



Blood supply challenges and transfusion care of patients with hemoglobinopathies during COVID19 pandemic

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The coronavirus disease 2019 (COVID-19) pandemic has led to a global health emergency since it was declared by the World Health Organization (WHO) as a pandemic in March 2020. COVID-19 has brought about immense challenges to the health care systems and economics in every country, with the impact being higher in countries of the developing world (1). The pandemic has had an impact on blood supply in several countries in particular during the early stages (2,3). Although the decline in donation number has been largely matched with reduced demand in many countries (4), the impact of the decline in blood supply on patients with hemoglobinopathies has not been universally assessed.

Inherited hemoglobinopathies, including sickle cell disease (SCD) and β -thalassemia major (BTM) are considered the commonest single-gene disorders worldwide. More than 80% of patients with these disorders live in developing and low-income countries with limited resources, which has resulted in challenges in maintaining their care (5). The emergence of the COVID-19 pandemic has jeopardized the already demanding and often suboptimal care of this group of patients in these countries (6). The fragility of the blood supply system in low and middle-income countries (LMICs) has made it particularly challenging for the blood banks in these countries to meet the ongoing demands during the pandemic. Many patients with BTM have limited access to regular and safe blood transfusions particularly in LMICs where the proportion of voluntary nonremunerated donors is low compared to that in more developed countries (7). This is

due to multiple factors including fragmented blood services, the lack of national blood policies, and the lack of facilities for the provision of phenotype-matched units. Not only do these countries suffer from fragmented blood systems, but they also have a major reliance on relatives and family members for blood supply (8), which threatens blood supply sustainability especially for patients with rare blood groups or complex alloimmunization. The same concerns apply in settings with restricted resources such as Sub-Saharan Africa where SCD is a major health burden (9), and in countries with humanitarian emergencies such as Yemen, Syria and Lebanon (8).

A multi-center survey run by the Thalassemia International Federation (TIF) among representatives from 42 countries (10), showed that the moderate to severe blood shortage during the COVID-19 pandemic has resulted in moderate to severe drop in hemoglobin (Hb) in BTM patients, with pre-transfusion Hb levels between 5–7 g/dL, with some reported to be very low (<5 g/dL) (5). Half of the respondents reported severe interruption with the frequency and/or the quantity of blood provided; all these respondents were from developing countries. This has resulted in the provision of unmatched or non-leukoreduced units, and even the reliance on whole blood for transfusion. Interruption and/or shortages in chelation therapy have also been reported. As expected, the impact on patients from western countries was mild to nil despite initial blood shortages.

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Mitigating blood transfusion challenges during COVID-19 pandemic

The WHO has published interim guidance on maintaining blood supply during the COVID-19 pandemic (11). It has recommended that blood transfusion services must be prepared to move quickly in response to changes in managing the demand for blood and blood products while mitigating the potential risk to staff and donors from exposure to COVID-19. In the event of anticipated blood shortages, there should be local strategies to increase supply, prioritize use, review the transfusion threshold of red cell transfusions for patients who are stable and low risk, and maximize use of alternatives for transfusion (4). An ongoing discussion with blood bank directors to identify strategies for support with blood products during such challenging situations is important.

For BTM patients on regular transfusion support, a chronic transfusion regimen must be maintained, and contingency plans should be put in place in case of possible reduction in blood availability for transfusion. The British Society of Hematology has set out guidelines regarding transfusion in this group of patients during the COVID-19 pandemic (12). This includes not mandating fresh red cells for patients with hemoglobinopathies if not available. For non-alloimmunized patients, it has recommended making a standard 7 days *group & save* to transfusion time. One particular aspect of optimizing blood use could be the use of erythropoietic simulants to reduce transfusion requirements. This is possible through different approaches such as the use of hydroxyurea (13), HbF production enhancers (14), and red cell maturation modifiers (e.g., luspaterecept) (15). However, these interventions would only benefit a proportion of patients considering limited access and unpredictable response.

For SCD patients, pre-established transfusion thresholds need to be reconsidered in view of the anticipated blood shortages during the pandemic, and transfusions should mainly be given for patients with severe anemia or with acute chest syndrome or stroke (16). Guidance has been provided to consider extending the *group & save* sample to transfusion time to 96 hours or a week for non-alloimmunized SCD patients who have had 100 units of blood (12). The American Society of Hematology (ASH) has provided guidance for transfusion in SCD patients as blood donation has dropped in the US, including reconsidering the Hb threshold for blood transfusion for common clinical situations (e.g., severe anemia, vaso-occlusive crisis), target

HbS after an exchange transfusion, or switching to simple transfusion instead of exchange transfusion for some patients (17). The provision of antigen-matched units to prevent alloimmunization may not be feasible all the time. Moreover, some providers are initiating hydroxyurea in patients on routine transfusion if severe blood shortages are expected or already occurring (12,17). Low-dose hydroxyurea (10 mg/kg per day) has been recommended to be considered in all paediatric patients at high risk of stroke, who receive regular blood transfusion for primary or secondary stroke prevention (18). Making this decision early is important considering the time required for hydroxyurea effect to take place. The ASH guidelines also recommended consideration of Voxelotor, a HbS polymerization inhibitor, in patients with low baseline Hb or difficult to transfuse because of alloantibodies (17).

The long-term effects of the challenges in maintaining blood supply in patients with hemoglobinopathies need to be studied. The consequences of under-transfusion of thalassemia patients, particularly in the pediatric age group, will need to be continually assessed considering the length of this pandemic. Previous experience from the early treatment of BTM patients in the mid 20th century suggests that this may result in growth retardation and/or increasing symptoms of ineffective erythropoiesis (e.g., bony changes, massive splenomegaly) and heart failure (due to severe anemia). Whether rates of recurrent strokes would increase in SCD patients will need to be assessed. Moreover, the impact of the current circumstances on the quality-of-life of this group of patients secondary to challenges in accessing hospitals during lockdown, providing sufficient blood for achieving target Hb or target HbS, more frequent hospital visits, and fear from risk of acquiring SARS-CoV-2 infection during hospital visits will also need to be studied.

Transfusion care of patients with SARS-CoV-2 infection

There are a few case series that have been reported of COVID-19 infection in BTM and SCD. The largest series among thalassemia patients has been reported from Iran, where, of 15,950 BTM and 2,400 non-transfusion dependant thalassemia patients (total 18,350), 15 cases of confirmed COVID-19 and 8 symptomatic cases, but not confirmed, were reported (19). A multicenter international survey reported 13 hemoglobinopathy patients with confirmed COVID-19; 10 of whom were with BTM (10). The global Secure-SCD Registry, Surveillance

Epidemiology of Coronavirus (COVID-19) Under Research Exclusion (<https://covidsicklecell.org>) was developed to provide data from international collaborators on the clinical characteristics, comorbidities, presenting manifestations, medications, and interventions performed in SCD patients with COVID-19. As of 23rd October 2020, there were 420 patients that have been reported in the registry of whom 12.68% were on chronic transfusion support. Moderate and severe disease developed in 15% of the patients. The commonest presenting manifestations were pain (55.95%) and pneumonia (27.14%). A third of the patients required blood transfusion support (70.99% simple transfusion, 29.01% exchange transfusion). A total of 16 deaths were reported (20).

It is recommended that physicians should closely monitor the blood counts of thalassemia patients with COVID-19 with caution for features of exacerbated intravascular and extravascular hemolytic anemia (10). Chelation should be temporarily stopped in patients with moderate to severe COVID-19. However, it can be safely continued in patients with mild disease (21). As for SCD, early, aggressive simple or exchange blood transfusions are recommended for SCD patients diagnosed with COVID-19 presenting with fever and cough, worsening anemia, evidence of hypoxia and/or pulmonary changes (16). In the event of progressively worsening hypoxemia and clinical deterioration, exchange transfusion with or without an early simple transfusion is recommended. One report described the use of Voxelator in a SCD patient during hospitalization for COVID-19 infection with a successful outcome (22).

Conclusions

In conclusion, there is a need for comprehensive and detailed reports to understand the impact of COVID-19 and the blood supply shortages during this pandemic on patients with hemoglobinopathies. Long-term follow-up is going to be essential. This is necessary to aid international medical experts in making evidence-based recommendations. Moreover, such information will aid policy-makers and governmental and non-governmental organizations to better plan for the care of these patients in future pandemics.

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