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COVID-19 and SCA: an old friend comes to the rescue

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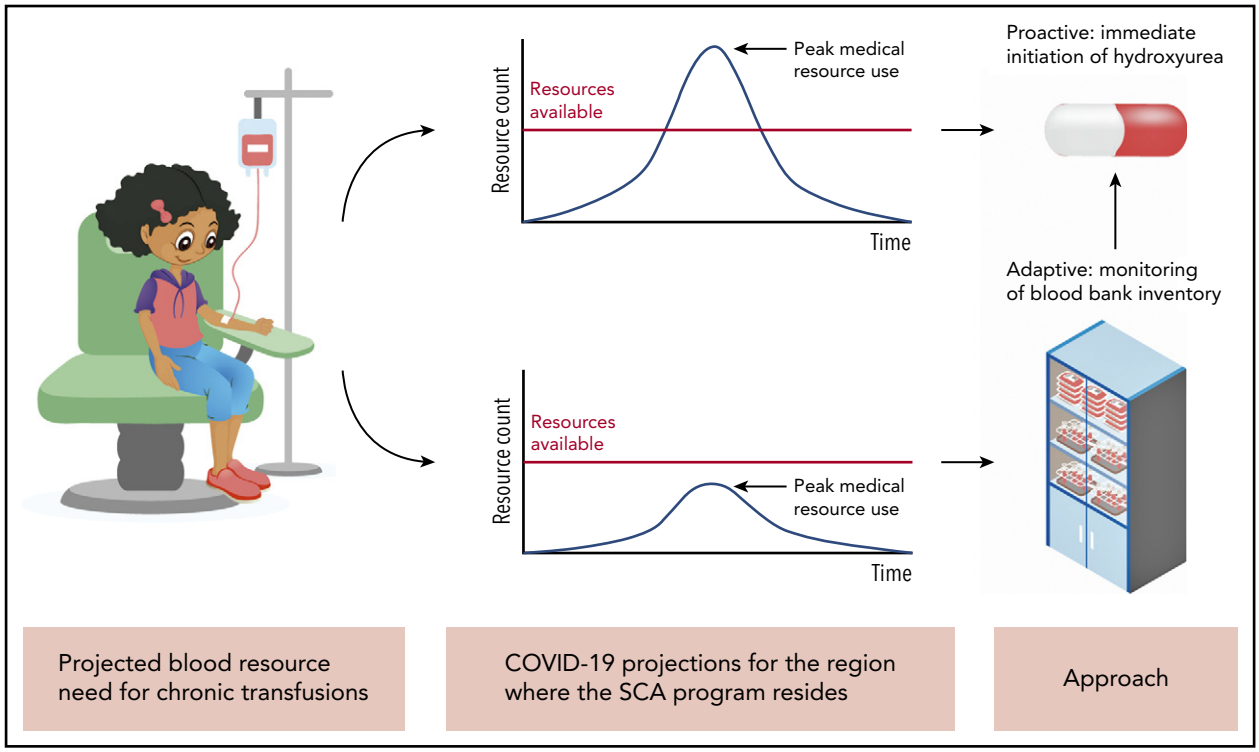
In this issue of *Blood*, DeBaun[1] proposes a forward-thinking evidence-based strategy to limit the impact of the SARS-CoV-2 coronavirus disease (COVID-19) pandemic on children with sickle cell anemia (SCA) at high risk for stroke. DeBaun argues that rapid initiation of low- and fixed-dose (10 mg/kg per day) hydroxyurea treatment while the children are receiving prophylactic chronic transfusions, and before blood supply is disrupted, ensures that when blood shortages do occur, the clinical benefit of hydroxyurea will be more quickly established, and the children will be better protected.

In COVID-19 hot spots around the world, health care resources, including blood products, have been rapidly depleted or reoriented toward emergency services, thereby exposing patients with chronic conditions to suboptimal care. However, some population centers and public health systems have weathered the crisis better by adopting a proactive approach, based on reasoned rationing of resources and protection of vulnerable populations like the elderly and the bearers of chronic diseases.

The prevention of pediatric stroke in SCA by administering prophylactic chronic transfusions has been a major success story in hematology and has reduced the incidence of stroke by ~90% (from 10.7 events per 100 person-years to 0.90 events per 100 person-years).[2] Yet, this strategy is dependent upon a reliable blood supply, which may not be guaranteed in chronically low-resource settings or during a pandemic crisis; abrupt interruption of transfusions can be devastating for children at risk, as shown in the STOP 2 trial.[3] Here enters hydroxyurea, the oldest and most extensively studied disease-modifying drug for SCA. For all of the concerns about myelosuppression, leukemogenesis, and teratogenesis, hydroxyurea has proven to be generally safe in SCA and has been approved by the US Food and Drug Administration for children with homozygous SCA beginning from 2 years of age. The evidence for the neuroprotective effect of hydroxyurea has also been mounting over the past decades.[4] Although the SWiTCH trial showed that hydroxyurea was not equivalent to transfusions (based on a composite end point) for secondary stroke prevention,[5] other studies showed that it was superior compared with no therapy, with 3.8 and 29 recurrent stroke events per



Children receiving chronic transfusions for stroke prophylaxis need a stable blood supply, which may be endangered during the COVID-19 pandemic. DeBaun proposes rapid initiation of hydroxyurea alongside transfusions in preparation for critical shortages of blood. This proactive approach could be particularly beneficial when the projected trajectory of the COVID-19 case burden indicates that the peak medical resource use will be superior to the available resources (upper branch). In other communities in which the projected trajectory will be less steep, an adaptive approach, with periodic assessment of regional blood bank inventory, may be preferable (lower branch).

100 person-years, respectively.[6] Therapy with hydroxyurea requires monitoring, primarily for myelosuppression; however, studies in low- to middle-income settings like Jamaica and sub-Saharan Africa have demonstrated that low-dose hydroxyurea treatment protocols are also beneficial in reducing transcranial Doppler velocity (a biomarker of stroke risk), without the need for frequent monitoring. Increasing the interval of laboratory monitoring and its attendant contact with health care facilities are paramount during the COVID-19 pandemic. Whether SCA is a significant risk for increased morbidity and mortality during SARS-CoV-2 infection is not yet known; however, it can be hypothesized that patients with SCA are particularly vulnerable based on their poor outcomes during the H1N1 influenza pandemic,[7] as well as the likelihood that the cytokine storm characteristic of severe cases of COVID-19[8] will exacerbate the hyperinflammatory milieu of SCA. COVID-19 and SCA share a propensity to cause acute lung injury, and data from the SECURE-SCA registry show that, as of 17 April 2020, 73 patients with SCA had contracted COVID-19 in the United States, with 27% developing pneumonia/acute chest syndrome and 12% succumbing to the disease, lending early validation to the concerns of the SCA community. Thus, it is critical to shield patients with SCA from hospital facilities via telemedicine appointments and by reducing blood draws.

In summary, the article makes a strong case that prompt initiation of hydroxyurea therapy alongside blood transfusions will allow safer interruption of transfusions when blood supplies are depleted and guarantee a measure of neuroprotection in children with SCA during a global health care emergency, while at the same time minimizing their exposure to health care facilities. The major question that remains unaddressed is whether the approach proposed by DeBaun is ideal for all SCA communities across the world. Although modeling the trajectory of the COVID-19 pandemic is proving to be challenging, a patchwork of COVID-19 risk is emerging. It is apparent that physical distancing and quarantine measures are effectively slowing the contagion in most medium- and small-sized urban areas in the United States, where the sharp decrease in elective surgery cases to minimize patient exposure (during procedures that can be safely postponed) has dramatically decreased blood demands to an extent disproportionate to the decline in blood donations; unexpectedly, this has resulted in regions with quite robust blood supplies. These conditions are likely to continue as long as elective surgery is postponed. For these settings, it can be argued that it may be more prudent to engage the local blood bank in deciding how to manage blood transfusions in patients with SCA, by assessing the blood inventory at key milestones of the pandemic and gradual reintroduction of elective surgery, as advocated by the American Society of Hematology/Sickle Cell Disease Association of America joint letter to blood groups on impact and management of blood shortages on sickle cell disease (available at https://www.hematology.org/covid-19/policy-resources) (see figure). In other words, a one-size-fits-all approach for patients in, for instance, New York City, which has been heavily battered by the pandemic, and Atlanta, GA (with COVID-19 deaths $<$ 1% of New York City's total) may not be ideal. In summary, acting in concert with the local blood bank and engaging local blood bank experts early on may be the most sensible approach for most communities, so that patients are not placed on hydroxyurea in combination with transfusions prematurely and for extended periods of time (and potentially without adequate laboratory monitoring), at least until a vaccine is available. Obviously, in both scenarios, shared decision making between providers and caregivers about initiation of hydroxyurea is paramount.

The COVID-19 pandemic is forcing us to reexamine how we practice medicine in high-resource settings like the United States. In the case of children with SCA, hydroxyurea, an old inexpensive drug whose benefits have been recently overshadowed by costly new treatments, may be pushed to the forefront once again; a low-cost fixed-dose treatment strategy being piloted in sub-Saharan Africa[9] may prove key to ease the transition to nontransfusion-based stroke prevention when resources wane during a pandemic in the United States. Thus, proactive, strategic repurposing may save the day.

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