

## Review Article

# Primary Immunodeficiency Diseases: An Overview of Clinical Presentation, Diagnosis, and Management

Izazi Arbain<sup>1</sup>, Zarina Thasneem Zainudeen<sup>1</sup>, Intan Juliana Abd Hamid<sup>1</sup>

### Author's Affiliation:

1- Primary Immunodeficiency Diseases Group, Department of Clinical Medicine, Institut Perubatan dan Pergigian Termaju, Universiti Sains Malaysia

### Correspondence:

Intan Juliana Abd, Email: intanj@usm.my

Received on: 09-Oct-2025

Accepted for Publication: 28-Dec-2025

### ABSTRACT

Primary immunodeficiencies (PIDs), recently reclassified as inborn errors of immunity (IEIs), represent a heterogeneous group of over 500 genetically defined disorders that impair the development or function of the immune system. Although individually rare, collectively they have a significant global health impact, contributing to recurrent infections, autoimmunity, autoinflammation, allergy, and malignancy. Advances in next-generation sequencing and immunological profiling have expanded the diagnostic landscape, enabling earlier recognition of atypical presentations and novel disease entities. Nevertheless, delayed diagnosis remains a challenge, particularly in low- and middle-income countries, where access to specialized testing and therapies is limited. Clinically, PIDs are diverse and may manifest from infancy to adulthood, often with overlapping phenotypes. The classical presentation of severe, recurrent, or unusual infections is increasingly recognized to be accompanied by immune dysregulation, including cytopenia, lymphoproliferation, and organ-specific autoimmunity. Early identification is essential, as timely interventions such as immunoglobulin replacement, antimicrobial prophylaxis, hematopoietic stem cell transplantation, and targeted biologic therapies significantly improve outcomes. This article provides an overview of the evolving understanding of PIDs, highlighting their clinical spectrum, diagnostic strategies, and therapeutic advances. By raising awareness among clinicians and health systems, it aims to reduce diagnostic delays and optimize patient care. Greater integration of molecular diagnostics, registries, and international collaboration is key to advancing precision medicine in the field of primary immunodeficiencies.

**Keywords:** Primary Immunodeficiency Diseases, Inborn Errors of Immunity, T cell defect.

## Introduction

The human immune system is an intricate network of organs, cells, and proteins essential for protecting the body from bacterial, viral, and fungal infections [1]. It secures the body by identifying and destroying destructive pathogens while conserving its own healthy cells. Primary immunodeficiency diseases (PIDs) constitute a diverse array of hereditary disorders marked by deficiencies in one or more elements of the immune system [2]. These conditions can manifest as autoimmunity, lymphoproliferation or malignancies, and recurrent, severe, or unusual infections. Individuals with PIDs are more susceptible to pathogens due to weakened immune defences. PIDs encompass a broad spectrum of diseases that impair the development, function, or regulation of the immune system. They are typically inherited and can follow autosomal or X-linked patterns.

Globally, primary immunodeficiency affects over 6 million individuals, however, an estimated 70% to 90% of these cases remain undiagnosed due to challenges in recognition and diagnosis. [3]. Over 400 varieties of primary immunodeficiency exist, differing in severity, which influences their detection timing [4]. The number of cases of untreated primary immunodeficiency considerably impacts morbidity and death, as lesser variants are frequently found late, often in adults, whereas severe versions manifest in infancy [5].

Primary Immunodeficiency Diseases (PID) are very important in paediatrics because many of them are present at birth and show up in infants or young children. Children with PID often get infections repeated, poor

respond to standard antibiotic treatments, and failure to thrive. If these infections have not been diagnosed and treated early, they can lead to serious long-term problems like organ damage, developmental delays, or even death. So, paediatricians need to keep an eye out for signs of PID so that they can diagnose and treat it quickly, which greatly improves the patient's quality of life and health. The purpose of this review is to examine recent advances in the understanding and management of Primary Immunodeficiency Diseases (PID), focusing on clinical manifestations, diagnostic approaches, and treatment options, with particular emphasis on their significance in paediatric populations.

## Classification

The group of Primary Immunodeficiency Diseases (PIDs) consists of more than 400 rare inherited disorders which affect the immune system development and operation [6]. People with PIDs experience multiple infections and higher chances of autoimmune diseases and sometimes develop cancer [7]. The disorders follow a systematic classification system recognised as IUIS Classification and continuously updated biennially [8].

The main category of combined immunodeficiency impacts both T-lymphocyte and B-lymphocyte immune system functions. The group includes Severe Combined Immunodeficiency (SCID) which causes life-threatening opportunistic infections and failure to thrive during infancy [9]. The disorders become fatal when left untreated so patients need hematopoietic stem cell transplantation as their only hope for survival [4]. The most prevalent form of PID consists of predominantly antibody deficiencies which result from insufficient immunoglobulin production [10]. The B-cell dysfunction in X-linked agammaglobulinemia and Common Variable Immunodeficiency (CVID) leads to recurring bacterial respiratory tract infections because T-cell function remains normal [11].

Various inherited defects of immunity can also be syndromic or involve immune deficiency along with defects of other organ systems. For example, DiGeorge syndrome is characterized by immune dysfunction plus congenital heart disease, hypocalcaemia, and distinctive facial characteristics, while Wiskott-Aldrich syndrome has a triad of eczema, thrombocytopenia, and immune deficiency [12]. There are also defined immune dysregulation disorders, which involve defects of mechanisms that would normally prevent autoimmunity. The most well-known example is IPEX syndrome due to mutations in the FOXP3 gene that can lead to severe autoimmune disease (e.g. enteropathy, endocrinopathies, dermatitis) [13].

Functional deficiencies of phagocytes such as chronic granulomatous disease (CGD) and the inability of immune cells to kill pathogens due to defective ROS generation are among the possible phagocyte defects [14]. Patients with CGD commonly present with deep-seated bacterial and fungal infections, especially catalase positive organisms, and granuloma formation [15]. Defects in pulmonary immunity, such as impairment in MyD88 or IRAK-4 that impairs early immune cell responses in addition to lack of pathogen recognition receptor signalling, result in susceptibility to significantly increased recurrent bacterial infection(s) [16]. In contrast, TLR3 contributed to susceptibility to herpes simplex virus encephalitis [16].

Auto inflammatory diseases are characterized by overwhelming and uncontrolled inflammation resulting from the fire-setting activity of the innate immune system. Diseases like Familial Mediterranean Fever, due to the MEFV gene mutations, present with recurrent episodes of fever, serositis, and systemic inflammation [17]. Complement deficiencies on the other hand, concern defective proteins in the complement cascade, resulting in an incapacity to clear immune complexes and susceptibility to infections [18]. Early component deficiencies (e.g., C1q, C2, and C4) are linked to autoimmune diseases, such as systemic lupus erythematosus, whereas terminal pathway deficiencies predispose to *Neisseria* infections [19].

Phenocopies of PIDs are defined as acquired disorders that resemble genetic PIDs in their clinical presentation, yet are caused by non-inherited factors, which include somatic genetic mutations or the production of host-derived autoantibodies directed against essential immune mediators [20]. These phenocopies may mimic inherited immunodeficiency and require a comprehensive and precise diagnostic assessment.

Early PIDs must be identified and diagnosed to prevent severe complications and differences in clinical outcome [21]. Therapeutic strategies should be aimed at the primary immunological abnormality e.g. immunoglobulin replacement therapy for defects of antibodies or curative measures (haematopoietic stem cell

transplantation) for severe combined immunodeficiency [22]. Advances in knowledge of PID pathogenesis have translated into the development of more specific treatments and better diagnostic options for improved care and long-term survival in these patients. Therefore, patients with recurrent, unusual, or severe infections and unexplained autoimmune or inflammatory manifestations should be adequately evaluated for the diagnosis, timely treatment, and correct management of primary immunodeficiencies [22].

### Clinical presentation

Primary immunodeficiency disorders (PID) embody a broad range of clinical presentation that affecting the immune system that have their own unique effect on immune system. Although it shares common symptoms with other conditions, careful diagnosis is essential to ensure accurate identification and appropriate treatment. People who suffer this diseases often experience recurrent or severe infection unlike healthy people. Most patients with antibody deficiency syndromes experience repeated infections with extracellular encapsulated bacteria, which can be resolved with proper antibiotic therapy [23].

Some patients with transient hypogammaglobulinemia or selective IgA deficiency may experience few or no infections. Patients with antibody deficiency rarely experience fungal or viral infections, with the exception of enterovirus. However, individuals with partial or complete impairments in T-cell function frequently have infections with low-grade or opportunistic bacterial, fungal, protozoal, and viral agents that are more severe than those in patients with antibody deficiency and for which there is no effective treatment [23]. Patients with primary T-cell defects rarely survive past infancy [23]. Individuals who have certain T-cell abnormalities may be both neutropenia and lymphopenia.

Severe combined immunodeficiency [SCID], are characterized by a near complete absence of immunological activity and functioning T cells. These conditions are uncommon and can be broadly classified as either T cell-deficient but B-cell-positive (T<sup>-</sup>, B<sup>+</sup>) or T and B-cell-deficient (T<sup>-</sup>, B<sup>-</sup>) [24]. In order to ascertain the genetic phenotype of SCID, natural killer (NK) cell counts are also important [25]. In addition to having the highest level of vulnerability to all types of infections, including opportunistic organisms, patients with SCID also completely lack of specialized immunity. They frequently have persistent diarrhea and failure to thrive [25].

B-cell immunodeficiency mainly manifest with recurrent sino-pulmonary infections with encapsulated bacteria, such as *Streptococcus pneumoniae* and *Haemophilus influenzae*, commonly commencing after 6 months of age. Additionally, patients may have fatigue, hearing loss, diarrhoea, and autoimmune symptoms [26].

Depending on the type of innate immune deficiency, symptoms may include autoimmune-like traits, poor wound healing, or frequent, severe infections. The Primary Immunodeficiency Resource Centre (Jeffrey Modell Foundation) listed 10 warning indicators to assist in identifying people with Primary Immunodeficiency Disease (PID) in table 1 and table 2.

Ten warning signs of PID in children
1. More than four ear infections in one year
2. More than two severe sinus infections in one year
3. More than two months treatment of antibiotics with little effect
4. More than two pneumonias over the year
5. Delay growth and insufficient weight gain
6. Recurrent organ or deep skin abscesses
7. Persistent fungal infection on skin or thrush in the mouth
8. Need for intravenous antibiotics to clear infections
9. More than two deep seated infection
10. Have a family history of a primary immunodeficiency
Source: Developed by the Jeffrey Modell Foundation Medical Advisory Board [27]

Table 1. Ten warning signs of PID in children as proposed by Jeffrey Modell Foundation

Ten warning signs of PID in adults
1. More than two ear infections in one year
2. More than two sinus infections in one year with absence of allergies
3. Recurrent need for intravenous antibiotics to clear infections
4. One pneumonias in a year for more than one year
5. Chronic diarrhoea with weight loss
6. Repeat viral infections
7. Persistent fungal infection on skin or thrush in the mouth or elsewhere
8. Recurrent, deep abscesses of internal organs or skin
9. Infection with normally harmless tuberculosis like bacteria
10. Have a family history of a primary immunodeficiency
<b>Source: Developed by the Jeffrey Modell Foundation Medical Advisory Board [27]</b>

Table 2. Ten warning signs of PID in adult as proposed by Jeffrey Modell Foundation

## Diagnostic method

The diagnostic approach for primary immunodeficiency disorders (PIDs) encompasses immunophenotyping, functional assays assessments, and genetic evaluation. The initial assessment often involves the quantification of T, B, and NK cells (TBNK) via flow cytometry to evaluate lymphocyte subsets, in addition to the detection of immunoglobulin levels (IgG, IgA, IgM). The evaluation of specific antibody responses (SAR) to vaccines like tetanus and pneumococcal assesses functional humoral immunity. Functional assays designed for suspected deficiencies, such as neutrophil oxidative burst tests for phagocyte diseases or lymphocyte proliferation assays for T-cell functionality, are also crucial. Genetic testing utilizing targeted gene panels encompassing over 500 genes associated with primary immunodeficiency (PID) or whole exome sequencing (WES) validates molecular diagnoses, informing management and familial counselling. This thorough approach is essential due to the diversity of primary immunodeficiency impacting various immunological compartments and functions.

The lymphocyte subset enumeration (TBNK) test is a flow cytometry-based assay that provides a quantitative measure of the predominant lymphocyte populations within the blood, T lymphocytes (CD3<sup>+</sup>), B lymphocytes (CD19<sup>+</sup>), and natural killer (NK) lymphocytes (CD16<sup>+</sup>/CD56<sup>+</sup>) [28]. The test is performed on venous blood collected in EDTA tubes [28]. Upon collection, the white blood cells (WBCs) from peripheral blood are stained with fluorescent-labelled monoclonal antibodies that bind specifically to these surface markers [29]. Once red blood cells have been lysed, the blood sample is analysed by flow cytometry. Flow cytometry counts and classifies lymphocytes based on the fluorescence intensity of the binding antibodies [28]. Results are reported as percentages and absolute counts of total T cells (CD3<sup>+</sup>), T-helper cells (CD4<sup>+</sup>), T-cytotoxic cells (CD8<sup>+</sup>), B-cells (CD19<sup>+</sup>), and NK cells (CD16<sup>+</sup>CD56<sup>+</sup>) groupings [30]. Age-related reference ranges are provided for interpretation [31]. Absolute counts are calculated using either internal bead standards or volumetric methods and there is ancillary reporting for further differentiation, such as the CD4/CD8 ratio [32]. Thus, the application of the TBNK test is key in the diagnosis of immunodeficiency and monitoring associated changes in the immune system. For example, a severe decline or absence of T cells from the above measurement indicates an increased likelihood of immunodeficiency for example Severe Combined Immunodeficiency- SCID and Di George Syndrome while the absence of a normal or near normal level of CD19 B cells may warrant an assessment for X-linked agammaglobulinemia. Reduced counts of NK cells can be genuinely found in GATA2 deficiency [30]. Furthermore, the assay is useful for monitoring immune status in HIV infection and other therapies depleting B cells, such as rituximab [30]. It is also an essential screening tool that can serve an important purpose for directing the diagnostic work up and treatment plans for abnormalities of the immune system [29].

Assessment of serum immunoglobulin levels--IgG, IgA, IgM, and sometimes IgE, is important for the evaluation of primary immunodeficiency diseases (PIDs) particularly those that are characterized by defects in humoral immunity. Each immunoglobulin performs different functions in host defence such as IgG which is the most abundant antibody in serum providing long-term immunity by neutralizing pathogens, opsonizing microbes and activating complement, IgA is the most abundant antibody in mucosal surfaces, such as the respiratory tract and gastrointestinal tract and prevents pathogen adherence and invasion, while IgM is the first antibody produced in response to a pathogen, it is also effective in activating complement and IgE is the least abundant and plays an important role in allergic reactions, and activation of mast cells against parasites [33].

In PIDs such as X-linked agammaglobulinemia (XLA), common variable immunodeficiency (CVID), and selective IgA deficiency (SIgAD), immunoglobulin levels are markedly abnormal. In XLA, nearly all classes of immunoglobulin are absent because of a developmental arrest in the maturation of B cell, and in CVID there is often low IgG but low IgA or IgM, with near-normal B cell counts. An absolute serum IgG concentration of less than approximately 200 mg/dL (2 g/L) is typically suggestive of significant antibody deficiency, but this must be further interpreted in conjunction with the patient's age and clinical context [34].

Serum immunoglobulin levels substantially lower than the normal range for a patient's age may indicate B-cell immunodeficiency. However, some individuals with B-cell immunodeficiency may have normal and only modestly decreased immunoglobulin levels. Due to this issue, antibody deficiency diagnosis is confirmed by measuring a patient's specific antibody responses (usually IgG) to vaccines. This involves immunizing the patient with protein antigens such as tetanus toxoid, and polysaccharide antigens such as pneumococcal vaccines. Serum antibody levels are obtained before and after vaccination, and in many primary immunodeficiency diseases, these antibody responses are absent or reduced [35].

Assessing specific antibody responses provoked by vaccines, such as a pneumococcal vaccine or a tetanus vaccine, is a fundamental way to assess functional humoral immunity in situations where antibody impairment is suspected but total immunoglobulin levels are normal. By measuring serotype-specific IgG antibodies towards 23-valent pneumococcal polysaccharide vaccine before and approximately 4 to 8 weeks after vaccination, vaccines can assess the functional humoral immune response and the production of T-cell independent antibody. A protective response typically defined as a four fold increase (or reaching a threshold of 1.3 µg/mL) in the majority (50–70%) of serotypes tested is evidence of normal B cell function and thus evidence that a defect with a component of humoral immunity (like SAD) is not present [36]. Tetanus vaccination assesses a T-cell dependent response by measuring IgG antibodies directed against tetanus toxoid [37]. Some inadequate responses may also indicate a more severe or combined immunodeficiency state if present. In summary, vaccine response testing provides critical functional information that goes beyond measuring static levels of immunoglobulins.

Whole Exome Sequencing (WES) and targeted genetic panels are crucial genetic methods in the diagnosis of primary immunodeficiency diseases (PIDs) [38]. WES sequences the entire exome of the genome in an unbiased manner, which is ideal especially when patients have complicated or unusual presentations that do not fall into known PID categories [39]. This approach has the potential to find rare or even novel genetic mutations that might otherwise be missed. It should be noted that WES requires specialized skill-set for analysis and interpretation; has a long turnaround time for interpretation can yield a significant number of variants of uncertain significance (VUS) and uninformative incidental findings that have no relevance to the patient's immune function [40]. Conversely, targeted gene panels are focused on curated list of PID associated genes, allowing for deeper coverage, quicker turnaround time, cost-effective testing, and easier interpretation of results which is preferable for patients presenting with classic clinical presentations and suggestive of known PIDs [40]. Clinician preference generally begins with targeted panel testing if the clinical features are clearly indicative of a familiar PID but will move to WES if negative or to further work-up of atypical or vague clinical symptoms of either unknown constellations of immunodeficiency or congenital immune depletion tend to warrant a more generic approach [38]. Some centres even claim that WES is considered the first-line investigation in atypical or multisystemic cases in order to maximize the diagnostic yield of next generation sequencing [41]. Targeted panels provide a relatively efficient pathway for uncomplicated cases while WES maximizes diagnostic utility for more complex cases [40]. The selection of one or the other depends on the clinical context, available resources, and specific aims of diagnosis, or patient management [40].

## Therapeutic Approach

Primary immunodeficiency diseases with chronic or severe diseases often need a lifelong therapy to prevent infection that severe or recurrent. This therapeutic approach is critical for improving disease development, minimizing complications, and improving patient health. The management of this diseases generally includes immunoglobulin replacement therapy to enhance immune function, antibiotics to reduce infection risk, and hematopoietic stem cell transplantation.

Individuals with immunodeficiency disorders that result in low levels or dysfunction of IgG often receive immunoglobulin replacement. Immunoglobulin G (IgG) is a type of antibody present in blood plasma. IgG used

for this treatment is a plasma-derived product obtained from healthy donors. The therapy can be administered either intravenously on a monthly basis or subcutaneously once a week or biweekly. Both routes are effective in restoring IgG to sufficient levels for infection protection [42]. The initial recommended dose for immunoglobulin (Ig) replacement therapy is typically 400–600 mg/kg every 4 weeks for intravenous (IV) administration and 100–150 mg/kg per week for the subcutaneous (SC) route [43]. The dosage adjustments may be necessary according to infection frequency which is important to monitor level of IgG regularly. Lower IgG trough levels have been linked to the worsening of chronic lung disease, even in patients without obvious symptoms [44]. This highlights the importance of maintaining adequate serum IgG levels, and clinicians should consider increasing the dose if the patient shows deteriorating lung function or continues to suffer from recurrent infections. In cases of frequent infections, preventive antibiotic therapy especially targeting *Streptococcus pneumoniae* and *Haemophilus influenzae* might be required in addition to Ig therapy. Depending on the specific B-cell immunodeficiency, antifungal prophylaxis may also be necessary.

Routine hearing evaluations and pulmonary monitoring are advised because B-cell disorders can be linked to hearing impairments and lung complications, Similar to T-cell deficiencies, patients with B-cell disorders should also be closely monitored for signs of malignancy and autoimmune diseases [45].

The long term antibiotics prophylaxis are crucial in improving the survival of individual with primary immunodeficiency diseases aiming to reduce the severity and frequency of infections [46]. Antibiotic therapy, particularly of azithromycin and trimethoprim-sulfamethoxazole (TMP-SMX), is a standard in preventing infective complications of the majority of primary immunodeficiency (PID), from chronic granulomatous disease (CGD) to severe combined immunodeficiency (SCID) and antibody deficiencies such as common variable immunodeficiency (CVID) [47]. TMP-SMX remains the drug of choice for prophylaxis of *Pneumocystis jirovecii* pneumonia, while azithromycin has been found effective in reducing the frequency of pulmonary exacerbations and preserving respiratory function in antibody-related immunodeficiency [48].

Hematopoietic cell transplantation (HSCT) is a key component of a permanent cure for SCID. Strong and long-lasting immunity reconstitution and over 90% long-term survival are guaranteed when the transplant is carried out with a HLA- matched sibling donor. HSCT from related donors who are HLA-mismatched can also produce excellent results, particularly if done during the first three and a half months of life [49]. The methodology for HSCT and the associated risk has evolved significantly over the last twenty years, with an increase in potential donor sources, improved targeting of preparatory chemotherapy protocols, and enhanced supportive care [50].

## Conclusion

Primary immunodeficiencies represent a diverse and evolving group of disorders that extend beyond recurrent infections to encompass immune dysregulation, autoimmunity, and malignancy. Advances in molecular diagnostics and newborn screening have transformed the landscape of early detection, while novel targeted therapies offer the promise of precision medicine. However, disparities in access to diagnostic resources and treatment remain a major global challenge. Strengthening awareness among clinicians, expanding registry data, and fostering international collaboration are essential to improve timely recognition and optimize patient outcomes. Ultimately, integrating clinical expertise with genetic and immunological insights will be key to advancing care for individuals with primary immunodeficiencies.

## References

1. Department of Health & Human Services. Immune system explained [Internet]. Better Health Channel. Available from: <https://www.betterhealth.vic.gov.au/health/conditionsandtreatments/immune-system>
2. McCusker C, Upton J, Warrington R. Primary immunodeficiency. Allergy Asthma and Clinical Immunology [Internet]. 2018 Sep 1; 14(S2). Available from: <https://doi.org/10.1186/s13223-018-0290-5>
3. Meyts I, Bousfiha A, Duff C, Singh S, Lau YL, Condino-Neto A, et al. Primary immunodeficiencies: a decade of progress and a promising future. Frontiers in Immunology [Internet]. 2021 Feb 18; 11. Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC7935502/>
4. CDC. [Internet]. Primary Immunodeficiency (PI). 2024. Available from:

- <https://www.cdc.gov/primary-immunodeficiency/about/index.html>
5. Bahrami A, Sayyahfar S, Soltani Z, Khodadost M, Moazzami B, Rezaei N. Evaluation of the frequency and diagnostic delay of primary immunodeficiency disorders among suspected patients based on the 10 warning sign criteria: A cross-sectional study in Iran. [Internet]. 2020 May 11; 48(6):711–9. Available from: <https://www.elsevier.es/es-revista-allergologia-et-immunopathologia-105-articulo-evaluation-frequency-diagnostic-delay-primary-S0301054620300641>
  6. McCusker C, Upton J, Warrington R. Primary immunodeficiency. *Allergy Asthma and Clinical Immunology* [Internet]. 2018 Sep 1; 14(S2). Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC6157160/>
  7. McCusker C, Warrington R. Primary immunodeficiency. *Allergy Asthma and Clinical Immunology* [Internet]. 2011 Nov 10; 7(S1). Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC3245434/>
  8. Bousfiha, A., Mounir, A., Tangye, S.G. et al. The 2022 Update of IUIS Phenotypical Classification for Human Inborn Errors of Immunity. *J Clin Immunol* 42, 1508–1520 (2022). <https://doi.org/10.1007/s10875-022-01352-z>
  9. Aranda CS, Guimarães RR, De Gouveia-Pereira Pimentel M. Combined immunodeficiencies. *Jornal De Pediatria* [Internet]. 2020 Dec 17; 97:S39–48. Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC9432339/>
  10. Fried AJ, Bonilla FA. Pathogenesis, diagnosis, and management of primary antibody deficiencies and infections. *Clin Microbiol Rev* [Internet]. 2009 Jul 1; 22(3):396–414. Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC2708392/>
  11. Immunodeficiency UK. Primary antibody deficiency - Immunodeficiency UK [Internet]. Immunodeficiency UK. 2025. Available from: <https://www.immunodeficiencyuk.org/immunodeficiency/primary-immunodeficiency/primary-antibody-deficiency/>
  12. Poplonyk AS, Begier K, Dorota A, Dabrowska M, Galecka D, Wawrzyniak K. Syndromic immunodeficiencies: A paediatricians perspective on selected diseases. *Allergologia et immunopathologia*, 2021. Doi:10.15586/aei.v49i4.200
  13. Immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome: MedlinePlus Genetics [Internet]. Available from: <https://medlineplus.gov/genetics/condition/immune-dysregulation-polyendocrinopathy-enteropathy-x-linked-syndrome/>
  14. Wolfe LC, Keefe E. Pediatric Chronic Granulomatous Disease. *eMedicine* [Internet]. Available from: <https://emedicine.medscape.com/article/956936-overview#a5>
  15. Dinuer MC. Chronic granulomatous disease and other disorders of phagocyte function. *Hematology* [Internet]. 2005 Jan 1; 2005(1):89–95. Available from: <https://pubmed.ncbi.nlm.nih.gov/16304364/>
  16. Maglione PJ, Simchoni N, Cunningham-Rundles C. Toll-like receptor signaling in primary immune deficiencies. *Annals of the New York Academy of Sciences* [Internet]. 2015 Apr 30; 1356(1):1–21. Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC4629506/>
  17. Jeong DC. Systemic autoinflammatory disorders. *Clinical and Experimental Pediatrics* [Internet]. 2023 Jun 19; 66(10):432–8. Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC10556796/>
  18. Complement blood test [Internet]. Available from: <https://medlineplus.gov/lab-tests/complement-blood-test/>
  19. Complement deficiencies | Immune Deficiency Foundation [Internet]. Available from: <https://primaryimmune.org/understanding-primary-immunodeficiency/types-of-pi/complement-deficiencies>
  20. Singh A, Jindal AK, Joshi V, Anjani G, Rawat A. An updated review on phenocopies of primary immunodeficiency diseases. *Genes & Diseases* [Internet]. 2019 Sep 24; 7(1):12–25. Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC7063430/>
  21. Battersby AC, Cant AJ. Advances in primary immunodeficiencies. *Paediatrics and Child Health*. 2017; 27:116–120. Available from doi:10.1016/j.paed.2016.11.001.
  22. Primary immunodeficiencies (PID) clinical update. Australian Society of Clinical Immunology and Allergy [Internet]. 2025. Available from: [https://www.allergy.org.au/images/stories/stories/pospapers/ASCIA\\_HP\\_Clinical\\_Update\\_PID\\_2025.pdf](https://www.allergy.org.au/images/stories/stories/pospapers/ASCIA_HP_Clinical_Update_PID_2025.pdf)

23. Buckley RH. Advances in the diagnosis and treatment of primary immunodeficiency diseases. *Arch Intern Med* [Internet]. 1986; 146(2):377. Available from: <https://doi.org/10.1001/archinte.1986.00360140207031>
24. McCusker C, Upton J, Warrington R. Primary immunodeficiency. *Allergy Asthma Clin Immunol*. 2018; 14:61. doi:10.1186/s13223-018-0290-5
25. Bonilla FA, Khan DA, Ballas ZK, Chinen J, Frank MM, Hsu JT, et al. Practice parameter for the diagnosis and management of primary immunodeficiency. *Journal of Allergy and Clinical Immunology* [Internet]. 2015; 136(5):1186-1205.e78. Available from: <https://doi.org/10.1016/j.jaci.2015.04.049>
26. McCusker C, Upton J, Warrington R. Primary immunodeficiency. *Allergy Asthma and Clinical Immunology* [Internet]. 2018 Sep 1; 14(S2). Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC6157160/#CR14>
27. Jeffrey Modell Foundation. 10 warning signs of primary immunodeficiency [Internet]. [info4pi.org](http://info4pi.org). Available from: <https://info4pi.org/library/educational-materials/>
28. Lymphocyte subsets (TBNK) - North West London Pathology [Internet]. North West London Pathology. Available from: <https://www.nwlp pathology.nhs.uk/tests-database/lymphocyte-subsets-tbnk/>
29. BD MultiTest™ 6-Color TBNK Kit | BD Biosciences [Internet]. BD Biosciences | Flow Cytometry Instruments and Reagents. 2023. Available from: <https://www.bdbiosciences.com/en-eu/products/reagents/flow-cytometry-reagents/clinical-diagnostics/multitest-6-color-tbnk-kit>
30. Lymphocyte surface marker analysis: CD4 count; TBNK Immunology Laboratory Oxford University Hospitals [Internet]. Available from: <https://www.ouh.nhs.uk/immunology/diagnostic-tests/tests-catalogue/lymphocyte-surface-marker-analysis/>
31. Apoil PA, Puissant-Lubrano B, Congy-Jolivet N, Peres M, Tkaczuk J, Roubinet F, et al. Reference values for T, B and NK human lymphocyte subpopulations in adults. *Data in Brief* [Internet]. 2017 Apr 21; 12:400–4. Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC5415546/>
32. Ward RY, Stevens M, Bashir S. Metrological traceability in flow cytometry? Evaluation of a new volumetric method for lymphocyte subsets. *International Journal of Laboratory Hematology* [Internet]. 2023 Dec 19; 46(3):488–94. Available from: <https://doi.org/10.1111/ijlh.14219>
33. Janeway CA Jr, Travers P, Walport M, Shlomchik MJ. The distribution and function of immunoglobulin isotype. *Immunobiology-NCBI Bookshelf* [Internet]. 2001. Available from <https://www.ncbi.nlm.nih.gov/books/NBK27162/>
34. Rezaei N, Hedayat M, Aghamohammadi A, Nichols KE. Primary immunodeficiency diseases associated with increased susceptibility to viral infections and malignancies. *Journal of Allergy and Clinical Immunology* [Internet]. 2011 Apr 25; 127(6):1329-1341.e2. Available from: <https://doi.org/10.1016/j.jaci.2011.02.047>
35. McCusker C, Upton J, Warrington R. Primary immunodeficiency. *Allergy Asthma and Clinical Immunology* [Internet]. 2018 Sep 1; 14(S2). Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC6157160/#Sec10>
36. Hansen AT, Söderström A, Jørgensen CS, Larsen CS, Petersen MS, Jensen JMB. Diagnostic vaccination in clinical practice. *Frontiers in Immunology* [Internet]. 2021 Sep 30; 12. Available from: <https://doi.org/10.3389/fimmu.2021.717873>
37. Orange JS, Ballou M, Stiehm ER, Ballas ZK, Chinen J, De La Morena M, et al. Use and interpretation of diagnostic vaccination in primary immunodeficiency: A working group report of the Basic and Clinical Immunology Interest Section of the American Academy of Allergy, Asthma & Immunology. *Journal of Allergy and Clinical Immunology* [Internet]. 2012; 130(3):S1–24. Available from: <https://doi.org/10.1016/j.jaci.2012.07.002>
38. Vorsteveld EE, Hoischen A, Van Der Made CI. Next-Generation Sequencing in the field of primary immunodeficiencies: current yield, challenges, and future perspectives. *Clinical Reviews in Allergy & Immunology* [Internet]. 2021 Mar 5; 61(2):212–25. Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC7934351/>

39. Borghesi A, Trück J, Asgari S, Sancho-Shimizu V, Agyeman PKA, Bellos E, et al. Whole-Exome sequencing for the identification of rare variants in primary immunodeficiency genes in children with sepsis: a prospective, population-based cohort study. *Clinical Infectious Diseases* [Internet]. 2020; 71(10):e614–23. Available from: <https://doi.org/10.1093/cid/ciaa290>
40. Engelbrecht C, Urban M, Schoeman M, Paarwater B, Van Coller A, Abraham DR, et al. Clinical utility of whole exome sequencing and targeted panels for the identification of inborn errors of immunity in a Resource-Constrained setting. *Frontiers in Immunology* [Internet]. 2021 May 21; 12. Available from: <https://doi.org/10.3389/fimmu.2021.665621>
41. Simon AJ, Golan AC, Lev A, Stauber T, Barel O, Somekh I, et al. Whole exome sequencing (WES) approach for diagnosing primary immunodeficiencies (PIDs) in a highly consanguineous community. *Clinical Immunology* [Internet]. 2020 Mar 3; 214:108376. Available from: <https://doi.org/10.1016/j.clim.2020.108376>
42. Immunoglobulin (IGG) Replacement Therapy defined | AAAAI [Internet]. Available from: [https://www.aaaai.org/tools-for-the-public/allergy,-asthma-immunology-glossary/immunoglobulin-\(igg\)-replacement-therapy-defined](https://www.aaaai.org/tools-for-the-public/allergy,-asthma-immunology-glossary/immunoglobulin-(igg)-replacement-therapy-defined)
43. Shehata N, Palda V, Bowen T, Haddad E, Issekutz TB, Mazer B, et al. The Use of Immunoglobulin therapy for Patients with Primary Immune Deficiency: An Evidence-Based Practice Guideline. *Transfusion Medicine Reviews* [Internet]. 2009 Dec 4; 24:S28–50. Available from: <https://doi.org/10.1016/j.tmr.2009.09.011>
44. Janssen WJM, Hoesein FM, Van De Ven AAJM, Maarschalk J, Van Royen F, De Jong PA, et al. IgG trough levels and progression of pulmonary disease in pediatric and adult common variable immunodeficiency disorder patients. *Journal of Allergy and Clinical Immunology* [Internet]. 2017 Jan 23; 140(1):303-306.e4. Available from: <https://doi.org/10.1016/j.jaci.2016.11.050>
45. McCusker C, Upton J, Warrington R. Primary immunodeficiency. *Allergy Asthma and Clinical Immunology* [Internet]. 2018 Sep 1; 14(S2). Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC6157160/#Sec11>
46. Marciano BE, Holland SM. Primary Immunodeficiency Diseases: Current and emerging therapeutics. *Frontiers in Immunology* [Internet]. 2017 Aug 8; 8. Available from: <https://doi.org/10.3389/fimmu.2017.00937>
47. Ballou M, Division of Allergy & Immunology, John Hopkins All Children's Hospital, University of South Florida. Prophylactic Antibiotics for Patients with Immunodeficiency. Should Prophylactic Antibiotics Be Used in Primary Antibody Immune Deficiency? [Internet]. Available from: <https://primaryimmune.org/sites/default/files/FOR%20WEB%20-%20Prophylactic%20Antibiotics%20PI.pdf>
48. Hanitsch L, Baumann U, Boztug K, Burkhard-Meier U, Fasshauer M, Habermehl P, et al. Treatment and management of primary antibody deficiency: German interdisciplinary evidence-based consensus guideline. *European Journal of Immunology* [Internet]. 2020 Aug 26; 50(10):1432–46. Available from: <https://doi.org/10.1002/eji.202048713>
49. Notarangelo LD. Primary immunodeficiencies. *Journal of Allergy and Clinical Immunology* [Internet]. 2009 Dec 30; 125(2):S182–94. Available from: <https://doi.org/10.1016/j.jaci.2009.07.053>
50. Segundo GRS, Condino-Neto A. Treatment of patients with immunodeficiency: Medication, gene therapy, and transplantation. *J Pediatr* [Internet]. 2020 Nov 9; 97:S17–23. Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC9432285/>