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The impact of COVID-19 in children post hematopoietic stem cell transplantation: Experience from a pediatric transplant unit in India

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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.

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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

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Abbreviations

HSCT	Hematopoeitic stem cell transplantation
GVHD	Graft versus host disease
CMV	Cytomegalovirus
ARDS	Acute respiratory distress syndrome
CRS	Cytokine release syndrome
MIS-C	Multisystem inflammatory syndrome in children
CTV	Cycle threshold value
RT-PCR	Reverse transcriptase polymerase chain reaction
ICMR	Indian Council of Medical Research
PRES	Posterior reversible encephalopathy syndrome
DVT	Deep vein thrombosis

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 moderate or severe illness, they were admitted for supportive care. We continued immunosuppressants for GVHD, including steroids, calcineurin inhibitors, and mycophenolate mofetil, as indicated. Moderate and severe COVID-19 illness was treated as per standard guidelines as proposed by the ICMR in the isolation ward and pediatric intensive care unit if clinically indicated. We recommended vaccination against COVID-19 for all contacts of children who underwent HSCT and standard precautions including social distancing and handwashing to minimize the risk of infections.

The study has been approved by the institutional review board (ASH-C-S-009/07–20) and written informed consent was obtained from parents/guardians of all children.

3. Results

Of the 265 children who underwent allogeneic HSCT in the unit in the aforementioned period, nine children (3.3%) acquired COVID-19 infection, 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 ($\leq$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 tacrolimus toxicity.

Fever was the only symptom at presentation for children who were at least 100 days post-HSCT. Children who acquired COVID-19 before D+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 thalassemia 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

Table-1
Demography, clinical and HSCT related parameters of children with COVID-19 infection post HSCT.

No	Age (Years)	Diagnosis	Post HSCT (D+)	Symptoms at diagnosis	COVID disease severity	CTV	Pre-COVID Co morbidity	Immunosuppressants at the time of infection	Indication for continued immunosuppression	Sequelae due to COVID-19 infection	Outcome
1	3	Mucopolysaccharidosis	360	Fever	Mild	NA	GVHD	Tacrolimus, tapering prednisolone	Chronic GVHD	None	Alive
2	18	Myelodysplastic syndrome	485	myalgia	Severe	17	GVHD	Cyclosporine, prednisolone	Chronic GVHD	Hyponatremia	Death due to MODS
3	12	Thalassemia Major	629	Fever	Moderate	12	None	Tacrolimus, tapering prednisolone	Chronic GVHD	MIS-C, DVT	Alive
4	9	Thalassemia Major	664	Fever	Severe	NA	AIHA	Cyclosporine, prednisolone	Chronic GVHD	ARDS	Dead due to MODS
5	14	Thalassemia Major	181	Fever	Mild	12	GVHD	Tacrolimus	GVHD prophylaxis	None	Alive
6	7	Fanconi Anemia	30	PRES	Mild	16	PRES	Tacrolimus	GVHD prophylaxis	CRS	Alive
7	10	Aplastic anemia	556	Fever	Mild	NA	Glomerulonephropathy	Prednisolone	Nephrotic syndrome-like renal disease	None	Alive
8	5	Myelodysplastic Syndrome	96	Lethargy	Mild	17	CMV Reactivation	Tacrolimus	GVHD prophylaxis	None	Alive
9	14	Acute Myeloid leukemia	112	Fever Myalgia	Severe	15	GVHD, Hyponatremia Hypoalbuminemia	Mycophenolate mofetil, cyclosporine, prednisolone	Acute GVHD	CRS, Rhizopus infection	Dead due Rinocerebral Rhizopus infection

PRES – Posterior Reversible Encephalopathy Syndrome, GVHD – Graft Versus Host Disease, DVT – Deep vein Thrombosis, MIS-C – Multisystem inflammatory Syndrome in Children, CRS – Cytokine Release Syndrome, AIHA- Auto Immune Hemolytic Anemia.

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.

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Declaration of competing interest

None.

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