Indian Society of Haematology and Blood Transfusion (ISHBT)

Resources: SARS-CoV-2 and Haematology

The outbreak of the SARS-CoV-2 (COVID-19) pandemic is a major global public health challenge. It is a challenge to deal with usual patients in this unusual time. Indian Society of Haematology and Blood Transfusion (ISHBT), in its commitment to serve the practice of haematology in India has compiled this set of broad question/answer-based guidance document providing recommendations based on expert opinion for physicians/ haematologists dealing with patients suffering from haematological disorders during the COVID-19 pandemic. The Society has mentioned the word recommendations (and not guidelines) as the Society is cognizant of the fact that there is inadequate published evidence in many of these areas to make evidence-based guidelines. The purpose of these recommendations is not to change practice, but to help practitioners faced with difficult situations.

These recommendations necessarily do not cover all the situations faced by the practitioner. These are compiled from various published and available online resources with inputs from subject experts. These recommendations are to serve as a guidance document for practitioners. The decisions in individual patients should be taken based on local / regional factors.

Since the evidence for many of these situations is still building up, hence these recommendations are in the present context, which may need modification as further data evolves. The Society reiterates that it is always the responsibility of the individual practitioner to decide on the appropriateness of these recommendations in the context of the care of any patient in the light of all the evidence available and the particular circumstances of that specific patient.

There are many stipulated guidelines and recommendations to strengthen patients' existing care with haematological disorders globally in the COVID 19 pandemic. These recommendations are an effort for addressal of issues in resource constraint settings or considering the problems faced in the management of haematological disorder in the developing world. Addressing the needs of our country, these are the adaptations from various guidelines and recommendations given by national and international bodies for managing haematological disorders like American society

of Haematology (ASH), European Haematology Association (EHA), British Society for Haematology (BSH), Thalassaemia International Federation (TIF), European Society for Blood and Marrow Transplantation (EBMT) and World Federation of Haemophilia (WFH), Indian Society for Blood and Marrow Transplantation (ISBMT), International Society on Thrombosis and Hemostasis (ISTH).

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1. General Recommendations

1.1 Proposed COVID-19 risk-categorisation of patients with haematological disorders

In the ongoing COVID-19 pandemic, every patient who is getting evaluated or getting treatment for haematological disorder requires assessment for concomitant COVID-19 exposure or illness. If there is an indication of COVID-19 testing based on assessment, it should be done before any further work up or treatment for haematological disorder is planned. The risk assessment and testing of patients is dynamic in nature and is based on current literature information on COVID-19. It is implied that haematologist treating these patients did not have any Influenza like Illness (ILI) symptoms or tested negative in the last two weeks and is taking appropriate protective measures.

All patients getting evaluation or coming for treatment should be put into the following categories (proposed):

Category 0: RT PCR negative (Not exposed or from non-containment zone)

Category 1: RT PCR negative (Exposed to COVID-19 positive patient or from containment zone)

Category 2: RT PCR positive, but asymptomatic

Category 3: RT PCR positive, symptomatic

1.2 Implications of categories

Category 0: Treat the patient as normal

Category 1: Treat if haematological condition warrants or call the patient after one week if clinically stable.

Category 2: Generally, should be deferred from immediate haematological intervention, however in certain diseases can go ahead with definitive management.

Category 3: Defer till COVID recovery, however in certain diseases can go ahead with therapy after explaining risk and benefit to the patient and relatives. Symptomatic COVID cases shall be managed at home or in hospital as per severity of symptoms and prevailing government guidelines. Definite therapy shall be considered after COVID-19 negative report.

1.3 General Instructions for all haematology patients

A) Minimizing hospital visits

i) During treatment, the patient must minimize hospital visits. They should visit hospital/doctor if the tests cannot be performed locally or if there are significant complaints. Patient's attendant (asymptomatic) can do the medication refill. Patients are encouraged to utilize the teleconsultation facility if available, to reduce face-to-face visits.

ii) Whenever possible, it is advocated to use oral medications/ treatment/ regimens after explaining the risk benefit as sometime the oral therapy may not be as efficient as the injectable.

iii) Elective procedures, if any, may be postponed or deferred for a while and reassessment of decisions periodically, depending on local circumstances.

B) Travel precautions

i) Patients may be encouraged to avoid crowded transport.

ii) Patients may preferably keep an attendant who should be asymptomatic for COVID related illness.

C) Measures to reduce exposure to SARS-CoV-2

At each visit reemphasize the importance of face mask, hand hygiene (frequent hand washing/use of alcohol-based hand rub) and maintaining a safe social distance of 2 meters.

D) Home care services

Home care services should be prioritized to avoid exposure to hospital and health care staff. All precaution to prevent spread of COVID infection should be followed.

1.4 Supportive Care for haematology patients

During the ongoing pandemic, there are several challenges to treatment of haematology patients due to constraints in resources like ICU bed, ventilators and trained staff being mobilized for COVID-19 patient care. Many of the haematology patients require supportive

care in the form of blood and blood products. Blood banks are facing severe shortage of blood and blood products due to lockdown in many parts of country, fear among donors of getting COVID-19 during blood donation and HCWs getting COVID-19 infection etc. The local situation needs to be explained to patient and their caregivers clearly before starting treatment.

A. Transfusion Support

In the current scenario, to avoid frequent hospital visits and to address the scarcity of blood products, it is advised to use blood products judicially in sync with various established guidelines.

Antifibrinolytic agents like tranexamic acid or epsilon amino caproic acid (EACA) should be used in case of bleeding or at-risk patients if clinically indicated.

B. Prevention and treatment of infection and reducing blood product requirements

Patients at risk of infection and febrile patients may need admission and antibiotics should be prescribed as per institutional protocol. Early discharge and switch to oral antibiotics or antifungal should be considered in stable patients. EPO, G-CSF and TPO should be liberally used if indicated.

C. Mental well being

Symptomatic patients are admitted in COVID care centres/COVID health centres/COVID hospitals and they are kept in isolation without any attendant. Because of the isolation, many patients with COVID-19 infection go through mental distress due to fear of death and associated stigma. Thus, wherever feasible involving mental health professional is desirable, and they may be approached for teleconsultations if possible.

2. COVID-19 and Chronic Myelogenous Leukaemia

1. **What are your recommendations for treating newly diagnosed CML- CP during COVID-19 pandemic?**

   Ans. For **category 0-1**, go ahead with planned therapy. For **category 2-3**, weigh the risks and benefits of starting Hydroxyurea or Imatinib. Upfront 2nd generation TKI may be delayed until resolution of COVID symptoms in categories 2-3.

2. **Do you propose any change in therapy for CML patients who are already on treatment?**

   Ans. Treatment need not be changed for **Category 0-1**. For **category 2-3**, discuss with COVID treating physician. In view of drug related adverse effects Dasatinib and Nilotinib should be avoided in category 2-3.

3. **How do you propose to treat patients with advanced phase of CML (accelerated phase and blast crisis)?**

   Ans. For **category 0-1** patient continue with therapy as planned. If planned for HSCT, consult HSCT guidelines. For **category 2-3** patients, weigh the risk and benefits for starting/continuation of therapy. As mentioned above, there is a theoretical risk of more complications with Dasatinib and Nilotinib. For category 2-3, single agent TKI (preferably imatinib) is to be considered until patient recovers from COVID-19 illness.

4. **How do you propose to monitor CML patients? Is there any change?**

   Ans. BCR- ABL PCR monitoring every 3 -6 months to continue; in cases with deep molecular response (DMR) 6 monthly monitoring can be considered. Avoid treatment free remission (TFR) trial as it warrants frequent BCR- ABL testing and hospital visits. Those already in TFR can decrease frequency of monitoring every 2-3 months. Hospital visits can be reduced for those in Major molecular response (MMR) and tele consult can be pursued.

3. COVID-19 and Chronic Lymphocytic Leukemia

1. **Is there any change in approach for initiating therapy for CLL patients during COVID-19 pandemic?**

   Ans. Category 0-1: Initiate therapy if indicated. **Category 2-3** wait until recovery. Initiate treatment only for symptomatic patients with proper indications for therapy. If indication was lymphocyte doubling time, then patient may be followed on monthly CBC instead of once at 3 months (telephonically). Ibrutinib is standard therapy for CLL and is preferable during the pandemic, as there appears to be lower risk for infection compared to

regimens like FCR or BR. Hence, whenever the drug can be arranged for a patient, this should be preferred choice. For young fit patients, where there is a preference to use FCR, caution is advised and consider postponing as there is significant risk of infections with FCR. In situations where Ibrutinib cannot be used BR/Chlorambucil are the options.

2. **Are CLL patients at a higher risk of severe COVID-19 infection compared to patients with other haematological malignancies?**

   Ans. CLL patients in general are considered at high-risk for infections, mainly bacterial and herpes virus family due to underlying immunodeficiency and inadequate immune response. However, based on limited data available, it seems that the risk for COVID-19 infection per se is not higher.

3. **Do you propose any change in therapy for CLL patients who are already on treatment?**

   Ans. Category 0-1: Ongoing CLL-directed therapies can continue. Minimizing hospital visits and tele consult for stable patients is a practical option. For **category 2-3**, wait until recovery.

4. COVID-19 and Acute Myeloid Leukaemia

1. **What are your recommendations for induction therapy in newly diagnosed AML during COVID-19 pandemic?**

   Ans-Category 0-1: Investigate and treat normally as per institutional guidelines. **Category 2-3** wait until 2-weeks. Supportive management in the form of Hydroxyurea, blood/blood products transfusion and treatment of infections with antibiotics/antifungals to continue along with treatment of COVID-19**.**

2. **Do you propose any change in consolidation therapy for AML patients?**

   Ans-Category 0-1: Consolidation as per institutional guidelines. May consider intermediate dose of cytarabine or hypomethylating agents. **Category 2-3** wait until recovery. Follow HSCT guidelines for patients in whom allogeneic SCT is indicated. Consolidative allogeneic hematopoietic cell transplantation may be limited at many

institutions during ongoing pandemic. Prophylactic antibiotics and supportive care as per institutional guidelines.

3. **How do you propose to treat patients with relapsed/refractory AML in COVID-19 pandemic time?**

   Ans-For refractory AML, palliation is recommended till recovery from COVID illness. For relapsed AML, follow guideline for new AML as above.

4. **Should APML therapy be modified in COVID-19 situation?**

   Ans-Category 0, 1 and 2: Induction with ATRA & ATO. For **category 3**: Wait until recovery. Use standard protocols preferably of ATRA & ATO combination. Chemo based protocol likely to have more blood product requirements and risk of neutropenia/infections.

5. COVID-19 and Acute Lymphoblastic Leukaemia

1. **What are your recommendations for initial induction and post-remission therapy in newly diagnosed Adult/Paediatric ALL during COVID-19 pandemic?**

   Ans-Category 0-1: Induction as per institutional practice. **Category 2-3**: Wait until recovery. Corticosteroids are generally part of standard treatment of COVID-19 infection and hence they can be continued in any category. For adults, may consider reducing anthracycline and L-asparaginase dose to 50%. Use GCSF to shorten the period of neutropenia.

2. **Do you propose any change in maintenance therapy for ALL patients?**

   Ans-Category 0-1 Continue maintenance therapy, avoid vincristine and dexamethasone in maintenance. **Category 2-3:** Hold until recovery.

3. **How do you propose to treat patients with relapsed/refractory ALL in COVID-19 pandemic time?**

   Ans- For refractory ALL, palliation is recommended during this time. For relapsed ALL, follow guideline for new ALL as above.

4. **Do any of the leukaemia drugs have known interactions with proposed COVID-19 therapies?**

Ans-Azithromycin can increase the toxicity of vinblastine, vincristine. Chloroquine, HCQ can increase cardiac toxicity of anthracycline. Azithromycin, HCQ, Chloroquine can increase QTc along with TKI (Imatinib, Dasatinib), Inotuzumab. Lopinavir/Ritonavir may increase the vincristine and methotrexate toxicity. Tocilizumab reduces dasatinib, Venetoclax concentration by inducing CYP3A4. Colchicine causes increased toxicity of vinca alkaloids.

5. **Do you propose any change in approach to Ph-positive ALL in Covid-19 situation?**

   Ans-Category 0-1, no change and continue therapy as per institutional practice. **Category 2-3**: Wait until recovery. Corticosteroids are generally part of standard treatment of COVID- 19 infection and hence they can be continued.

6. COVID-19 and Multiple Myeloma

1. **Are you recommending any change in approach to treatment of newly diagnosed Multiple Myeloma during COVID-19 pandemic?**

   Ans- Category 0-1: Normal therapy. **Category 2-3**: Weigh the risks and benefit based on impending organ dysfunction. Corticosteroids are generally part of standard treatment of COVID-19 infection and hence they can be continued. Anti-myeloma therapy can be put on hold until recovery for patient with additional myeloma defining events (SLiM criteria) **Initial therapy**- VRD/VTD/VCD 4-6 cycles followed by autologous transplant for transplant eligible. Post induction therapy for transplant ineligible: High-risk: Continue triple therapy as per institutional practice. Standard risk: Consider lenalidomide maintenance after MRD negativity or as per institutional practice. Prefer subcutaneous bortezomib at home. **Zoledronic Infusion**: monthly for 1st six months then change to every 3 months. Consider denosumab if affordable instead of Zoledronic acid as it can be administered subcutaneous at home. However, Denosumab cannot be stopped abruptly because of increased risk of vertebral fractures and bone loss.

Elderly myeloma: can consider two drug induction and maintenance based on respective institutional practice. Consider dexamethasone 10-20 mg/week to decrease the chance of infection. Prophylactic antibiotics: As per institute protocol.

2. **Do you propose any change in maintenance therapy for MM patients?**

   Ans- No for **category 0, 1 and 2**. Hold therapy for **category 3**.

   Zoledronic Infusion: defer if no bone lesion or change to every 3monthly schedule.

3. **How do you propose to treat relapsed/refractory MM cases during COVID-19 pandemic?**

   Ans- Oral regimens should be preferred- PCD, MPT, Bortezomib-containing regimen if the patient was not exposed at first line. Bortezomib regimens are quite safe and need not be avoided if the patient can be instructed to get the injections at local place with the help of a nurse/ doctor nearby.

   For indolent biochemical relapse, patient can be monitored instead of initiating anti-myeloma therapy.

   Consider: Carfilzomib can be administered as weekly infusions. Avoid other schedules.

   Consider: Daratumumab can be converted to once monthly regimens.

4. **What is your advice regarding transplant-eligible patients?**

   Ans- If patient is transplant eligible, follow HSCT guidelines.

   Stem cell transplant may be delayed after stem cell collection if the facility for stem cell cryopreservation/ liquid nitrogen system is available. If no such storage facility is available, then patient can be taken up for auto HSCT as per institutional practice and following HSCT guidelines.

7. COVID- 19 and Myelodysplastic Syndrome and Ph (-) Myeloproliferative Neoplasm

1. **Are MDS patients at a higher risk of severe COVID-19 infection?**

   Ans-Patients with MDS are more likely to have neutropenia or functional neutrophil defects which makes them more susceptible to bacterial or fungal infection. There are no data available till date to convincingly say that they are at higher risk of contracting COVID-19 infection. However, if they contract COVID-19 infection the severity is expected to be more because of presence of neutropenia and immune dysfunction. If frequent hospitalization required for the above conditions, they are also more prone to develop COVID-19 infection and subsequently higher mortality rate as similar to other cancer patients. Therefore, it is highly recommended to maintain personal hygiene, social distancing, and utmost caution with other contacts outside their residential place. (Reemphasized here)

2. **Is there any change in approach to therapy (initiation, choice of treatment, transplant options) for MDS patients during COVID-19 pandemic?**

   Ans- Low to intermediate-risk MDS: **Category 0-1:** Follow institutional practice. Consider ESA and TPO mimetic agents. For **category 2-3**, hold until recovery.

   High-risk MDS: **Category 0-1:** Hypomethylating agents (HMA), **Category 2-3:** Palliation until the patient recovers from COVID followed by treatment as per institutional policy.

3. **What is your approach to patients with MPN/MDS and Ph negative MPN? Is there any consideration regarding thrombosis risk and adjustment of dose of anticoagulation?**

   Ans-Category 0, 1 and 2: Hydroxyurea can be administered. Rest of the treatment as per institutional practice

   Category 3: Hydroxyurea/Phlebotomy in consultation with COVID physician. May consider higher hematocrit > 48-50% for phlebotomy along with aspirin as prophylaxis. Heparin administration is standard management in the treatment of Covid pneumonia and it can be given in consultation with Covid physician.

8. COVID- 19 and Lymphoma

1. **Are you recommending any change in approach to treatment of early stage of Hodgkin Lymphoma during COVID-19 pandemic?**

   Ans. For **Category 0-1**: Standard therapy with 2-4 cycles of ABVD and IF(S) RT can be done during the COVID-19 pandemic. **Category 2-3**: Hold until recovery. Protocols using Escalated BEACOPP (2+2 as per HD 14 and HD 17 trials) despite having higher EFS may be avoided during the pandemic. In hospital situations where radiation is not possible or frequent visits need to be avoided, can consider PET guided omission of radiation with the understanding that outcomes may be inferior.

2. **Are you recommending any change in approach to management of advanced stage of Hodgkin Lymphoma during COVID-19 pandemic?**

   Ans. For **category 0-1:** A PET-guided approach gives good outcome in advanced Hodgkin lymphoma (aHL) and reduces use of bleomycin in PET -ve patients (RATHL study). For PET+ve patients BEACOPP-14 may be safer than Esc BEACOPP. Again, upfront BEACOPP may be avoided to reduce neutropenia risks and prefer ABVD based therapy as standard. **Category 2-3:** Hold chemotherapy until recovery

3. **How do you propose to treat relapsed/refractory Hodgkin Lymphoma cases during COVID-19 pandemic?**

   Ans. Category 0-1: Follow institutional practice. **Category 2-3:** Hold until recovery. For young fit patients' standard of care is salvage and transplant. Salvage regimens with nivolumab and brentuximab have high response rate and less neutropenia – however they are expensive and can't be used for majority in India. Some of the salvage regimens like Gemcitabine vinorelbine dexamethasone, or Gemcitabine Cisplatin dexamethasone (GDP) may have lower risk of neutropenic complications than older regimens like DHAP or ICE and may be preferred. GDP can be administered in Day Care setting and is preferable over other intensive regimens warranting prolonged hospitalization. Auto

transplant should not be withheld if the center can manage the logistics during the pandemic. For older patients prefer oral metronomic chemotherapy options during the pandemic and reduce risk of neutropenia.

4. **Are you recommending any change in approach to treatment of Aggressive/High grade non-Hodgkin Lymphoma during COVID- 19 pandemic?**

   Ans. Category 0-1: Treat as per your institutional practice. **Category 2-3:** Corticosteroids are generally part of standard treatment of COVID 19 infection and hence they can be continued. Hold chemotherapy until recovery.

5. **What is your approach to patients with other low- grade NHL/CLPD? Do you propose any modification in therapy?**

   Ans. The treatment of low-grade lymphomas is done only if there is a clear indication. **Category 0-1:** Treatment can be initiated if indicated. **Category 2-3:** Except corticosteroids, hold rest of the treatment until recovery. Relapsed patients use oral metronomic therapy to reduce frequency of hospital visits and consider teleconsultation as far as possible.

9. COVID-19 and Aplastic Anemia

1. **What are your recommendations for treating severe AA patient during COVID-19 pandemic?**

   Ans-Management of AA broadly encompasses supportive care and definitive treatment. Basic principles of supportive care have been discussed under general recommendation. All patients of severe and very severe AA may need admission and antibiotics should be prescribed as per institutional protocol. Early discharge and switch to oral antibiotics or antifungal should be considered in stable patients. G-CSF is of no benefit in case of severe and very severe aplastic anemia patients.

   The definitive treatment options and recommendations are as follows:

   Allogenic SCT- Category 0-1: Should not be delayed whenever possible (considering disease severity, infection risk, blood product immunization) specially in case of matched related donor transplant in view of risk of COVID-19 infection and BMT may be a lifesaving

treatment in many patients, so can't be deferred. However, follow HSCT guidelines. **Category 2-3:** Transplant to be deferred until recovery and can be considered after 2 negative RT PCR reports one week apart (follow ISBMT guidelines)

Immunosuppressants (applies only to acquired AA)- **Category 0-1:** Treat as per institutional practice. In case of severe or very severe AA, ATG should be used as per standard protocol and precautions. Hospital stay should be minimized, and all effort should be put to use home care services. **Category 2-3:** Hold until recovery. Alternative agents in combination like Eltrombopag, low dose cyclosporine (2-3 mg/kg/day), danazol/stanazolol can be considered for patients who can stay at home.

2. **Can febrile neutropenia be treated at home?**

   Ans- Low-risk**:** probably yes. High-Risk FN: Hospitalization

   Earlier discharge with continued oral antibiotics may be possible in stable patients.

10. COVID-19 and Immune thrombocytopenia

1. **For a newly diagnosed ITP in children and adults requiring treatment due to severe thrombocytopenia, what is your recommendation for initial treatment options in the setting of the COVID-19 pandemic?**

   Ans- For **category 0-1**, follow institutional guidelines. Steroids and IVIG can be given for **category 2-3.** In case of non-response 2nd line agents based on affordability of patient should be given.

2. **Do you propose any change in therapy for chronic ITP patients during COVID-19 Pandemic?**

   Ans- Chronic ITP patient who is stable (on low dose steroid) to continue the same (dose of steroid). For patient on higher doses (0.5 to 1mg/kg/day) of corticosteroids or immunosuppressive drugs (Cyclosporin, Azathioprine), dose can be lowered to minimum

level or change to TPO agonists (Eltrombopag or Romiplostim), if affordable and according to institutional practice.

3. **Do you propose any change in frequency of blood count monitoring or threshold to initiate treatment to reduce hospital visits?**

   Ans- Follow institutional practice. Frequent visits to hospital and laboratory should be avoided as mentioned in general recommendations. If there is severe thrombocytopenia and/or bleeding symptoms, admission to hospital may be required according to institutional practice.

4. **What is the approach to a hospitalized patient with ITP who develops a serious COVID-19 infection? What are the concerns if the patient has had a splenectomy?**

   Ans: Steroids are standard form of therapy to treat symptomatic COVID patients with hypoxia. Both steroids and IVIG can be considered to treat ITP in this setting. Treatment of a febrile splenectomised patient with ITP remains unchanged in the setting of COVID-19 infection.

11. COVID-19 and Haemophilia

1. **Are there any concerns for patients with bleeding disorders COVID-19 pandemic?**

   Ans- Minimize hospital visits. Management to continue same as per institutional practice for **category 0, 1 and 2**. For **category 3**: There is increased risk of thrombosis in category 3 patients and heparin is administered as part of standard protocol. A close liaison with COVID Physician/Specialist is must. Overall Paracetamol is a safe antipyretic/analgesic while ibuprofen and Non-steroidal anti-inflammatory drugs should be avoided.

2. **What are your recommendations for People with Haemophilia who are already on treatment/prophylaxis with Factor VIII/IX/Cryoprecipitate concentrates during COVID-19 pandemic?**

Ans-Category 0, 1 and 2: There is no need to change the recommended treatment regimen for the people with haemophilia (PWH). It is also recommended for haemophilia centers to maintain adequate supply of blood and plasma in the current scenario.

For category 3: There is increased risk of thrombosis in category 3 patients and heparin is administered as part of standard protocol. A close liaison with COVID Physician/Specialist is must. Plasma derived products are safe and switching to other product is not recommended. For treatment with other blood-derived products like cryoprecipitate, platelets (which are not virally inactivated), risk/benefit ratio of bleeding vs any residual risk of acquiring another infection should be judged

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12. COVID-19 associated Coagulopathy

1. **What is COVID-19-associated coagulopathy (CAC)? Is it similar to DIC?**

Ans-Most of the patients with SARS-CoV2 infection in **category 3** show derangement in the baseline coagulation prolife which includes mild thrombocytopenia or thrombocytosis and raised fibrinogen and D-dimer levels with no/ minimal prolongation of APTT and PT-INR. These findings parallels with acute phase reactants like C-reactive proteins (CRP) as a marker of inflammation. Rarely lupus-like inhibitors have been reported as a cause for mild APTT prolongation. These are the usual features of COVID-19-associated coagulopathy (CAC). This entity is different from DIC.

However, if the patients with severe COVID-19 infection develop multi-organ failure, they may subsequently meet the criteria of overt DIC according to ISTH criteria. Moderate to severe thrombocytopenia, prolongation of PT-INR, APTT, TT and severe hypofibrinogenemia and moderate to marked elevation of D-dimer or FDP characterize this.

2. **What treatment or intervention should be given to a patient with CAC/DIC?**

Ans-Although majority of the COVID-19 patients have mild abnormality in coagulation parameters, they rarely bleed. It is emphasized that blood products should not be used to correct the deranged laboratory parameters if the patient is not bleeding; rather this might aggravate the already compromised respiratory reserve and increase the risk for thrombosis. Heparin administration (prophylactic or therapeutic) is part of standard treatment for categories 2-3. Hence, liaison with COVID physician/specialist is must for overall management of this group of patients. Institutional practice to be followed in case of bleeding symptoms in DIC.

13. COVID-19 and Thalassemia Major

1. **Do Thalassemia Major Patients' have increased risk of getting COVID-19 or its complications?**

Ans-Thalassemia patients, especially young adults/adults, have a chronic condition which may be associated with several co-morbidities, the underlying disease as well as complications of chronic transfusions; hence it seems possible that there could be an increased risk of severe COVID-19 disease in category 2-3 patients. Patients in category 3 should undergo additional adrenal function evaluation as this complication goes unrecognized in most patients. If recognized, it should be treated appropriately.

2. **Does splenectomy confer a higher risk for COVID-19 infection?**

Ans-Splenectomy doesn't confer high risk for viral or severe viral infection and there is no specific experience regarding SARS-CoV2.

3. Due to the ongoing COVID-19 pandemic is any change in transfusion schedule or threshold is required?

Ans -Threshold to transfuse blood is same as in pre- COVID phase, though due to lockdown and fear among donors of getting COVID there is possibility of suboptimal transfusion. NGOs, society working for thalassemia, should encourage and raise awareness among donors

through social media for blood donation and blood bank should ensure safe donation and transfusion environment.

4. Can SARS-CoV2 be transmitted through donated blood?

Ans-At present there is no evidence of transmission through transfused blood.

5. Should thalassemia patients continue iron chelation if exposed to or detected to have confirmed SARS-CoV2?

Ans-No data are currently available regarding iron chelation and susceptibility or severity of COVID-19 infection. **Category 0, 1 and 2**, continue. **Category 3:** Hold until recovery.

6. What about use of Luspatercept during COVID-19 pandemic?

Ans-No evidence of any harmful effect, so patient who are on, should continue it. It is more beneficial rather, as reducing transfusion frequency will reduce clinic visit and exposure to SARS-CoV2.

7. What are the recommendation for stem cell transplant during COVID –19 pandemic?

Ans-There is no evidence that SARS-CoV2 can be transmitted through hematopoietic stem cell product. There is no urgency/emergency of HSCT in younger patients. In view of need of hospitalization and myeloablation, leading to increased risk of infection, stem cell transplant should be postponed during initial part of pandemic. With fall in number of cases of COVID-19 coming to hospital, family and haematologist can discuss for moving forward for planned procedure. Consult HSCT guidelines.

14. COVID-19 and Haematology Laboratory

1. **What are the derangements in haematologic laboratory parameters reported in patients' with COVID-19 infection?**

   Ans – Lymphopenia, alteration in ANC/ALC >3.5 (considered a poor prognostic marker), thrombocytopenia, thrombocytosis, presence of activated lymphocytes in peripheral blood film (designated as COVIDocytes) – similar to activated lymphocytes seen in any viral infection, alteration in coagulation parameters like elevated D-dimer, elevated fibrinogen, prolonged PT and APTT and presence of FDP (seen in severe COVID-19 with ARDS and DIC) are some of the derangements in haematologic laboratory parameters.

   Eosinopenia defined as a reduction of circulating eosinophils <0.02 $X10^9$/L along with elevated C reactive protein (CRP)> 40mg/L has been used as markers based on which patients with fever can be triaged effectively. In addition, serum biochemical abnormalities comprising of elevated ALT, AST, LDH, Serum ferritin, IL6, CRP are frequently seen.

2. **What are the common laboratory investigations anticipated in patients with COVID-19 infection?**

   Ans-Complete Blood counts (CBC), complete coagulogram (Prothrombin time, APTTK, D-dimer, Fibrinogen), Liver function tests, LDH, urea, creatinine, CRP procalcitonin, IL 6 , Vit D, Calcium and serum Ferritin or as per institutional protocol.

3. **How do you recommend sending samples of suspected/ confirmed COVID-19 patients to haematology laboratory?**

   Even though there is no evidence that COVID-19 is transmitted through blood, consider all samples sent to the laboratory as potentially infectious.

   - All samples are to be collected in appropriate anticoagulated vials and should be further placed in a secondary container (small plastic airtight container would be preferred to keep the samples upright) to minimize potential breakage or spill. All these containers must be sent in a large plastic box with **biohazard label** (COVID-19).

- These plastic surfaces can be sterilized with alcohol wipes/ 0.5% hypochlorite prior to handling the samples.
- Ideally ONLY online requisitions for COVID-19 patient samples should be sent.
- Avoid physical forms. In case, physical forms are being used, requisition form should have proper patient label and BIOHAZARD label
- Samples should NOT be sent in pneumatic tubes
- Do not transport haematology samples rolled up in the requisition forms
- Follow local institutional/government protocol for the same.

4. What is the proportion of viremia in Covid-19 infection?

Ans. Approximately 1%

5. What are your recommendations for sample processing and handling by laboratory staff?

- The technician or doctor handling the samples should have appropriate Personal Protective Equipment (PPE) - mask, goggles, face shield, head cover, gown and gloves. It is preferable to have a dedicated staff, by rotation, who will perform the tests.
- It is recommended to have a separate dedicated auto-analyzer for COVID samples. CBC values could be directly uploaded to HIS if the facility is available.
- Peripheral smears should be performed, with care, and if indicated. Prefixation in methanol before staining can be done.
- Proper decontamination of surface and machines necessary.
- Minimal handling of requisition forms and other potential fomites.

Since coagulation work up needs centrifugation, which is aerosol generating, it is necessary to use closed centrifugation system and preferably in a BSL class 2 lab facility if available using appropriate PPE with face shield.

7. **If a patient with known/suspected haematologic abnormality requiring special investigation additionally has COVID-19 infection, what is your recommendation for sample processing?**

Ans-A liaison with COVID physician/specialist and clinical haematologist is must. Non-urgent investigations may be postponed until the person turns negative. Urgently required investigations (e.g. Flow cytometry for haematological malignancies, bone marrow aspiration and trephine biopsy) should be performed after prior discussion with the laboratory/hematopathologist. In case of critical and urgent requirements, same precautions apply.

8. **How to discard biomedical waste generated in laboratories while testing COVID-19 samples?**

Ans- Handle laboratory waste from testing suspected or confirmed COVID-19 patient specimens as all other biohazardous waste in the laboratory. Follow institutional/ government guidelines and discuss with the hospital biomedical waste management team for safe disposal.

15. COVID-19 and Haematopoietic Stem Cell Transplantation (HSCT)

General Guidelines

We need to realize that ongoing pandemic is dynamic in nature and recommendations may change as the pandemic evolves. Recommendations also have to be evaluated based on local conditions. In some places, the pandemic seems to past its peak while it continues to enter new regions in India.

1. We feel comfortable doing HSCTs in these times also. What are the challenges?

Ans. An important consideration in regions which are yet to peak is availability of adequately trained BMT staff, ICU beds, ventilators, as well as availability of the stem cell product. One may feel comfortable performing a BMT but primary transplant physician may fall sick or be quarantined. A whole lot of BMT nurses may be quarantined. Many

nurses stay in hostels and hostel itself may be declared a containment zone. This has already happened in Delhi.

Similarly, availability of adequate blood products during myeloablative phase is required. These days, donors are unwilling to come to hospitals for blood donation. This needs to be accounted for.

2. What kind of transplants can be performed and what can be deferred?

Ans. In regions where pandemic is in community stage, non-urgent transplants need to be deferred like those for multiple myeloma and benign conditions like thalassemia. However, where insignificant transmission is there or regions which are past its peak, a gradual return to normalcy is advised including transplants for multiple myeloma and benign conditions.

3. What to do if patient for HSCT is infected with SARS-CoV2?

Ans. Category 1, 2 and 3: Hold until recovery. Wherever possible, HSCT should be deferred for 3 months if patient itself has been positive. In patients with high risk disease, such a deferral is not possible. Then we should wait for at least 2 weeks, till patient become asymptomatic and 2 negative PCRs one week apart have been documented.

4. What to do if patient for HSCT had a contact with a person with confirmed COVID-19?

Ans. This is category 1. Patient should be isolated for 2-3 weeks. In patients with high risk disease, such a deferral is not possible. Then we should wait for at least 2 weeks, till patient is asymptomatic and 2 negative PCRs 24 hours apart have been documented.

5. What to do if HSCT donor is infected with SARS-CoV2 or had a contact with a person with confirmed COVID-19?

Ans. Although data is limited for a recommendation but If donor is positive then HSC donation should be deferred by 3 months weeks in category 1-2. In case BMT is urgent

then asymptomatic donor after 2 weeks of isolation with 2 negative PCRs 24 hours apart can be allowed. For category 3, liaison with COVID physician/specialist is advised for best timing of donation.

6. In otherwise normal situation, does patient need to be tested?

Ans. Testing for SARS-CoV2 is strongly recommended both for patient and donor even if they are asymptomatic during current times. All patients should be RT PCR negative at least 72 hours before start of the conditioning.

7. Do we need to modify conditioning regimen?

Ans. If a transplant is being performed as lifesaving or urgent/emergent measure then this is not suggested. However, wherever possible, reduced intensity conditioning instead of myeloablative conditioning should be seriously considered.

In unrelated donor setting, procure the stem cell graft and cryopreserve before starting the conditioning. Cryopreserve separate graded dose aliquots of lymphocytes for potential donor lymphocyte infusions from donor stem cell harvests, when possible. In unprecedented times, stem cell source may not reach transplant center in time for several reasons.

8. Do we need to modify graft source?

Ans. Wherever feasible, a peripheral blood stem cell (PBSC) graft is preferable over bone marrow graft for faster engraftment and early discharge from hospital. There may be a situation where one may have to stick with bone marrow as source of stem cells.

9. **Do we need to modify mobilisation regimen?**

Ans. Whenever, low stem cell yield is suspected, prefer using Plerixafor and G-CSF. Avoid chemotherapy based mobilisation and its complications.

10. What supportive precautions can we take?

Ans. During this pandemic, a liberal use of G-CSF is allowed. In thrombocytopenic patients, off label thrombopoietin receptor agonists like Eltrombopag or romiplostim can be considered. Centres not routinely using prophylactic antimicrobials should consider prophylactic antibiotics, antifungal and antiviral agents as appropriate.

11. What to do if patient has symptoms suggestive of SARS-CoV2?

Ans. Test both nasal and pharyngeal swab by RT PCR. BMT units are positive pressure units. The pressure needs to be changed to negative or neutral. If there is possibility of shifting to isolation room in COVID designated area, then transfer patient. If not, all staff to use PPE as per institutional guidelines and management to be done in liaison with COVID care physician of the hospital.

12. What additional precautions to be taken after discharge from BMT unit?

Ans. Post BMT patients are at high risk of infection and therefore need to avoid contact with suspected individuals. Hand hygiene and social distancing as per local norms to be followed. Avoid travel. If urgent, use hired/private vehicle instead of public transport.

To reduce risk of exposure, minimise hospital visits and use telemedicine as much as possible.

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