Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
The impact of COVID-19 in children post hematopoietic stem cell transplantation: Experience from a pediatric transplant unit in India

Rumesh Chandar, Venkateswaran Vellaichamy Swaminathan, Satishkumar Meena, Harika Varla, Ramya Uppuluri*, Revathi Raj

Department of Pediatric Hematology, Oncology, Blood and Marrow Transplantation, Apollo Hospitals, 320, Padma Complex, Anna Salai, Teynampet, Chennai, 600035, India

**ARTICLE INFO**

**Article history:**
Received 17 October 2021
Received in revised form 28 November 2021
Accepted 17 December 2021
Available online 20 December 2021

**Keywords:**
COVID – 19
HSCT
Hyponatremia
Cytokine release syndrome
Cytopenia
Mucormycosis

**ABSTRACT**

**Introduction:** Hematopoietic stem cell transplantation (HSCT) has been particularly challenging during the COVID-19 pandemic. We aimed to analyse the impact of infection with COVID-19 in children post-HSCT and describe the clinical syndromes and the disease manifestations in this cohort. Patients and methods: Children who underwent HSCT between January 2019 to June 2021 and acquired COVID-19 infection were included in the study. The symptomatic children were hospitalized for supportive care. Asymptomatic children were treated in home isolation with azithromycin and zinc supplements. Children who were on immunosuppressants were continued on it. Results: A total of 9/265 children who underwent HSCT in the study period were diagnosed with COVID-19, the incidence being 3.3%. The cycle threshold value in all children was low (<17), indicating a profound viremia. All children had cytopenia, four had hyponatremia, and two had grade 2 cytokine release syndrome. The severity of the disease was mild in 5 children, moderate in 1 child, and severe in 3 children. Post COVID sequelae included ARDS (n = 1), MIS-C and DVT (n = 1), rhinocerebral rhizopus infection (n = 1). Three children with severe infection died, two due to multiorgan dysfunction and one due to fungal infection. Conclusion: The presence of GVHD, opportunistic fungal infection, and hyponatremia help predict a severe course and mortality in children post HSCT who are diagnosed to have COVID-19 infection. Prophylaxis for mucormycosis in high-risk children with GVHD is an essential aspect of management.

*Corresponding author.
E-mail address: ramya.december@gmail.com (R. Uppuluri).

Peer review under responsibility of Pediatric Hematology Oncology Chapter of Indian Academy of Pediatrics.

1. Introduction

Ever since the onset of the severe acute respiratory syndrome - Corona Virus 2 (SARS-COV2) pandemic in December 2019, the disease burden in the pediatric population seems to be a mixed bag, probably due to their enigmatic immune system. The initial surge of COVID-19 had a lesser impact in children; however, the second surge, especially with the onset of the emerging delta variant and the occurrence of Multisystem Inflammatory Syndrome in Children (MIS-C), continues to have a more significant disease burden.

Allogeneic hematopoietic stem cell transplantation (HSCT) has been particularly challenging and there is paucity of data on the impact of COVID-19 infection in this group of children. Timely diagnosis due to the marked absence of clinical features, and a predisposition to opportunistic infections are some of the challenges faced by the transplant physicians. Like any other viral illness, once infected, COVID-19 usually undergoes two phases inside a host. The initial viremia and subsequent stages are characterized by host immune response to the viremia in the form of cytokine-mediated response, which is the primary cause of morbidity and mortality, causing end-organ damage, multiorgan dysfunction syndrome, and thrombosis [1]. Children post HSCT represent a unique cohort as disease manifestations and severity may vary depending on the adequacy of immune reconstitution and the level of immune suppression.

The lack of classic symptoms at presentation could delay the diagnosis of COVID-19 illness in children post-HSCT. A number of reasons can cause cytopenia in children post HSCT, including poor graft function, change in recipient blood group in the early post HSCT period, graft versus host disease (GVHD), viral reactivation, and the drugs used to treat the condition [2]. The prolonged period...
of immunosuppression predisposes them to opportunistic fungal infections, especially mucormycosis. The clinical features manifest only after the recovery in the neutrophil count or around the time of withdrawal of immune suppression [3].

As a novel pandemic, the knowledge on its impact on children who have undergone HSCT emerges from small retrospective studies. We aimed to analyse the impact of infection with COVID-19 in children post-HSCT and describe the clinical syndromes and the disease manifestations in this cohort.

2. Patients and methods

We performed a prospective study in the pediatric blood and marrow transplantation unit. The study included all the children, up to 18 years of age, who underwent allogeneic HSCT between January 2019 and June 2021 and acquired COVID-19 infection. Clinical suspicion of COVID-19 infection was based on the Indian Council of Medical Research (ICMR) criteria. Diagnosis was confirmed by a Reverse Transcriptase-Polymerase Chain Reaction (RT-PCR) result at the time of admission to our unit. Children requiring elective procedures, chemotherapy, and hospitalization on an emergency basis for supportive care also underwent an RT-PCR test. Exclusion criteria were children who had not undergone infusion of stem cells and those with equivocal RT-PCR reports. Data was analysed on the severity of infection, presentation, associated co-morbid conditions, sequelae and outcome.

The severity of COVID-19 infection was classified based on the criteria proposed by the ICMR [4]. Children whose family members acquired COVID-19 were advised home isolation and subsequently RT-PCR in case of symptoms. Children who had a mild COVID-19 infection were advised home isolation and were given oral azithromycin and zinc supplements. The families informed oxygen saturation reports two times a day, and we initiated a video consultation daily until asymptomatic. In case of progression to severe COVID-19, two during the initial surge and seven children during the second surge. The demography, clinical characteristics, and HSCT-related parameters in the children who acquired COVID-19 in our study are described in Table 1. The median age of children with COVID-19 was ten years (3–18 years). The majority of the children (n = 7) were well beyond day +100. Three children were over 18 months post-HSCT, four children were a year post-HSCT, and one child was six months post-HSCT. In our cohort, all the nine children were on immunosuppressants at the time of infection, the details of which are presented in Table 1. The cycle threshold value (CTV) in 6 children (where CTV was available) was low (<17). The children who required hospitalization were three children with severe disease, one child with moderate disease, one child for otitis externa, and one child with posterior reversible encephalopathy syndrome due to tacrolium toxicity.

Fever was the only symptom at presentation for children who were at least 100 days post-HSCT. Children who acquired COVID-19 before day +100 were either asymptomatic (one child was admitted for PRES and subsequently found to have COVID-19) or had non-specific symptoms like lethargy (n = 1). Laboratory parameters at the time of diagnosis of COVID-19 included worsening cytopenia (n = 9), hyponatremia (n = 4), and grade 2 cytokine release syndrome (CRS) (n = 2). Cytopenia noted in all children predominantly included neutropenia with absolute neutrophil counts dropping to below 1000/cu.mm. The two children with CRS were treated with steroids (methylprednisolone at 1 mg/kg/day in two divided doses) and had resolution of symptoms within 48 h.

The comorbidities documented were GVHD in four children; autoimmune hemolytic anemia (AIHA), calcineurin inhibitor-induced glomerulonephropathy, and Cytomegalovirus (CMV) reactivation in one child each. The severity of COVID-19 was mild in five children, moderate in one child, and severe in three children. Post-COVID sequelae included Multisystem Inflammatory syndrome in Children (MIS-C) and deep vein thrombosis in a child with thiabasemia major. She was treated with low molecular weight heparin for six months.

One child with high risk acute myeloid leukemia (FLT3-ITD positive) with severe illness around four months post HSCT, had hyponatremia and hypoalbuminemia. Two weeks later, she developed facial puffiness, which was clinically suspected to be sinusitis. MRI of the brain and a diagnostic nasal endoscopy revealed rhinocerebral rhizopus infection. The opportunistic fungal infection was observed to emerge in these children around the time of immune recovery. All children who had adequate immune reconstitution before COVID-19 did not manifest opportunistic fungal infection.

The three children with severe COVID-19 infection died. Two children died due to COVID-19 related multiorgan dysfunction syndrome (MODS), at 15 months and 20 months post HSCT respectively. Both the children were on immunosuppressants due to chronic GVHD. One child succumbed to rhinocerebral rhizopus infection, at 4 months post HSCT. She was on immunosuppressants including mycophenolate mofetil, cyclosporine and prednisolone for GVHD.

4. Discussion

The study describes clinical syndromes and outcome of COVID-19 infection in children post HSCT. The incidence was 3.3% (n = 9), with majority of children being over 100 days post HSCT. Unexplained and sudden onset cytopenia was the earliest manifestation
of COVID-19 infection in all the children. Hyponatremia (serum sodium <125 meq/dl) was observed in four among the nine children without any apparent cause. MIS-C was documented in one child and rhinocerebral rhizopus in one child. Three children died, all of whom fulfilled criteria of severe disease at presentation.

Children who underwent HSCT tend to have profound viremia and prolonged viral shedding. This is due to poor immune reconstitution and the concomitant use of immune suppressants. Our study noted that all the children had a cycle threshold value of less than 17 in RT-PCR (CTV of <25 indicated high viral load) [5]. During the early post HSCT period, there is neither a robust NK/regulatory and cytotoxic T cell immunity nor do they develop adequate anti-SARS-CoV-2 antibodies to protect them [6]. Therefore, the usual clinical manifestations of COVID-19 viremia as observed with immuno-competent children may not be evident. Cytokine excess pathognomonic of severe viral illness may not manifest in the immediate post HSCT period. However, it does occur in children over six months post HSCT with adequate immune reconstitution. Our study observed that two children developed milder (grade 2 CRS), which responded to steroids alone.

Cytopenia could be a result of viral-induced marrow suppression and should alert the clinician for a possible COVID-19 infection. Hyponatremia can indicate a moderate to severe COVID-19 infection [7]. Children post HSCT who require hospitalization for moderate and severe disease, even with inadequate immune reconstitution, can mount a cytokine release syndrome at varying intensities [8]. Like immunocompetent children, MIS-C can be a presenting feature in children post-HSCT, especially at the time of withdrawal of immunosuppression. Parameters like serum ferritin, D-dimer, IL-6, and C-reactive protein can indicate the ongoing inflammation and an impending cytokine excess and guide the resolution of viremia. Serial monitoring can guide further management with steroids or Tocilizumab [9,10].

We recommend early imaging of the paranasal sinuses and skull base for any possible rhinocerebral mucormycosis and diagnostic nasal endoscopy and posaconazole prophylaxis for children on immunosuppression. All children post HSCT detected to have COVID-19 infection, irrespective of the disease severity, were started on posaconazole prophylaxis for 4 weeks, in discussion with the infectious disease specialists. Sinusitis during and post-HSCT should be considered as an indication for imaging to rule out mucormycosis as, before HSCT, most of these children might have had asymptomatic COVID-19. Laboratory parameters and imaging modalities play a vital role in the early and appropriate initiation of treatment modalities.

There has been a rapid accrual of knowledge about COVID-19 infection and its impact on the immunocompromised population. Until we have prospective multicentric study data, best practice recommendations need to be derived from case series. The United Kingdom and United States of America experience have highlighted the lower risk of COVID-19 in the initial 100 days post-HSCT, feasibility of relatively safe conduct of HSCT, and cellular therapy in children amidst the COVID-19, and the need for seamless HSCT services in the future surges in the pandemic [11–15].

As depicted in our study, most children tend to contract SARS-CoV-2 from the community despite maximal precautions. Hence vaccinating the close contacts against SARS-CoV-2 should be an early initiative. Screening for SARS-CoV-2 in case of a close contact infection is also mandatory, even if asymptomatic. Care of the stem cell donor before conditioning therapy, including completely vaccinating the potential adult donors one month before HSCT, is necessary, for paediatric donors’ routine precautions need to be undertaken.

Since viremia from SARS-CoV-2 is usually profound, at least in children beyond 12 years of age, giving REGEN-COV (Casirivimab and Imdevimab) that bind to non-overlapping epitopes of the spike protein receptor-binding domain (RBD) of SARS-CoV-2 and reducing viremia could be beneficial [16]. Especially in children less than six months post HSCT and those on immunosuppressants where the immune system is not at its adequacy, this monoclonal antibody cocktail can help reduce viremia and the associated cytokine-mediated morbidity.

5. Conclusion

The presence of GVHD, opportunistic fungal infection, and hyponatremia help predict a severe course and mortality in children post HSCT who are diagnosed to have COVID 19 infection. While primary prevention is vital, early suspicion of COVID-19 in asymptomatic children is the key to optimal outcomes.
Acknowledgments

We wish to acknowledge the contribution of our infectious disease specialists Dr Ram Gopalakrishnan and Dr Abdul Chafur for their constant support in the management of our HSCT patients and providing a framework of guidelines for prevention and management of patients during the pandemic.

References

[1] Belsky JA, Tullius BP, Lamb MG, Sayegh R, Stanek JR, Auletta JJ. COVID-19 in immunocompromised patients: a systematic review of cancer, hematopoietic cell and solid organ transplant patients. J Infect 2021 Mar;82(3):329–38. https://doi.org/10.1016/j.jinf.2021.01.022. Epub 2021 Feb 4. PMID: 33549624; PMCID: PMC7859698.

[2] Nakamae H, Storer B, Sandmaier BM, Maloney DG, Davis C, Corey L, et al. Cytopenias after day 28 in allogeneic hematopoietic cell transplantation: impact of recipient/donor factors, transplant conditions and myelotoxic drugs. Haematologica 2011 Dec;96(12):1838–45. https://doi.org/10.3324/haematol.2011.044966. Epub 2011 Aug 31. PMID: 21880629; PMCID: PMC3232267.

[3] Centers for Disease Control and Prevention; Infectious Disease Society of America; American Society of Blood and Marrow Transplantation. Guidelines for preventing opportunistic infections among hematopoietic stem cell transplant recipients. MMWR Recomm Rep (Morb Mortal Wkly Rep) 2000 Oct;49(RR-10):1–125. CE1-7. Erratum in: MMWR Recomm Rep. 2004 May 14;53(19):396. PMID: 11718124.

[4] Indian Council of Medical research. Guidelines for the management of COVID-19 in children below 18 years. Ministry of health and family welfare. https://www.mohfw.gov.in/pdf/GuidelinesforManagementofCOVID19inCHILDREN18June2021final.pdf; 2021.

[5] Coperchini F, Chiavato L, Croce L, Magri F, Rotondi M. The cytokine storm in COVID-19: an overview of the involvement of the chemokine/chemokine-receptor system. Cytokine Growth Factor Rev 2020 Jun;53:25–32. https://doi.org/10.1016/j.cytogfr.2020.05.003. Epub 2020 May 11. PMID: 32446778; PMCID: PMC7211650.

[6] Ogunek J, Kralj Juric M, Glimir S, Varanasi PR, Holler E, Greinix H, et al. Immune reconstitution after allogeneic hematopoietic stem cell transplantation. Front Immunol 2016 Nov 17;7:507. https://doi.org/10.3389/fimmu.2016.00507. PMID: 27909435; PMCID: PMC5112259.

[7] Gheorghe G, Ilie M, Bungas S, Stoian AMP, Barbaceta N, Diaconu CC. Is there a relationship between COVID-19 and hyponatremia? Medicina (Kausa) 2021 Jan 9;57(1):55. https://doi.org/10.3390/medicina57010055. PMID: 33435405; PMCID: PMC7827625.

[8] Zhang C, Wu Z, Li JW, Zhao H, Wang GQ. Cytokine release syndrome in severe COVID-19: interleukin-6 receptor antagonist tocilizumab may be the key to reduce mortality. Int J Antimicrob Agents 2020 May;55(5):105954. https://doi.org/10.1016/j.ijantimicag.2020.105954. Epub 2020 Mar 29. PMID: 32234467; PMCID: PMC7118634.

[9] Hennon TR, Penque MD, Abdul-Azziz R, Alibrahim OS, McGreavy MB, Prout AJ, et al. COVID-19 associated Multisystem inflammatory syndrome in children (MIS-C) guidelines; a western New York approach. Prog Pediatr Cardiol 2020 May 23;101232. https://doi.org/10.1016/j.ppedcard.2020.101232. Epub ahead of print. PMID: 32837142; PMCID: PMC7244417.

[10] Radia T, Williams N, Agrawal P, Harman K, Weale J, Cook J, et al. Multi-system inflammatory syndrome in children & adolescents (MIS-C): a systematic review of clinical features and presentation. Paediatr Respir Rev 2021 Jun;38:51–7. https://doi.org/10.1016/j.prrv.2020.08.001. Epub 2020 Aug 11. PMID: 32891582; PMCID: PMC7417920.

[11] Vicent MC, Martinez AP, Trabajo Del Castillo M, Molina B, Sisini L, Morin-Cazalilla G, et al. COVID-19 in pediatric hematopoietic stem cell transplantation: the experience of Spanish Group of Transplant (GETMON/GETH). Pediatr Blood Cancer 2020 Sep;67(9):e28514. https://doi.org/10.1002/pbc.28514. Epub 2020 Jun 23. PMID: 32573924; PMCID: PMC7361142.

[12] Lucchini G, Furness C, Lawson S, Gibson B, Wynn R, Slatter M, et al., UK and Ireland Paediatric BMT Group. COVID-19 infection in paediatric recipients of allogeneic stem cell transplantation: the UK experience. Br J Haematol 2021 Aug;194(4):e74–7. https://doi.org/10.1111/bjh.17547. Epub 2021 Jun 20. PMID: 34132400; PMCID: PMC8444814.

[13] Maurer K, Saucier A, Kim HT, Achariya U, Mo CC, Porter J, et al. COVID-19 and hematopoietic stem cell transplantation and immune effector cell therapy: a US cancer center experience. Blood Adv 2021 Feb 9;5(3):861–71. https://doi.org/10.1111/bloodadvances.202003883. PMID: 33603937; PMCID: PMC7869610.

[14] Zamperlini-Netto G, Fernandes JF, Garcia JL, Ribeiro AAF, Camargo LFA, de Moraes Terra C, et al. COVID-19 after hematopoietic stem cell transplantation: report of two children. Bone Marrow Transplant 2021 Mar;56(3):713–5. https://doi.org/10.1038/s41409-020-01041-8. Epub 2020 Sep 16. PMID: 32934304.

[15] Ljungman P, de la Camara R, Mikulska M, Tridello G, Aghado R, Zahrani MA, et al. COVID-19 in patients with hematopoietic stem cell transplantation; results from an EBMT and GETH multicenter prospective survey. Leukemia 2021 Jun 2;1:1–10. https://doi.org/10.1038/s41375-021-01302-5. Epub ahead of print. PMID: 34079042; PMCID: PMC8117362.

[16] Razoonable RR, Pawlowski C, O’Horo JC, Arndt LL, Arndt R, Bierle DM, et al. Casirivimab-Imdevimab treatment is associated with reduced rates of hospitalization among high-risk patients with mild to moderate coronavirus disease-19. EClinicalMedicine 2021 Aug 30:101102. https://doi.org/10.1016/j.eclinm.2021.101102. Epub ahead of print. PMID: 34485873; PMCID: PMC8404031.