Immunodeficiency States in Children

A Comprehensive Clinical Review for Medical Students

1) Osmonova Gulnaz
2) Ahala Muhammed
3) Muhammed Salim
4) Charalil Ashehad Anifer

(1.Teacher, International Medical Faculty Osh State University, Osh, Kyrgyz Republic . 2,3,4, Students, International Medical Faculty Osh State University, Osh, Kyrgyz Republic)

Abstract: *Immunodeficiency states in children comprise a heterogeneous group of disorders resulting from defects in one or more components of the immune system. These are classified into Inborn Errors of Immunity (IEI), formerly Primary Immunodeficiency Disorders, and Secondary Immunodeficiencies. This review explores the physiological basis, clinical warning signs, diagnostic logic, and contemporary management of these conditions, emphasizing the role of early detection in reducing pediatric morbidity and mortality.*

1. Introduction and Epidemiology

The pediatric immune system is a dynamic network that evolves significantly from gestation through adolescence. Immunodeficiency occurs when this network is compromised, leaving the host susceptible to infections that are unusually frequent, severe, or caused by opportunistic pathogens. While secondary immunodeficiencies (e.g., due to HIV or malnutrition) are globally more prevalent, the understanding of primary immunodeficiencies has expanded exponentially due to advances in molecular genetics.

Recent data suggest that the prevalence of Inborn Errors of Immunity (IEI) may be as high as 1 in 1,000 to 1 in 2,000 individuals when milder forms are included. For medical students, distinguishing between physiological "normal" childhood infections and underlying immune defects is a foundational clinical skill.

2. Classification of Immunodeficiency

2.1 Inborn Errors of Immunity (IEI)

The International Union of Immunological Societies (IUIS) periodically updates the classification of IEI. Major clinical categories include:

- **Immunodeficiencies affecting cellular and humoral immunity:** Including Severe Combined Immunodeficiency (SCID) and combined immunodeficiencies (CID).
- **Combined immunodeficiencies with associated or syndromic features:** Such as Wiskott-Aldrich syndrome and DiGeorge syndrome.
- **Predominantly antibody deficiencies:** The most common category, including Agammaglobulinemia and CVID.
- **Diseases of immune dysregulation:** Conditions where autoimmunity or lymphoproliferation dominates the clinical picture.
- **Phagocyte defects:** Disorders affecting the number or function of neutrophils (e.g., Chronic Granulomatous Disease).

2.2 Secondary (Acquired) Immunodeficiencies

In the pediatric population, secondary immunodeficiency is often overlooked during the search for rare genetic markers. Key drivers include:

Major Causes of Secondary Immunodeficiency:

- **Malnutrition:** Protein-energy malnutrition leads to atrophy of the thymus and impaired T-cell function.
- **Infection:** Viral pathogens, most notably HIV, but also measles and CMV, can cause transient or permanent immunosuppression.
- **Therapeutic Agents:** Chemotherapy for pediatric malignancies, long-term corticosteroid use for asthma or nephrotic syndrome, and biologics.
- **Critical Illness:** Severe burns or trauma lead to massive immune system exhaustion.

3. Pathophysiology and Immunology

3.1 The Adaptive Immune Defect

Adaptive immunity relies on the specificity of T and B lymphocytes. In **X-linked Agammaglobulinemia (XLA)**, a mutation in the Bruton tyrosine kinase (BTK) gene prevents B-cell maturation. Consequently, these children lack mature B-cells and plasma cells, leading to a profound deficiency in all immunoglobulin classes. Because maternal IgG crosses the placenta and persists for several months, these infants typically remain asymptomatic until the second half of their first year of life.

Conversely, **SCID** represents the "pediatric emergency" of immunology. Whether caused by an IL-2 receptor gamma chain defect (X-linked) or Adenosine Deaminase (ADA) deficiency, the lack of functional T-cells prevents the maturation of the entire adaptive response. These children are susceptible to viruses, fungi (like *Pneumocystis jirovecii*), and bacteria within weeks of birth.

3.2 Defects in Innate Immunity

The innate system is the first line of defense. In **Chronic Granulomatous Disease (CGD)**, the phagocytes can ingest bacteria but cannot produce the "oxidative burst" (reactive oxygen species) needed to kill catalase-positive organisms like *Staphylococcus aureus* or *Aspergillus*. This leads to the formation of granulomas as the body attempts to wall off infections it cannot clear.

4. Clinical Presentation: The 10 Warning Signs

Early identification is often hindered by the fact that young children naturally experience 6-8 viral respiratory infections per year. Clinicians must look for "red flags" that deviate from this norm.

Sign	Description/Criteria	Commonly Associated Defect
Recurrent Otitis	4+ ear infections within one year.	Antibody deficiency
Sinus Infections	2+ serious sinus infections within one year.	B-cell/Humoral defects
Antibiotic Failure	2+ months on antibiotics with little effect.	General Immunodeficiency
Failure to Thrive	Failure of an infant to gain weight or grow normally.	T-cell / Combined (SCID)
Deep Abscesses	Recurrent skin or organ abscesses.	Phagocyte defects (CGD)
Persistent Thrush	Oral candidiasis persisting after age 1.	T-cell deficiency
IV Antibiotics	Need for intravenous antibiotics to clear infections.	Severe Antibody defects
Family History	A family history of IEI/PID.	Genetic predisposition

5. Diagnostic Evaluation Strategy

A systematic "tiered" approach prevents unnecessary testing while ensuring critical diagnoses like SCID are not missed. For students, the history remains the most powerful diagnostic tool.

Step 1: The Initial Screen (First Tier)

Every suspected case should begin with a CBC and Differential. A low absolute lymphocyte count (ALC) in a neonate is SCID until proven otherwise. Following this, quantitative immunoglobulins (IgG, IgA, IgM) should be measured. Note that IgA deficiency is the most common single antibody defect but is often asymptomatic.

Step 2: Functional Assessment (Second Tier)

If initial screens are normal but suspicion remains high, functional tests are required:

- **Vaccine Response:** Measuring titers before and 4 weeks after a booster (e.g., Pneumococcal vaccine) determines if the B-cells can actually produce specific antibodies.
- **DHR Flow Cytometry:** Replaces the older NBT test for CGD; it measures the oxidative burst in neutrophils.
- **Flow Cytometry for Lymphocyte Subsets:** Counting CD3+ (T), CD4+ (Helper T), CD8+ (Cytotoxic T), CD19+ (B), and CD16/56+ (NK) cells.

Step 3: Genetic Analysis (Third Tier)

Definitive diagnosis now increasingly relies on molecular genetics. Whole Exome Sequencing (WES) has revolutionized the field, allowing for the identification of rare variants that dictate specific biological therapies.

6. Therapeutic Interventions

Management of pediatric immunodeficiency has shifted from purely reactive (treating infections) to proactive (preventing damage and curative attempts).

6.1 Immunoglobulin Replacement Therapy (IRT)

For patients with antibody failure, lifelong IRT is life-saving. It provides passive immunity via pooled IgG from thousands of donors. Modern SCIG (subcutaneous) administration allows families to manage therapy at home, significantly improving quality of life.

6.2 Hematopoietic Stem Cell Transplantation (HSCT)

HSCT is the curative treatment of choice for SCID and many other severe cellular defects. The goal is to replace the patient's defective hematopoietic stem cells with those from a healthy donor. Success rates are highest (over 90%) when performed in the first 3.5 months of life, highlighting the importance of Newborn Screening (NBS) for SCID using TREC (T-cell Receptor Excision Circles) assays.

7. Special Considerations in Pediatric Care

7.1 Vaccination Precautions

This is a critical area for medical board exams. Children with significant T-cell or B-cell defects should **not** receive live-attenuated vaccines. These include:

- BCG (Tuberculosis)
- OPV (Oral Polio)
- Rotavirus
- MMR (Measles, Mumps, Rubella)
- Varicella

In a child with SCID, the rotavirus vaccine can cause life-threatening diarrhea, and the BCG vaccine can lead to disseminated "BCG-osis."

7.2 Psychosocial Impact

Chronic illness in childhood imposes a significant burden on the family unit. "Isolation" protocols to protect the child from community-acquired infections can lead to developmental delays and social anxiety. A multidisciplinary team involving psychologists and social workers is essential.

8. Conclusion and Future Directions

The field of pediatric immunology is moving toward a precision medicine model. As we identify more specific genetic mutations, we are moving away from broad immunosuppression toward targeted biologicals (e.g., CTLA4-Ig for LRBA deficiency). For the student, the core mission remains the same: identify the child who is "too sick, too often" and initiate the diagnostic workup that could save their life.

9. References

1. **StatPearls. (2023).** *Immunodeficiency in Children.* StatPearls Publishing. Comprehensive overview of pathophysiology and clinical presentation for board review.

2. **McCusker, C., Upton, J., & Warrington, R. (2018).** *Primary immunodeficiency*. Allergy, Asthma & Clinical Immunology. A detailed guide on the 10 warning signs and initial laboratory workup.

3. **Royal Children's Hospital Melbourne. (2023).** *Clinical Practice Guidelines: Immunodeficiency*. Evidence-based guidelines for the acute management of pediatric immune defects.

4. **Bucciol, G., & Meyts, I. (2020).** *Recent advances in primary immunodeficiency: from molecular diagnosis to treatment.* F1000Research. High-level review of genomic sequencing and gene therapy.

5. **Chapel, H., et al. (2014).** *Primary Immune Deficiencies – Principles of Care*. Frontiers in Immunology. Global consensus on the management of PID patients.

6. **Tangye, S. G., et al. (2020).** *Human Inborn Errors of Immunity: 2019 IUIS Phenotypic Classification.* Journal of Clinical Immunology. The gold-standard classification used by immunologists worldwide.

7. **Peddi, N. C., et al. (2023).** *Guardians of Immunity: Advances in Primary Immunodeficiency Disorders*. Cureus. Review of recent therapeutic breakthroughs including biologicals.