven pneumonia within 3 years	4. Chronic diarrhea with weight loss
5. Infection with unusual localization or unusual pathogen	5. Recurrent viral infections (colds, herpes, warts, condyloma)
6. A family history of primary immunodeficiency	6. Recurrent need for intravenous antibiotics to clear infections
	7. Recurrent, deep abscesses of the skin or internal organs
	8. Persistent thrush or fungal infection on skin or elsewhere
	9. Infection with normally harmless tuberculosis-like bacteria
	10. A family history of primary immunodeficiency

be diagnosed later in life [14]. CVID is defined by reduced levels of immunoglobulins G (IgG) along with low levels of IgA and/or IgM, defective responses to immunizations, and abnormal B cell immunophenotype, often with significant reduction of isotype-switched memory B cells [15]. CVID represents a heterogenous group of disorders with variable clinical phenotypes, contributing to delayed diagnosis. Most patients are diagnosed between 20 and 45 years of age after multiple consultations and hospitalizations [16]. While genetic variants are identified in 25–30% of cases, novel disease-causing mutations continue to be discovered [17]. The clinical presentation and potential complications can vary according to the underlying genetic defect.

The main clinical feature of CVID is recurrent respiratory tract infections, such as pneumonia, sinusitis, and otitis media, mainly due to *Streptococcus pneumoniae* and *Haemophilus influenzae*, which have been reported in over 90% of patients in large studies [16]. Viral (e.g., herpes zoster), fungal (e.g., *Pneumocystis jirovecii*), and parasitic (e.g., *Giardia*) infections are less frequent [16]. In adults with recurrent respiratory infections, the presence of allergy, autoimmunity, and/or granulomatous disease should raise the suspicion of underlying CVID [18]. Patients with predominant non-infectious complications (autoimmunity, lymphoproliferation, enteropathy) are increasingly recognized as a distinct subgroup of CVID with different pathophysiology and outcomes compared to those with mainly infectious manifestations [19]. Additional complications affecting CVID patients include atopy, immune thrombocytopenic purpura, hemolytic anemia, lymphoproliferation, splenomegaly, protein-losing enteropathy, and granulomatous lymphocytic interstitial lung disease (GLILD) [20]. Bronchiectasis and interstitial lung disease are major complications of pulmonary infections and represent key signs for CVID diagnosis.

Secondary Immunodeficiency

SID conditions are acquired, tend to appear later in life, and can be transient or permanent. They result from external factors that impair immune function. Identifying the underlying cause is crucial, as targeted interventions can often alleviate or reverse immune dysfunction.

SID Inducing Drugs

Medications represent one of the most frequent causes of SID in adults. Various drug classes can impair the immune system, including cytotoxic agents, glucocorticoids, traditional immunosuppressants, biological and targeted therapies, and cellular therapies, as well as certain antiepileptic and antipsychotic drugs (Table 2). A comprehensive review of current and past medication history is crucial for the recognition of drug-induced immunosuppression.

Glucocorticoids exert anti-inflammatory and immunosuppressive effects in a dose and duration-dependent manner [31], and may lead to hypogammaglobulinemia and CD4 lymphopenia [22, 32]. Similarly, biological agents used to treat autoimmune disorders and malignancies increase the risk of infection through mechanisms specific to their targets and off-target enzyme inhibitions. For example, anti-CD20 monoclonal antibodies, such as rituximab, cause prolonged B-cell depletion, while hypogammaglobulinemia can also occur, especially with prolonged courses [33]. Some patients also develop late-onset neutropenia, which is believed to result from immune dysregulation, including cytokine imbalance that impairs neutrophil production [34]. Impaired vaccine responses, severe respiratory infections, reactivation of hepatitis B virus, and even progressive multifocal leukoencephalopathy (PML) in rare cases are reported [33]. Tumor necrosis factor alpha (TNF-α) inhibitors are consistently associated with an increased risk of tuberculosis and potentially a higher risk of serious infections, particularly early in treatment, as well as with reactivation of hepatitis B infection [25].

Of note, immunosuppressive drugs are often used in combination, leading to an increased immunosuppressive state. For example, combined drug regimens used after solid organ transplantation (SOT) to avoid transplant rejection often include glucocorticoids, calcineurin inhibitors, lymphocyte

Table 2 Most common medications causing secondary immune deficiency

Medication family	Examples
B cell targeting monoclonal antibodies [21]	Rituximab, daratumumab, belimumab
Immunosuppressants and cytotoxic agents [22–24]	Prednisone and derivates, methotrexate, cyclophosphamide, mycophenolate mofetil, cyclosporin, calcineurin inhibitors, purine analogs
Tumor necrosis factor alpha inhibitors [25]	Infliximab, etanercept
Tyrosine kinase inhibitors [26]	Ruxolitinib, tofacitinib, baricitinib
Others [27–30]	Anticonvulsivants: carbamazepine, phenytoin, lamotrigine Antipsychotics: clozapine Antimalarials: chloroquine and hydroxychloroquine

proliferation inhibitors and/or mechanistic target of rapamycin (mTOR) inhibitors, while anti-thymocyte globulins (ATG) and anti-IL-2 receptor antibodies are also frequently used at induction. These agents are known to cause profound immunosuppression, especially of the cell-mediated immunity and lead to a high infection risk after SOT [35].

The list of biological and targeted molecules with immunosuppressive potential is rapidly expanding, reflecting the continuous development of novel agents in oncology, autoimmunity, and transplantation. It is increasingly challenging for non-specialists to remain familiar with their diverse mechanisms of action and infectious risks. For this reason, updated consensus documents, such as those from the ESCMID Study Group for Infections in Compromised Hosts (ESGICH), are valuable resources that provide comprehensive, regularly revised guidance on infection risk stratification and management [36].

Metabolic Causes

Diabetes mellitus is the most common metabolic disorder associated with immune dysfunction, leading to an increased susceptibility to infections [37]. Chronic hyperglycemia impairs both innate and adaptive immunity, affecting neutrophil chemotaxis, phagocytosis, and cytokine responses. Obesity without diabetes is also associated with autoimmunity and immune dysfunction, suggesting a causal relationship [38]. Patients with Cushing's disease are at a higher risk of infection due to increased endogenous glucocorticoid production, which suppresses inflammatory and immune responses [39]. To a lesser extent, thyroid dysfunction can contribute to weakening immune function due to its effect on T-cell function. Other hormonal dysfunctions that can impact the immune system include hypopituitarism, adrenal insufficiency, growth hormone deficiency, and imbalances in sex hormones.

Infectious Causes

Chronic infections can contribute to SID by directly targeting immune cells or inducing prolonged immune activation and exhaustion. HIV is the most well-known infectious cause. In the absence of antiretroviral therapy, HIV infection progressively leads to CD4 + T-cell depletion and impaired cell-mediated immunity, increasing vulnerability to encapsulated bacteria (*S. pneumoniae*) and severe opportunistic infections including viral (reactivation of herpesviruses, JC virus), fungal (including *Pneumocystis jirovecii*, *Cryptococcus* spp, *Candida* spp), parasitic (toxoplasmosis), and mycobacterial pathogens. Infection risk is strongly correlated with CD4 T-cells counts. HIV also disrupts innate immunity, impairing alveolar macrophage function, reducing neutrophil and NK cell activity, and altering B-cell responses, leading to defective antibody production and poor vaccine-induced immunity [40, 41]. Additionally, chronic immune activation and gut barrier disruption contribute to systemic immune dysfunction.

Protein Loss

Protein-losing conditions can lead to hypogammaglobulinemia due to excessive immunoglobulin loss that is not adequately compensated by synthesis. In nephrotic syndromes, proteins including immunoglobulins are lost in the urine, with hypogammaglobulinemia further exacerbated by impaired IgG synthesis and by the use of B-cell-targeting medications [42, 43]. Protein-losing enteropathy (PLE) results from excessive protein loss through the gastrointestinal tract and can complicate various conditions, including inflammatory bowel disease, systemic lupus erythematosus, coeliac disease, graft versus host disease, bacterial overgrowth, and intestinal infections such as viral or parasitic enteritis and Whipple disease. PLE may also be associated with cardiovascular disorders and neoplasms [44]. Additionally, PLE can occur as a complication of IEI, such as CVID, further exacerbating hypogammaglobulinemia.

Lymphatic Malformations and Primary Intestinal Lymphangiectasia

Lymphatic malformations and primary intestinal lymphangiectasia (PIL) are rare but significant causes of SID. These conditions are characterized by abnormal development or dysfunction of lymphatic vessels, leading to excessive loss of lymphatic fluid rich in proteins, lymphocytes, and immunoglobulins [45, 46]. As a result, affected individuals often develop hypogammaglobulinemia, lymphopenia, and impaired humoral and cellular immune responses, increasing their susceptibility to infections. Clinically, it manifests with peripheral edema, chylous ascites, chronic diarrhea, and recurrent infections, particularly with encapsulated bacteria [47]. Patients with PIL may also present with profound and selective lymphopenia, further compromising immune defenses [48]. Generalized lymphatic malformations, as seen in certain congenital syndromes (e.g. Hennekam syndrome), can also lead to SID due to systemic lymphatic leakage [49, 50].

Hematological Malignancies

Patients with hematological malignancies have a high infectious risk due to the underlying malignancies and treatments. Infectious risk is highest in those with acute leukemia receiving induction and consolidation chemotherapies resulting in prolonged neutropenia (> 10 days), and in recipients of allogeneic hematopoietic cell transplantation

(HCT), especially in the context of additional immunosuppression for prevention or management of graft versus host disease (GVHD) [51, 52]. Novel cellular therapies such as chimeric-antigen-receptor (CAR) T-cell therapies are increasingly used in B-cell and plasma cell malignancies and lead to profound and persistent immune deficits in cellular and humoral immunity [53]. Importantly, emerging treatments—including bispecific T-cell engagers and CAR T-cell therapies—further underscore the need for heightened vigilance in assessing infection risk. The duration of neutropenia is a key determinant of infection risk in these "high risk" patients with hematological malignancies, increasing risk for bacterial and fungal infection and dictating preventive strategies. Cellular immunodeficiency after allogeneic HCT increases the risk of herpesvirus infection, especially cytomegalovirus (CMV), that requires special prophylactic strategies in this setting. Finally, humoral immune deficits are also frequent, both after HCT and CAR T-cell therapies ("on-target off-tumor effects"), and lead to frequent sinopulmonary infections.

Other hematological malignancies, such as myeloma and lymphoma, can lead to immunodeficiencies through multiple mechanisms [54]. Multiple myeloma disrupts normal antibody production through the expansion of clonal plasma cells that produce large quantities of dysfunctional monoclonal immunoglobulins, while simultaneously suppressing normal immunoglobulin synthesis. In lymphoma, immune dysfunction arises due to bone marrow involvement, chemotherapy-induced myelosuppression, and direct impairment of B- and T-cell function. Patients with these malignancies are at increased risk for recurrent bacterial infections, particularly with encapsulated organisms, due to impaired humoral immunity.

Hypogammaglobulinemia is frequent in patients with chronic lymphocytic leukemia (CLL) due to the progressive loss of normal B-cell function, leading to impaired immunoglobulin production and defective humoral immunity [55]. The severity of B-cell dysfunction correlates with disease progression and treatment exposure, particularly with anti-CD20 monoclonal antibodies and Bruton tyrosine kinase (BTK) inhibitors, which further deplete B-cell populations.

Thymoma can also be associated with B-cell lymphopenia and hypogammaglobulinemia, leading to a rare form of secondary immunodeficiency known as Good's syndrome [56]. The immune defect in Good's syndrome extends beyond B-cell deficiency and may include T-cell abnormalities, resulting in susceptibility to both bacterial and opportunistic infections.

Malnutrition and Aging

Malnutrition is a leading cause of SID worldwide and affects both children and adults, particularly in low-income countries. Chronic caloric and protein deficiencies impair immune cell development, proliferation, and function, increasing susceptibility to infections. Micronutrient deficiencies, including zinc, vitamin A, vitamin D, iron, and selenium, weaken mucosal barriers, and impair innate and adaptive immune responses [57]. Hypoproteinemia results in decreased T cell generation and function, with immunosuppression correlating with the severity of protein depletion [58].

Immunosenescence, the gradual decline of immune function with age, results in reduced naïve T-cell production, impaired B-cell responses, and diminished innate immune activity. Elderly individuals experience weakened vaccine responses, increased susceptibility to infections, and a higher prevalence of chronic inflammation ("inflammaging"), which contributes to immune dysregulation [57]. These age-related changes along with a higher burden of comorbidities make older individuals particularly vulnerable to pneumonia, influenza, and other infectious diseases, often with more severe outcomes.

Other Causes

Chronic kidney disease (CKD) and liver cirrhosis can also lead to SID by multiple mechanisms. In CKD, uremic toxins impair neutrophil chemotaxis, phagocytosis and oxidative burst, reducing innate immune defenses and increasing susceptibility to bacterial infections [59]. Furthermore, CKD leads to T-cell dysfunction, with decreased activation, proliferation, and cytokine production, further compromising adaptive immunity [60]. Liver cirrhosis results in the dysfunction of Kupffer cells, the resident macrophages of the liver, resulting in impaired pathogen clearance and endotoxin tolerance. Additionally, it is associated with decreased acute-phase reactant production, impaired neutrophil function, and complement deficiency, all of which contribute to the increased risk of spontaneous bacterial peritonitis and systemic infections [61].

Other causes of SID include splenectomy, functional hyposplenia or asplenia, thymectomy, radiation therapy, and plasmapheresis. Splenectomy results in impaired clearance of encapsulated bacteria, predisposing individuals to overwhelming post-splenectomy infections syndrome (OPSI) [62]. Functional hyposplenia, as found in sickle cell disease patients, alters immunophenotype and also predisposes to bacterial infections [63]. Thymectomy, particularly when performed early in life, can significantly reduce T-cell output, leading to a weakened adaptive immune response [64]. Radiation therapy, especially when targeting the bone marrow or lymphoid tissues, leads to lymphopenia and neutropenia, increasing the risk of infections [65]. Plasmapheresis, used to remove pathogenic antibodies, can also deplete protective immunoglobulins [66].

Workup for Suspected Immunodeficiency

When immunodeficiency is clinically suspected, investigations should begin with a detailed patient history and thorough physical examination. The history should assess recurrent, severe, or unusual infections, the age of onset, response to antibiotics or prophylactic treatments, and any history of chronic inflammatory, autoimmune, or allergic manifestations. A family history suggestive of IEI, the presence of comorbidities that could lead to SID, past and current medications, and prior immune evaluations must be reviewed. Finally, vaccination records and symptoms suggestive of hematologic malignancies or other occult neoplasia should be assessed. Physical examination should look for signs of chronic infections, autoimmune disorders, or systemic immune dysfunction, including splenomegaly, lymphadenopathy, malnutrition, signs of chronic lung or gastrointestinal diseases and skin abnormalities.

Investigations should be completed with a laboratory workup [6]. A reasonable, two-step approach is described in Table 3**.**

The first step, which can be conducted by a primary care physician, includes the evaluation of secondary causes, as well as of a full blood count and total serum immunoglobulin levels. Step two includes a more in-depth evaluation of cellular and humoral immunity, as well as the complement activity. This step should ideally be interpreted by an immunologist or immunodeficiency specialist. Investigations are tailored to each case and may include IgG subclass analysis, lymphocyte proliferation assay, neutrophil function test, and genetic screening. In specific situations, baseline lung functions and chest CT imaging should be considered to evaluate for interstitial lung disease, bronchiectasis, or thymoma.

Abnormal quantitative results for serum immunoglobulins or blood cell count may transiently occur during acute infection. Therefore, it is generally recommended to wait 4 to 6 weeks after the resolution of last acute infection before performing an immunodeficiency assessment. An unremarkable baseline biological workup does not exclude an underlying immunodeficiency, particularly in patients suffering from recurrent, severe, or unusual infections. If clinical suspicion remains high despite normal initial results, referral to an immunology specialist for further evaluation and long-term follow-up is warranted [6].

Management of Immune Deficiency in Adults

The management of SID relies on two pillars: identifying and treating the underlying cause and preventing infections. The treatment of the etiology focuses on addressing the underlying disease process to reverse or slow down the progression of the immune deficiency whenever possible.

The risk of infection varies significantly depending on the underlying condition, immunosuppressive treatment, and patient characteristics. Generally, infection risk is low in young patients without significant comorbidities receiving a single immunomodulatory agent for inflammatory diseases, while SOT and HCT recipients, patients with hematologic malignancies undergoing intensive chemotherapy, and patients with HIV infection and CD4 counts below 200 cells/mm^3 are at the highest risk. Older patients with cancer and other comorbidities on combined immunosuppressive regimens are at intermediate risk. We propose a framework

Table 3 Laboratory workup for clinically suspected immunodeficiency

Step 1	Step 2
• Full blood count[a] • Serum level of immunoglobulin G, A and M and IgG subclasses[a] • Renal and liver function tests • Albumin • CRP, ESR • Exclusion of chronic infections: HIV, HBV, HCV, tuberculosis • TSH and HbA1c • Serum protein electrophoresis and immunofixation • Nutritional assessment[CC]	• Lymphocyte subset analysis (at minimum T CD3 +, T CD4 +, T CD8 +, B and NK cells) • Specific antibody response to both protein/conjugated antigens (e.g. tetanus, diphtheria and *Haemophilus influenzae serotype b*) and polysaccharide antigens (e.g. *Streptococcus pneumoniae*) • CH50 (screening for classical complement pathway; AP50 if alternative pathway defect suspected)

Additional autoimmunity testing (e.g. Antinuclear Antibody (ANA), Extractable Nuclear Antigen (ENA)) can be considered when clinical suspicion of immune dysregulation exists but is not part of the systematic first-line evaluation

IgG subclasses interpretation requires correlation with clinical findings and vaccine-specific antibody responses

CRP C-reactive protein, *ESR* erythrocyte sedimentation rate, *TSH* Thyroid Stimulating Hormone, *HbA1c* glycated hemoglobin, *CD* cluster of differentiation, *NK* natural killer

[a]Repeat testing 4–6 weeks after acute infection

[CC]On a case-by-case basis

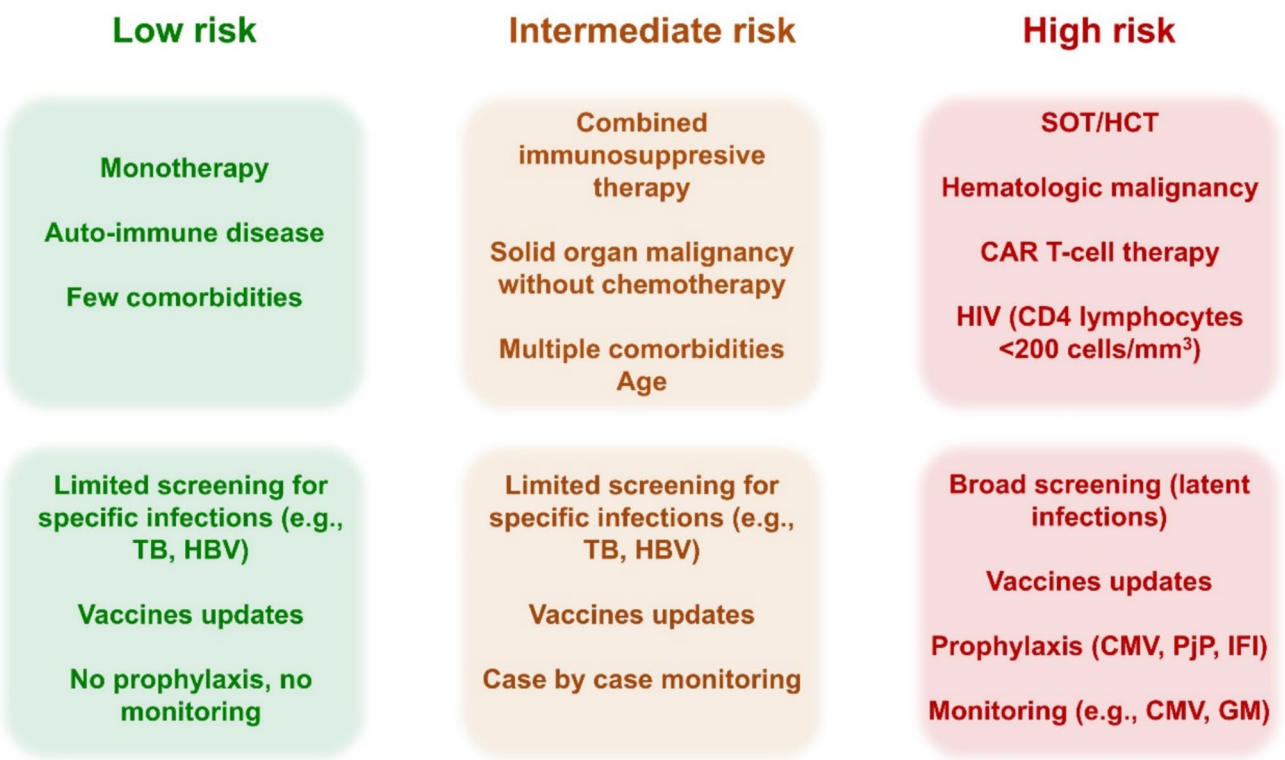


Fig. 1 Conceptual framework for infectious risk stratification and preventive measures. Abbreviations: TB, tuberculosis; HBV, hepatitis B virus, SOT, solid organ transplant; HCT, hematopoietic cell transplantation; CAR T-cell, chimeric antigen receptor T-cells; HIV, human immunodeficiency virus; CMV, cytomegalovirus; PjP, *Pneumocystis jirovecii* pneumonia; IFI, invasive fungal infection; GM, galactomannan

for infection risk stratification based on the patient, disease, and treatment characteristics (Fig. 1). Low-risk patients may benefit from targeted screening (e.g., latent TB in anti-TNF) and vaccination, while high-risk patients additionally require more extensive screening, antiviral and antifungal prophylaxis, and monitoring (e.g., CMV). In the following paragraphs, we outline general preventive measures applicable to all SID patients, as well as specific strategies tailored to different levels of infectious risk.

General Preventive Measures

Prevention of infection primarily includes general hygiene measures, such as hand disinfection, wearing protective face masks during winter months in case of contact with crowds in closed spaces, and avoiding close contact with sick individuals [67].

Patients with SID require regular follow-ups with their primary care physician. Depending on their estimated infectious risk, they might also require follow-up with specialists to monitor immune function, infection risk, and treatment response. Follow-up visits should include clinical assessments, laboratory monitoring, and individualized adjustments to prophylactic or therapeutic strategies based on disease progression and emerging complications.

Early infection detection and intervention are crucial, as infections may present atypically, progress rapidly, and lead to severe complications. Patients should be educated on recognizing early signs of infection, including fever, persistent cough, shortness of breath, unexplained weight loss, recurrent diarrhea, or localized pain and swelling. Patients should be instructed to seek prompt medical attention if they develop any of these symptoms to facilitate early diagnosis and timely treatment.

Antimicrobial Prophylaxis Based on Infectious Risk

Patients at high risk for infection (e.g., transplant recipients, cellular therapies recipients, HIV with CD4 counts below 200 cells/mm^3) (Fig. 1) may require specific antimicrobial prophylaxis. *Pneumocystis jirovecii* prophylaxis is recommended in patients with cellular immunodeficiencies [68, 69]. First-line prophylaxis is trimethoprim–sulfamethoxazole (TMP-SMX), which also provides protection against *Toxoplasma gondii*. If TMP-SMX cannot be used, alternatives for *Pneumocystis jirovecii* include atovaquone or aerosolized pentamidine. Toxoplasmosis prophylaxis is

also recommended in patients at high risk, including toxoplasma-seropositive HIV-infected persons with CD4 counts below 200 cell/mm^3 and toxoplasma-seronegative heart transplant recipients receiving an allograft from a seropositive donor [69]. When TMP-SMX cannot be used, patients at risk for toxoplasmosis may require dapsone combined with pyrimethamine and folinic acid. Given their complexity and potential toxicities, they should preferably be prescribed with input from an infectious diseases or immunology specialist.

Other bacterial prophylaxis may also be required in specific setting. Long-term penicillin prophylaxis is recommended in patients with active graft versus host disease (GVHD) after allogeneic HCT due to increased susceptibility to recurrent bacterial infections with encapsulated bacteria [70]. Penicillin prophylaxis is recommended for patients who have not been vaccinated against *Neisseria meningitidis* and are treated with the anti-C5 antibody eculizumab. The optimal duration of prophylaxis, and its necessity in vaccinated individuals, remains a matter of debate [71, 72].

Antifungal prophylaxis with fluconazole or mold-active azoles (posaconazole) is warranted during periods of prolonged severe neutropenia in patients with hematologic malignancies receiving intensive chemotherapies and/or allogenic HCT [73]. A preemptive approach based on monitoring of galactomannan and early work-up with imaging and initiation of antifungal therapy in patients with persistent neutropenic fever can also be implemented [74]. Antiviral prophylaxis against HSV and VZV is also generally recommended in high-risk patients, particularly those with cellular immunodeficiencies [75]. CMV prophylaxis (letermovir, (val)ganciclovir) or or CMV monitoring with blood PCR and preemptive therapy at detection above certain viral-load thresholds is generally reserved for transplant recipients at risk [76, 77]. Prophylaxis for hepatitis B virus (HBV) may be needed in certain high-risk patients (e.g., patients with HBsAg + chronic infection and treated with rituximab, prolonged corticosteroid therapy, or chemotherapy) [78, 79]. Treatment of latent tuberculosis infection (LTBI), should generally be considered, especially for patients receiving TNF-α inhibitors, prolonged corticosteroid therapy, or chemotherapy [80].

Vaccines

Vaccination is crucial for reducing infection risk, morbidity, and mortality in patients with SID. Due to the heterogeneous nature of SID and limited clinical data, vaccination recommendations are mainly based on expert opinion [81].

To maximize efficacy, vaccines must be administered as soon as immune deficiency is diagnosed or before initiating immunosuppressive therapy. Live attenuated vaccines, such as measles/mumps/rubella (MMR), live-attenuated influenza, varicella, and yellow fever vaccines should generally be avoided in immunocompromised individuals and, in some cases, by their household members, due to the risk of uncontrolled replication of the weakened pathogen in immunocompromised individuals. The immunogenicity of non-live vaccine is considered to be suboptimal in immunocompromised patients. Revaccination after receipt of HCT, SOT and cellular therapies is recommended. The quality of vaccine response in SID patients is often suboptimal, depending on the underlying disease. For this reason, household members, close contacts, and caregivers should also be vaccinated to reduce exposure risk.

Annual seasonal influenza and Covid-19 vaccinations are recommended in the fall/winter. For pneumococcal infections, the conjugate pneumococcal vaccine (preferably 20-valent) is recommended. Recombinant adjuvanted zoster vaccine is recommended in all VZV-seropositive individuals. Additional vaccinations may be recommended depending on immune deficit (e.g., *Neisseria meningitidis* in asplenic patients or patients treated with eculizumab) and exposures. Assessing the immune response by measuring vaccine-specific anti-pneumococcal antibodies can help to estimate protection level and monitor changes over time. Other vaccination strategies depend on the specific underlying disease or treatment and are outlined in Table 4.

Vaccination against respiratory syncytial virus (RSV) is recommended by the Centers for Diseases Control and Prevention for all adults aged 75 and older and for adults aged 60 to 74 at increased risk for severe RSV. Vaccination before the age of 60 must be evaluated on a case by case basis [95]

Adapted from [81, 84, 96]

Immunoglobulins Replacement Therapy

Immunoglobulins replacement therapy (IGRT) plays a crucial role in reducing the risk of infections in patients with hypogammaglobulinemia, particularly those with PID. While a total serum IgG level below 4 g/L is often considered a strong indicator for further evaluation, the ESID diagnostic criteria emphasize a comprehensive assessment, including Ig levels, vaccine response, and clinical history. The decision to initiate IGRT should therefore be based not solely on IgG levels, but on the overall immunological and clinical context.

Studies in patients with CVID have shown that the risk of infections, particularly pneumonia, rises significantly when serum IgG levels fall below 3.0 g/L [97]. Furthermore, patients with persistent very low IgG levels (< 1.0 g/L) are generally considered at high risk for severe and potentially life-threatening infections. In such cases, IGRT is typically initiated even in the absence of a significant history of infections [98].

Table 4 Vaccination suggestions according to the secondary immunodeficiency etiology

Condition	Recommended vaccinations
Liver cirrhosis [82]	- Annual Influenza and Covid-19 - Pneumococcal PCV20 - Hepatitis A upon diagnosis - Hepatitis B upon diagnosis - Tetanus, Diphtheria, Pertussis (Tdap) if not up to date
Anatomical or functional asplenia (including sickle cell disease) [83]	- Annual Influenza and Covid-19 - Pneumococcal PCV20 - *Haemophilus influenzae* b: one dose - Meningococcal (serogroups A, C, W, Y + serogroup B) - Tetanus, Diphtheria, Pertussis (Tdap) if not up to date
Chronic kidney disease [84]	- Annual Influenza and Covid-19 - Pneumococcal PCV20 if clearance < 30 ml/min or worsening (stages 4–5, National Kidney Foundation) - Recombinant zoster vaccine from age 50 and in end-stage disease (stages 4–5, National Kidney Foundation) or dialysis - Hepatitis B before hemodialysis initiation - Tetanus, Diphtheria, Pertussis (Tdap) if not up to date
Nephrotic syndrome [85]	- Annual Influenza and Covid-19 - Pneumococcal PCV20 - Tetanus, Diphtheria, Pertussis (Tdap) if not up to date
Diabetes with impact on renal function or cardiovascular disease [86]	- Annual Influenza and Covid-19 - Pneumococcal PCV20 if clearance < 30 ml/min or worsening (stages 4–5, National Kidney Foundation) - Recombinant zoster vaccine from age 50 in type 1 diabetes - Hepatitis B - Tetanus, Diphtheria, Pertussis (Tdap) if not up to date
Neoplasms: lymphoma, leukemia, myeloma, solid tumors treated with chemotherapy [87]	- Annual Influenza and Covid-19 - Pneumococcal PCV20 - Recombinant zoster vaccine from age 18 - Tetanus, Diphtheria, Pertussis (Tdap) if not up to date
Transplantation [88, 89]	**Solid Organ Transplantation** - Annual Influenza and Covid-19 - Pneumococcal PCV20 pretransplant and a booster after transplant - Poliovirus: 3 doses of inactivated vaccines 6–12 months after transplantation - Varicella: pre-transplantation if no evidence of varicella immunity - Recombinant zoster vaccine from age 18 - Hepatitis B pre-transplantation and at 12 months post-transplantation - Hepatitis A pre-transplantation and at 12 months post-transplantation - Measles, rumps and rubella (MMR) if not immune and pre-transplantation - Tetanus, Diphtheria, Pertussis (Tdap) if not up to date **Hematopoietic Stem Cell Transplant Recipients** - Annual Influenza and Covid-19 - Pneumococcal: 3 doses of PCV20, starting 3 months post-transplantation - *Haemophilus influenza* serotype b: 3 doses 6–12 months after transplantation - Hepatitis B: 3 doses 6–12 months after transplantation - Poliovirus: 3 doses of inactivated vaccines 6–12 months after transplantation - Varicella: 2 doses 24 months after transplantation if varicella seronegative - Recombinant zoster vaccine from age 18 - MMR if not immune and pre-transplantation - Tetanus, Diphtheria, Pertussis (Tdap) if not up to date

Table 4 (continued)

Condition	Recommended vaccinations
Immunosuppressive medication (including long-term systemic corticosteroids and radiotherapy) [90]	- Annual Influenza and Covid-19 - Pneumococcal PCV20 during maintenance therapy - Shingles (exclusively non-live vaccine) according to age - Tetanus, Diphtheria, Pertussis (Tdap) if not up to date
Human immunodeficiency virus [91]	- Annual Influenza and Covid-19 - Pneumococcal: Pneumococcal PCV20 - Shingles (exclusively non-live vaccine) ■ from age 50 if CD4 ≥ 200 cells/ml ■ from age 18 after immune reconstitution if CD4 < 200 cells/ml - Hepatitis A upon diagnosis - Hepatitis B upon diagnosis - Tetanus, Diphtheria, Pertussis (Tdap) if not up to date
Congenital or acquired immunodeficiency, common variable immunodeficiency (CVID), selective anti-polysaccharides antibody deficiency [92]	- Annual Influenza and Covid-19 - Pneumococcal PCV20 - Meningococcal (serogroups A, C, W, Y + serogroup B) - If T-cell deficit: Shingles (exclusively non-live vaccine) from age 18 - Tetanus, Diphtheria, Pertussis (Tdap) if not up to date
Complement deficiency (terminal or alternative pathway), mannose-binding lectin deficiency [93, 94]	- Annual Influenza and Covid-19 - Pneumococcal PCV20 - Meningococcal (serogroups A, C, W, Y + serogroup B) - Tetanus, Diphtheria, Pertussis (Tdap) if not up to date

The consensus is that IGRT should aim to maintain trough serum IgG levels of at least 5.0 g/L [99]. Higher target levels (8–10 g/L) are advised for certain high-risk patient groups, such as those with bronchiectasis or chronic lung diseases [100]. In contrast, the role of IGRT in patients with hematologic malignancies and SOT recipients is less well established and remains controversial [53].

For selected patients with severe forms of IEI, curative approaches such as hematopoietic stem cell transplantation or gene therapy may be considered in specialized centers. While these modalities are beyond the scope of this review, they represent important therapeutic advances that complement supportive measures such as IGRT.

Conclusion

Immunodeficiency in adults is more prevalent than commonly recognized and often remains underdiagnosed due to its heterogeneous presentation. This review highlights the most frequent causes of adult-onset immunodeficiency and provides a structured approach to its evaluation. Early recognition and appropriate workup are crucial, as delayed diagnosis may lead to recurrent, severe, or opportunistic infections with significant morbidity. It is essential to emphasize that a normal initial workup does not exclude underlying immunodeficiency, particularly in high-risk patients. Therefore, individuals with recurrent infections, poor vaccine responses, or other clinical features suggestive of immune dysfunction should be referred to an immunology specialist for comprehensive assessment and tailored management. A multidisciplinary approach involving primary care providers, immunologists, infectious diseases physicians, and other specialists is key to optimizing patient outcomes and preventing long-term complication.

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Data Availability No datasets were generated or analysed during the current study.

Declarations

Conflict of Interest EK received consulting fees from Merck and honoraria from Takeda and Merck.

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