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Inborn Errors of Immunity: New Insights

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Abstract
This paper presents a comprehensive and updated overview of inborn errors of immunity (IEIs), focusing on the optimal treatment strategies. IEIs or primary immunodeficiencies (PIDs) are a heterogeneous group of approximately 500 disorders, classified into ten categories according to the affected component of the immune system. The clinical presentation varies, based on the type of the disorder and the patient's age. Early diagnosis is essential to prevent recurrent severe infections and potential organ damage. Treatment strategies, including hematopoietic stem cell transplantation, enzyme replacement therapy, thymus transplantation, or gene therapy, primarily focus to restore immune function. Emerging therapeutic approaches aiming to modify the immune response comprise small molecule inhibitors, biological therapies, and adoptive transfer of virus-specific T-cells. Given the complexity and diversity of PIDs, as well as evolving novel therapies, continuous education of the physicians on timely diagnosis and effective intervention, significantly improves patients' management and outcomes. **Conclusion.** Early diagnosis and individualized treatment plans are crucial for effectively managing IEIs. As treatment options evolve, ongoing education and the integration of new approaches are key to improving patient outcomes and quality of life.

Key Words: Inborn Errors of Immunity ▪ Bone Marrow Transplantation ▪ Gene Therapy ▪ Biological Therapy.

Introduction

Primary immunodeficiencies (PIDs) are a diverse group of inherited disorders that are typically caused by pathogenic germline variants in single genes. These alterations result in specific disruptions in the development and function of the immune system. It has been recently proposed to replace the term "PIDs" with "inborn errors of immunity" (IEIs) to emphasize the diversity of clinical presentations, including not only immune deficiencies, but also excessive or dysfunctional immune responses (1).

IEIs present clinically as increased susceptibility to infections, autoimmunity, autoinflammatory diseases, bone marrow failure, and/or malignancy. The estimated prevalence ranges from 1 to 5 per 1,000 individuals (2). Over the past two decades, advances in genomic analysis, combined with biochemical and cellular testing, have enabled a more precise identification of IEIs (3), with more than 480 classified disorders nowadays compared to approximately 150 in 2009 (4, 5). Better classification, based on the underlying molecular, cellular, and immunological mechanisms, led to significant improvements in management and outcome (4).

Many IEIs, such as severe combined immunodeficiency (SCID), have been effectively treated for several decades with hematopoietic stem cell transplantation (HSCT) (5). Recently, precision medicine strategies have emerged, including the targeted modulation of intracellular pathways affected by genetic alterations, and gene therapy using viral vectors for selected disorders (6).

The aim of this review is to provide a comprehensive and updated overview of IEIs, with a particular focus on optimal treatment strategies. By

exploring the classification, clinical presentation, and advancements in therapeutic approaches, this review highlights the importance of early diagnosis and tailored interventions in improving patient outcomes. Furthermore, it underscores the role of emerging therapies and the need for continuous education among healthcare professionals to enhance the management of these complex disorders.

Classification

The most recent classification identifies a total of 485 distinct IEIs. The International Union of Immunological Societies (IUIS) divides IEIs into nine main categories, based on the component of the immune system affected and most likely clinical presentation. A tenth category encompasses IEI phenocopies (Table 1). Each category of IEI is characterized by unique pattern of infections, autoimmunity, and/or inflammation, which aids in guidance for the initial diagnostic evaluation (2).

Category I - Combined Immunodeficiencies without Syndromic Features

This category includes combined immunodeficiencies (CIDs) that affect both cellular and humoral immunity but lack distinct syndromic features. Patients with T-cell lineage defects are predisposed to a range of viral, fungal, and bacterial infections, including opportunistic infections (e.g., *Pneumocystis jirovecii* pneumonia) and adverse reactions to live vaccines (e.g., measles, mumps, rubella, and varicella) (1). SCID is the most severe disorder within this category, typically manifesting in early childhood (7). While the most common SCID type is X-linked, autosomal recessive inheritance also exists, caused by mutations in genes such as Janus kinase 3 (*JAK3*), protein tyrosine phosphatase, and recombination activation genes *RAG1* and *RAG2* (8). Another autosomal recessive form is adenosine deaminase (ADA) deficiency, caused by mutations in the *ADA* gene, which result in the toxic accumulation of metabolites that are particularly harmful to developing lymphocytes, leading to profound defects in both T- and B-cell immunity (7).

Table 1. IUIS* Classification of Primary Immunodeficiencies

Category	Primary immunodeficiency	Genetic defects (N†)
I	Cellular and humoral immunodeficiencies	60
II	Syndromic combined immunodeficiencies	65
III	Antibody deficiencies	43
IV	Immune dysregulatory diseases	47
V	Phagocytic diseases	42
VI	Innate immunodeficiencies	71
VII	Autoinflammatory diseases	49
VIII	Complement deficiencies	36
IX	Diseases due to bone marrow failure	43
X	Phenocopies of PIDs‡	13
Total		469

*International Union of Immunological Societies; †Number; ‡Primary immunodeficiencies.

Category II - Combined Immunodeficiencies with Syndromic Features

This heterogeneous group consists of CIDs with distinctive clinical features and well-defined underlying immune system abnormalities. Chediak-Higashi syndrome (CHS) is a rare autosomal recessive disorder caused by mutations in the *LYST* gene, impacting lysosomal trafficking and resulting in partial oculocutaneous albinism, immunodeficiency, and mild bleeding tendency. Around 85% of CHS patients progress to an accelerated phase or hemophagocytic lymphohistiocytosis (9). Wiskott-Aldrich syndrome (WAS) is an X-linked rare condition, caused by mutations in *WASP* gene that encodes the Wiskott-Aldrich syndrome protein (WASP), essential for B- and T-cell signaling. WAS presents with purpura, bleeding tendency, eczema, and recurrent infections. DiGeorge syndrome is characterized by congenital heart defects, craniofacial abnormalities, thymic dysgenesis or agenesis, and developmental delays. It is primarily caused by deletions in the 22q11 region or mutations in genes at chromosome 10p13 (7).

Category III - Predominantly Antibody Deficiencies

Predominantly antibody deficiencies are the most common type of PIDs, characterized by recurrent bacterial infections particularly in the upper and lower respiratory tract, such as otitis, sinusitis, and pneumonia. The genetic basis is diverse, reflecting the immunological heterogeneity of these disorders. Mutations in genes such as *BTK* (Bruton tyrosine kinase), *CD3γ*, *CD40L*, and *ZAP-70* contribute to the variability in the clinical presentation and underlying mechanisms (4). X-linked agammaglobulinemia (XLA) or Bruton agammaglobulinemia is caused by mutations in *BTK* gene on the X chromosome, that lead to a severe block in B-cell development and immunoglobulin (Ig) production (10).

Category IV - Immune Dysregulation Diseases

This group involves defects in self-tolerance mechanisms, either central or peripheral, which often lead to autoimmunity or significant lymphoproliferation. Autoimmune lymphoproliferative syndrome (ALPS) is characterized by impaired lymphocyte homeostasis. Initial manifestations typically include lymphocyte expansion with lymphadenopathy, splenomegaly, and hepatomegaly, as well as cytopenias, including thrombocytopenia and hemolytic anemia, and lymphoma in later stages. ALPS is caused by germline and somatic variants in the *FAS* gene (specifically *ALPS-FAS* and *ALPS-sFAS*), which hinder Fas/Fas ligand (FasL)-mediated apoptosis necessary for lymphocyte regulation. In addition to *FAS*, mutations in other genes, such as *FASLG* (encoding Fas ligand) and *CASP10* (encoding caspase-10), have been implicated in ALPS. These mutations disrupt the apoptotic pathways critical for immune homeostasis, leading to the accumulation of autoreactive lymphocytes and associated clinical features (11).

Category V - Phagocyte Number/Function Defects

This category includes disorders affecting the number and/or function of phagocytes. Neutrophils, essential for pathogen clearance via phagocytosis and activation of proteolytic enzymes, are the first line of immune defense. Patients with compromised phagocytosis typically suffer from severe bacterial and fungal infections. Chronic granulomatous disease (CGD) is characterized by inability of phagocytes to produce reactive oxygen species, leading to impaired microbial killing. Clinical manifestations include recurrent infections, granulomatous lesions in the lungs, liver, lymph nodes, and gastrointestinal tract, lymphadenopathy, hypergammaglobulinemia, and anemia. CGD is inherited in an X-linked and autosomal recessive pattern (12). The X-linked form of CGD is caused by mutations in the *CYBB* (Cytochrome B[-245] Beta chain) gene. The autosomal recessive forms are caused by mutations in *CYBA* (Cytochrome B[-245] Alfa chain), *NCF1* (Neutrophil Cytosolic Factor 1) and *NCF2* (Neutrophil Cytosolic Factor 2) genes (4).

Category VI - Defects in Intrinsic and Innate Immunity

This group encompasses a wide range of disorders resulting from defects in innate immune system, such as natural killer (NK) cells, Toll-like receptors (TLRs), various cytokines and other essential signaling molecules. Chronic mucocutaneous candidiasis involves persistent or recurrent *Candida* infections limited to mucous membranes, skin, and nails, due to T-cell defects. It is inherited in an autosomal dominant pattern linked to *STAT1* mutations or in an autosomal recessive pattern, most commonly linked to mutations in *AIRE* gene (13).

Category VII - Autoinflammatory Disorders

Autoinflammatory disorders are characterized by excessive activation of the innate immune system, leading to the overproduction of proinflammatory cytokines and subsequent tissue damage. Familial Mediterranean Fever is an autosomal recessive disorder caused by mutations in the *MEFV* gene which encodes pyrin (a protein found in neutrophils), resulting in recurrent fever, peritonitis, arthritis, pleuritis, skin lesions, and, in some cases, renal amyloidosis with kidney failure (14).

Category VIII - Complement Deficiencies

This group of disorders include deficiencies in the complement system, as an integral component of innate immunity. Early deficiencies in the classical component pathway (C1q, C1r, C1s, C2, C4) are associated with increased susceptibility to infections, often by encapsulated bacteria, and with autoimmune diseases such as systemic lupus erythematosus (SLE). Terminal complement component deficiencies (C5 to C9) present as recurrent meningitis, particularly with *Neisseria*. Factor H and Factor I deficiencies, affecting complement regulation, may cause atypical hemolytic uremic syndrome or increased susceptibility to *Neisseria*, depending on the underlying mutation. Hereditary angioedema results from a deficiency or dysfunction of C1 inhibitor (C1-INH), which regulates the classical and lectin complement activation, as well as kinin, procoagulant, and fibrinolytic pathways. The main manifestations are recurrent episodes of the facial, oral, and upper airway swelling (15).

Category IX - Bone Marrow Failure Defects

Bone marrow failure syndromes include genetic conditions that affect hematopoiesis, and are often accompanied by significant immune dysfunction. Fanconi anemia (FA) is autosomal recessive disorder, associated with more than 23 FA complementation genes (*FANC*) which are all involved in DNA repair. Most patients present with skeletal abnormalities or other congenital malformations, including short stature, skin, eyes, ears, heart, urinary tract, gonads, gastrointestinal tract, and central nervous system. Bone marrow failure typically occurs by the age of seven, and almost all patients experience this complication by age 40 years. There is an increased risk for developing hematological malignancies (myelodysplastic syndrome, acute myeloid leukemia) and solid tumors (squamous cell cancers of skin and head/neck/tongue, skin basal cell carcinoma, anogenital cancers) (16).

Category X - IEI phenocopies

This group includes disorders that exhibit symptoms resembling those of IEIs. They are characterized by somatic mutations (as opposed to germline mutations in IEIs) or are associated with the presence of autoantibodies (17).

Diagnosis

In children with recurrent infections, especially those confined to a single organ system, the underlying causes are often related to increased exposure to pathogens, allergies, or anatomical abnormalities, rather than immune defects. However, a significant number of PIDs remain undiagnosed or are misdiagnosed, leading to extended periods of inappropriate or ineffective treatment. Therefore, early identification and accurate diagnosis of PIDs are essential to achieve favorable patient outcomes (18).

History and Physical Examination

In a child with the suspected IEI, a detailed medical history and thorough physical examination can often help narrow the diagnosis to the specific component of the immune system. Various diagnostic models have been developed to differentiate PIDs from those with other causes of recurrent infections. These models assume that children with PIDs are more likely to experience serious, persistent, unusual and/or recurrent infections, often referred to as "SPUR" infections. The models serve as valuable tools for raising suspicion of PIDs, which in turn prompts a more focused diagnostic approach.

The European Society for Immunodeficiencies (ESID) developed guidelines for the assessment of patients with suspected PID, which were updated in 2011, and categorize these disorders into seven clinically recognizable presentation patterns (Table 2) (19). O'Sullivan and Cant proposed several key warning signs of PIDs in the first year of life, which warrant prompt evaluation and referral to an immunologist. These signs include chronic oral thrush, persistent diarrhea, failure to thrive,

Table 2. Clinical Presentation of Primary Immunodeficiencies

Clinical presentation	Other relevant indicators	Possible immune deficiency
Frequent ENT* and lower respiratory tract infections	Bronchiectasis	Antibody deficiency Phagocytic diseases Wiskott-Aldrich syndrome Complement deficiencies
Failure to thrive from early infancy	Persistent diarrhea, rashes, or *Candida* infections	T-lymphocyte deficiencies Severe combined immunodeficiency Neutrophil disorders
Recurrent pyogenic infections	Inflammation with poor wound recovery Chronic granulomatous inflammation due to *Aspergillus* or *Burkholderia*	Neutrophil disorders Chronic granulomatous disease
Severe and/or unusual infections	Pneumococcal meningitis Herpes simplex encephalitis	T-lymphocyte deficiencies Severe combined immunodeficiency Wiskott-Aldrich syndrome Innate immunodeficiencies
Recurrent infections with the same pathogen	Infections with meningococci or other encapsulated bacteria or with uncommon serotypes; *Candida* infections	Antibody deficiencies / Complement deficiencies (Encapsulated bacteria) T-lymphocyte deficiencies (*Candida*) Macrophage disorders / T-cell interaction defects (*Mycobacteria*)
Autoimmune or persistent inflammatory conditions	More frequently recognized as a characteristic of PID†	Common variable immunodeficiency Hemophagocytic lymphohistiocytosis
Syndromic features	PID† diagnosis becoming more common in genetic conditions	DNA repair defects Hyper-IgE‡ syndrome DiGeorge syndrome

*Ear, Nose, and Throat; †Primary immunodeficiency; ‡Immunoglobulin E.

recurrent infections from bacterial or opportunistic pathogens, pneumonitis unresponsive to treatment, extensive skin lesions, delayed umbilical cord detachment, hepatosplenomegaly, congenital heart defects, and a family history of PIDs, or history of early childhood deaths. Laboratory indicators such as lymphopenia and low immunoglobulin levels, and absence of a thymus shadow on X-ray should also prompt further investigations (20).

Laboratory Evaluation

The initial evaluation of PIDs should target the most likely affected component of the immune system, based on the clinical assessment. B-cell abnormalities and combined B- and T-cell defects account for the majority of PIDs and should be prioritized in the evaluation. Standard initial laboratory tests include a complete blood count (CBC) with differential, biochemical panel, immunoglobulin levels, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), and urinalysis. Special attention should be given to the absolute lymphocyte count. Other findings such as anemia, thrombocytopenia, thrombocytosis, leukopenia, or leukocytosis should also be noted. The biochemical panel may reveal signs of liver or renal disease, hemolysis, and hypoalbuminemia due to protein loss or malnutrition. Elevated inflammatory markers (e.g., ESR, CRP) may point towards chronic infection or autoimmunity. Ig levels should be compared with age-appropriate reference ranges. Low Ig levels suggest antibody deficiency or combined immunodeficiencies: an IgG level <300 mg/dL, total Ig (IgG + IgM + IgA) less than 500 mg/dL, or complete absence of IgA and/or IgM in a child older than six months indicates an antibody deficiency. Significantly elevated IgE levels (>2,000 IU/mL) may indicate a monogenic atopic disorder or one of the hyper-IgE immunodeficiency syndromes. Disorders of

functional antibody production can occur despite normal IgG levels, and normal Ig levels do not rule out disease. Additional tests such as microbiological cultures and imaging studies should be performed when indicated by the initial findings (the absence of a thymus shadow on chest X-ray is a common finding in severe T-cell deficiencies) as well as human immunodeficiency virus (HIV) tests in children with a delayed onset of severe infections or unexplained lymphopenia. Total complement (CH50) is recommended for patients with a history of sepsis or *Neisseria* infections. Flow cytometry analysis detects T- and B-cell subsets, and NK-cells (21).

Genetic Testing

Genetic testing plays a crucial role in diagnosing IEIs. With the growing accessibility of next-generation sequencing (NGS) technologies, including whole exome sequencing (WES), whole genome sequencing (WGS), and targeted gene panels, genetic testing has become an integral component of the diagnostic work-up for patients suspected of having PIDs. The decreasing costs and broader availability of these technologies have led to their more widespread use, with testing being conducted earlier in the diagnostic pathway. The results of genetic tests often help determine further laboratory investigations. Targeted NGS offers a cost-efficient method to screen for mutations in known immunodeficiency-related genes. It can identify atypical presentations of established genetic defects and pinpoint the underlying cause in cases where multiple candidate genes may be involved. Additionally, most NGS panels can detect copy number variations due to their high read depth. When targeted NGS does not provide conclusive results, WES is commonly employed as the next step.

WES analyzes approximately 2 percent of the genome, focusing on the exonic regions and nearby splice sites. In contrast, WGS sequences the entire genome, including the non-coding intronic regions. Although WES is less expensive, less labor-intensive, and easier to analyze, it is less effective in identifying mutations in deep intronic or promoter regions compared to WGS. These regions are more difficult to interpret independently, so WGS is typically used in research settings and often combined with RNA sequencing to investigate alternative splicing and gene expression patterns. Both WES and WGS are valuable tools for identifying rare genetic mutations, particularly in patients with severe, early-onset conditions. However, confirming the pathogenicity of new variants in known or novel genes remains a complex challenge (21).

Diagnosis in Neonates

Diagnosing PIDs in neonates presents unique challenges due to the innate characteristics of the neonatal immune system, which can mask the clinical manifestations of immune deficiencies (22). The immune system of the newborn is structurally developed but has limited exposure to infections and weaker inflammatory responses, which makes neonates more vulnerable to infections. While most newborns remain healthy due to innate immunity and transferred maternal IgG, certain features, such as a positive family history, unusual infections, or syndromic appearance, should raise suspicion of IEI. A positive family history is particularly important, as it may indicate a genetic predisposition to PIDs and prompt early evaluation. Screening laboratory tests, including CBC with differential and Ig levels, should be conducted if the risk factors are present. Additional evaluation, such as lymphocyte immunophenotyping and T-cell receptor excision circles (TREC) analysis, are valuable for early detection of T-cell deficiencies. TRECs are circular DNA fragments produced during T-cell development, and can be detected using polymerase chain reaction (PCR) from dried blood spot on Guthrie cards. The absence of TRECs indicates defects in T-cell maturation. Therefore, the inclusion of TREC testing in newborn screening would represent significant progress in the early diagnosis of PIDs (23).

Treatment

The treatment of PIDs depends on the underlying disorder. Some PIDs manifest with subtle and intermittent signs and symptoms, while others may progress rapidly to life-threatening conditions. Early recognition and accurate diagnosis are crucial for effective treatment (19). Children with recurrent or chronic bacterial infections (e.g., otitis, sinusitis, bronchitis, pneumonia) should be treated promptly with empiric antibiotic therapy pending culture results (7).

Immune Reconstitution

Reconstitution of immune function can be achievable in certain IEIs through various treatments, including HSCT, enzyme replacement therapy, thymus transplantation, or gene therapy (24). The range of available therapies has expanded to encompass small molecule inhibitors, biological drugs, and the adoptive transfer of virus-specific T-cells to combat viral infections in immunocompromised patients (6).

Hematopoietic Stem Cell Transplantation

Allogeneic HSCT has been a standard treatment for severe IEIs for over five decades, and remains a cornerstone for treating conditions such as SCID, WAS, hyper-IgM syndrome, CGD, familial hemophagocytic lymphohistiocytosis (FHL), severe congenital neutropenia, and other combined immunodeficiencies. However, there are numerous serious adverse effects of allogeneic HSCT, including treatment-related mortality. Graft-versus-host disease (GvHD) is a common complication that can significantly impair immune function, different organs (skin, gastrointestinal tract, liver, lungs, kidneys, eyes, and hematopoietic system), and post-transplant quality of life. Therefore, a careful evaluation of risks and benefits of HSCT for individual patients is essential. Unlike in hematological malignancies, where the goal is to eradicate immune cells, the aim of HSCT in IEIs is to achieve immune system reconstitution. Reduced intensity conditioning (RIC) regimens, such as busulfan combined with fludarabine, are recommended for non-SCID IEIs. The optimal conditioning regimen should be tailored to each specific IEI (25). A matched related or sibling donor (MRD/MSD) is a preferred donor option. However, advances in graft processing, conditioning regimens, and the prevention of post-transplant complications, have rendered HSCT from matched unrelated donors (MUD) and mismatched related donors (MMRD) suitable alternatives, with survival rates exceeding 70% (26).

Thymus Transplantation

Allogeneic thymus transplantation is a therapeutic option for patients with thymus deficiency and athymia due to complete DiGeorge syndrome, since conditioning and HSCT could exacerbate their immunodeficiency. Despite advances in techniques and treatment outcomes, thymus transplantation still carries a relatively high complication rate. Cultured thymus organoids present a new promising therapeutic approach (5).

Biological Therapy

As the ability to establish molecular diagnosis for patients with PIDs improves, there is a growing interest in targeted therapies that can replace, enhance, or modulate immune responses. Biological drugs, including monoclonal antibodies and recombinant proteins, specifically target cytokines or their receptors. Fusion receptors have significantly increased the ability to modulate the immune system by linking extracellular domains of various transmembrane proteins to other molecules. For example, treatments for CTLA-4 (Cytotoxic T-Lymphocyte-Associated Antigen 4) and LRBA (Lipopolysaccharide Responsive and Beige-like Anchor protein) deficiencies have benefited from abatacept therapy. Abatacept is a soluble fusion protein that consists of the extracellular domain of human CTLA-4. It inhibits T-cell activation and prevents autoimmune reactions mediated by regulatory T-cells (Tregs). Enzyme replacement therapy, such as for SCID due to ADA, addresses

metabolic deficiencies associated with specific PIDs. Currently, for most IEIs, no approved therapies exist, and "off-label" use is based on limited data (6).

Small Molecule Inhibitors

Small molecule inhibitors are low molecular weight compounds that can easily penetrate cells and target intracellular signaling pathways, such as JAK/STAT pathway that transmits signals downstream of various cytokines. Small molecule JAK inhibitors, ruxolitinib and tofacitinib, have demonstrated clinical improvement in patients with STAT1 or STAT3 gain-of-function syndromes. Despite the potential side effects including thrombocytopenia, elevated liver enzymes and viral infections, long-term treatment resulted in the significant amelioration of immune dysregulation (6).

Adoptive Transfer of Virus-Specific T-Cells

Adoptive transfer of virus-specific T-cells (VSTs) provides a therapeutic option in controlling viral infections in immunocompromised patients, such as cytomegalovirus, Epstein-Barr virus, and adenovirus. Derived from either stem cell donors or HLA-matched third-party donors and serving as "ready-made" therapies, VSTs have shown efficacy, particularly in patients undergoing HSCT (6).

Gene Therapy

Gene therapy (GT) has become a feasible and effective treatment for several PIDs that are restricted to hematopoietic cell lineages. GT involves the transduction of autologous hematopoietic stem cells with a vector containing the corrected gene product, which is subsequently administered to the patient as an autologous bone marrow transplant. Early phase I trials of GT using gamma-retroviral vectors to treat SCID, WAS, and CGD demonstrated immune reconstitution post-engraftment, but were complicated by multiple cases of leukemia and myelodysplastic syndrome due to insertional mutagenesis. Recent advances in vector engineering have minimized these risks. Current self-inactivating lentiviral vectors have been successfully administered in phase I trials to treat patients with X-linked SCID and ADA, WAS, and CGD without reported cases of leukemia. The concept of GT has evolved from retroviral or lentiviral gene delivery to gene editing (GE), which aims to correct disease-causing genes using techniques such as Zinc Finger Nucleases (ZFN), Transcription Activator-Like Effector Nucleases (TALEN), and CRISPR/Cas9 (CRISPR-associated protein 9). GE creates double-strand DNA breaks at specific sites, triggering endogenous repair mechanisms that permanently edit the genome through non-homologous end joining (NHEJ) or homology-directed repair (HDR). Unlike GT, GE eliminates the need for viral vectors, offering more precise gene correction with fewer complications, such as insertional mutagenesis and transgene silencing. However, GE is still experimental and is not yet widely implemented in clinical practice (27).

As our understanding of PIDs underlying mechanisms expands, new opportunities arise for research and development of targeted therapies, along with broader use of potentially curative treatments like GT. With increased survival rates, it is now crucial to establish best practice guidelines and coordinated healthcare for all adolescents with PIDs in the transition from pediatric to adult services (28).

Conclusion

IEIs represent a rapidly expanding group of genetic disorders of the immune system. Although not very rare, IEIs are frequently misdiagnosed or diagnosed late due to their complex or atypical clinical presentation, which severely diminishes patients' quality of life and survival. Timely recognition and referral to an experienced immunologist can significantly improve outcome. Therefore, continuous education of healthcare professionals on early diagnosis and advanced therapeutic strategies is crucial for minimizing complications and mortality related to PIDs.

What is Already Known on This Topic:

IEIs are a group of diverse monogenic disorders mainly characterized by deficient or dysfunctional immune system, and are associated with significant morbidity and mortality. Until recently, the mainstay of the management included prompt treatment of infections, antimicrobial prophylaxis, and Ig replacement. The advent of precision-based therapies has dramatically enhanced the quality of life and outcome of patients with IEIs. Timely referral to immunology services is critical, enabling patients to receive an accurate molecular diagnosis and targeted therapy when available.

What This Study Adds:

Lack of knowledge and awareness among healthcare professionals regarding the diversity of IEI manifestations in children and adults contributes to diagnostic and treatment delays. This review briefly describes new insights in the pathophysiology of PIDs, and discusses revolutionary treatment armamentarium, with the aim of improving recognition, timely diagnosis and management of these disorders.

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