Review Article

Primary Immunodeficiency Diseases: An Overview of Clinical Presentation, Diagnosis, and Management

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Received on: 09-Oct-2025 Accepted for Publication: 28-Dec-2025

ABSTRACT

Primary immunodeficiencies (PIDs), recently reclassified as inborn errors of immunity (IEIs), represent a heterogeneous group of over 500 genetically defined disorders that impair the development or function of the immune system. Although individually rare, collectively they have a significant global health impact, contributing to recurrent infections, autoimmunity, autoinflammation, allergy, and malignancy. Advances in next-generation sequencing and immunological profiling have expanded the diagnostic landscape, enabling earlier recognition of atypical presentations and novel disease entities. Nevertheless, delayed diagnosis remains a challenge, particularly in low- and middle-income countries, where access to specialized testing and therapies is limited. Clinically, PIDs are diverse and may manifest from infancy to adulthood, often with overlapping phenotypes. The classical presentation of severe, recurrent, or unusual infections is increasingly recognized to be accompanied by immune dysregulation, including cytopenia, lymphoproliferation, and organ-specific autoimmunity. Early identification is essential, as timely interventions such as immunoglobulin replacement, antimicrobial prophylaxis, hematopoietic stem cell transplantation, and targeted biologic therapies significantly improve outcomes. This article provides an overview of the evolving understanding of PIDs, highlighting their clinical spectrum, diagnostic strategies, and therapeutic advances. By raising awareness among clinicians and health systems, it aims to reduce diagnostic delays and optimize patient care. Greater integration of molecular diagnostics, registries, and international collaboration is key to advancing precision medicine in the field of primary immunodeficiencies.

Keywords: Primary Immunodeficiency Diseases, Inborn Errors of Immunity, T cell defect.

Introduction

Hematopoietic stem cell transplantation (HSCT) is a potentially curative treatment for a wide range of malignant and non-malignant hematologic disorders, including leukemias, thalassemia, aplastic anemia, and hemoglobinopathies[1,2]. However, access to transplant facilities in India remains highly skewed toward metropolitan areas and private sector hospitals, leaving large populations in tier-2 and tier-3 cities without affordable access[3,4].

Recognizing this gap, the Department of Pediatrics at **NSCB Medical College, Jabalpur**, initiated the development of a government-supported pediatric bone marrow transplant (BMT) unit in early 2023. Located in central India, the institution serves as a tertiary referral center catering to Madhya Pradesh and neighboring states.

The objectives were to:

1. Establish a sustainable and infection-controlled BMT unit within a government hospital framework;
2. Develop trained multidisciplinary manpower capable of performing HSCT safely;
3. Implement cost-effective and collaborative strategies for investigations and donor workup; and

4. Evaluate early transplant outcomes to assess feasibility and safety.

This article describes the planning, establishment, and operationalization of the unit and presents outcomes of the first four transplants performed, highlighting the feasibility of setting up BMT programs in government medical colleges with structured planning and phased implementation.

Methods

1. Planning and Approval Process

The initial planning began in **February 2023** when a detailed proposal outlining the clinical need, infrastructure design, and projected costs was submitted to the state health authorities. The proposal was approved the same year, with **a sanctioned budget of ₹8 crore**—₹5 crore allocated for infrastructure development and ₹3 crore for procurement of essential medical equipment. The funding was released in phases, allowing progressive construction and commissioning of the unit.

2. Infrastructure and Design

A dedicated area within the pediatric block was identified and remodeled according to transplant-specific architectural and infection-control standards. The **BMT unit comprises 10 single-occupancy HEPA-filtered isolation rooms**, each equipped with:

- **Positive-pressure air handling units** and individual HEPA filters ensuring laminar airflow;
- **Centralized air conditioning** with temperature and humidity control;
- **Negative-pressure anterooms** for staff entry and doffing;
- ICU-grade beds, multiparameter monitors, syringe pumps, and crash carts;
- Facilities for in-room ventilation and ICU care for patients developing respiratory complications;
- Dedicated nursing stations with restricted access and separate donning/doffing areas.

An adjoining **procedure and apheresis room** was established with installation of a **cell separator machine**, biosafety cabinets, and appropriate sterilization facilities. A **central nursing observation area** was integrated to allow continuous monitoring of all patients.

3. Blood Bank Upgradation

Parallel to unit development, the **blood bank was upgraded** to support transplant-specific requirements.

- **Leucodepletion filters** were installed to provide leukoreduced blood components for all transfusions.
- An **irradiation facility** was commissioned to prepare irradiated cellular components, preventing transfusion-associated graft-versus-host disease (TA-GVHD).
- Standard operating procedures (SOPs) were developed for blood component preparation, storage, and bedside transfusion monitoring.
  These steps ensured that all transfusion products adhered to international HSCT safety standards.

4. Equipment Procurement

Essential equipment procured included:

- **Ten ventilator-compatible ICU beds**
- **Multiparameter monitors and infusion pumps**
- **Apheresis machine** for stem cell harvest
- **Laminar air flow cabinets**
- **Refrigerated centrifuges and freezers (-80°C)** for cryopreservation

- **Autoclaves, UV sterilizers, and backup power systems**
  All equipment was purchased through government e-tendering channels with technical specifications vetted by expert committees.

5. Human Resource Development and Training

To ensure sustainability, both clinical and technical staffs were trained prior to unit commissioning.

- **Three staff nurses and two laboratory technicians** were deputed to a **government-run BMT unit** for a **three-month structured training program**, gaining hands-on exposure to aseptic techniques, line care, infection control, and supportive management.
- The **medical team**, consisting of pediatric hemato-oncologists and intensivists, had prior training in transplant medicine at high-burden tertiary centers.
- Regular **infection-control workshops**, mock drills, and protocol-based teaching were conducted after their return to Jabalpur.
- Nursing teams were trained in 1:1 patient assignment, HEPA maintenance, and biomedical waste segregation.

6. Laboratory and Diagnostic Collaborations

To minimize cost and dependence on private agencies, a **hub-and-spoke laboratory model** was implemented:

- **In-house laboratory services** provided complete blood counts, biochemistry, and microbiology culture support.
- **ICMR-NIRTH, Jabalpur**, located adjacent to the college, extended collaboration for **viral PCR assays** (CMV, EBV, adenovirus).
- A **Memorandum of Understanding (MoU)** was signed with **Sukalp India Foundation**, an NGO facilitating advanced transplant diagnostics including **HLA typing, chimerism analysis, and donor-specific antibody (DSA)** testing.
  This collaborative approach allowed timely and cost-efficient access to essential investigations.

7. Infection Control Measures

Comprehensive infection control protocols were established, covering:

- HEPA integrity testing every three months;
- Regular microbial air sampling;
- Strict hand hygiene and barrier nursing;
- Prophylactic antimicrobial regimens in accordance with institutional policy;
- Restricted visitor entry and routine environmental decontamination.
  Monthly audits were performed by the hospital infection control committee.

8. Patient Selection and Conditioning Regimens

Patients were selected after multidisciplinary review and family counseling. Donor selection followed standard HLA typing.

- **Conditioning regimens** were tailored to disease and donor type:
  - **Allogeneic transplants:** Fludarabine–Busulfan–Cyclophosphamide with Anti-thymocyte globulin (Flu-Bu-Cy-ATG) or Thiotepa–Treosulfan–Fludarabine–ATG (Thio-Treo-Flu-ATG).
  - **Autologous transplants:** Fludarabine–Busulfan–Melphalan (Flu-Bu-Mel).
- **GVHD prophylaxis** included post-transplant cyclophosphamide (PTCy), cyclosporine, and mycophenolate mofetil (MMF) for haploidentical and matched transplants.

- Stem cells were infused fresh or cryopreserved based on graft source and logistics.

9. Post-Transplant Monitoring

Patients were monitored daily for engraftment, infection, GVHD, and organ toxicities.

- Neutrophil engraftment was defined as ANC > 500/μL for three consecutive days.
- Platelet engraftment was defined as counts > 20,000/μL without transfusion for 7 days.
- Regular chimerism analysis and infection surveillance were conducted as per protocol.
- Supportive care included irradiated, leukoreduced blood components, antifungal prophylaxis, nutritional support, and psychosocial counseling.

Results

Between **March and September 2025**, four HSCTs were performed—two allogeneic and two autologous. All patients achieved hematologic recovery and were discharged in stable condition. A summary of cases and outcomes is shown in Table 1 (excluded from word count).

Case 1: Haploidentical Allogeneic HSCT for Refractory AML ($FLT3^+$)
A 9-year-old girl with refractory AML, persistent MRD positivity after multiple salvage therapies (Sorafenib along with 3+7 induction, one cycle of FLAG-Ida, and four cycles of Venetoclax–Azacitidine), underwent haploidentical HSCT using her mother as a 6/10 HLA-matched donor. Conditioning included Flu-Bu-Cy-ATG with PTCy, CSA, and MMF prophylaxis. The bone marrow graft (6×10^6 $CD34^+$ cells/kg) engrafted for neutrophils on day +20. She had delayed thrombocytopenia but remained afebrile and was discharged on day +34

Case 2: Matched Sibling HSCT for Sickle Cell Disease
A 5-year-old boy with transfusion-dependent sickle cell disease and recurrent vaso-occlusive crises underwent HSCT using his 14-year-old HLA-matched sister (12/12 match) as donor. Conditioning with Thio-Treo-Flu-ATG was followed by PBSC infusion (4.8×10^6 $CD34^+$/kg). Engraftment for both neutrophils and platelets occurred on day +12. Apart from transient febrile episodes during engraftment, his course was uneventful. Chimerism at day +30 showed 100% donor cells. He was discharged in stable condition.

Case 3: Autologous HSCT for High-Risk Neuroblastoma
A 4-year-old boy with suprarenal neuroblastoma, post-COJEC chemotherapy and radiotherapy, underwent autologous HSCT with Flu-Bu-Mel conditioning. Stem cells were cryopreserved for 72 hours with 98% post-thaw viability (4×10^6 $CD34^+$/kg). Engraftment occurred by day +13, and he was discharged on day +30 .

Case 4: Autologous HSCT for High-Risk Neuroblastoma
A 3-year-old boy post-COJEC chemotherapy underwent autologous HSCT with glycated Flu-Bu-Mel conditioning. Engraftment occurred on day +10, with minor upper respiratory infection managed conservatively. He was discharged on day +32 .

There were **no transplant-related mortalities**. Median duration to ANC recovery was 13 days (range 10–20), and median hospital stay was 31 days (24–34). All patients remain on regular follow-up with stable counts.

Discussion

The experience from NSCB Medical College demonstrates the feasibility of developing a BMT unit within a government institution in a tier-2 city through **strategic planning, phased investment, and human resource development**.

Infrastructure and Infection Control

Adequate infrastructure and infection control are essential for transplant success. Previous Indian studies emphasize that infection control measures, especially HEPA filtration and positive-pressure environments, significantly reduce nosocomial infections and transplant-related mortality[5,6]. By incorporating these standards, our unit maintained aseptic conditions equivalent to private centers.

Training and Manpower

Developing skilled human resources is the cornerstone of any new transplant program. Our model of deputing nurses and technicians for short-term intensive training mirrors approaches adopted by AIIMS, Delhi, and CMC Vellore[7,8]. Continuous in-house education and mock drills further reinforced staff confidence and procedural uniformity.

Collaborations and Resource Optimization

Partnerships with ICMR laboratories and NGOs proved vital. The **hub-and-spoke model** reduced dependency on costly private facilities, ensuring cost-effective access to molecular testing and chimerism analysis. Such collaborative frameworks have been recommended by the Indian Society for Blood and Marrow Transplantation (ISBMT) to scale transplant capacity in government sectors[9].

Cost and Sustainability

Financial constraints remain a major barrier in low- and middle-income countries (LMICs). Even with state support, the **average per-transplant cost was ₹4–5 lakh for allogeneic and 3-4 lakh for Autologous Transplant**, consistent with national estimates[10,11]. Integration with government health schemes and NGO donations ensured that families incurred **no out-of-pocket expenses**. However, sustainability requires **dedicated BMT-specific budget lines**, bulk procurement of essential drugs, and a central funding mechanism for investigations—each transplant needing approximately ₹5 lakh for medications and disposables.

Clinical Outcomes

All four patients in our initial cohort engrafted successfully without mortality—an encouraging finding comparable with early outcomes from mature Indian centers reporting survival rates of 85–95% in pediatric HSCT[12,13]. As summarized in **Table II**, these early results from our center align with national benchmarks and indicate that, despite a small sample size, the new unit has achieved clinical safety and operational readiness. Though our sample size is small, these results validate the clinical safety and readiness of the new unit.

Challenges and Future Directions

Challenges encountered included delays in specialized tests due to lack of in-house flow cytometry and the limited number of trained staff. Addressing these through **equipment expansion**, **staff recruitment**, and **training fellowships** is planned. In the long term, we aim to expand to 20 beds and initiate unrelated donor transplants, CAR-T collaborations and gene therapy for benign genetic diseases mainly hemoglobinopathies.

Conclusion

The establishment of a fully functional pediatric bone marrow transplant unit at NSCB Medical College, Jabalpur, within a government framework, demonstrates that advanced hematologic therapies can be effectively decentralized beyond metro cities. Strategic state funding, targeted manpower training, and inter-institutional collaborations enabled successful early transplants with favorable outcomes.

To sustain and expand such programs, it is imperative for government policy to:

- Allocate dedicated **BMT funding through Ayushman Bharat Yojna exclusively for government institution. (≥₹5 lakh per case)**;
- Foster **training networks between established and emerging centers**; and
- Encourage **public–NGO partnerships** for specialized investigations.

With structured planning and state commitment, regional government medical colleges can evolve into **centers of excellence for HSCT**, ensuring equitable access to curative therapies for children across India.

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