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Human inborn errors of immunity: diagnosis and management

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Abstract

Primary immunodeficiency disease (PID) now known as inborn errors of immunity (IEI) is genetic disorder(s) that impair the immune system. IEI is a heterogeneous group of diseases of more than 485 lifelong genetic disorders mainly due to intrinsic defect(s) in human immune system. Adults, children, and neonates can be affected by IEI diseases. The first IEI defects were reported in the 1950s, but Bruton's use of immunoglobulin in 1952 to treat an 8-year-old boy suffering from pneumonia and other bacterial sino-pulmonary infections brought the PID or IEI and associated diseases into limelight. This review will focus on a general description of IEI (history, epidemiology, pathophysiology, and diagnosis), inborn errors of metabolism, and the management (cure or therapy) of IEI diseases.

Keywords

Primary immunodeficiency disease, inborn errors of immunity, classification of inborn errors of immunity by International Union of Immunological Societies, in born error of metabolism, diagnosis and management of inborn errors of immunity

Introduction

Primary immunodeficiency disease (PID) is a group of genetic disorders that impairs the immune system. PID is a heterogeneous group of diseases of more than 485 lifelong genetic disorders mainly due to intrinsic defects in human immune system [1–3]. Adults, children, and neonates can be affected by PID [4–6]. PID is characterized by impaired antibody production. Antibody production defects can lead to X-linked agammaglobulinemia, common variable immune deficiency (CVID), X-linked or autosomal hyper immunoglobulin M syndrome, and selective immunoglobulin A deficiency [7]. PIDs are now referred to as inborn errors of immunity (IEI).

This review will focus on a general description of IEI (history, epidemiology, pathophysiology, and diagnosis), inborn errors of metabolism (IEM), and the management (cure or therapy) of IEI diseases.

IEI

Disorders of IEI lead to the mutation of genes that regulate immune system that causes dysfunction in the immune system [3, 8]. Mutation leads to deletions or abnormal changes in a gene that causes it to behave abnormally. Depending on the gene, several diseases or abnormalities may occur in a person and can be described as follows.

Autoinflammatory disease may occur due to the malfunction in the innate immune system [2].

- Malfunction in the immune system can cause viral, bacterial, fungal, or mycobacterial infections [2, 9].
- Autoimmune disease can be a result of malfunction in the adaptive immune system [2]. Hypersensitivity of immune system can cause allergic disease [2].
- Abnormalities in the bone marrow results in the decreased number of circulating blood cells [10].
- Mutations of various oncogenes can cause hematological and non-hematological cancers [2, 10–12].
- Excessive proliferation of T-cell or B-cell lymphocytes in the lymph nodes, gastrointestinal tract, liver, and skin can cause non-malignant lymphoproliferative disorders [13].

The first IEI defects were reported in the 1950s [8]. In 1950, Kostmann described a patient with severe congenital neutropenia [8]. Janeway et al. [14] reported in 1954 a patient with recurrent infections and elevated serum immunoglobulins. In 1950, Glanzmann and Riniker [15] described an infant who succumbed to infections early in life due to severe lymphopenia and atrophy of lymphoid tissues [15]. However, PID as a serious life-threatening disease came to limelight in 1952. In 1952, Bruton [16] used immunoglobulin (Ig) to treat an 8-year-old boy who suffered from pneumonia and other bacterial sino-pulmonary infections. Bruton [16] noted that gamma globulin was absent in this boy despite having normal total protein and he did not respond to four different pneumococcal antigens. Bruton [16] administered 3.2 grams of immune human serum gamma globulin subcutaneously. After the administration of gamma globulin, the boy was free from pneumococcal sepsis for more than a year, whereas he had sepsis at least 19 times in the previous four years. With this experience, Bruton [16] suggested that there were possibilities to control and treat many diseases (agammaglobulinemia) with gamma globulin(s).

Hitzig reported that there were infants with life-threatening infections and lacked both gamma globulins and lymphocytes [8]. This condition is now termed as severe combined immune deficiency (SCID) [8]. The discovery of agammaglobulinemia and SCID have provided critical information regarding the role played by humoral and cellular immunity, respectively, in protection against infections [8].

Several reports and studies related to IEI from 1946 to 1952 indicated that severe infectious diseases in humans can be due to a single-gene IEI with incomplete penetrance [17]. Casanova and Abel [17] described the nature of severe fevers related to IEI in three steps and these steps are PIDs which were discovered from 1985 onward, Mendelian infections from 1996 onward, and monogenic infections but not Mendelian infections from 2007 onward [17]. Casanova and Abel [17], have defined PIDs, Mendelian infections, and monogenic infections as follows.

- PIDs comprise more than 400 monogenic IEIs disrupting host defense against various infections. They are also associated with immunological abnormalities.
- Mendelian infections are 5 monogenic IEIs disrupting host defense against one or a few infections. These infections were considered idiopathic but with the discovery of disease-causing genes it was recognized that these were immunological abnormalities.
- Monogenic infections comprise at least 10 monogenic IEIs disrupting host defense against one or a few infections. These infections were considered idiopathic but with the discovery of disease-causing genes it was recognized that these were immunological abnormalities.

Expression of IEI genes

An IEI gene may be defective because it is not expressed normally. These expressions may be under expressed, over-expressed, or a gene can be formed with reduced, increased, or without any activity [8, 17]. The defective IEI gene in parents may not be expressed in their offspring due its location in the X or Y chromosome, or one of 46 remaining non-sex chromosomes (known as autosomes) [8, 17]. The offspring who inherit IEI gene may not show symptoms due to the following reasons [17, 18].

- The gene is under expressed (reduced penetrance) or not expressed (non-penetrance) in males or females.
- The presence of other genes that modify the activity of the inherited IEI gene (genetic modifiers).
- Exposure to environmental factors that modify the activity of the inherited IEI gene (environmental modifiers).
- Factors that regulate the expression of the IEI gene without changing the gene's nucleic acid sequence (epigenetic regulation).

International Union of Immunological Societies classification of IEI

A committee of the IEI was established by the World Health Organization (WHO) in 1973 [19]. The objectives of this committee were to describe and classify the types of primary immune defects or diseases affecting humans [19]. In the 1990s, WHO decided to focus on more common diseases of IEI, and a committee was formed known as the International Union of Immunological Societies (IUIS). In the 1980s [20], the number of genes when mutated to cause specific IEI disorders was < 10 but by 2022 the number rose to 485 mutated genes causing these disorders [21]. It is anticipated that with more DNA sequencing the number of mutated genes will increase. In 2023, the number of IEIs was estimated to be between 1 in 1,000 and 1 in 5,000 individuals but this may be as high as 1 in 500 individuals [3, 22].

The IUIS report was updated in 2022 (previously published January 2020) and in this report the classification of IEI consisted of key clinical and laboratory features of 55 monogenic gene defects and 1 phenocopy due to autoantibodies [2]. The report indicated that in 2022 there were 499 (increased from 485) known genetic defects [21]. It is expected that this report will help immunologists and geneticists to pursue and identify cellular and molecular mechanisms of monogenic infections and related human immune disorders [2]. Currently, IUIS (2022 report) classified IEI into 10 categories and these are described below [2, 21, 22]. These categories are summarized in Table 1.

Table 1. IUIS classification of IEI diseases

IUIS classification	PID disease category	Disorders	# of diseases	# of genetic defects
1	Cellular and hormonal immunodeficiencies	SCID	58	66
2	Syndromic combined immunodeficiencies	T cells and B cells	68	69
3	Predominantly antibody deficiencies	Hypogammaglobulinemia	51	45
4	Immune dysregulation disease	Hemophagocytic lymphohistiocytosis	51	52
5	Congenital defects of phagocytes	Defects in phagocyte function	35	42
6	Defects in intrinsic and innate immunity	Bacterial, fungal, and viral infections	63	74
7	Autoinflammatory diseases	Autoinflammatory diseases	59	56
8	Complement deficiencies	Decrease in the levels of a component protein	30	36
9	Bone marrow failure diseases	Reduction in the levels of red and white blood cells	43	44
10	Phenocopies of inborn errors of immunity	Various diseases	15	15*

* It was assumed that these are genetic defects or pathogenesis

- Combined immunodeficiencies (cellular and hormonal immunodeficiencies) consisting of 66 defective genes and 58 diseases. The diseases in this classification are SCID diseases that are associated with low levels of CD3 protein-expressing T cells.
- Combined immunodeficiencies with syndromic features consisting of 69 defective genes and 68 diseases. The disorders include combined immunodeficiencies of T cells and B cells.
- Predominantly antibody deficiencies consist of 45 defective genes and 51 diseases. The disorders include hypogammaglobulinemia.
- Diseases of immune dysregulation consist of 52 defective genes and 58 diseases. The disorders include hemophagocytic lymphohistiocytosis.
- Congenital defects of phagocytes in intrinsic and innate immunity consisting of 42 defective genes and 35 diseases. The disorders include neutropenia not caused by antibodies directed against neutrophils and defects in phagocyte function.
- Defects in intrinsic and innate immunity consist of 74 gene defects and 63 diseases. The diseases include a predisposition to develop bacterial, fungal, parasite and/or viral infections.
- Autoinflammatory diseases consist of 56 defective genes and 59 diseases. The disorders include various types of autoinflammatory diseases.
- Complement deficiencies consisting of 36 defective genes and 30 diseases. The disorders lead to decrease in the levels of a component protein in the complement system function.
- Bone marrow failure disorders consist of 44 defective genes and 43 diseases. The disease leads to bone marrow failure which in turn causes a reduction in the levels of red and white blood cells, and/or platelets.
- Phenocopies of IEI consist of 15 genes and 15 diseases causing various PIDs.

Diagnosis and diagnostic tests for IEI

Impaired antibody production can lead to X-linked agammaglobulinemia, common variable immunodeficiency, X-linked or autosomal hyper IgM syndrome, and selective IgA deficiency [22]. Complications of PIDs can lead to autoimmunity and malignancies and after infection cancer is the second most leading cause of death in patients with PIDs [2, 6]. Early diagnosis and treatment of IEI is very important [23]. IEI can be divided into two groups:

- Immune deficiency disorders (infections): For example, current or recurrent infections, severe infections, unusual pathogens, and restricted pathogen pattern [24].
- Immune dysregulation disorders (non-infections): For example, autoimmune cytopenia, lymphoproliferation, cancer predisposition, eczema, erythroderma, endocrinopathy, enteropathy, and systemic autoimmunity [24].

Immunodeficiency can be classified as [25]:

- Primary immunodeficiency: Genetically determined and typically occur during infancy or childhood. Primary immunodeficiency can be characterized by humoral or cellular immunity, combined humoral and cellular immunity, phagocytic cells, or complement proteins.
- Secondary immunodeficiency: This is acquired immune deficiency and can be characterized as follows:
  - Systemic disorders such as diabetics, under-nutrition, HIV infection.
  - Immunosuppressive treatments.
  - Prolonged serious illness.

Initial tests to diagnose immune disorders should include [25]:

- Complete blood count (CBC).
- Quantitative Ig measurements.
- Antibody titers.
- Skin testing for delayed hypersensitivity.
- Prenatal testing. Parents who have a child with a PID disorder might want to be tested for certain immunodeficiency disorders during future pregnancies. Samples of the amniotic fluid, blood, or cells from the tissue that will become the placenta (chorion) should be tested for any abnormality [26].

Antibody deficiency (or humoral immune function)

The standard humoral immune function test is the measurement of Ig levels in blood [26]. There are five classes of Igs in humans. These are known as IgG, IgM, IgA, IgE, and IgD, IgG being the most abundant of these Igs [27]. The tests include IgG, IgA, IgM, and sometimes IgE levels. The results should be compared with age- and sex-matched controls [26].

There are two tests which are conducted to evaluate the specific antibody production [26].

- The T cell dependent pathway measured by the antibody response to protein antigens, such as tetanus and diphtheria toxoids.
- The T cell independent pathway measured by the antibody response to carbohydrate antigens, such as those found in the pneumococcal polysaccharide vaccine (PPSV).

There is an additional test to evaluate the antibody deficiencies [26]. This test evaluates different types of lymphocytes in the blood using flow cytometry. B cells produce antibodies and its absence can be attributed to disorders of antibodies such as X-linked agammaglobulinemia [26]. In addition, DNA testing can be done to check for a genetic defect for the child to be born so that treatment of the defect can begin immediately [25, 26]. Genetic testing can confirm a variant in the gene encoding Bruton tyrosine kinase (BTK) associated with X-linked agammaglobulinemia [26]. Furthermore, Ig production can be assessed by cultured lymphocytes in response to a variety of different kinds of stimuli [26].

Immune Deficiency Foundation in its laboratory tests states [26] "It is important to note that in a person with a previously confirmed defect in antibody production, stopping therapy to recheck for antibody levels and immunization response is unnecessary and may place the individual at risk of acquiring an infection during the period when the Ig replacement therapy is stopped. In someone whose diagnosis of an antibody immunodeficiency is unclear, it may be necessary to stop Ig replacement therapy for a period of four to six months so that the individual's humoral immunity can be adequately assessed".

Cellular or T-cell immunity

Cellular or T cell immunity determines the number of different types of T cells and evaluate the function of these cells. In the USA, there is newborn screening test which screen the levels of T cells [26]. The infants may be healthy looking but this screening test helps in detecting treatable genetic defects [26]. This newborn screening test makes it easier to treat SCID and other related severe T cell immunodeficiencies since infants with these conditions were identified at birth [26].

CBC

CBC test is the simplest method to evaluate the decrease or absence of T cells. The total blood lymphocyte count is an appropriate test for the assessment of decreased T cell numbers. The rationale behind this is that since 75% of the circulating lymphocytes are T cells and a reduction in T cells indicates that the total number of lymphocytes or total lymphocyte count has decreased [26].

Neutrophil function test

Neutrophil function test focuses on the white blood cells counts with differentials. This test determines if there is neutropenia that is a decrease in the absolute neutrophil count [26]. If these initial screening tests of neutrophil numbers are found normal then the testing is focused on two PIDs. Chronic granulomatous disease (CGD) and leukocyte adhesion deficiency (LAD). Both of these disorders have normal or elevated numbers of neutrophils. At this time, for testing both of these two disorders, flow cytometry is considered reliable [26].

Complement deficiency test

The standard screening test for complement deficiency is the total hemolytic complement assay or CH50 [26]. The CH50 will be almost negative if there is a defect in one complement component. In rare cases, there may be defects in other complement pathway that can be screened by a functional test directed specifically at this pathway, the AH50 test [26].

Innate immunity test

Innate immunity tests determine the number and activity of lymphocytes such as natural killer (NK) cells and the function of various cell surface receptors [26].

Genetic testing

Laboratory immunological testing initially confirms IEIs by showing altered numbers or function of T cells, B cells, neutrophils, complement or innate immune system [28–37]. Since 1985, the genetic defects leading to IEIs led to the molecular confirmation of many immunological diagnoses of IEIs. These days the evaluation of IEIs mainly relies on direct genetic confirmation, and genetic testing has become an integral part of diagnostic process of IEIs [9, 17]. Genetic tests help in rapid screening for mutations in hundreds of genes that affect the immune system [26].

It appears that there is too much focus on the infectious diseases in IEI but one should also focus on other diseases related to IEI [38]. These diseases can be manifestations of early onset and/or refractory to conventional treatments [39], severe and difficult to control allergic conditions [40], recurrent or persistent inflammatory processes with or without fever [41], and malignant diseases [42]. Considering these onset of diseases, early diagnosis is of immense importance to reduce morbidity and mortality from these diseases [43]. It has been also recommended that screening for SCID using T cell receptor excision circle (TREC) and kappa recombining excision circles (KREC) be incorporated in neonatal screening programs [44].

The aforementioned tests are initial evaluation of IEI but with the discovery of many other diseases associated with IEI new tests may be needed for other defects [45]. Some of these are summarized below.

- The measurement of the enzymatic activity of adenosine deaminase (ADA) and purine nucleoside phosphorylase (PNP) in peripheral blood can help in the diagnosis of SCID. Furthermore, the measurement of uric acid can identify PNP deficiency (very low levels of uric acid) [46].
- Cytotoxicity tests are useful when defects in NK cells are suspected with major viral infections such as the human papillomavirus (HPV) or the herpes virus. These tests can be conducted by assessing the release of chromium in the supernatant from the lyzed target cell or the expression of CD107a on the cell surface [47].
- Functional tests to identify the defects of IFNγ-IL-12 axis which causes Mendelian susceptibility to mycobacteria are performed by evaluating IL-12 production in-vitro [47].
- In order to assess the innate immunity deficiency (restricted to one type of infectious agent), toll like receptors using CD62L shedding assay can be performed [47].
- Serum type I interferon measurement known as interferonopathies can be used to assess a group of autoinflammatory diseases [48].

IEM

IEM, also known as inherited metabolic disorders or hereditary metabolic disorders, are a group of genetic conditions that affect the metabolic function of a person [49]. Metabolism is a complex biochemical process through which living organisms maintain the cellular activities to sustain their life [49]. These biochemical processes convert food into energy and remove toxins from the body [49]. There are specific metabolic pathways which depend on specific enzymes and substrates. IEM occur when activity in a metabolic pathway becomes deficient. Majority of the IEM are inherited in an autosomal recessive manner [49, 50].

IEM are individually rare but collectively causes mortality and morbidity in the neonatal period. IEM are identified by either newborn screening tests or clinician-initiated targeted biochemical screening [50]. IEM are a heterogeneous group of over 1,000 diseases affecting different components of the metabolic pathways and may not be identified in the neonatal period [51]. Due to the heterogeneity and individual rarity of IEM, physicians use a combination of biochemical tests and a selection of second-line metabolic tests before proceeding to specific metabolic tests [52, 53].

IEM occur in 1 out of 2,500 births [54]. Due to the heterogeneity of IEM, different disorders have different epidemiological and clinical presentation. The IEM disorders may lead to a complete dysfunction of enzymes or can be partial or incomplete [54].

Nosological classification of IEMs

IEM diseases are inherited biochemical disorders with specific enzyme defects that interfere with normal metabolism of a person. IEM diseases are classified as disorders of carbohydrate metabolism, protein metabolism, organic acid metabolism, fatty acid oxidation, glycogen, or lysosomal storage diseases [54, 55]. The major subtypes of IEM can be classified into three broad groups according to the pathogenesis and clinical presentations. These classifications are as follows.

Intoxication disorders

Accumulation of toxic compounds due to the metabolic dysfunction is responsible for the symptoms of intoxication disorders [56].

- Amino acids metabolism disorder leads to organic acidemias, urea cycle disorders, phenylketonuria, and homocystinuria [56].
- Urea cycle disorders cause the impaired removal of ammonia from the blood resulting in the accumulation of ammonia. Ammonia is extremely toxic, particularly to the central nervous system [55].
- Phenylketonuria (PKU) is a rare inherited disorder that causes phenylalanine (an amino acid) to build up in the body. PKU is caused by a change in the phenylalanine hydroxylase gene. In the absence of the enzyme which is necessary to break down phenylalanine a buildup of phenylalanine occurs in the body when a person consumes food that contain protein. Signs and symptoms of untreated PKU can be neurological problems, skin rashes, hyperactivity, and behavioral, emotional, and social problems [57].
- Alteration in carbohydrate metabolism leads to galactosemia and fructosemia. Galactosemia prevents galactose from turning it into energy in the newborns and can be life-threatening if not treated. Vomiting, jaundice, and diarrhea are the early symptoms of galactosemia. Without treatment a child can develop cataracts [58].
- Hereditary fructosemia is an autosomal recessive metabolic disorder caused by a loss of function in the aldolase B gene [58]. This leads to fructose 1-phosphate accumulation [58]. Severe liver and kidney dysfunction, seizures, coma, and death can occur if not treated [58].
- Metal metabolism disorders cause metals build up to toxic levels in the body. Wilson disease (excess copper levels) and hemochromatosis (excess iron levels) are examples of metal metabolism disorders [55].

Energy metabolism disorders

Mitochondrial and fatty acid oxidation disorders are classified in this category [56].

- **Mitochondrial diseases:** This disease is characterized by defective oxidative phosphorylation, resulting in inefficient energy production and changes in the reduction-oxidation balance. The disease subsequently affects the function of many organ systems such as brain, muscles, liver, kidneys, etc. [55, 56].
- **Fatty acid oxidation disorders (FAODs):** FAODs disorders are due to unbalance of either mitochondrial β-oxidation or the fatty acid transport using the carnitine transport pathway [56]. Gluconeogenesis, ammonium metabolism, and the formation of ketone bodies are affected by the defects of this metabolic pathway and consists of a group of 20 diseases [59]. This results in non-ketonic hypoglycemia, hyperammonemia, and lactic acidosis in catabolic scenarios [60]. Liver, heart, and muscles are the most dependent organs on the fatty acid beta-oxidation pathway for energy production. In the neonatal period, cardiomyopathy and during infancy and childhood liver dysfunction, hypoketotic hypoglycemia (low blood glucose and low ketones), and rhabdomyolysis are common [55, 59].

Storage diseases

- **Lysosomal storage disorders:** These disorders do not remove or break down waste products leading to the accumulation of toxins in the body (hyperammonemia). Lysosomal storage disorders include Hurler syndrome, Gaucher disease, and Tay-Sachs disease [54, 55].
- **Glycogen storage disease:** The disease causes low blood sugar (hypoglycemia) by not allowing the storage of sugar in the body from food.
- Peroxisomal disorder is caused by impairment in the biogenesis of peroxisomes. Peroxisomal disorder leads to toxins build up in the body and in most cases results in neurologic dysfunction [54, 55].
- **Glycosylation disorders:** Congenital disorders of glycosylation (CDG) are a hereditary disorder and presents from early childhood to adulthood [61]. CDG are a group of clinically heterogeneous disorders which are due to the defects in the synthesis of glycans [61]. Glycosylation is essential for the normal function of proteins and lipids throughout the body and many enzymes are involved in the process of glycosylation [61]. Lack of any one of these enzymes lead to the defects of glycosylation which affect all the organs of the body and its functions including those in the brain, liver heart, gastrointestinal, muscle, hormone, and immune systems. The common signs and symptoms may be slow growth, nerve damage, muscle weakness, liver, heart and bone diseases, and low blood sugar levels [61].

Clinical presentations

IEM is a heterogeneous disease and may have many signs and symptoms. Some of the common signs and symptoms of IEM are presented below [54–56].

- Development or growth delay and weight loss.
- Loss of appetite or poor oral intake resulting in low energy (lethargy).
- Recurrent vomiting, diarrhea, abdominal pain.
- Unusual odors of urine, sweat, or breath.
- Seizures, changes in tone or reflexes.
- Skin rash and abnormal pigmentation.

Diagnosis of IEMs

Due to nonspecific clinical presentation, diagnosis of IEMs is difficult and challenging. IEMs have a wide clinical spectrum but the nervous (slow growth, movement disorders, coma, seizures, and psychiatric symptoms) and gastrointestinal (vomiting and severe abdominal pain) systems are most frequently observed [62–64]. Early diagnosis of IEMS in infants, children, and adults is vital for the prevention of death and serious physiological damage. Appropriate laboratory tests should be used to diagnose the IEMs so that appropriate treatment can be initiated. Some laboratory tests for the diagnosis of IEMS have been suggested in infants and adults and are as follows [56, 65, 66].

- CBC with differential (neutropeniaor thrombocytopenia)
- Blood gases
- Blood glucose
- Plasma ammonia
- Plasma and urine amino acids (quantitative)
- Plasma lactate and pyruvate concentrations
- Serum electrolytes
- Urinalysis
- Urine reducing substances
- Urine ketones if acidosis or hypoglycemia present
- Urine organic acids
- Liver function tests
- Plasma carnitine and acylcarnitine
- CSF amino acid analysis
- Peroxisomal function test

Treatment of IEMs

Treatment for disorders of IEM varies based on the type of the disease. Due to the heterogeneous nature of the diseases involved with IEMs a detailed description of the treatment of these disorders associated with IEMs is beyond the scope of this manuscript. Therefore, only a brief description of the treatment of well-known diseases due to IEMs is presented here.

The treatment of IEM was initially focused in reducing undesirable metabolites [67]. The first treatments in this direction involved dietary restrictions to decrease the production of undesirable metabolites. Later, steps were taken to eliminate toxic metabolites such as by using dialysis or ammonia scavengers in urea cycle disorders or organic acidemias [67].

For the treatment of PKU, the initial therapy involved dietary restriction of phenylalanine with supplementation of tyrosine. Two other treatments involved supplementation with large neutral amino acids to block entry of phenylalanine into the brain and supplementation of the enzyme's cofactor, tetrahydrobiopterin [67].

In this century, the treatments of IEMs are involved in correcting the metabolic defects [67]. Orthotopic liver transplantation is now a treatment of choice for a number of IEMs such as severe urea cycle defects. In some cases, in place of entire organ, cells were transplanted such as muscle cell transplantation for neuromuscular disorders or liver cell transplantation for PKU. Stem cell bone marrow transplantation can be of therapeutic benefit particularly in some storage disorders (Hurler syndrome), and pre-symptomatically in some degenerative white matter leukodystrophies [67].

The only effective treatment for hereditary fructosemia is a fructose- and sucrose-free diet [68].

For the management of (FAODs), the main focus is on avoidance of fasting, aggressive treatment during increased metabolic stress, and if needed supplementation of carnitine [69]. Infants (0–4 months) should be fed every 3 hours, up to 8 hours till the age of 12 months, and after infancy no more than 10–12 hours. Aggressive treatment includes oral or enteral carbohydrate-rich fluids given every 3–4 hours in case of mild to moderate illness [69].

The treatment programs for IEMs can be summarized as follows [55]:

- **Changing diet:** Since patients with IEMs have difficulty in processing foods and beverages, removing certain food items will be beneficial.
- **Medicines:** Certain medicines can be helpful in improving metabolism function. Medicines could include enzyme or chemical replacements.
- **Dialysis:** Dialysis can remove toxins from blood.
- **Organ transplant:** To treat severe cases of IEMs, a liver transplant might be needed.

Treatment or management of IEI

Early diagnosis and primary prevention and prophylaxis is helpful to avoid serious infection and morbidity and mortality from IEI diseases. Since IEIs consists of a wide variety of disorders, it is necessary to have an appropriate diagnosis of the disorder(s) and the subsequent treatment. Not all drugs for the treatment of IEIs have been approved by the regulatory agencies and off-label use is common [70]. The treatment options for IEIs are antimicrobial prophylaxis, Ig replacement therapy, allogeneic hematopoietic stem cell transplantation (HSCT), and gene therapy [70]. The details of all forms of therapy in the disorders of IEIs is beyond the scope of this manuscript hence, salient features of such therapies are discussed below.

Antimicrobial prophylaxis

Antimicrobial prophylaxis is regularly used in the treatment for CGD or leucocyte adhesion deficiency [71]. These patients have multiple deep skin infections. Antimicrobial prophylaxis treatment is based on the known risk of infection. Infants with severe SCID are typically given multiple forms of antimicrobial prophylaxis such as trimethoprim/sulfamethoxazole [71]. It should be however, recognized the adverse effects (mainly skin rashes, allergy, photosensitivity, and kidney damage) of sulfonamides in infants, children, and elderly. Infants with SCID due to their immunocompromised status are also given prophylaxis against viral and fungal infections such as acyclovir and fluconazole, respectively. However, patients with antibody deficiencies are treated at higher doses or longer period of antimicrobial dosing than those patients who do not have antibody deficiencies [71].

Practice parameter for the Diagnosis and Management of PIDs states: “The standard dose and duration of antimicrobial regimens might not be adequate to eradicate infections in immunocompromised hosts. Early combined antimicrobial therapy and prolonged courses should be considered.” [72]. The selection of an antimicrobial agent based on the culture of an adequate sample (sputum or tissue sample) is considered the preferred approach [71].

In children with antibody deficiency, doses of 20 mg/kg once or twice daily, trimethoprim/sulfamethoxazole given either daily or three times weekly at 5 mg/kg, or azithromycin 5 mg/kg thrice weekly has been found to be beneficial. In adults with antibody deficiency, either amoxicillin 500–1,000 mg daily or twice daily, trimethoprim/sulfamethoxazole 160 mg daily or twice daily, or azithromycin 500 mg once weekly or 250 mg every other day were found to be beneficial [72, 73].

Although, prophylactic antibiotics in primary antibody deficiency is widely used, there are very little data to show the effectiveness of these antibiotics. There are no controlled studies on the use of adjunct prophylactic antibiotics in patients with PID [73].

IEIs can lead to increased susceptibility to fungal infections. Patients with CGD deficiency can suffer from aspergillosis [74]. Mold-active antifungal prophylaxis should be prescribed to these patients immediately after diagnosis [74]. Most patients with IEI and invasive fungal infections can be managed using prolonged duration of antimicrobial prophylaxis and antifungals [74].

Ig therapy

Following Bruton's [16] use of Ig to treat an 8-year-old boy suffering from pneumonia and other bacterial infections, Igs have become an integral part of PID treatment. Today, Ig products are widely used for the treatment of immunodeficiency syndromes and autoimmune diseases such as chronic inflammatory demyelinating polyneuropathy (CIDP), immune thrombocytopenic purpura (ITP), and PID [1, 75]. Almost 75% of PIDs (impaired antibody production) are treated with Igs. The objective of the Ig replacement therapy is to maintain stable and optimum concentrations of IgGs for the therapeutic or clinical management of patients with PID [76].

Igs are endogenous proteins produced by B lymphocyte cells. In humans, there are five classes of Igs: IgG, IgM, IgA, IgE, and IgD [3, 4]. The IgG is the most abundant of these Igs and are further divided into four subclasses: IgG1, IgG2, IgG3, and IgG4 [77, 78]. Igs are manufactured from pooled human plasma and contain more than 95% IgG with intact Fc-dependent effector functions [77, 78].

Oral administration of IgGs is not possible because IgGs are unstable in the acidic pH of the stomach and also due to the proteolytic degradation in the stomach and intestine [79]. In early days, IgGs were administered by intramuscular route but these days intramuscular administration is rarely used. These days, IgGs are administered either by intravenous (IV) or subcutaneous (SC) route [79].

IgGs are distributed to the kidneys, lungs, liver, spleen, heart, and lymph. The distribution of IgGs to the tissues takes place by the lymph [80, 81]. Since IgGs are intact antibodies and are not filtered by the kidneys therefore, their elimination occurs via catabolism. Other elimination pathways are binding to specific receptors, receptor-mediated endocytosis, recycling via FcRn, non-specific uptake by tissues, binding via Fc receptors, and anti-product antibodies [80, 81]. Antibody fragments are filtered and reabsorbed as well as metabolized by proximal tubular cells. Receptor-mediated drug disposition generally leads to the saturation of IgG clearance resulting in nonlinear pharmacokinetics (PK) of IgGs [80, 81].

The IV route of administration is preferable over SC mainly because larger volumes of IgGs can be administered [79]. However, SC mode of administration is becoming popular due to the ease of administration. The FDA guidance [82] suggests a dose of IVIG ranging from 200 to 800 mg/kg every 3 or 4 weeks. The minimum trough level required for protection against bacterial infection is considered to be 500 mg/dL [82]. However, studies have shown that IgG concentrations of 700 to 1,000 mg/dL, are more efficient to prevent infections, particularly pneumonia [76, 83, 84]. Higher IgG concentrations provide protection from infection especially, to patients with chronic pulmonary disease [85–87]. IgG concentrations widely vary among patients therefore, treatment should be individualized. It is very important that IgG dose, trough level, and the risk of serious and non-serious bacterial infections be established in order to provide right dose to the patients with PID.

Although, the SC route of administration is becoming popular but many caveats of SC administration of IgGs should be recognized [79, 88]. The dosing frequency of SCIg is weekly and the increase in IgG concentrations is not as rapid as IVIg. It takes several days to reach the maximum concentrations of IgGs. Large doses of IgGs (> 500 mg/dL) cannot be administered due to the limited solubility of IgG products [79, 88]. Another issue with the SC administration is the adjustment of bioavailability of SCIgs [82]. The concentrations of SCIgs are lower than the concentrations of IVIG [89]. This leads to lower trough and area under the curve (AUC) values of SCIg products than the IVIg products. The US FDA [82] recommends that SCIg dose be adjusted when patients are switched from IVIg to SCIg based on the patients previous IVIg dose. The average dose adjustment for SCIg is generally from 130% to 153% depending on the product [90]. On the other hand, the European studies do not account for the SCIg dose adjustment based on the bioavailability of SC product [91].

PK dosing of Igs

PK plays a very important role in modern day drug development irrespective of small or large molecules [92]. PK-based dosing of Igs is now a regular clinical practice and is advocated in the literature [82, 91–94]. The PK of Igs is characterized from plasma concentration-time profiles and from these profiles several PK parameters are derived. These parameters can be half-life, area under the curve, clearance, volume of distribution, maximum and (C_{max}) and minimum (C_{min}) concentrations [90, 93]. The PK of IgGs has been extensively studied in adults following IVIg and SCIg administration [79, 91–94]. Although, Igs are also used in neonates, infants, and children but limited PK data are available for these age groups [95–98].

Several factors such as age (neonates, infants, and children), obesity, pregnancy, and immunogenicity can influence the PK and dosing of Igs. Therefore, these factors should be taken into account [90, 93, 94, 97]. In Table 2, the half-life and clearance values of some IgGs are shown.

Table 2. Half-life and clearance of immunoglobulins following intravenous dosing

Product	Dose (mg/kg)	Half-life (day)	CL (mL/day/kg)	References
ASCENIV 10%	291–760	29 ± 5	1.68 ± 0.40	[110]
BIVIGAM 10%	300–800	20 ± 4	1.97 ± 0.22	[111]
FLEBOGAMMA 10%	339–597	34 ± 10	1.64 ± 0.44	[112]
PANZYGA 10%	200–800	32 ± 12	1.44 ± 0.24	[113]
PRIVIGEN 10%	200–714	28 ± 6	1.30 ± 0.10	[114]

Allogeneic HSCT

In SCID, one of the treatment options is allogeneic HSCT [99]. In a patient with IEI, the patient's hematopoietic stem cells (HSCs) are replaced by healthy donor HSCs [99]. Since the first successful HSCT in 1968 in patients with SCID, HSCT has emerged as a lifesaving therapy [99]. However, HSCT in many cases has resulted as a partial or insufficient cure mainly due to graft failure (GF) [100]. The risk of GF is known to be higher in non-malignant disorders and 8–16% patients with IEI were reported to suffer from GF in multi-center studies [101, 102]. A second allogenic HSCT may be an option for GF. Laberko et al. [100] conducted a study in 48 patients with IEI who received a second HSCT and the authors found the results encouraging. The authors' conclusion was that an individualized approach is required for the second HSCT in patients with IEI [100].

Gene therapy

The objective of gene therapy (GT) is to fix, correct, or modify a faulty gene and replace it with a healthy gene in order to cure diseases or make the body better able to fight diseases [99]. GT offers an alternative to HSCT by modifying autologous hematopoietic stem cells. This method does not require a suitable allogeneic donor and eliminates the risk of graft versus host disease [99]. There are two approaches in GT: ex-vivo or in-vivo GT therapy. In ex-vivo GT therapy, generally, $CD34^+$ hematopoietic stem and progenitor cells are genetically modified outside the body and then transplanted the cells back into the patients. For in-vivo gene therapy, the genetic material is directly delivered to target cells in the body [103]. Viral gene addition (viral vectors) currently in use for IEIs or gene editing are two main approaches for gene therapy for the treatment or management of IEIs [99].

Viral vectors

Viral vectors are used for a broad spectrum of gene therapy for both acute and chronic diseases. Since a gene cannot be easily inserted directly into cells, it is delivered using a carrier called a vector and these vectors are viruses. The vectors carry a correct copy of therapeutic gene (transgene) along with promoters and enhancers [99]. This process replaces genes that cause diseases with genes needed to cure or manage diseases.

Gene editing

Gene editing is a genetic engineering in which a single or double strand DNA is inserted, deleted, modified or replaced at a specific target site in the DNA. The basic mechanism involved is using engineered nucleases such as zinc-finger nuclease, transcription activator-like effector nucleases and CRISPR-Cas (clustered regularly interspaced short palindromic repeat)-Cas (CRISPR-associated) [99, 104].

In 2016, the European Commission approved ex vivo hematopoietic cell gene therapy for the treatment of ADA-deficient SCID [105]. The approved product is known as Strimvelis and is an advanced therapy medicinal product. The market approval was based on data obtained from 18 ADA-SCID children treated from 2000 to 2011 with a median follow-up of about seven years. Survival rate was 100% [105].

There are challenges with GT treatment in terms of safety, therapeutic effectiveness, and how easy for patients to access gene therapy treatment [99]. There are still safety and efficacy concern for gene editing strategies using engineered nucleases for IEI [99]. Further risks from cell and GT can be summarized as follow [106].

- The inserted viruses may be considered as intruders by the body's immune system resulting an immune reaction that can range from swelling to organ failure.
- Healthy cells can be targeted by the inserted viruses which will lead to damage to the healthy cells.
- The inserted viruses can cause disease(s).

Reverse genetics and gene reversal

Phenotype is described as an individual's observable trait(s) or character(s). A person's phenotype such as height, color of eyes and hair, and blood type is determined by both their genomic makeup (genotype) and environmental factors [107].

Reverse genetics is used to understand the function(s) of a gene by examining the changes to phenotypes of cells or organisms. The alteration in phenotypes is caused by genetically engineering specific nucleic acid sequences within the gene (DNA or RNA). Mutations are induced by radiations or chemicals and mutant cells or organisms are isolated based on their phenotype and genomic mapping is performed to confirm phenotype to genetics [107, 108].

The reverse genetics is opposite to forward genetics. In forward genetics, one attempts to find the genetic basis of a phenotype or trait, whereas, in reverse genetics one attempts to find the phenotypes that are influenced by particular genetic sequences [107, 108].

Reverse genetics is a powerful tool that can be used to understand the function of genes so that new treatments for genetic disorders and diseases can be developed. Reverse genetics has its therapeutic benefits. The main therapeutic application of reverse genetics is in the engineering of vaccines against viruses and in the reconstruction of a viral genome [108]. Live attenuated vaccines have higher immunogenicity than traditional inactivated vaccines and reverse genetics can be used to modify viral genomes by altering their pathogenicity in the development of live attenuated vaccines [108]. Besides, it's application in vaccine development, the therapeutic applications of reverse genetics are in GT, gene editing, cancer therapy, and protein engineering.

Gene reversal, also known as gene conversion is a process in which an inactivated gene is reactivated [109]. For example, effects of a genetic mutation or disease can be reversed by inserting a normal copy of the gene into cells or organisms. However, the drawback of a gene reversal is that the process can lead to loss or alteration of genetic information affecting an organism's development and function. It should be noted that the gene reversal and reverse genetics are two different things.

Gene reversal is in the early stages of research and it will take some time to understand its full therapeutic benefit. At the moment, gene reversal technique is focused on gene therapy, cancer treatment, regenerative medicine, treatment of congenital defects, aging, and management or cure of genetic disorders [109].

Conclusions

Although, immune deficiencies are characterized as monogenic disorders affecting T cells, B cells, combination of T and B cells, or innate immune disorders, in recent years, it has been recognized that there are also a variety of phenotypes associated diseases with one genotype or similar phenotypes causing IEI. IEIs are genetic disorders causing diverse manifestations of immune dysregulation. It is now well recognized that IEIs are beyond just infections and complications from autoimmunity, hypersensitivity, lymphoproliferation and cancer risks leading to morbidity and mortality.

For years, the management of IEIs was mainly the treatment of infections by antimicrobial prophylaxis or IgGs. These days, the management of IEIs has been expanded to small molecule inhibitors, biologics, GT, and the use of adoptive transfer of virus-specific T cells. Early diagnosis and treatment are crucial for the survival from IEI diseases. The newborn screening tests have helped to identify severe SCID in the early stage of the disease resulting in improved outcomes. Rapid improvement in genetic sequencing has helped to identify new IEI diseases. Advances in GT, bone marrow, and HSCT have led to better managements of IEI diseases and outcome.

It is anticipated that in coming years the management of IEIs will improve due to the improvement in technology to screen or identify IEI related diseases and management options. Reverse genetics and gene reversal techniques are slowly emerging and can lead to a better understanding of relationship between phenotypes and genetics hence, more opportunities to treat diseases.

Abbreviations

ADA: adenosine deaminase

Cas: CRISPR-associated

CBC: complete blood count

CDG: congenital disorders of glycosylation

CGD: chronic granulomatous disease

CRISPR: clustered regularly interspaced short palindromic repeat

CVID: common variable immune deficiency

FAODs: fatty acid oxidation disorders

GF: graft failure

GT: gene therapy

HSCs: hematopoietic stem cells

HSCT: hematopoietic stem cell transplantation

IEI: inborn errors of immunity

IEM: inborn errors of metabolism

Ig: immunoglobulin

IUIS: International Union of Immunological Societies

IV: intravenous

NK: natural killer

PID: primary immunodeficiency disease

PK: pharmacokinetics

PKU: phenylketonuria

PNP: purine nucleoside phosphorylase

SC: subcutaneous

SCID: severe Combined Immune Deficiency

WHO: World Health Organization

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