Practice Parameter: Algorithmic Management of Inborn Errors of Immunity

Indian Academy of Pediatrics – Allergy and Applied Immunology Chapter

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I. Primary Immunodeficiencies (PID) / Inborn Errors of Immunity (IEI)

Primary Immunodeficiency Diseases (PIDs), now more commonly known as Inborn Errors of Immunity (IEIs), are a diverse group of inherited conditions that impair the function of the immune system. Found in approximately 1 in 2,000 live births, more than 500 unique types have been identified. These disorders not only lead to increased frequency and severity of infections but also contribute to immune dysregulation, such as autoimmune diseases, chronic inflammation, abnormal lymphocyte growth, and a heightened risk of cancer.

The symptoms of IEIs vary widely and are not limited to infections alone. Early involvement of a clinical immunologist is vital to ensure prompt diagnosis and management, which are crucial to reducing illness and death. A solid understanding of how to classify, identify, diagnose, and treat these conditions is essential to improving the quality of life for patients and supporting their families.

II. Classification of IEIs

IEIs are broadly classified based on the primary component of the immune system that is affected . Classification systems, such as those from the World Health Organization and the International Union of Immunological Societies, group disorders based on mechanistic and clinical characteristics . Table 1 summarises this as below

Table-1. Simplified classification for IEI based on IUIS approach

Category	Description	Examples
Combined Immunodeficiencies (CID)	Affects both cellular (T cell) and humoral (B cell) immunity.	Severe Combined Immunodeficiency (SCID), Hyper-

		IgM syndromes (CD40L, CD40 defects)
Predominantly Antibody Deficiencies	Primarily affects B cell development and antibody production.	X-linked Agammaglobulinemia (XLA), Common Variable Immunodeficiency (CVID), Selective IgA Deficiency (SIGAD)
Phagocytic Cell Defects	Affects the number or function of phagocytes (neutrophils, macrophages).	Chronic Granulomatous Disease (CGD), Leukocyte Adhesion Deficiency (LAD)
Defects of Innate Immunity	Affects the first line of defense mechanisms (TLRs, NK cells).	NEMO deficiency, Chronic Mucocutaneous Candidiasis (CMCC) syndromes
Disorders of Immune Dysregulation	Characterized by autoimmunity, autoinflammation, or lymphoproliferation.	Hemophagocytic Lymphohistiocytosis (HLH), Autoimmune Lymphoproliferative Syndrome (ALPS), IPEX syndrome
Autoinflammatory Disorders	Characterized by recurrent episodes of inflammation and fever.	Cryopyrin-Associated Periodic Syndromes (CAPS), Familial Mediterranean Fever (FMF), TRAPS
Complement Deficiencies	Affects components of the complement system.	C1, C2, C3, C4, C5-C9 deficiencies, Factor H, Factor I, Properdin deficiencies
Immunodeficiency Syndromes	Disorders with other characteristic features in addition to immune defects.	Wiskott-Aldrich syndrome (WAS), DiGeorge syndrome (DGS), Ataxia-Telangiectasia (AT), Hyper-IgE syndromes (HIES)
Immunodeficiency Associated with Autoantibodies	Conditions where autoantibodies cause immune dysfunction.	Anti-cytokine autoantibodies (e.g., anti-IFN-gamma, anti-GM-CSF)
Primary Atopic Disorders	Monogenic disorders with predominant pathogenic allergic/atopic symptoms.	CADINS, SAM syndrome

III. Primary atopic disorders

The term 'Primary Atopic Disorders' (PAD) was coined by Lyons and Milner in 2018. The PADs are heritable monogenetic disorders presenting with predominant atopic or allergic manifestations. They are a subgroup of IEI with phenotype that includes allergic diseases as well as genetic disorders of the skin barrier.

Primary atopic disorders (PADs) are often associated with significantly elevated IgE levels, frequently exceeding 2000 U/L. However, the term **"Hyper IgE Syndrome" (HIES)** specifically refers to a limited group of genetic defects—such as **STAT3, IL6ST, and ZNF341 mutations**—that present with a classic triad: **eczema, recurrent Staphylococcal infections**, and **connective tissue abnormalities**.

Therefore, **"PAD" and "HIES" are not interchangeable terms** and should be used distinctly to reflect their underlying pathophysiology and clinical manifestations.

Current diagnostic guidelines for IEI maybe inadequate to diagnose PAD as it primarily focus on infectious manifestations but PAD present solely or primarily as allergic manifestations. IEI may go unrecognised if atopy is the predominant symptom.

Frequency of atopy in IEI is estimated to be 10-28%, and, IEI initially presenting as isolated atopy is in the range of 5-25 %. Therefore, it is important that allergists need to be aware of the PADs and they play a vital role in early recognition of the affected patients.

Classification of Primary Atopic Disorders based on clinical presentation

1. Atopic Features as Primary Presentation

A. CADINS (CARD11-associated atopy with dominant inheritance of immunodeficiency)

• May initially present with severe atopic dermatitis

• Inherited in an autosomal dominant pattern

• Progresses to include recurrent infections, autoimmunity, and malignancy

B. STAT6 gain of function

- Caused by germline GOF mutations in STAT6, leading to overactive allergic responses.
- Includes refractory eczema, asthma, food allergies, and eosinophilic gastrointestinal disease.
- Targeted biologics: Dupilumab (anti-IL4Rα) may be considered

C. **JAK1 gain of function**

- Autosomal dominant inheritance
- Presents with severe atopic dermatitis, food allergies, asthma, and eosinophilic gastrointestinal disease
- In addition to allergy, may show autoimmunity, lymphoproliferation, and even growth failure
- JAK inhibitors (e.g., ruxolitinib) show therapeutic promise.

D. **IPEX Syndrome (Immune dysregulation, Polyendocrinopathy, Enteropathy, X-linked)**

- Early manifestations include atopic dermatitis and food allergies
- Followed by immune dysregulation and increased susceptibility to infections

2. Recurrent Infections

A. Omenn syndrome (infantile-onset):

- Opportunistic infections such as Candida or Pneumocystis jirovecii usually seen
- Diffuse erythroderma (often misdiagnosed as atopic dermatitis) accompanied by scaling, loss of scalp hair or eyelashes.
- Generalized lymphadenopathy can be seen.
- Has lymphocytosis, eosinophilia, and high IgE levels

B. Combined immunodeficiencies with predominant atopy:

- DOCK8 defect or CBM defects (CARD11/ BCL10/ MALTI defects): Common cutaneous infections with Staphylococcus aureus, Candida, HSV, Varicella-Zoster Virus, and also unusual cutaneous infections such as extensive warts or molluscum contagiosum

C. Hyper IgE syndrome (HIES)

- Defects in STAT3 (dominant negative), IL6ST (autosomal recessive/ dominant negative), IL6R (autosomal recessive) and ZNF341 (autosomal recessive)
- Predisposition to staphylococcal infections and mucocutaneous candida infections
- Pneumatocele formation in lungs are typically seen

3. Predominant Autoimmunity

Autoimmunity with concurrent atopy is suggestive of **T-cell signaling defects** or **actin cytoskeleton disorders (actinopathies)**

A. **DOCK8 Deficiency**
- Autosomal recessive inheritance
- Features: autoimmunity (e.g., hemolytic anemia, autoimmune thyroiditis, SLE, uveitis), severe allergic disease, and cutaneous/pulmonary infections

B. **IPEX Syndrome**
- X-linked recessive
- Presents with severe atopy, autoimmune endocrinopathies (e.g., Type 1 diabetes, thyroiditis)

C. **ARPC1B Deficiency**
- Features include severe atopic dermatitis, food-induced anaphylaxis, elevated serum IgE, and immunodeficiency with vasculitic manifestations

D. **Wiskott-Aldrich Syndrome (WAS)**
- Eczema is a hallmark; scoring systems include it as a key parameter
- Classic triad: eczema, thrombocytopenia, and severe or recurrent infections; however, autoimmunie manifestation such as autoimmune hemolytic anemia or features of lymphoproliferation can also be seen

4. Malignancy Association

- IEIs with elevated risk of malignancy, particularly hematologic or virus-associated cancers
- Conditions: DOCK8 deficiency, CADINS, Wiskott-Aldrich Syndrome (WAS)
- Red flags, if seen with atopic features, consider primary antibody deficiency (PAD):

  • Childhood-onset malignancy

  • Malignancies with viral associations (e.g., EBV-related lymphomas)

  • Associated autoimmunity, infections.

5. Short Stature and Growth Failure

- Seen in IEIs such as IPEX Syndrome, STAT5B defect, and occasionally with MALT1 Deficiency and DOCK8 Deficiency
- STAT5b is essential for IGF-1 production STAT5b dysfunction leads to IGF-1 deficiency and GH insensitivity

- Clinical clue: Atopy, normal birth weight followed by severe postnatal growth failure, and poor response to growth hormone (GH) therapy

6. Connective Tissue Abnormalities

- Seen in HIES associated with defects in STAT3 (dominant negative), IL6ST (autosomal recessive/ dominant negative), and ZNF341 (autosomal recessive)
- Characteristic features include:
    - Dental anomalies (lack of fall of primary dentition)
    - Joint hypermobility
    - Frequent bone fractures
    - Scoliosis
    - Facial dysmorphism
    - Vascular anomalies

Suggested Reading: Inborn Errors of Immunity

1. Stiehm's Immune Deficiencies: Inborn Errors of Immunity
   A comprehensive reference text covering pathophysiology, clinical features, diagnostics, and management of immunodeficiency states.
2. Inborn Errors of Immunity: A Practical Guide
   A clinically oriented handbook designed for practitioners, with emphasis on diagnosis, work-up, and management.

3. Inborn errors of immunity — recent advances in research on the pathogenesis. Yamashita et al. *Inflammation & Regeneration* (2021)
   Reviews emerging mechanisms, genotype–phenotype correlations, and recent progress in IEI research.
4. Inborn Errors of Immunity: A field without frontiers. Bucciol et al. *Immunological Reviews* (2023)
   A broad perspective on the evolving landscape of IEI, highlighting new discoveries and challenges.
5. Human inborn errors of immunity: 2024 update on the classification (JHI)
   Updated classification reporting ~508 genes and new phenocopies, reflecting the expanding molecular spectrum.
6. Unmasking inborn errors of immunity: identifying the red flags of immune dysregulation**.** Cortesi et al. *Frontiers in Immunology* (2024)
   Focuses on clinical clues, presentations beyond infections (autoimmunity, hyperinflammation, lymphoproliferation), and the importance of early recognition.
7. Inborn errors of immunity (primary immunodeficiencies). PMC review (2025)
   A general, up-to-date open-access review covering the breadth of IEI: epidemiology, diagnostic strategies, and therapeutic options.

Flow chart for approach to Primary Atopic Disorders