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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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Care of patients with hemoglobin disorders during the COVID-19 pandemic: An overview of recommendations

To the Editor:

The outbreak of Coronavirus Disease 2019 (COVID-19) caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has led to a global health emergency.¹ Compared to the general population, patients with hemoglobin disorders such as sickle cell disease (SCD) or thalassemia are expected to be more severely affected by COVID-19 due to their preexisting chronic morbidities.² The Centers

for Disease Control and Prevention does not report any specific indications for patients with hemoglobinopathies. However, it can be hypothesized that the rapid spread of the virus may render these patients fragile when fighting the infection.

SCD, a hematological condition with functional asplenia, puts patients at a greater risk to develop acute pulmonary complications, including viral infections.² A study by Hussain et al reported four SCD cases that tested positive for COVID-19.³ These cases initially presented to the emergency department for a typical vaso-occlusive crisis (VOC), and the clinical course of their SARS-CoV-2 infection was rather mild. Patients had a history of respiratory complications, such as acute chest syndrome (ACS), asthma, or pulmonary embolism, which may be potential risk factors for progressive COVID-19 pulmonary disease in patients with SCD.³ A series of isolated cases of ACS in SCD patients positive for COVID-19 has been recently reported.^{4,5} Therefore, very little clinical experience of infected patients with SCD currently exists. For this reason, we believe that certain recommendations must be followed by healthcare professionals treating any SCD patient infected with SARS-CoV-2.

First, it is important to recognize the clinical manifestations suggestive of rapidly progressive ACS, including multi-organ failure, hepatic dysfunction, thrombocytopenia, and acute kidney injury. Healthcare professionals should differentiate between pneumonia or ACS, and the more diffuse ground glass appearance that is commonly associated with SARS-CoV-2 infection. Caution should be taken towards increased pulmonary pressures and right heart failure as symptoms suggestive of pulmonary hypertension, which can increase the risk of complications of a SARS-CoV-2 infection. Pulmonary and cardiac specialists should be consulted in case of suspicion of pulmonary hypertension. It is also important to recognize the high risk of life-threatening sepsis among SCD patients, whose functional hyposplenism renders them vulnerable to superimposed bacterial infections.

In terms of the therapeutic options for these patients, we recommend early aggressive simple or exchange blood transfusions for SCD patients diagnosed with COVID-19 and manifesting fever and cough, have worsening anemia, evidence of hypoxia and/or lung imaging changes. Exchange transfusions should be initiated in case of progressively worsening hypoxemia and clinical deterioration. Blood products shortage is anticipated during the pandemic, so pre-established transfusion thresholds should be adjusted to include mainly patients with severe anemia or with complications, namely ACS or stroke. There currently exists no evidence that being on hydroxyurea would increase SARS-CoV-2 infection risk. However, it is advisable to avoid the routine use or increasing doses of hydroxyurea to reduce the need for repeated phlebotomy and hospital visits.^{2,6} In areas where severe blood shortages are expected due to the pandemic, a low dose of hydroxyurea is recommended in all pediatric patients with sickle cell anemia, who receive regular blood transfusion therapy for primary or secondary stroke prevention.⁷ In the absence of regular blood transfusion therapy, hydroxyurea treatment will also decrease the incidence rates of acute vaso-occlusive pain and ACS events.⁷ Noteworthy, a treatment with one single dose of tocilizumab (8 mg/kg) was successfully used to treat an adult SCD patient with

pneumonia; it was related to COVID-19 infection associated with ACS.⁸

Respiratory measures for these patients should not include aerosol-based interventions, but rather nebulizers and metered-dose inhalers, if the room is non-negative pressure. A negative pressure room for non-invasive ventilation, high flow oxygen, and bronchoscopy should also be used.⁹ Patients with SCD are often prescribed non-steroidal anti-inflammatory drugs, angiotensin converting enzyme inhibitors, and angiotensin II receptor blockers. There is emerging data regarding the possible negative effects of these classes of drugs on SCD patients being treated for COVID-19.⁹ As data is emerging on a day-by-day basis, clinicians should search for the latest evidence in that regard when encountering patients on these medications.

There is emerging evidence from case series and retrospective studies that severe SARS-CoV-2 infection can be complicated by an increased risk of coagulopathy. In addition, SCD patients often experience an increased frequency of viscosity-related events, and have an increased risk for venous thromboembolic events. This suggests that they may even be at higher risk compared to COVID-19 patients who do not have SCD. Although data suggests that pediatric COVID-19 patients have a milder clinical course compared to adults, thrombosis has been reported. All adult or pediatric SCD patients with severe COVID-19 should therefore be given prophylactic doses of anticoagulant, unless there is an indication for full anticoagulation.¹⁰ Recent data suggests a reduced 28-day mortality in severely ill COVID-19 patients who received low-molecular-weight heparin or unfractionated heparin. Moreover, therapeutic anticoagulation strategies in these patients should also be taken into consideration. The active application of anticoagulants, such as heparin, has been recommended but still needs validation by evidence. There is a close association between elevated D-dimer levels and pro-inflammatory cytokines with disease severity in patients with COVID-19.¹¹ Blood tests on admission should include platelet count, fibrinogen, and D-dimer levels. It is also recommended to check D-dimer levels every 24-48 hours during hospitalization. Stem cell transplants and gene therapy approaches should be deferred for these patients until the pandemic resolves. If the patient is on one of the recently approved drugs for SCD such as voxelotor or crizanlizumab, it is advised that they continue therapy. If not yet started, delaying the new drug initiation should be considered.¹⁰

While thalassemia patients do not have the same risk for pulmonary infections as patients with SCD, they also have underlying comorbidities (stemming from ineffective erythropoiesis, chronic hemolytic anemia and primary or secondary iron overload) that may also make them vulnerable to complications of the SARS-CoV-2 infection.² A study by Motta et al provided preliminary data from an Italian experience, showing that patients with thalassemia have mild clinical presentation of SARS-CoV-2 infection.¹² They included 10 cases of transfusion-dependent thalassemia (TDT) and one case of non-transfusion-dependent thalassemia (NTDT), all of whom had thalassemia-related comorbidities and were diagnosed with COVID-19. Six patients required hospitalization and none died. Except for one patient with myelosuppression, there was no increase in blood

requirements.¹² A larger sample is required to better understand the impact of COVID-19 in thalassemia patients, but these data suggest that it may not be more severe than the general population. While there is very little clinical experience of infected patients with thalassemia, we believe that certain recommendations must be followed by healthcare professionals treating any thalassemia patient with COVID-19.

Clinicians dealing with COVID-19 thalassemia patients should take into consideration the possibility of adrenal insufficiency, particularly in patients with hemodynamic instability. The need for low dose glucocorticoid supplementation should be considered, while keeping in mind that corticosteroids slow down clearance of viral RNA from respiratory tract in SARS-CoV-2 infection, and increase the complication rate. Both, intravascular and extravascular hemolysis, can occur in thalassemia patients. Clinicians should therefore closely monitor blood counts of thalassemia patients with COVID-19, and caution should be maintained towards the possibility of exacerbated hemolytic anemia in the setting of acute viral infection. As for those patients with cardiac disease, routine monitoring for iron overload and related cardiomyopathy should be continued. Although thalassemia is known to be associated with a hypercoagulable state, there is currently no data on increased risk of thromboembolic events among thalassemia patients with COVID-19. However, since there is emerging evidence that severe SARS-CoV-2 infection has an increased risk of coagulopathy, we recommend giving prophylactic anticoagulation to all patients with severe COVID-19.

Patients with thalassemia, particularly those in the older age group, are most likely to have been splenectomized. If these patients are infected with SARS-CoV-2, the risk of developing a superimposed secondary bacterial infection, and triggering a life-threatening sepsis should be considered. Therefore, thorough evaluation of any splenectomized thalassemia patient presenting with fever should be made and antibiotics should be initiated for possible bacterial infection. As for blood transfusions, the patient's chronic transfusion regimen must be maintained, as there is no evidence to date that COVID-19 may be transmitted through blood. If thalassemia patients are exposed to SARS-CoV-2 but are asymptomatic, iron chelation therapy should not be stopped. However, should the patient become symptomatic, it is advisable to interrupt iron chelation therapy.^{6,13} Unless conditioning has already been initiated, stem-cell transplants and gene therapy should be deferred for these patients until the pandemic resolves.¹³ Should a patient be on the novel erythropoiesis maturation agent luspatercept, therapy should be maintained even if the patient is diagnosed with COVID-19, as there is no evidence that it should be discontinued in this case scenario. If not yet started, delaying the new drug initiation should be considered.¹³

The consequences of COVID-19 in patients with SCD and thalassemia are not yet well delineated. Comprehensive and detailed reporting by international medical experts, policy makers, governments, and non-governmental organizations of the clinical course and outcomes in this patient population is needed. This will enhance the understanding of the infection in this patient group and will lead to





more evidence-based management recommendations for these patients. Until more data arise, the recommendations we provide herein can be used based on clinicians' best judgment.

CONFLICTS OF INTEREST

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Granulocyte-colony stimulating factor in COVID-19: Is it stimulating more than just the bone marrow?

To the Editor:

Granulocyte-colony stimulating factor (GCSF) is routinely administered in cancer patients as prophylaxis or treatment of neutropenia. Although the safety profile of GCSF use in patients with symptomatic COVID-19 disease is unclear, lung findings from autopsies of patients showed neutrophil extravasation in the alveolar space.¹ It is known that severe cases of COVID-19 have been reported to have a higher absolute neutrophil count (ANC)-absolute lymphocyte count (ALC) ratio²; both reported findings raise questions about the appropriate timing of administering growth factors to neutropenic patients with SARS-CoV-2 infection.

Although clear causal evidence of GCSF administration leading to worse outcomes in COVID-19 patients does not yet exist, there