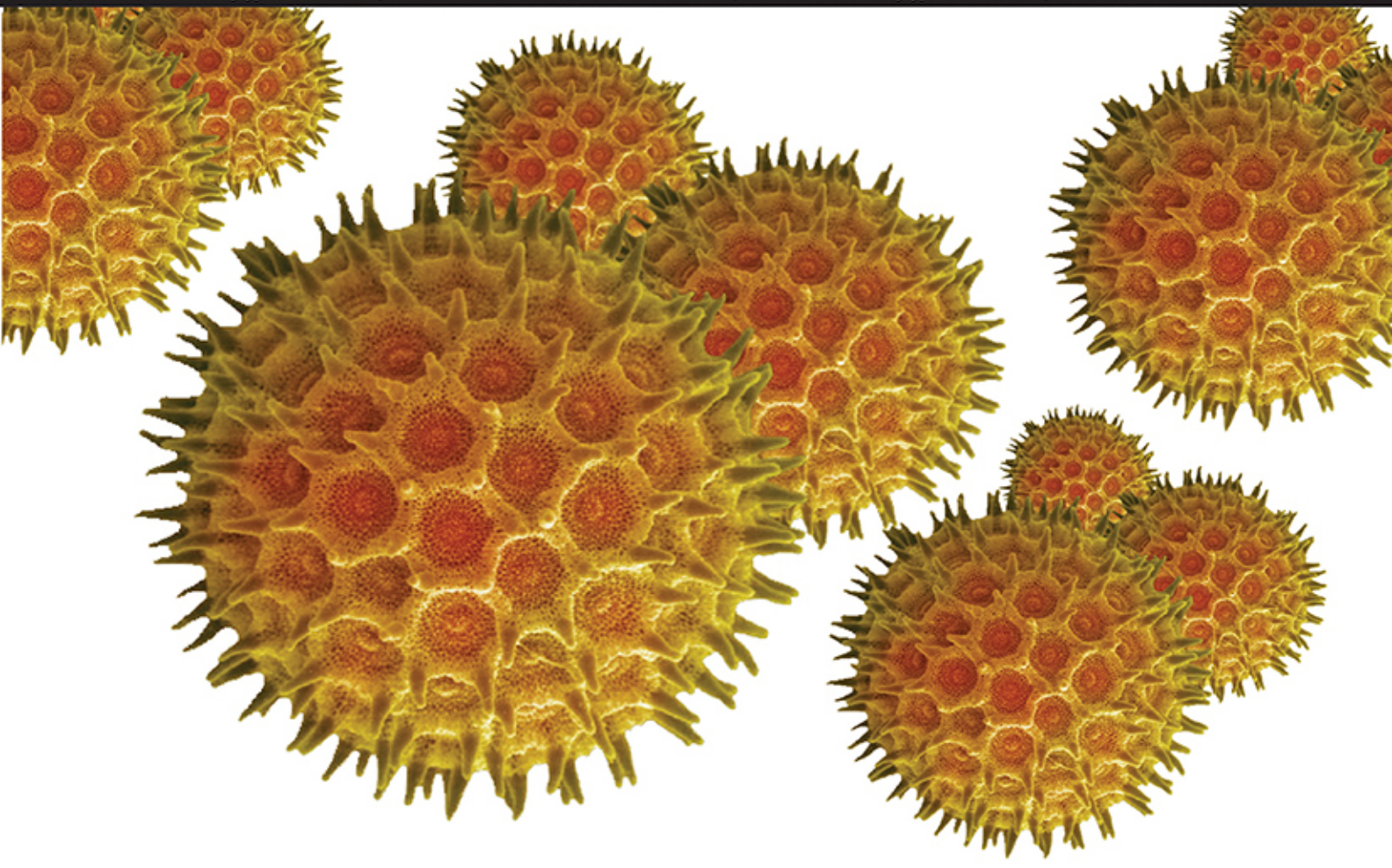
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Comprehensive Textbook of ALLERGY

Striking the Right Balance

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JAYPEE

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CHAPTER

4 Inborn Errors of Immunity

Swati Bhayana, Manas Kalra, Anupam Sachdeva

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INTRODUCTION

Primary immune system defects are traditionally called primary immunodeficiencies (PIDs). PIDs are a rare and heterogeneous group of disorders that occur due to a defect in the development and/or function of the innate or adaptive immune system. Humoral immune deficiencies are characterized by impaired antibody production, while cellular immune deficiencies are caused by defects in T cells.

Inborn errors of immunity (IEI) now comprise 406 distinct disorders with 430 different gene defects listed in the 2019 International Union of Immunological Societies (IUIS) classical classification. There has been an exponential increase in the number of published literatures on IEI. Increased awareness among treating physicians, better molecular diagnostic techniques, improved accessibility for both research and clinical applications, availability of intravenous immunoglobulin (IVIg), facilities for hematopoietic stem cell transplant (HSCT), and postdoctoral training courses have all contributed to early diagnosis and improved outcomes.

Due to the diverse clinical manifestations, investigations should be guided by clinical history. Early diagnosis is essential for referral to specialized care centers and prompt initiation of appropriate therapy which provides the opportunity for appropriate genetic counseling to the patient and his or her family.

PREVALENCE

Studies in the United States have reported the prevalence of IEI as high as 1 in 1,200 population. Prevalence rates may be higher in communities with a high occurrence of consanguineous and endogamous marriages. In India, antibody deficiencies, familial hemophagocytic lymphohistiocytosis (HLH), Wiskott–Aldrich syndrome (WAS), hyper-IgE syndrome (HIES), ataxia–telangiectasia, and hereditary angioedema are among the common diagnoses.

INHERITANCE PATTERN

Most of the IEI are single-gene defects and follow a Mendelian inheritance pattern. However, some of them, such as common variable immunodeficiency (CVID), may have a complex polygenic inheritance. They can be dominant or recessive, autosomal or X-linked, and with complete or incomplete penetrance **(Box 1)**.

BOX 1 Pattern of inheritance of common inborn errors of immunities (IEIs).

- *X-linked recessive*:
  - Severe combined immunodeficiency (SCID)
  - X-linked immunodeficiency
  - Chronic granulomatous disease
  - Hyper-IgM deficiency
  - Wiskott–Aldrich syndrome
- *Autosomal dominant*:
  - Hyper-IgE syndrome
  - Hereditary angioedema
  - STAT1 gain-of-function mutation
  - CTLA-4 haploinsufficiency
- *Autosomal recessive*:
  - Hyper-IgE (DOCK8 deficiency)

CLASSIFICATION

In 1990, the Jeffrey Modell Foundation proposed 10 warning signs to help physicians suspect the diagnosis of PID **(Box 2)**.

The IUIS Expert Committee for Primary Immunodeficiency gave an update on the phenotypic classification of IEI, based on the 2019 IEI classical classification in 2020 **(Box 3)**.

CLINICAL FEATURES

Age of Presentation

Patients may present during the newborn period or in adulthood. The most common age at presentation is infancy and early childhood.

- *Disorders presenting in the first few weeks or months of life*:
  - Severe combined immunodeficiency (SCID)
  - Severe congenital neutropenia (SCN)
  - DiGeorge syndrome
  - Leukocyte defect
- *Disorders presenting from 6 months to 5 years of life*:
  - X-linked agammaglobulinemia (XLA)
  - WAS
  - Chronic granulomatous disease (CGD)
- *Disorders presenting after 5 years of life*:
  - CVID
  - Specific antibody defect
  - Complement defects
  - Ataxia–telangiectasia

COMMON PATHOGENS

Suspect IEI in any patient presenting with severe, disseminated infection by viruses, bacteria, fungi, protozoa, and opportunistic microorganisms. Common pathogens responsible are as follows:

- *Virus*: *Cytomegalovirus*, herpesvirus, enterovirus (polio vaccine), norovirus, Epstein–Barr virus (EBV), human papillomavirus (HPV)-disseminated warts rotavirus
- *Bacteria*: Mycobacteria, Pneumococcus, *Neisseria* sp., *Haemophilus*, *Mycoplasma*, *Giardia lamblia*, *Campylobacter* sp., *Salmonella* sp., *Staphylococcus* sp., *Klebsiella* sp., *Serratia* sp., *Pseudomonas* sp., *Shigella*
- *Fungus*: *Candida* sp., *Aspergillus* sp.
- *Protozoa:* Toxoplasmosis, *Cryptosporidium* sp.
- *Pneumocystis jirovecii* (PJP)
- Reaction to Bacillus Calmette–Guérin (BCG) vaccine

BOX 2 Ten warning signs of primary immunodeficiency (PID) proposed by Jeffrey Modell Foundation.

1. Four or more new ear infections within 1 year
2. Two or more serious sinus infections within 1 year
3. Two or more months on antibiotics with little effect
4. Two or more pneumonias within 1 year
5. Failure of an infant to gain weight or grow normally
6. Recurrent, deep skin or organ abscesses
7. Persistent thrush in mouth or fungal infection on skin
8. Need for intravenous antibiotics to clear infections
9. Two or more deep-seated infections including septicemia
10. A family history of PID

BOX 3 Primary immunodeficiency (PID) classification.

The International Union of Immunological Societies (IUIS) Expert Committee Classification of Primary Immunodeficiency Diseases:

- *Immunodeficiencies affecting cellular and humoral immunity*
  [e.g., severe combined immunodeficiency (SCID)]
- *Combined immunodeficiencies with associated or syndromic features*
  [e.g., Wiskott–Aldrich syndrome, hyper-IgE syndrome, and deoxyribonucleic acid (DNA) repair defects such as ataxia–telangiectasia]
- *Predominantly antibody deficiencies*
  [e.g., Xlinked and autosomal recessive agammaglobulinemia and common variable immunodeficiency (CVID)]
- *Diseases of immune dysregulation*
  (e.g., familial hemophagocytic lymphohistiocytosis)
- *Congenital defects of phagocyte number, function, or both*
  (e.g., neutropenia, chronic granulomatous disease, and leukocyte adhesion defect)
- *Defects in intrinsic and innate immunity*
  [e.g., Mendelian susceptibility to mycobacterial disease, STAT1 deficiency, STAT1 gain of function, and interleukin (IL)17 deficiency; majority of them also predispose to chronic mucocutaneous candidiasis (CMC)]
- *Autoinflammatory disorders*
  [e.g., familial Mediterranean fever, neonatal-onset multisystem inflammatory disease (NOMID), deficiency of IL1 receptor antagonist (DIRA), deficiency of IL36 receptor antagonist (DITRA), and neonatal inflammatory skin and bowel disease]
- *Complement deficiencies*
  (e.g., C1q deficiency presenting as early-onset lupus and C1-inhibitor deficiency presenting as hereditary angioedema)
- *Bone marrow failure syndromes*
  (e.g., Fanconi anemia, dyskeratosis congenita)
- *Phenocopies of PID*
  (e.g., antibodies to IL-17 or IL-22 presenting as CMC and antibodies to C1inhibitor presenting as angioedema)

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COMMON MANIFESTATIONS OF INBORN ERRORS OF IMMUNITY (TABLE 1)

- *Skin*: Eczematous dermatitis, chronic mucocutaneous candidiasis, skin viral infections such as disseminated molluscum contagiosum, extensive eczema ichthyosis, ectodermal dysplasia, partial oculocutaneous albinism, panniculitis, lipodystrophy, severe acne, pustular psoriasis, erythroderma
- Chronic diarrhea, bloody diarrhea, severe inflammatory bowel disease
- Failure to thrive, growth impairment, short stature
- Absence of tonsils, thymus, adenoids
- Deep abscesses, necrotizing pneumonia, osteomyelitis
- Mouth ulcers, oral thrush
- Delayed umbilical cord fall
- IgA nephropathy, vasculitis
- Microcephaly with or without facial dysmorphism
- Deafness, recurrent otitis media
- Cataracts, oculocutaneous telangiectasias
- Bone dysplasia, fracture, scoliosis, lytic bone lesions, arthritis
- Pancreatic insufficiency
- *Autoimmune diseases*: Lupus-like, autoimmune hemolytic anemia and autoimmune thrombocytopenia, autoimmune endocrinopathies
- *Malignancies*: Kaposi sarcoma, EBV-associated lymphoproliferative disorders, lymphomas colorectal carcinoma, brain tumors
- Granulomatous disease including lung
- Bruising, bleeding
- Cerebellar ataxia, global development delay, intellectual deficit
- Increased radiosensitivity
- Family history

INVESTIGATION IN A CASE OF SUSPECTED INBORN ERRORS OF IMMUNITY

Baseline Testing

- *Complete blood count with peripheral smear*:
  - Anemia
  - Thrombocytopenia with or without small platelets (mean platelet volume < 7 fL)
  - Leukocytosis > 20,000/μL
  - Lymphopenia (lymphocyte count < 3,000/mm^3) in infancy, neutropenia, monocytopenia, eosinophilia, and/or giant granules in neutrophils
- *Immunoglobulin profile* **(Table 2)**:
  - Immunoglobulin A, M, G, and E measurements
  - IgG total and subclass: A value of <3 g/L (300 mg/dL) in an adolescent or adult as well as values clearly below the age-appropriate reference (95% confidence interval) in a child.
- Lymphocyte subpopulation counts (CD3, CD4, CD8, CD19, CD56, respectively T, T4, T8, B, and NK) and comparison with age and population appropriate reference range. CD3 is usually <300/cumm in case of SCID.

TABLE 1: Common manifestations of inborn errors of immunity (IEI) and causative agents.

Affected cell line	Sites of infection	Common organisms
B cells	• Sinopulmonary tract • Gastrointestinal (GI) tract • Joints • Central nervous system (CNS)	• *Pyogenic bacteria*: Streptococci, Staphylococci, *Haemophilus influenzae* • *Enteroviruses*: Enteric cytopathic human orphan (ECHO), polio • *Mycoplasma* species
T cells	• Multisystem involvement • Sepsis • Lung • GI tract • Skin	• *Viruses*: *Cytomegalovirus* (CMV), adenovirus, measles, molluscum • *Fungi*: *Candida* and *Aspergillus* species, *Pneumocystis jirovecii* • Pyogenic bacteria • *Protozoa*: *Cryptosporidium* species
Phagocytes	• Skin infections • Lymphadenitis • Liver • Lung • Bone • GI tract • Gingivitis/periodontitis	• *Bacteria*: Staphylococci, *Serratia marcescens*, *Burkholderia cepacia*, *Klebsiella* species, *Escherichia coli*, *Salmonella* species, *Proteus* species • *Fungi*: *Candida*, *Aspergillus*, and *Nocardia* species
Complement	• Systemic infections • Meningitis	*Pyogenic bacteria*: Streptococci, *Haemophilus influenzae*, *Neisseria* species

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TABLE 2: Differentials of low immunoglobulin levels.

IgG	IgM	IgA	B cell number	Likely diagnosis
Low	Variable	Low	Usually, normal	Common variable immunodeficiency
Normal	Normal	Low	Normal	Selective IgA deficiency
Low	Low	Low	Undetectable or very low	Congenital agammaglobulinemia
Normal	Normal	Normal	Normal	Specific antibody deficiency
Low	Variable	Low	Low	Agammaglobulinemia with thymoma
Low	Normal, low, or high	Low	Normal	Hyper-IgM syndromes
–	–	Low	–	Ataxia–telangiectasia syndrome
Low	–	Low	–	Transient hypogammaglobulinemia of infancy

- Nitro blue tetrazolium (NBT) or dihydrorhodamine (DHR) test for CGD
- *Flow cytometry for leukocyte adhesion defect (LAD)*: Assessment of the neutrophil adhesion molecules CD11 and CD18, the expression of which is absent or decreased on neutrophils (and other leukocytes) from patients with LAD type I (LAD I). CD15 (Sialyl–Lewis X) expression is absent on neutrophils from patients with LAD type II (LAD II).
- *Rule out secondary immunodeficiencies*: Human immunodeficiency virus (HIV) and drug-induced
- *HLH*: High ferritin and circulating soluble CD25 levels

Advanced Testing

- *Flow cytometry evaluation*:
  - In combined T- and B-cell defects without intense lymphopenia, it is necessary to evaluate subpopulations of T lymphocytes: Naïve ($CD3^+$ $CD45RA^+$), memory ($CD3^+$ $CD45RO^+$), double negative ($CD3^+$ TCR, $CD4^-$ $CD8^-$) and T helper (Th) 17, subpopulations of natural killer (NK) cells (CD56 and CD16).
  - Expression of proteins such as BTK (XLA), WASp (Wiskott–Aldrich syndrome protein), CD40/CD40L (hyper-IgM syndrome), CD11/CD18, and interleukin (IL)-10R (LAD I).
  - Functional in vitro assays to assess lymphocyte proliferation and activation, interferon-gamma (IFN-γ)-IL-12 axis activity, CD62L shredding assay, oxidative burst in phagocytes.
- *Genetic testing*: Chromosomal microarray analysis, genetic sequencing using the Sanger method, and complete sequencing of the exome or genome using the new-generation sequencing technology.
- Total hemolytic complement activity (CH50) assay and AH50 assay screen for defects in the alternative complement pathway.
- *Adenosine deaminase (ADA) and purine nucleoside phosphorylase (PNP)*: To assist diagnosis of cases with SCID.

To assess the response to protein antigens, the vaccine response is evaluated like serological tests for measles, rubella, mumps, tetanus, poliovirus, and diphtheria. In patients who are already receiving immunoglobulin replacement, we assess the response to the rabies vaccine.

The response to polysaccharide antigens should be obtained by requesting IgG measurements for 23 pneumococcal serotypes before and 4–6 weeks after the unconjugated 23-valent pneumococcal vaccine. Intradermal hypersensitivity tests can be used to screen for cell immunity. The antigens used are candidin, streptokinase/dornase, staphylococcal toxin, trichophytin, and purified protein derivative (PPD). Patients older than 1 year must respond (3-mm papule) to at least one of the tested antigens in 48–72 hours. This type of assessment has been abandoned as a result of widespread access to flow cytometry.

- T-cell receptor excision circles (TREC) allow assessing the presence of naïve T cells that recently left the thymus and kappa-deleting recombination excision circles (KREC) assess the presence of immature B lymphocytes. Generally used in the neonatal screening for T- and B-cell defects, this count can also be useful in the investigation of an IEI.

Special cases:

- *SCN (Kostmann syndrome)*: Neutrophil counts of $<0.5 \times 10^9$/L on several occasions
- *Cyclic neutropenia*: Weekly serial hemograms
- Measurement of uric acid, which is extremely low in PNP deficiency and acts on purine metabolism
- *Alpha-fetoprotein level*: High in patients with ataxia–telangiectasia

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Severe Combined Immunodeficiency

Severe combined immunodeficiencies are a group of monogenic diseases with impaired adaptive immunity due to a severe lack of T lymphocyte number and function, with or without low B and NK lymphocyte numbers. SCID infants have grave prognosis due to severe recurrent infections with common pathogens such as respiratory syncytial virus (RSV), myxovirus, adenovirus, and opportunistic microorganisms such as PJP and CMV, intestinal infections with rota-, noro-, or adenovirus, and vaccines such as BCG vaccine. They may also present with failure to thrive and signs of immune dysregulation caused by autologous or allogeneic T cells. They can have manifestations such as cytopenias, chondrosternal dysplasia, deafness, dysmorphisms, congenital alopecia, nail dystrophy, lymphoproliferation, granuloma, and autoimmunity.

They are often seemingly well at birth and present within their first weeks or months of life, after the protective effect of residual transplacental maternal IgG weans off. Atypical or leaky SCID caused by hypomorphic mutations have a less severe clinical phenotype and may present after 1 year in life.

In the laboratory, SCID infants usually have absolute lymphocyte counts lower than 3×10^9/L. Primary Immunodeficiency Treatment Consortium diagnostic criteria for typical SCID require <300 autologous T cells/mm^3 in peripheral blood sample with <10% response to phytohemagglutinin (PHA) when compared against control or demonstration of maternal engraftment. A lack of naïve T lymphocytes (e.g., $CD3^+$, $CD4^+$, $CD45RA^+$, $CCR7^+$) or more specifically of recent thymic emigrant cells ($CD4^+$, $CD45RA^+$, $CD31^+$) is an important laboratory finding suggestive of thymic dysfunction. Atypical or leaky SCID, such as Omenn syndrome, is characterized by less severe T lymphopenia. The presence and absence of B cells and NK cells distinguish the type of SCID. Absence of thymic shadow on thoracic radiographs is a characteristic feature of ADA deficiency. It is very important to look for and rule out DiGeorge syndrome or any other thymic disorder.

Infections must be carefully investigated (including invasive measures such as biopsies or bronchoalveolar lavage) to provide specific therapy.

An Indian multicentric study on 57 SCID patients revealed a heterogenous genetic basis of SCID. The most common underlying defect was Rag1/2 defect followed by IL2RG and JAK3 abnormalities. Very few patients proceeded to HSCT, revealing the huge delay in presentation, evaluation, and appropriate management.

Chronic Granulomatous Disease

Chronic granulomatous disease is an inherited PID caused by functional impairment of the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase complex in neutrophilic granulocytes and monocytes with defective reactive oxygen species (ROS) production and characterized by recurrent and severe infections, dysregulated inflammation, and autoimmunity. Patients with X-linked CGD have a more severe disease course with earlier age at presentation and earlier age of death. Superoxide production can be measured by NBT reduction test and DHR-1,2,3 assay by flow cytometry by quantifying oxidative capacity of the phorbol 12-myristate 13-acetate (PMA)-stimulated neutrophils. Mutation analysis should be performed in patients with CGD to confirm the genetic defect and is needed for genetic counseling and prenatal screening.

Chronic granulomatous disease may present at any age from infancy to late adulthood; however, the majority of patients are diagnosed at <5 years of age. Infections are primarily with a subset of catalase-positive microorganisms, and the most common sites of infection are the lungs, skin, lymph nodes, and liver. Pathogens are *Aspergillus* spp., *Staphylococcus aureus*, *Burkholderia cepacia*, *Serratia marcescens*, *Nocardia* spp., *Salmonella*, BCG, and tuberculosis in developing countries. Mulch pneumonitis is a severe inflammatory lung pathology seen in patients with CGD who are exposed to decayed living wastes. Fungal pneumonia due to *Aspergillus* sp., *Fusarium dimerum*, *Penicillium* sp., *Paecilomyces variotii*, and *Scedosporium* sp. in CGD may warrant prolonged antifungal treatment.

Improved recognition and early diagnosis leading to earlier therapies, including more efficacious antimicrobial and antifungal prophylaxis, use of IFN-γ supplementation for infection prophylaxis, and use of HSCT, have led to a marked improvement in life expectancy. Recent reports have shown the beneficial effects of addition of glucocorticoids with intravenous antibiotics for the management of liver abscess in CGD in terms of reduction in the need of surgical intervention and enhanced resolution of abscess.

Multicentric data from an Indian CGD cohort of 236 patients revealed a higher proportion of autosomal recessive disease and much more mycobacterial infection as compared to the western cohorts. The study identified differences in the genetic basis of disease based on the regional distribution (CYBA more common in south and western regions and NCF2 more common in North India). The most common underlying mutation in Indian patients was CYBB followed by NCF1 and NCF2 variants.

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Mendelian Susceptibility to Mycobacterial Disease

Mendelian susceptibility to mycobacterial disease (MSMD) is a type of IEI, which predisposes the individual to develop infections from intracellular organisms such as mycobacteria and *Salmonella*. It generally consists of defects in the IFN-γ–IL-12/23 circuit that is crucial for immunity against intracellular microorganisms and often leads to recurrent or persistent infections to bacteria which may be weakly virulent to the general population like the BCG strain-related infection that is produced from serial subcultures of *Mycobacterium bovis*. These individuals may develop recurrent candidiasis and other fungal infections such as histoplasmosis.

Authors from India performed the largest study on a cohort of 55 MSMD patients and identified BCGosis as the most common form of presentation at a median age of 6 months. *Salmonella* and fungal/CMV infections were also identified in patients with these defects. IFN2R defects seem to be more common than reported in western literature.

Hyper-IgE

Hyper-IgE syndrome was first described in 1966, in two girls suffering from recurrent cold staphylococcal abscesses, pneumonia, and neonatal eczema. They are characterized by a triad of atopic dermatitis (distributed on the scalp, face, neck, axillae, and diaper area, typically pruritic owing to the histamine released by IgE-triggered intradermal mast cells), recurrent skin and lung infections (cold abscesses and chronic candidiasis), and elevated IgE levels. The nonimmunological manifestations of HIES include skeletal and connective tissue abnormalities, such as scoliosis, osteoporosis, fracture following minor trauma, hyperextensive joints, retained deciduous teeth and conjunctivitis, keratitis, spontaneous corneal perforation, recurrent giant chalazion, extensive xanthelasma, tumors of the eyelid, strabismus, and bilateral keratoconus.

Job syndrome or autosomal dominant HIES is the more common form and occurs because of heterozygous loss-of-function mutations with dominant negative effect in signal transducer and activator of transcription-3. HIESs including autosomal recessive mutations in the *DOCK8*, *ZNF431*, and *PGM3* genes and heterozygous mutations with dominant negative effects in the *CARD11* gene are increasingly identified in the last decade.

Total leukocyte counts are generally within the normal limits in the absence of infection and often fail to rise in the occurrence of active infection. Eosinophilia (2 standard deviations above normal values) in the blood, sputum, and abscesses are seen in virtually all patients. An IgE level 10 times higher than the 95th percentile of the age norm seems to be an acceptable level for the diagnosis of HIES. A lower limit of 2,000 IU/mL is used as an arbitrary cutoff for this syndrome. In newborns, normal levels of IgE are very low to undetectable; therefore, normal adult IgE levels in infants (100–200 IU/mL) are pathological. Serum concentrations of the other immunoglobulins (IgG, IgA, IgM, and IgD) and IgG subclasses are normal in the patients.

High-dose IVIg and subcutaneous injection of IFN-γ with a dose of 0.05 mg/m^2 three times weekly have been shown to reduce IgE production. Bone marrow transplant and a monoclonal anti-IgE (omalizumab) are hoped to be successful treatment in the future.

Indian patients with HIES either have no genetic basis identified or harbor rare variants of heterozygous *STAT3* mutations. The diagnosis in such cases rests on clinical scenario, eczema, eosinophil counts, IgE levels, and infections by pathogens such as *Staphylococcus* and *Candida* (additionally mycobacteria which is seen mainly in the Indian subcontinent).

Familial Hemophagocytic Lymphohistiocytosis

In a cohort of 101 molecularly characterized HLH patients, FHL2 and FHL3 together constituted 84% of the patients. Perforin assays were abnormal in FHL2, and CD107a degranulation assay was helpful in predicting FHL 4/5 and 3, respectively. We reported the largest single-center series of HLH patients from India. Out of 118 patients, 27 (23%) were primary HLH. The median age at diagnosis was 4 years and the median ferritin value was 6,504 ng/mL. Hyponatremia, hyperbilirubinemia, increased sIL2 receptor, and coagulopathy predicted poor outcomes.

Primary Antibody Deficiency

Primary antibody deficiencies lead to severe and/or recurrent infections by encapsulated bacteria. They generally have suboptimal response to antibiotics and need repeated hospitalizations for parenteral therapy.

The entity includes the following scenarios:

- Severe deficiency of all immunoglobulin isotypes with marked decreased or absent B cells, agammaglobulinemia (X-linked or autosomal recessive)
- Severe deficiency in at least two serum immunoglobulin isotypes with normal or low number of B cells, CVID phenotype
- Severe reduction in serum IgG and IgA with normal/elevated IgM and normal numbers of B cells, hyper-IgM phenotype
- Isotype, light chain, or functional deficiencies with generally normal numbers of B cells

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Severe form: XLA or autosomal recessive agammaglobulinemia (ARA) patients have absent to reduced size of tonsils, Peyer's patches, spleen, adenoids, and lymph nodes where B cells undergo maturation and differentiation.

X-linked agammaglobulinemia is caused by defects in *Btk (gene)* encoding Bruton's tyrosine kinase (Btk). The disease presents in males after 6 months of age when maternally transmitted antibodies have waned off.

Quantitative serum levels of IgM, IgG, IgA, IgE, and antibody titers in response to vaccines (tetanus and diphtheria toxoids, *Haemophilus influenzae*, measles, mumps, rubella, varicella, pneumococcus, hepatitis A or B, influenza virus) are the initial line of investigation. Lymphocyte subsets reveal normal T-cell numbers but <1–2% B cells. *Btk* gene testing identifies the variant that is mutated.

These patients are likely to develop sepsis, meningitis, otitis, sinusitis, or cellulitis due to *H. influenzae* and *Streptococcus pneumoniae. Other pathogenic organisms are Pseudomonas, Staphylococcus, Campylobacter jejuni, and enterovirus infections.* Enteroviruses such as norovirus, vaccine-associated polio, and ECHO virus infections can be very severe in these patients. These patients can develop meningoencephalitis and polio secondary to these infections. *G. lamblia*, *Enterovirus*, rotavirus, *Campylobacter*, *Salmonella,* and cryptosporidia can lead to recurrent diarrhea. Arthritis and inflammatory bowel disease are frequent autoimmune manifestations. Regular immunoglobulin replacement prevents serious bacterial infection and hospitalizations. Trough level of IgG should be maintained above 400–600 mg/dL. Subcutaneous Ig obviates the need for regular admission and IV infusion. Patients should be monitored for the development of chronic lung disease. HSCT carries the risk of toxicity associated with the procedure. As the transplant becomes more safe, it may replace regular IVIg supplementation.

A multicentric Indian study on 145 children revealed a 48-month delay in diagnosis of XLA. Most patients presented with pneumonia and the most common infectious agent isolated was *Pseudomonas* sp. followed by *S. pneumoniae*, *S. aureus*, and *Klebsiella pneumoniae*. *BTK* gene abnormalities seen in Indian patients were missense (36%) and frameshift (22%), followed by nonsense (21%) variants. Administering regular IVIg still continues to be a major challenge in our country due to lack of resources.

Common Variable Immunodeficiency

Most CVIDs are polygenic. Only 10% of cases will have a genetic basis that can be identified. The diagnosis relies on low Ig levels. In most cases, patients have low IgG with or without low IgA and/or IgM. Class switch memory B cells are low ($CD10^+$, $CD27^+$, IgM^-, IgD^-). Patients may present with autoimmune or granulomatous manifestations, chronic lung or liver disease, splenomegaly, lymphadenopathy, meningitis, and sometimes with cancer.

Wiskott–Aldrich Syndrome

This X-linked disorder is characterized by thrombocytopenia, eczema, and recurrent infections. The condition occurs because of loss-of-function mutations in the *WAS* gene that is expressed only in hematopoietic cells and encodes the WASp, a key actin cytoskeletal regulator that coordinates assembly of actin filaments in response to cell signaling events. An easy screening tool is measuring the MPV (mean platelet volume), which is typically <7 fl. It is frequently misdiagnosed as immune thrombocytopenic purpura (ITP) as the latter is a much more common cause of thrombocytopenia in young children. Both the conditions may have a normal megakaryocyte number in marrow. WAS also presents with other features of autoimmunity and has increased predisposition to malignancy.

Leukocyte Adhesion Defect

Polymorphonuclear leukocytes migrate from blood to the site of inflammation in an organized fashion and this process involves several adhesion molecules, the defect of which impairs the attachment to endothelium and subsequent migration to extravascular space. These defects are clubbed together and known as LAD. Four classes of LAD are discovered. LAD I is the most common and the most serious form. It leads to life-threatening bacterial sepsis without pus formation and death at a very young age. It is caused by loss of function of common chain, CD18 of b2 integrin family. Patients have very high white blood cell (WBC) count with predominant neutrophilia as these cells are unable to migrate out of the vessel to the site of infection/inflammation. The diagnosis is based on CD11b/CD18 expression on stimulated and unstimulated neutrophils. In LAD II, the severity of illness is less but children still develop bacteremia and mental retardation. This results from a general defect in fucose metabolism. Antibiotic prophylaxis is needed. Bombay blood group phenotype is also observed in these patients. LAD type III (LAD III) is caused by abnormal integrin activation. LAD III leads to severe bacterial and fungal infections. Patients frequently show delayed detachment of umbilical cord (seen in types III and I), impaired wound healing, and increased tendency to bleed (Glanzmann type of defect). Bone marrow transplant is needed for curative therapy in types I and III. LAD type IV (LAD IV), a newly described entity, is caused by defects in b2 and

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a4b1 integrins, which impairs lymphocyte adhesion. LAD IV patients have a monogenic defect in cystic fibrosis transmembrane conductance regulator (*CFTR*) gene, resulting in cystic fibrosis.

India largely has LAD I (>96%) variant and very few LAD III patients (~4%). Majority of these patients presented by 3 months of life. Patients with LAD III have bleeding tendencies due to defects in platelet function along with defective immunity. Common underlying defects were ITGβ2 and FERMT3. Patients with higher CD18 expression presented later in life with nonhealing skin ulcers.

PREVENTION AND TREATMENT

- *Isolation and hygiene practices*: Once any severe form of PID is diagnosed, patients should be isolated to prevent life-threatening infections. This is particularly important for candidates for HSCT. Patients with SCID can be either managed carefully at home while awaiting HSCT or hospitalized in an isolation room. Caregivers should receive counseling regarding safe isolation practices and avoidance of public outings. Family members and staff entering the patient's room should wash hands thoroughly with soap and water and use a mask, gown, and gloves. The number of guests/visitors to the home should be minimized. For HSCT, the patient should be placed in a positive-pressure room with high-efficiency particulate air (HEPA) filtration.
- *Health care*: Health maintenance in patients with PID includes dental, audiologic, and vision care. Routine dental visits at least twice annually are essential. Sugary drinks should be avoided. Routine dental X-rays should be avoided in patients with radiosensitivity, including ataxia–telangiectasia, Artemis deficiency, and related disorders. All patients with IEI should have baseline audiologic screening. Hearing loss can be a potential risk due to infections such as CMV or medication toxicities such as aminoglycosides. ADA deficiency has been associated with an elevated risk of sensorineural hearing loss after bone marrow transplantation.

  Patients with IEI are at a risk for infection of the eye as herpesviruses (CMV, herpes simplex virus ½, and varicella zoster), toxoplasma, and inflammatory complications that may impact vision.
- *Prophylactic antibiotics*: Infections are the most common forms of presentation, and treatment in patients with IEI requires long-term use of broad-spectrum medications. The use of prophylactic antibiotic therapy is widespread aiming to reduce the frequency and severity of infections, especially sinopulmonary infections caused by common bacteria. The scientific evidence for the use of antibiotic prophylaxis in PIDs such as CGD and SCID shows that it is known to reduce annual exacerbations in patients with antibody defects (CVID and agammaglobulinemia). Agents used are sulfamethoxazole-trimethoprim, azithromycin, amoxicillin, ciprofloxacin, and dapsone.

  Antiviral (herpesvirus family) prophylaxis is indicated in some patients with recurrent mucosal or skin herpes simplex outbreaks. Antifungal prophylaxis may be required in disorders with high susceptibility to recurrent fungal infection, such as defects in the IL-12/23/Th17 pathway. Itraconazole prophylaxis has an established role in CGD and HIES.
- *Immunoglobulin replacement therapy*: Most IEI patients require immunoglobulin replacement. Immunoglobulin can be replaced intravenously (IVIg) or subcutaneously (SCIg). The indications of immunoglobulin replacement therapy are proven beneficial in immune system defects that affect B cells and hypogammaglobulinemia, likely benefit in a qualitative defect in the specific antibody production. They are known to have no benefit/contraindicated in selective IgA deficiency and IgG4 deficiency. The European Immunodeficiency Society (ESID) recommends immunoglobulin replacement therapy at IgG < 200 mg/dL for all patients, IgG 200–500 mg/dL associated with repeated infections, and IgG > 500 mg/dL in specific antibody deficiency associated with severe or repeated infections.

  Specific immunodeficiencies that require immunoglobulin replacement therapy are as follows:
  - Agammaglobulinemia
  - Hypogammaglobulinemia such as CVID
  - Hyper-IgM syndrome, HIES, WAS, and ataxia–telangiectasia in case of repeated infections

  The IVIgs are given every 3–4 weeks, with an initial dose of 400–600 mg/kg, so that the IgG level is >500 mg/dL. Higher doses, around 800 mg/kg, help in the control of pulmonary problems and are recommended for patients with chronic pulmonary disease and/or chronic sinusitis. The dose regimen is similar and follows the equivalent of 100–150 mg/kg/week. IgG level monitoring should be carried out three monthly. Stable values are reached after the sixth infusion and interval must be adjusted. Good patient hydration and reduced infusion rate are effective measures in preventing adverse events. Subcutaneous infusions may cause local irritation effects but have the advantage of outpatient-based treatment.

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Serum from donors with high levels of antibodies directed against particular infectious organisms may be pooled such as CMV immune globulin and varicella-zoster immune globulin. Anti-RSV antibody palivizumab is used for prevention of RSV infection in immunocompromised patients.

- *HSCT*: The approach to HSCT has changed substantially in the past two decades, with more potential donor sources, better conditioning regimens, and better support care.
  - *Human leukocyte antigen (HLA) typing and match*: High-resolution, allele-level HLA-A, -B, -C and -DRB1, -DQB1 typing is mandatory for all donors (except unrelated CB). For unrelated donors, allele-level matching at all 10 loci is the gold standard.
  - *Donor choice*: HLA identical siblings as the first donor choice, matched unrelated donor (MUD), and HSCT performed with mismatched family have increasingly improved.
  - *Conditioning*: While until 15–20 years ago, myeloablative conditioning with (oral) busulfan and cyclophosphamide was the norm, over the years, extensive experience has been obtained with a number of different, and increasingly less toxic, conditioning regimens.
  - *Stem cell dose*: In case of unmanipulated bone marrow grafts in matched family or unrelated donors, the recommended cell dose is 2–4 × 10^8 TNC/kg. In case of T replete peripheral blood stem cell (PBSC) grafts from matched donors, the recommended $CD34^+$ cell dose is 5–8 × 10^6/kg. In case of higher doses, the T-cell dose should not exceed 3–5 × 10e8 $CD3^+$ T cells/kg in order to limit the risk for graft-versus-host disease (GvHD).

  Approach to common IEI transplant:
  - *SCID*: These may include no conditioning to busulfan/fludarabine or treosulfan/fludarabine.
  - *CGD and other phagocyte disorders*: Busulfan/fludarabine or treosulfan/fludarabine are the preferred regimens. In X-CGD, carrier family donors should generally be avoided as they may have inflammatory and autoimmune symptoms.
  - *HLH*: Regardless of the underlying genetic cause of primary HLH, disease remission at the time of HSCT is the key factor in overall survival. Veno-occlusive disease (VOD) is common in this group of patients, mainly due to treatment-related toxicity and disease. Use of prophylactic defibrotide in infants under 18 months of age or those over 18 months with clear hepatic involvement is recommended. Outcomes post HSCT have significantly improved with the advent of reduced toxicity conditioning protocols and better HLH control prior to conditioning. Stable high-level donor chimerism is desired, and mixed chimerism is seen more commonly after treosulfan- and melphalan-based regimens. XIAP-deficient patients have significantly worse outcomes than for other forms of primary HLH even in the context of RIC regimens. These patients are particularly sensitive to alkylating agents and appear to suffer from more severe GvHD, which leads to higher mortality. Conditioning regimens include MAC regimens such as busulfan/fludarabine and treosulfan/fludarabine/thiotepa. Serotherapy should also be considered as part of the conditioning to control the disease if not in complete remission.
- *Gene therapy*: It consists of the genetic modification of hematopoietic stem cells of the individual with a vector containing the corrected gene product and administered to the patient as an autologous bone marrow transplant. The great advantage of this procedure is that there is no need to find compatible donors. However, the initial trials with retroviral vectors were complicated with cases of leukemia and myelodysplasia. Lentiviral vectors are currently considered safer, and trials with SCID due to ADA deficiency, X-linked SCID, WAS, and DCG have shown good immunological reconstitution in phase I.
- *Vaccination of patient, family members, and caregivers*: Live vaccines are contraindicated in patients with moderate-to-severe forms of PID, but expert consensus recommends that healthy family members and close contacts receive all vaccines.
  - *Blood transfusions*: Patients with suspected or known T-cell immunodeficiencies, such as SCID, WAS, nuclear factor-kappa-B essential modifier (NEMO) deficiency, and complete DiGeorge syndrome, should not be given blood or blood components that may contain viable lymphocytes because of the risk of fatal transfusion-associated GvHD. Any cellular blood products given to these patients must be irradiated. Leukocyte reduction is also highly recommended in order to minimize chances of transmission of CMV.

    Packed cells and platelet transfusion are given at usual indications. Granulocyte transfusion has value in treating serious bacterial and fungal infections.
- *Infectious disease*: When a suspected bacterial infection develops, attempts should be made to culture and identify the pathogen and initiate antibiotics as rapidly as possible. Delayed clearance and response to anti-infective therapy warrant prolonged antibiotic courses.

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- *Enzyme replacement and metabolic therapy*: Adenosine deaminase deficiency accounts for roughly 20% of SCID and can be treated via enzyme replacement with recombinant ADA stabilized with polyethylene glycol (PEG-ADA), which is administered intramuscularly once to twice weekly.
- *Thymic transplantation*: This is done in patients with complete DiGeorge syndrome and forkhead box N1 (FOXN1) deficiency.
- *Genetic testing and counseling*: Appropriate interpretation is beneficial for education of the patient and family regarding the prognosis and impact on subsequent pregnancies. Parental genetic sequencing should be offered to families of children with suspected PID to confirm variant phase (cis/trans) and aid in interpretation of pathogenicity.

CONCLUSION

Inborn errors of immunity are uncommon but serious health conditions which requires a high index of suspicion and an interdisciplinary team for diagnosis and management. Some of the conditions can manifest in young adults. The majority of the conditions are because of antibody defects or combined antibody and cellular defects. Recent advances in treatment including bone marrow or stem cell transplantation has improved the prognosis of most of these conditions.

KEY POINTS

- IEI are rare and heterogeneous disorders that require a high index of suspicion.
- Antibody defects are the most common type among this group of disorders.
- Some disorders may be detected after 5 years of age or in adults.
- Meticulous history is the cornerstone in diagnosis.
- Simple investigations such as chest roentgenogram or complete blood count can be the first pointers toward diagnosis.

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Printed in India

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ISBN 978-93-5696-190-6