proportion of the affected neonates requiring intensive care and mechanical ventilation suggests that the disease in neonates is more severe than older children [3-8], which correlates with our study as well.

Contributors: BS, SR, VD, SP, MB: conceived, designed the study, finalized the manuscript; BS,VD,SR: data collection, data analysis, writing manuscript; BS,VD,SR,SP: data collection, data analysis, managed the babies; BS,VD,SR,SP: Literature search, interpretation of data, writing manuscript.
Ethic clearance: IEC - Bai Jerbai Wadia Hospital for Children; No. IEC-BJWHC/88/2020 dated 26 August, 2020.
Funding: None; *Competing interests:* None stated.

BHAVYA SHAH, VAIDEHI DANDE, SUDHA RAO,* SANJAY PRABHU AND MINNIE BODHANWALA
From Department of Pediatrics, Bai Jerbai Wadia Hospital for Children, Mumbai, Maharashtra, India
**c_sudha@hotmail.com*

REFERENCES

1. Cook J, Harman K, Zoica B, Verma A, D'Silva P, Gupta A. Horizontal transmission of severe acute respiratory syndrome coronavirus 2 to a premature infant: Multiple organ injury and association with markers of inflammation. Lancet Child Adolesc Health. 2020;4:548-51.
2. Corondao A, Nawaratne U, Mcmann D, Ellsworth M, Meliones J, Boukas K. Late- onset neonatal sepsis in a patient with Covid-19. N Engl J Med. 2020;382:e49.
3. Castagnoli R, Votto M, Licari A, et al. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in children and adolescents: A systematic review. JAMA Pediatr. 2020;174:882-88.
4. Rodriguez-Morales AJ, Jaime A. Cardona-Ospina, et al. Clinical, laboratory and imaging features of COVID-19: A systematic review and meta-analysis. Travel Med Infect Dis. 2020;34:101623.
5. Meena J, Yadav J, Saini L, Yadav A, Kumar J. Clinical features and outcome of SARS-CoV-2 infection in children: A systematic review and meta-analysis. Indian Pediatr. 2020;57:820-26.
6. Ludvigsson JF. Systematic review of COVID-19 in children shows milder cases and a better prognosis than adults. Acta Paediatr. 2020;109:1088-95.
7. Dong Y, Mo X, Hu Y, et al. Epidemiological characteristics of 2143 pediatric patients with 2019 coronavirus disease in China. J Emerg Med. 2020; 58:712-13.
8. Bernado G, Giordano M, Zollo G, et al. The clinical course of SARS-CoV-2 positive neonates. J Perinatol. 2020;40:1462-69.

Hematopoietic Stem Cell Transplantation for Children With Inborn Errors of Immunity

This is a retrospective analysis of clinical characteristics of children with inborn errors of immunity who underwent hematopoietic stem cell transplant (HSCT). Although the mean age at diagnosis was 24.4 months, it was 51.9 months at HSCT. There is an urgent need to improve awareness, expand donor registries and initiate newborn screening for inborn errors or immunity.

Key words: *Primary immune deficiency disorders*.

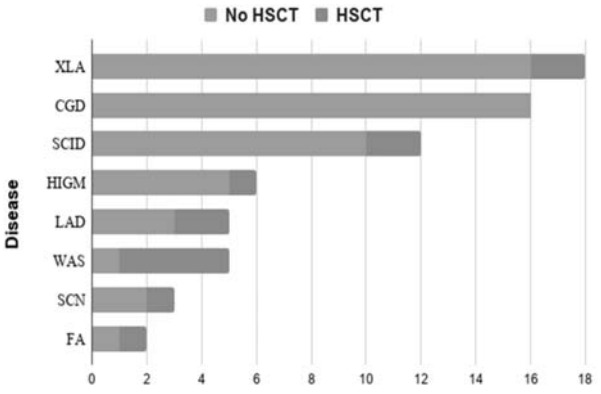
Inborn errors of immunity or primary immune deficiency disorders (PIDDs) occur with a frequency of 1 in 5000 to 1 in 1000 [1], and are frequently misdiagnosed resulting in avoidable morbidity and mortality [2]. Diagnostic tests and hematopoietic stem cell transplant (HSCT) are not uniformly accessible [3].

Government Medical College, Kozhikode, a tertiary care hospital in Kerala, and CSIR Institute of Genomics and Integrative Biology, Delhi have been conducting a program on primary immune deficiency disorders over the last five years. Although HSCT is often the only curative option, we are dependent on centers outside the state. The study was designed to document the clinical characteristics of children who underwent HSCT for an inborn error of immunity.

Hospital records of children with PIDDs who attended the immune deficiency clinic from June, 2015 to May, 2020 were obtained and data of those who underwent HSCT were analyzed. Only children who had completed at least 3 months post-HSCT were included. Variables studied included age at onset diagnosis and at HSCT, gender, relationship with stem cell donor, time since HSCT and diagnostic genetic or phenotypic marker. Quantitative variables were entered on an Excel data sheet and frequency and associations calculated using the statistical package Epi Info (version 7.2.3.1).

HSCT was performed in 13/67 (19.4%, 11 boys). The indications included Wiskott-Aldrich syndrome (4, 30.8%), and leukocyte adhesion deficiency, severe combined immune deficiency, and *X*-linked agammaglobulinemia in two each (15.4%) congenital neutropenia Fanconi anemia, and hyper IgM syndrome were diagnosed in one child each. The median (IQR) age at diagnosis of children who underwent HSCT was 14 months (first quartile, III quartile). The median (IQR) age at HSCT was 27.5 (first quartile, III quartile) months and the median (IQR) interval between diagnosis and HSCT was 7 (first quartile, III quartile) months. Recurrent pneumonia was the commonest presenting feature in 7 (54%) children, followed by frequent skin and soft tissue infections in 6 (46%) and recurrent otitis media in 4 (30.8%). Frequent abscesses, recurrent diarrhea and bleeding were presenting features in 2 (15%) children each. HSCT was done in an asymptomatic child with Fanconi anemia after his elder sister succumbed to the same disease.

Of the 13 children who underwent HSCT, 9 (69%) children had a matched sibling donor and 2 children each (15%) had matched unrelated donor transplants (MUDs) [4] and haploidentical stem cell transplants. Reduced intensity conditioning (RIC) [5] with treosulfan and fludarabine was



SCN: Severe congenital neutropenia; FA: Fanconi anemia; HIGM: Hyper-IgM syndrome; LAD1: Leukocyte adhesion deficiency; SCID: Severe combined immune deficiency; WAS: Wiskott–Aldrich syndrome; XLA: X-Linked agammaglobulinemia.

Fig. 1 Number of patients with primary immune deficiency disorders who underwent hematopoietic stem cell transplants (HSCT).

used and 12 children had sustained engraftment. There was one graft rejection with autologous reconstitution, and a second HSCT resulted in sustained engraftment. Post-HSCT complications included bacterial sepsis, cytomegaloviral reactivation, steroid-induced hypertension and graft versus host disease. There was no mortality and the mean duration of post-transplant event-free survival was 25.1 months.

HSCT was performed for 2 (15%) children with XLA. Although this is not the standard treatment, but it has been found to be a feasible option where availability and cost of immunoglobulin replacement therapy are limiting factors and parents are not keen on lifelong replacement [6].

The median interval between onset of symptoms to diagnosis was 9 months. This emphasizes the need to improve awareness among pediatricians [2]. The mean interval between diagnosis and HSCT was 40.9 months, accounting for the high mortality. Improved outcomes are described with HSCT before 3.5 months of age before onset of infectious complications [7,8]. The youngest child who underwent HSCT in this series was 5 months.

The outcome of HSCT for children with matched unrelated donors (MUDs) and haploidentical donors has improved globally [4,9] both children in this series had good outcomes. Limitations of the study include the small sample size and the variable time since HSCT with possible recall bias.

The main stumbling blocks to wider use of HSCT remain the cost and non-availability of suitable donors. National rare disease policy addressing the major concerns of affected families would be the way forward. Awareness regarding PIDDs should be rapidly scaled up, donor registries expanded and government funding streamlined. A newborn screening program would help to reduce mortality.

***Acknowledgements*:** Dr. Dhanasooraj, Scientist, MRU, Govt. Medical College, Kozhikode; Dr. Ajith Kumar VT and Dr. MP Jayakrishnan, Department of Pediatrics, Government Medical College, Kozhikode; Athulya EP, Junior Research Fellow; and Abhinav Jain and Dr. Sridhar Sivasubbu at the CSIR - Institute of Genomics and Integrative Biology, Delhi.

Ethics clearance: GMCKKD/RP2020/IEC/428; dated May 29, 2017.

Contributors: GMG: conceptualization of the study, data analysis and writing the paper. RR and RU oversaw the work-up and procedure for HSCT; VS: did the genetic work up for the patient. All authors approved the final draft of the paper.

Funding: Science and Engineering Research Board, Delhi, and Foundation for Primary Immune Deficiency Diseases (FPID); *Competing interesst*: None stated.

GEETA M GONVINDARAJ,[1*] U RAMYA,[2] TP ASHRAF,[1] REVATHI RAJ[2] AND VINOD SCARIA[3]

*From [1]Departments of Pediatrics, Government Medical College, Kozhikode, Kerala; [2]Paediatrics Hematology Oncology, Blood and Marrow Transplantation Apollo Hospitals, Chennai, Tamil Nadu; [3]CSIR Institute of Genomics and Integragative Biology (CSIR-IGIB), Delhi, India. *geetakkumar@gmail.com*

REFERENCES

1. Tangye SG, Al-Herz W, Bousfiha A, et al. Human Inborn Errors of Immunity: 2019 Update on the Classification from the International Union of Immunological Societies Expert Committee. J Clin Immunol. 2020;40:66-81.
2. Kapoor N, Raj R. Hematopoietic stem cell transplantation for primary immune deficiency disorders. Indian J Pediatr. 2016;83:450-54.
3. Jindal AK, Pilania RK, Rawat A, Singh S. Primary immunodeficiency disorders in India – A situational review. Front Immunol. 2017; 8:714.
4. Dalal I, Reid B, Doyle J, et al. Matched unrelated bone marrow transplantation for combined immunodeficiency. Bone Marrow Transplant 2000;25:613-21.
5. Rao K1, Amrolia PJ, Jones A, et al. Improved survival after unrelated donor bone marrow transplantation in children with primary immunodeficiency using a reduced-intensity conditioning regimen. Blood. 2005;105:879-85.
6. Ikegame K,Imai K, Yamashita M, H, et al. Allogeneic stem cell transplantation for X-linked agamma-globulinemia using reduced intensity conditioning as a model of the reconstitution of humoral immunity. J Hematol Oncol. 2016; 9:9.
7. Szabolcs, M. Cavazzana-Calvo, A. Fischer, Veys P. Bone marrow transplantation for primary immunodeficiency diseases. Pediatr Clinics North Am. 2010;57: 207-237.
8. Mitchell R, Nivison-Smith I, Anazodo A, et al. Outcomes of Hematopoietic Stem Cell Transplantation in Primary Immunodeficiency: A Report from the Australian and New Zealand children's Haematology Oncology Group and the Australasian Bone Marrow Transplant Recipient Registry. Biol Blood Marrow Transplant. 2013;19:338-43.
9. Yadav SP. Bone marrow transplantation for primary immune deficiency disorders in India: Past, present and future. Indian Pediatr. 2018;55:657-58.