Guidance for Pediatric Hematology-Oncology (PHO) and Hematopoietic Stem Cell Transplant Services during COVID-19 Pandemic: A Consensus Statement by PHO Chapter of Indian Academy of Pediatrics

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A B S T R A C T

With the recent Pandemic of Covid-19 affecting more than 180 countries across the globe, services to children with blood disorders and cancers are likely to be affected. Children, in general, are at lesser risk of developing severe diseases and mortality, and mostly recover from it; fortunately, till date, very few cases have been reported in children with cancers. However, since this is an unprecedented pandemic, there is a felt need for guidance on the challenges faced in providing care to children with cancers and various blood disorders including those requiring Hematopoietic Stem Cell Transplantation (HSCT). This document will provide guidance on how to maintain continuity of care for children with blood disorders & cancers during the COVID-19 pandemic while exercising all precautions to reduce the risk of Covid-19 in this vulnerable group and if infected, what optimum care should be provided to these children.

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1. Introduction

Corona virus disease 2019 (COVID-19) pandemic caused by SARS-CoV-2 started first time in December of 2019 in Wuhan, China and has affected more than 200 countries [1,2]. Children who are immunocompromised either by virtue of their disease like cancer or by the treatments like anti-cancer chemotherapy, immunotherapies etc are assumed to be at a higher risk of severe COVID-19 disease than healthy counterparts [1,2]. This, however, is an assumption and not documented in big data sets in children.

Experience on a small number of pediatric cancer patients from New York suggest that these patients do not demonstrate higher morbidity with only 5% requiring hospitalization for COVID-19 [3]. Children with various blood disorders such as hemoglobinopathies, aplastic anemia and immune cytopenias are also faced with challenges due to multiple hospital visits, or due to various immunomodulatory therapies used as a standard of care such as in acquired and constitutional bone marrow failure syndromes, immune thrombocytopenia etc. With strategies aimed at limiting the spread of COVID-19 like lockdown in various countries & states, stoppage of all modes of transport between countries as well as within the country, the delivery of care for children with cancers and blood disorders is definitely expected to be adversely affected around the world [4,5]. This guideline is aimed at providing insight into how care for children with blood disorders and cancers at this...
difficult time is to be continued, precautions to be exercised to so that the risk of Covid-19 infection in them can be reduced as well as how to manage Covid-19 infection if it occurs.

There is little data on COVID-19 in children and its effect on children with cancers and blood disorders is also limited and evolving [6]. Based on the scant literature available regarding Covid-19 in children, fortunately, the overall incidence of COVID-19 in children is low and generally the disease is mild (especially in children above 5 years of age) [6]. Children below one year of age are likely to have severe disease [6]. However, given the immunocompromised state of children with cancers and blood disorders as alluded to earlier, it is assumed that they would suffer severe disease and a consequent unfavourable outcome compared to healthy children. This however is extrapolation from the adult data with limited data in children [2]. In March 2020, from Wuhan China a child with Acute Lymphoblastic Leukemia with COVID-19 was reported who developed acute respiratory distress syndrome and needed respiratory support [2,6]. However, experience from New York on about 20 pediatrics oncology patients who tested positive for SARS-CoV-2, manifestations were mild with mortality [3].

 Interruption or postponement of treatment would be an additional challenge either due to Covid-19 infection or inability to reach the centers for treatment due to lockdowns. Individualized and personalized treatment incorporating multidisciplinary meetings (through teleconsultation and/or virtual online platforms) would help reduce this impact on outcomes [1,4–7].

As of June 9, 2020, a total of 6.9 million cases have been reported globally with 400,000 deaths (5.7%). In India more than 250,000 cases of COVID-19 and more than 7000 deaths have been reported so far [8]. A Chinese study indicated that hospital related transmission may be responsible for up to 41% of the COVID-19 cases [2]. Appropriate measures are needed to prevent infection in them both within the hospital as well as in the community, while ensuring continuation of care for these children during the COVID-19 pandemic [1,2,6].

The guidance is discussed under the following sections:

1) General measures to prevent Covid-19 infection in children with cancers and blood disorders.
2) Ensuring continuity of care for children with cancers, children with blood disorders and those undergoing HSCT.
3) Preventive strategies for Health Care Providers and the care takers

2. General measures for prevention of Covid-19 and continuity of care

In general, the pediatric hematology oncology (PHO) units shall remain open and daily activities of the unit should continue, of course with necessary precautions. During this pandemic children with suspected cancers or blood disorders including those on treatment already should not be turned away [1,2,6,7,10]. Lockdowns are likely to cause disruptions in hospitals on availability of human and material resources, thereby affecting the PHO & HSCT services [4,5]. This could lead to short-term deviations from standard of care or well-established therapies in areas experiencing major surge of COVID-19 cases or severe resource constraints [2,6,7]. Policies must therefore remain flexible and continue to evolve to adapt with the prevailing local situation. Staff shortages need to be anticipated either due to their own illness, or unable to travel due to travel restrictions, or the need to care a sick family member, or requirements to self-isolate due to contact with a COVID-19 positive case, or even diversion to COVID-19 care areas [2,6]. "Short staff" rotations might ensure minimum required staff, always to manage the patients. This can be done by developing teams of staff members who can be rotated with adequate period of quarantine. This will not only ensure continuity of care but also help to maintain morale and adequate “rest”.

Staff also needs to be provided with appropriate personal protective equipment (PPE) to avoid transmission infection as well as information on appropriate use by a dedicated Infection Prevention Committee (IPC) [6,11].

It is essential that the PHO units provide clear information for the parents and families on various aspects of this infection [6,11]. All children with cancer and on treatment shall practice physical isolation whether at home or in the hospital. Virtual modes of communication like phone calls, and video communication should be encouraged to minimize outpatient visits [1,2,6,7].

Irrespective of the structure of the hospital - pediatric, general hospitals or oncology centers, all the patients reporting to the hospital need to go through screening for symptoms suggestive of infection. In the clinics and ward areas, social distancing (at least six feet) between individuals, one parent/attendant policy to be promoted and enforced [6]. As much as possible and where feasible, cancer care to be delivered in areas which are “COVID-19 free”.

COVID-19 task force should be established in every hospital to make necessary policies and recommendations [2]. This committee or task force should include, infectious disease specialists, Infection control/prevention team, laboratory specialists, pharmacists, and administrators [2]. This task force should keep all the medical and non-medical staff updated with the latest information on COVID-19 and review this from time to time including proper use of PPE. Hematology and oncology physicians should draft SOPs for the department which should be ratified by the task force.

Wherever possible and feasible, hospitals can create four zones for efficient screening of suspected cases and reduce cross infection:

Zone-1 (screening zone): This is the first “point of contact” and done by a consultant/health care provider. As they can be potentially infected with SARS-CoV-2; each patient should be seen in a single room and HCP with adequate PPE.

Zone-2 (suspected quarantine zone): This is for patients with symptoms suspicious of COVID-19; each patient should be isolated in a single room.

Zone-3 (COVID-19 confirmed zone): This is where treatment of the confirmed COVID-19 is provided. Some hospitals may not have capacity or capability to have this “zone”, in which case the confirmed patients shall be transferred to specialised centers.

Zone-4 (Pediatric hematology-oncology ward): Area where patients with haematological malignancies or blood disorders who are negative for COVID-19 are treated [2].

To ensure safe medical care, reduce risk of transmission and protect themselves HCPs should wear adequate and appropriate PPEs depending on the ‘zone’ they are working, IPC should lay down guidelines on appropriate PPE use in different zones and ensure the compliance. Hospital administration are duty bound to ensure smooth supply of PPE, such as protective clothing, helmets, goggles, or other garments and equipment. Donning and doffing guidelines and charts should be displayed in the concerned areas where PPE is mandatory [2,11].

We recommend mandatory testing for the patients with symptoms suspicious of COVID-19 prior to admission. Due to high prevalence of asymptomatic carriers testing for all the asymptomatic patients and caregivers is desirable, however, units need to comply with their IPC and national/state government guidelines on this.
3. Outpatient department & triage

Promote tele-consultation or video-consultation where possible, if the hospital visit is mandatory it is recommended to advance book the visits online or by phone. Avoid main hospital visits just for blood tests (like patients of acute lymphoblastic leukemia on maintenance therapy needing CBC every 2 weekly or monthly). While waiting in the clinic and at the blood test facility, avoid over-crowding and maintain social distancing. Patients can wait in carpark to get blood test done or meet the doctor. Children and accompanying care takers should be provided face masks on entry to the health care facility, epidemiological history elicited, symptoms and temperature recorded by the triage staff. Patients with suspicious positive epidemiological history or symptomatic (fever, cough, and other respiratory symptoms) should be directed to the dedicated area as mentioned before where screening and testing if required for COVID-19 [1,2,6,7,12].

Patients requiring admission to the hospital for chemotherapy, complications of the treatment or requiring management of their disease (cancer or blood disorders) should go through the clinical assessment and screening process. Cancer and blood disorder patients on regular follow up (like maintenance chemotherapy or surveillance) can avoid hospital visits. Most outpatient consults in this group of patients can be done on virtual platforms like video consult, or phone call. Patients and families should not visit the hospital if they have respiratory symptoms with fever or contact history. Instead, they must call the center and seek advice. Patients/family members who have symptoms suspicious of COVID-19 or any close contact with a known patient should call the primary care team and seek guidance [2,6].

4. Policy for respiratory symptoms (cough, breathlessness, sore throat and fever)

Patients who are already enrolled at the center with diagnosis of cancer or blood diseases-if they have respiratory symptoms with high fever or if there is contact history with COVID-19 patients should be directed to consult the Infection Prevention Committee (IPC). If they need to come to the centre, they should follow the system of triage and proceed accordingly [2,12].

5. Policy for patient attendants (family members)

Screen them for possible exposure history, contact history, travel history and suspected symptoms. Families need to sign a consent form stating self-disclosure and taking responsibility. Educate them periodically on facts and clear myths [2,6,12].

6. Admissions for febrile neutropenia

All neutropenic children, especially those with hematological malignancies on intensive chemotherapy or within 3–6 months post HSCT would require emergency admission for supportive care. Patients should be ideally admitted in single room. If that is not feasible an attempt should be made to keep them away from those receiving intensive chemotherapy. If they have respiratory symptoms along with febrile neutropenia, the isolation protocol should be followed. They should be admitted in single isolation rooms and the infection prevention & control (IPC) team should be immediately alerted [1,2,6,7,12].

7. Admissions for non-neutropenic fever or supportive care

Most patients can be managed on outpatient basis if they are not on high risk treatment and clinically well. Those that require admission—they should be admitted in single isolation rooms if feasible. If not feasible, do not admit with patients receiving intensive chemotherapy. Patients with respiratory symptoms—please follow the protocol, admit in single isolation room and inform IPC team. Children requiring blood component transfusions can be admitted only after blood products have been arranged and in single isolation room preferably. Admissions for other supportive care like severe mucositis can be done if necessary while following all necessary precautions [1,6,7].

8. Policy for in-patients

Patients and caregivers should be admitted to the pediatric hematology oncology ward after due diligence of screening. Ideally one attendant per patient allowed in the ward not allowed to leave the ward during hospitalization. Visitors should be prohibited from visiting the wards. If feasible and resources permit, all inpatients should be kept in single isolation ward [2,6,7].

Respiratory infections in pediatric patients post chemotherapy are not uncommon. These patients should be isolated as soon as possible, and COVID-19 screening process should be applied again. Inpatients and caregivers should be briefed and preferably given written handouts of the “Dos” and “Don’ts” and must strictly abide by the relevant rules. Display notices and pamphlets on how to perform hand hygiene, wear a mask, and follow social distancing etc. Psychological support for children, parents and the caretakers especially in the isolation rooms should be readily available. Patients and care takers should also be advised of not concealing COVID-19 symptoms [2].

9. Role of prophylactic antiviral therapy

There is no evidence or published literature on the use of prophylactic antivirals to prevent COVID-19 in children with cancers or blood disorders. Many studies are underway to explore effectiveness of antiviral medications (e.g. chloroquine, oseltamivir, hydroxychloroquine, remdesivir, lopinavir, and favipiravir). Most of these trials are in treatment settings and not studying the prophylactic role and hardly any in the settings of cancer and blood diseases in children [1,13].

10. Guidelines for some special situations in pediatric oncology

For children undergoing planned therapy, we recommend the following:

a) Unless COVID-19 is diagnosed, induction therapy for children with acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML) should continue as planned [2,6].

b) For patients already diagnosed, on treatment and enrolled; curative chemotherapy for leukemia (ALL, AML) and high-grade lymphomas, high-risk neuroblastoma etc. should be continued. Needless to say, all standard precautions to reduce risk of Covid-19 must be followed each time they come to the hospital [2,6].

c) Incubation period COVID-19 ranges from 2 to 14 days (median 5 days), a treatment delay of no more than 7 days is recommended for patients with ALL and AML in consolidation or intensification phase [2,6].

d) Children with solid tumours (e.g., Wilms tumor, hepatoblastoma, neuroblastoma, and germiimona) and lymphomas have a high chance of cure. We recommend that they should be treated according to their chemotherapy schedule, and without delay, and get them in complete remission. Once
complete remission is achieved in these patients, we recommend a treatment delay of no more than 7 days to allow a short period of observation to screen for COVID-19 if required [2,6].
e) Oncologists should decide whether to continue, withhold or postpone radiotherapy keeping in mind the risk of delaying or continuing treatment while balancing the risk of COVID-19 due to repeated hospital visits [2].
f) Surgical excision of tumor should not be postponed unless anaesthesia services or post-operative care is not available [2].

A joint publications of SIOP, COG, SIOP-E, SIOP-PODC, IPSO, PROS, CCI and St Jude Global, provides a good guideline for managing specific pediatric malignancies during this pandemic including “acceptable” modifications and deviations from the “standard of care” and can be referred to Ref. [7].

11. Children with benign blood disorders

Various hematological conditions such as hemoglobinopathies, acquired and constitutional bone marrow failure syndromes, immune cytopenias etc. need chronic care with regular transfusions and/or medical treatment. During the pandemic, these children as children with cancers, would be affected due to disruptions in hospitals, affected by lock downs. Therefore, it is imperative to ensure that mandatory treatment is not interrupted and the risk of contracting the COVID-19 infection is minimised in them too. All the general measures are also applicable to this group of vulnerable children. Additionally, certain special requirements of these children need to be dealt with as follows:

11.1. Children with transfusion dependent thalassemia and other hemoglobinopathies

Blood shortage is a major hurdle in management of these children who are on regular 2 to 3 weekly transfusions to maintain their hemoglobin at 9 to 10.5 gms%. However, encouraging blood donations by healthy volunteers in community directly at the blood banks with all due precautions to ensure their safety, would go a long way in keeping the hospitals blood sufficient! Additionally, due to reduced number of elective surgeries, blood shortage can be averted to a large extent anyway!

Additionally, adolescents with thalassemia have co-morbidities due to cardiac iron overload, diabetes mellitus etc, and it would be presumed that they would suffer more serious complications of COVID-19 infection. However, fortunately, a small cohort of patients, who were closely followed up in Italy, showed only mild to moderate disease. Chelation should be temporarily halted in those with moderate to severe COVID-19 disease but can be safely continued in those with mild disease [9].

HSCT should be deferred until the situation is under total control and near normalcy resumes as this is an elective procedure in thalassemic children.

11.2. Children with bone marrow failure syndromes

Those with constitutional Bone Marrow Failure Syndromes need supportive care and this can be easily continued keeping in mind the general measures for all children.

For those with acquired bone marrow failure syndromes, immunosuppressive therapy (IST) is mandatory for those who do not have HLA-matched donor for HSCT. If ANC >200/µL, one may advise oral Cyclosporine and Eltrombopag to avoid hospitalization for ATG. In those with lower ANC, however, the hATG and Cyclosporine can be given. These are not severely immunosuppressive but due monitoring and exercising all precautions to reduce the risk of COVID-19 infection is important.

HSCT should be deferred until possible. In severe cases with emergent need, it may be considered with appropriate counselling of patient and parents regarding the higher risks in the present circumstances.

11.3. Children with immune cytopenias

Immune thrombocytopenia requires immunosuppressive therapy such as steroids, IVlg, Rituximab etc. for treatment. Steroids and Rituximab are best avoided whereas IVlg can be given, though it requires infusion in the hospital. Thrombopoietic oral agents are also effective and can be safely administered at home. All other general precautions should be adopted for all children who are visiting the hospital and/or are admitted. They should be discouraged from attending hospital outdoor as much as possible and be treated based on clinical symptoms rather than blood tests.

12. Children undergoing HSCT

Elective allogeneic hematopoietic stem cell transplantation (HSCT) in diseases which are well controlled or managed with conventional treatment, for example, beta-thalassemia major children on regular PRBC transfusion and chelation, sickle cell disease children or supportive should be delayed as much as possible [2]. Diseases like high-risk leukemia which need allogeneic HSCT; it would be difficult to postpone HSCT for too long. It is better to assess each case in an individualized manner and proceed accordingly. Autologous HSCT for patients like high risk neuroblastoma or relapsed high-risk lymphomas also should be scheduled on time. There is likely to be prolonged period of shortage of blood and blood products in all blood banks and this should be considered while HSCT planning [2,10]. Regardless of upper respiratory symptoms or other symptoms, all patients proceeding to HSCT should have testing for SARS-CoV-2 [19]. Due to possibility of false negative test and median incubation of 5 days, we recommend repeat test after 7 days and strict quarantine before proceeding for HSCT. For autologous HSCT, screen the patient and the attendant for COVID-19 before starting HSCT. For allogeneic HSCT, screen the patient and the donor, along with attendant for COVID-19 before starting the process of transplant. For patients who are Covid-19 negative, proceed to HSCT. For patients who are COVID-19 positive, follow national guidelines [14,15]. Primary disease treatment would be deferred until COVID-19 is treated. Personalized approach and multidisciplinary meeting to decide when to proceed with HSCT once COVID-19 is treated is suggested.

If there is a close contact with a known COVID-19 patient of the patient or the donors, procedures like peripheral blood stem cell (PBSC) collection, bone marrow harvest or conditioning shall be postponed for at least 14 days, and preferably 21 days from the last contact. For matched unrelated donors (MUD) (especially through registries like DATRI, NMDP or DKMS); it is advisable to procure the stem cell product and cryopreserve before starting the BMT so as to avoid any last minute hitches of delivery of the product considering the current scenario of travel and transport issues. Have another back up donor if possible or autologous back-up wherever applicable. Prefer PBSC product over bone marrow
harvest [10].

For patients, who are post HSCT; especially allogeneic (sibling, MUD or haploidentical), more importantly in the first 6 months; careful monitoring with routine protocols, minimize hospital visits and hospital stay, low threshold for screening for Covid-19 in case of suspected symptoms is advisable. Visitors or caregivers and staff with respiratory symptoms should never come in contact with these patients [1,2,6,7,10].

13. Children with cancers and blood disorders diagnosed with Covid-19 infection

Children with cancers and or blood disorders who are diagnosed with COVID-19 to be managed by a multidisciplinary team including the intensive care team, infectious disease expert and others. In these patient’s treatment of COVID-19 should be prioritised and chemotherapy/immunosuppressive medications to be stopped, suspended or reduced depending on the primary condition and the remission status [1,2,6,7,10,12]. Delays in treatment of the primary condition should be minimised as much as possible and treatment alternatives which are less intense or less immunosuppressive to be employed without compromising the outcomes significantly, wherever feasible.

14. COVID-19 and Health Care Providers

Doctors, nurses, paramedical staff, laboratory personnel, housekeeping staff and other HCP are at high risk of acquiring coronavirus infection in the hospital settings. One of the reports from Italy in March 2020, indicated that approx. 8.3% of all the cases were HCPs. Many HCPs have died due to COVID-19 last few months [1,2,6,7]. HCPs experiencing symptoms of cough, sore throat, fever, breathing difficulty etc should report immediately to the IPC and may require testing. Those who have been exposed to a known case of COVID-19 may require quarantine for 14 days and sometimes admission and testing (follow national guidelines) [11,14,15].

HCPs have been working under difficult circumstances during these testing times especially those working in COVID, intensive care as well as PHO areas. Feeling of stress and exhaustion (physical and mental) as well as long working hours and inadequate sleep is very common in health care professionals catering to cancers and blood disorders. It is extremely important to have a system of psychological support, counselling services and other addressal systems in place [1,2,6].

15. Advice to patients’ families regarding hospital visits

Families should be advised to avoid travel as much as possible and advised to visit hospital only in case of an emergency or for follow up visits advised by their treating team. Children with thalassemia and other disorders on regular blood transfusions should be advised to relocate temporarily to centers in proximity to their homes. It is also recommended that they confirm availability of blood before reporting to the centre. The patient as well as the parent/guardian accompanying the child are advised to practise social distancing and wear a face mask, from the time they leave their homes and till they get back home. They should be advised to carry hand sanitizer and wear face mask during the hospital visit. The patient and the family should be encouraged to report any symptoms such as fever, cough, cold or difficulty in breathing, to the treating team over the phone before starting from home and should visit only if advised to do so. The centre should arrange for them to be tested and treated for SARS-COV-2 at the nearest facility, if needed. If they have been in contact with a person who has been diagnosed with COVID or a person who has travelled from abroad recently and has been self-quarantined, families should inform their treating team. Follow https://www.mohfw.gov.in/or https://www.cdc.gov/coronavirus/2019-ncov/index.html or your respective state health department advisory for more information [4–6,12,14,15].

16. Conclusion

COVID-19 pandemic has posed significant challenges for children with cancers and blood disorders. Literature related to this group of vulnerable children and COVID-19 is scanty, with lockdowns posing a threat to continuity of the treatment of the basic disease in them. Additionally, there are rapid changes in guidelines for screening, testing and treatment of COVID-19 based on latest available information. With the present evidence, it is not recommended to routinely withhold critical chemotherapy, other anti-cancer treatments or immunosuppressive therapy. Careful weighing of the risks versus benefits of delaying or interrupting treatment needs to be done. If the treatment is stopped, delayed or modified, it may increase the risk of cancer progression/relapse, and hence these decisions should be individualized. Recommendations for treatment considerations/modifications during this pandemic in specific disease conditions are available from international organisations as a joint publication and may be referred to Ref. [7]. The effort of everybody should be directed to help these children fight their disease by continuing disease specific care as well as safeguarding them from the risk of acquiring COVID 19 or developing complications of the same during this pandemic.

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