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WIDER PERSPECTIVES

The wider perspective: Barriers and recommendations for transfusion support for patients with sickle cell disease in low- and middle-income countries

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Summary

Globally, sickle cell disease (SCD) is the most common inherited haemoglobinopathy. The highest burden of SCD is encountered in low- and middle-income countries (LMICs), most of which lack the resources to contend with the disease. There is a marked divide between care for individuals with SCD in high-income countries (HICs) versus LMICs, whereby the few disease-modifying therapies and curative regimens are only accessible to those in HICs. As such, blood transfusion remains central to the emergent treatment and prevention of complications of SCD. However, there are a myriad of related challenges in LMICs, which have impeded efforts to treat patients with SCD effectively. In addition to blood safety and availability, examples that impact SCD specifically include capabilities to detect and/or manage red blood cell alloimmunization, capacity for automated red cell exchange, limited immunohematology, suboptimal quality oversight with a lack of safeguards to prevent transfusion of incompatible blood and limited or absent post-transfusion surveillance to detect and/or manage transfusion-associated adverse events. Consequently,

clinical practices that are otherwise regarded as standard of care in HICs remain the exception in LMICs, highlighting disparities in care. A multifaceted approach that prioritizes transfusion support in LMICs is needed to improve care for patients with SCD.

KEYWORDS
alloimmunization, haematology, red blood cells, sickle cell disease, transfusion medicine, transfusion support, transfusion-transmitted infection

INTRODUCTION

Sickle cell disease (SCD) is a chronic, debilitating haematological disorder that arises from a point mutation in the β-globin gene.[1] This mutation produces an abnormal form of haemoglobin (i.e. haemoglobin S, HbS), which polymerizes under low oxygen conditions, resulting in 'sickled' red blood cells (RBCs). The pathophysiology of SCD is a complex interplay of chronic haemolysis, thrombosis, vascular occlusion and systemic inflammation. SCD is a systemic disorder whereby all organs may be affected. Notable acute and chronic sequelae include vaso-occlusive crises, anaemia, acute chest syndrome (ACS), ischaemic and haemorrhagic stroke, renal injury, chronic pain, pulmonary hypertension and cardiac failure. Some of the therapies in use to manage SCD (e.g. blood transfusion) also pose risks (e.g. alloimmunization, hyperhaemolysis, haemosiderosis/iron overload, infections) to patients.

The highest burden of SCD is still encountered in low- and middle-income countries (LMICs), most of which have limited resources to contend with the disease.[2–4] In 2021 alone, an estimated 7.7 million people were living with SCD worldwide, and 515 000 babies were born with SCD,[2] most (~80%) of whom were in sub-Saharan Africa, particularly Nigeria and the Democratic Republic of Congo.[1–3]

There is a marked divide between care for individuals with SCD in high-income countries (HICs) versus LMICs. The care of individuals with SCD has improved substantially in HICs, where over 90% of children with SCD now survive into adulthood.[4] Interventions that have contributed favourably to improvements in outcomes include newborn haemoglobinopathy screening, transcranial Doppler (TCD) ultrasound, penicillin prophylaxis, immunization programs, access to a safe and sufficient blood supply and hydroxyurea therapy.[4] By contrast, LMICs lag far behind. Indeed, 50%–90% of children with SCD in LMICs die before their fifth birthday.[2,5]

TREATMENT OPTIONS FOR SCD

Historically, treatment options globally for SCD were limited to red cell transfusion and hydroxyurea. While this is notably still the case in LMICs,[3,6] recognition of the growing burden of SCD in HICs has spurred some—albeit modest—investment in disease-modifying therapies. Three agents—voxelotor (a HbS polymerization inhibitor), L-glutamine (an amino acid) and crizanlizumab (a P-selectin inhibitor)—were developed and approved for use in the United States and other HICs given their effects on the mitigation of haemolysis and vaso-occlusive crises.[7,8] However, crizanlizumab's market authorization has subsequently been revoked in multiple regions (e.g. in Europe and Brazil) due to lack of efficacy,[9] and voxelotor has been voluntarily removed from the global market and all clinical trials discontinued by the manufacturer due to safety concerns.[10]

While these newer agents have generally been underwhelming in regard to improved outcomes, hydroxyurea therapy has emerged as a cornerstone in the management of SCD. Hydroxyurea is an antimetabolite that selectively inhibits ribonucleoside diphosphate reductase, offering clinical benefits by reducing the frequency of vaso-occlusive crises, ACS and the need for blood transfusions.[11–16] The therapeutic effects of hydroxyurea are primarily attributed to its ability to increase fetal haemoglobin (HbF) levels, which reduces haemoglobin polymerization and subsequent erythrocyte sickling under deoxygenated conditions.[16,17] In addition to HbF induction, hydroxyurea decreases leucocyte, reticulocyte and platelet counts and reduces their surface expression of adhesion receptors, thereby attenuating inflammation and vascular adhesion, which are critical contributors to the pathophysiology of SCD.[18,19] Long-term studies have demonstrated its efficacy and safety in both paediatric and adult populations.[11,20] However, the overall use of hydroxyurea varies widely (yet remains low) as compared to HICs.[21] Some countries have expanded use through subsidized healthcare programmes and partnerships with global health organizations.[22] For instance, the Novartis Africa SCD programme was implemented to overcome barriers in SCD care and ensure access to therapies.[22] Further efforts to increase its adoption in LMICs require coordinated interventions, including local production, integration of SCD care into primary healthcare systems and public health campaigns to increase awareness.

While there is a paucity of disease-modifying agents available, there are potentially curative treatments for patients with SCD, including haematopoietic stem cell transplantation (HSCT) and gene editing therapies.[23,24] The American Society of Hematology (ASH) recommends human leukocyte antigen-matched related HSCT for those patients with SCD who have abnormal TCD ultrasound findings or a history of stroke. Nonetheless, this remains a conditional

recommendation (i.e. it relies on individualized decision-making).[25] Additional indications for HSCT include recurrent pain that is refractory to standard of care and recurrent episodes of ACS. The difficulty in identifying compatible blood for patients who have developed multiple antibodies is another consideration in the decision to proceed with transplantation. For those patients who do not have a matched sibling donor, ASH *suggests* considering alternative methods of transplant (unrelated HSCT and haploidentical related donors).[25]

Two autologous cell-based gene therapies were approved by the US FDA in December 2023 as another potentially curative option for patients with SCD.[23] One utilizes CRISPR/Cas9 to target *BCL11A*, which—under normal circumstances—functions to repress transcription of the γ-globin gene; disruption of *BCL11A* results in an increased production of HbF.[26] The other approved therapy uses a viral vector to insert a modified β-globin gene variant into cells. Despite the promise of a cure, access to these therapies is limited even in HICs. Given the high cost (minimum of $2 million USD per treatment),[27,28] coupled with the infrastructure required to implement these therapies (e.g. the ability to perform autologous haematopoietic stem cell collection and ex vivo modification), it is highly unlikely that these therapies will become available in LMICs in the near future. Moreover, myeloablative conditioning is required irrespective of the type of curative therapy, necessitating, in addition to fertility preservation and late effects follow-up care, blood transfusion support, the capacity for which may be limited in LMICs.

BLOOD TRANSFUSION FOR PATIENTS WITH SCD

Blood transfusion remains both a major treatment—as well as a commonly employed preventive strategy—for complications of SCD. Almost nine in 10 adults with SCD in LMICs receive an RBC transfusion in their lifetime.[29] In LMICs, the primary driver for blood utilization in patients with SCD occurs in the emergency setting, as many patients are severely anaemic upon arrival at the hospital. Complications such as malaria-associated anaemia, acute splenic sequestration, ACS, sepsis, acute stroke and multiorgan failure are major indications for emergent blood transfusion. The scarcity of blood contributes to an increase in the mortality rate in these patients during their hospitalization.[30]

Chronic transfusion therapy is also employed and may be administered as simple transfusion (infusing blood without removing or exchanging the patient's own blood), partial manual exchange transfusion (phlebotomy is undertaken immediately prior to simple transfusion) or automated exchange transfusion (concomitant removal of a patient's blood and infusion of donor blood via apheresis technology).

Chronic transfusion therapy has been shown to benefit patients with SCD, particularly those individuals with a history of stroke. Prophylactic transfusion therapy may also confer benefits to pregnant patients with SCD.[31–33] In the Stroke Prevention Trial in Sickle Cell Anaemia (STOP trial), children with SCD and elevated TCD velocities who received prophylactic transfusion therapy had a 92% lower risk of stroke than those children who received standard of care.[34] In the STOP II trial, the incidence of high-risk TCD findings or overt stroke was significantly greater in those children whose TCDs had normalized after 30 months of transfusion therapy and subsequently stopped transfusions compared to those who continued chronic transfusion therapy.[35] Additional studies have assessed whether children with a history of stroke or abnormal TCDs can be transitioned from chronic transfusion therapy to hydroxyurea after a particular amount of time; the findings have demonstrated that hydroxyurea may not be inferior to chronic blood transfusion in certain patients.[36,37] Thus, this may be cost-effective, reducing the transfusion burden.[38] Nevertheless, transfusion remains the standard of care for acute neurological events and ACS.

The ASH recommends automated red cell exchange (RCE) for stroke and severe ACS in SCD.[39] Automated RCE reduces the HbS level more rapidly, and in a more predictable manner, as compared to simple transfusion. Automated RCE is also euvolemic: with modern instrumentation, the patient's RBCs are removed, and donor RBCs are returned in a continuous manner, thus minimizing the risk of fluid overload (patients with SCD are at risk of renal impairment and cardiorespiratory failure).[40,41] Furthermore, iron accumulation and hyperviscosity can be controlled through the adjustment of target parameters. Nonetheless, automated RCE remains the exception in LMICs. Barriers to its wider adoption include the need for specialized equipment, skilled personnel (i.e. with specialized training in apheresis), adequate vascular access (potentially necessitating central venous access) and a requirement for a greater number of RBCs as compared to other RBC transfusion modalities (e.g. 4–10 units of RBCs for RCE as compared to 1–3 units for an adult undergoing simple transfusion).[42] As such, the British Society of Haematology recommends that all hospitals that treat patients with SCD should have the capability to perform manual exchange, asserting that this may be life-saving in emergent situations.[43] However, automated RCE remains the preferred approach.[43] Manual exchange is enormously labour intensive, inefficient and—arguably—not amenable to high throughput treatment of large numbers of patients with SCD. Furthermore, acceptance of suboptimal practices impedes progress towards the standard of care.[44]

CHALLENGES TO BLOOD TRANSFUSION SUPPORT FOR PATIENTS WITH SCD IN LMICS

Despite recognition of the importance of blood transfusion therapy in SCD, there are a myriad of challenges that impact blood transfusion safety and availability in LMICs.[45–48]

These have impeded efforts to treat patients with SCD effectively. The first challenge is the availability of blood for patients with SCD when it is needed. Most LMICs, including those where SCD is prevalent (i.e. parts of Africa and India) do not have sufficient blood to meet the needs of the population.[46,47,49,50] Furthermore, in many regions, the amount of blood that is needed to support individual populations has yet to be quantified, hindering efforts to optimize the blood supply.[51]

Even when blood is available, all of the risks of blood transfusion are accentuated in a low-resource setting, irrespective of the mode (i.e. simple vs. automated) of administration. For one, the transfusion-associated infectious risk in many LMICs is considered to be high. This stems from a host of associated challenges spanning high background prevalence for the major transfusion transmissible infections (TTIs), suboptimal blood donor selection (specifically, collection of blood from first time, family replacement and paid donors), testing (variable use of quality-controlled assays, lack of standardized algorithms with inconsistent use of repeat and confirmatory testing) and largely absent post-transfusion surveillance.[44,52–54] Individuals with SCD are often chronically transfused, either prophylactically or for treatment of SCD-associated complications, conferring cumulative risk of TTIs.

Second, immunohematology is lacking in LMICs.[49,55] This is reflected by the limited capacity for RBC antigen phenotyping, antibody detection and antibody identification. In part, this stems from the need for specialty training (e.g. specialist in blood banking, medical laboratory scientist and related education), the costs and availability of evaluation (reagents, RBC panels), and storage capabilities for reagents, panels and blood products. While not unique to immunohaematology, there are systemic challenges in low-resource settings pertaining to the maintenance of supply chains, from procurement through distribution. Prophylactic matching strategies for blood transfusion, whereby the antigen profiles of allogeneic RBC units are "matched" to those of the recipient's profile, are rarely available in LMICs, despite evidence suggesting a reduction in alloimmunization.[55,56] Even if there were the infrastructure and human capacity to perform the testing and laboratory services, there are not sufficient blood, financial resources or operational capability to integrate partial or complete phenotypic matching into routine practice.

Alloimmunization to RBC antigens is a formidable challenge, even in HICs, as it reduces the pool of compatible donors to support a given patient. In HICs, access to RBC reagents (e.g. antisera, test cells, enzymes, etc.) and rare donor registries, in conjunction with high-throughput phenotyping and genotyping of donors, enables the identification of suitable donor units. Furthermore, there is ease of blood distribution across large geographic areas, such that sample and blood product shipping, even across state/provincial/country borders, is undertaken routinely. These capabilities are not available in most LMICs. To some extent, greater homogeneity in the blood group antigen frequencies between the blood donor and recipient populations in many African countries may offset the risks and consequences of RBC alloimmunization.[56] However, mutations in the genes that encode for RBC antigens are relatively frequent in patients with SCD, contributing to challenges in finding compatible donors, even when RBC transfusions are phenotypically matched (i.e. using serological typing). A mitigation strategy, whereby both donors and recipients are genotyped, is infrequently performed in HICs and is not undertaken in LMICs due to technological, operational, and financial barriers.[57] Moreover, there are additional risks for alloimmunization due to transfusion practices in LMICs, such as the absence of leucoreduction and transfusions that occur predominantly for acute circumstances or in patients with underlying inflammatory states.[58] While leucoreduction decreases human leucocyte antigen alloimmunization (and potentially decreases RBC alloimmunization) by removing donor white blood cells,[59,60] it is a high-cost intervention and has not been widely implemented in LMICs. Even in HICs (such as those in Europe and North America) where advanced methods are in place to reduce RBC alloimmunization, high rates of alloimmunization continue to occur due to the pervasive antigen mismatch between the blood donor pool (which is largely composed of individuals of European descent) and individuals with SCD, who tend to be of African descent.[61] However, it is possible that studies, which suggest a comparatively lower incidence of alloimmunization in LMICs, do not take into account the patient's antibody and/or transfusion history, which are typically unknown in a low-resource setting. Moreover, antibody screening and identification are the exceptions in LMICs.[55] Therefore, given the evanescence of RBC antibodies, the incidence of alloimmunization is likely underestimated in LMICs.

There are further challenges that have not been considered in the context of immunohaematology. A third of patients with SCD who are transfused with blood from African donors may develop alloantibodies to antigens that are not included on a standard RBC test panel.[62] Even if routine immunohematology testing capabilities (e.g. antibody screening using a standard two- or three-cell panel, antibody identification using a standard 11- or 14-cell panel, etc.) were to be implemented, the lack of access to reagent RBCs that express low-prevalence or lack high-prevalence antigens that are important in the African population, and specialized testing to resolve antibody identification (e.g. the use of enzymes/lectins, adsorption/elution techniques, molecular analysis) would still fail to identify a substantial proportion of individuals with alloantibodies. A high incidence of alloimmunization in patients with SCD, coupled with limited laboratory capacity to identify these antibodies, confers a risk of delayed haemolytic transfusion reactions and hyperhaemolysis.[63] The latter is characterized by 'bystander haemolysis' of the patient's own RBCs and can result in profound anaemia, cardiovascular collapse and death.[64] As haemovigilance systems are limited or absent in LMICs,

it is difficult to determine the impact of these antibodies on patients and the frequency of post-transfusion haemolysis, as the patients' symptoms are likely to be attributed to SCD itself.

By extension, the lack of quality oversight and measures to ensure safe transfusion (e.g. prevention of haemolytic transfusion reactions due to ABO incompatibility) poses a substantial risk. Major acute haemolytic transfusion reactions due to ABO incompatibility are considered sentinel events in HICs. Indeed, all processes are designed specifically to mitigate this risk. Examples include a requirement for dual specimen collection for determination of the patient's ABO type, intolerance of clerical discrepancies pertaining to patient and specimen identification, barcode scanning using an electronic medical record, redundant checks on specimen testing and patient identification, through to electronic safeguards against mistransfusion.[65] By contrast, many LMICs do not have systems in place to prevent adverse outcomes, and a lack of post-transfusion surveillance and the ability to capture and track data precludes identification of, and appropriate treatment for, transfusion-associated adverse events.[66,67]

STRATEGIES TO IMPROVE BLOOD TRANSFUSION FOR PATIENTS WITH SCD IN LMICS

Transfusion management of patients with SCD in LMICs is subsumed by broader considerations surrounding global blood transfusion safety and sufficiency.[46,47] Despite ongoing challenges, there are examples where progress in blood transfusion is occurring. These include projects and health programs aimed at improving the safety of blood products through quality assurance and regulatory initiatives,[68] haemovigilance/post-transfusion surveillance programmes[69] and the development of formal education in haematology and transfusion medicine, particularly focusing on immunohaematology.[70,71]

To improve the care of patients with SCD, increasing the capacity of blood banking and laboratory medicine must be prioritized. Specific areas of need span the quality system of laboratory practice and the procurement of reagents and equipment (e.g. analysers) for pre-transfusion testing, to health management information systems that enable documentation and tracking of patients with alloantibodies or a history of transfusion reactions. There are few examples of success in this domain. Leveraging partnerships with societies such as ASH, the International Society of Blood Transfusion, the Association for the Advancement of Blood and Biotherapies, the Asian Association of Transfusion Medicine and the Africa Society for Blood Transfusion could be instrumental in developing and reforming immunohaematology capabilities and transfusion support for patients with SCD.[72] This could include individual grants for dedicated technical training, as well as virtual education for staff.

Additional policy initiatives to strengthen health systems (e.g. through collaboration with the World Health Organization and the Africa Centres for Disease Control and Prevention) would also advance transfusion services in LMICs. For example, the establishment of SCD Centres of Excellence that have the capability to perform reference testing (e.g. serological and molecular immunohematology) may assist in facilitating country-wide programmes. Alternatively, integrating SCD care into settings that provide services for patients with other conditions could increase access to regular blood transfusion therapy. For example, in Angola, an SCD programme was established at a maternal and child health hospital, thus facilitating access to SCD treatment for this patient population.[73]

Furthermore, investment in donor recruitment, particularly retention of a stable, diverse voluntary donor pool, could improve the availability of units that have a similar antigen composition to that of the intended recipient population. Establishing local donor outreach programmes that incorporate a welcoming atmosphere could be effective in developing a repeat, volunteer donor pool. This was exemplified by a programme at the Kumasi Teaching Hospital Blood Centre in Ghana where the hospital partnered with a local radio station to encourage individuals to donate three times annually using music, entertainment and token gifts as incentives.[74,75] A total of 3801 individuals participated, of whom over 90% were eligible to donate.[74] Likewise, education is critical to donor recruitment; there is often a lack of knowledge regarding the importance of blood donation, community understanding of when it is not safe to donate blood (e.g. if the individual is in poor health or at risk of transmitting TTIs), and how to contend with stigma regarding attitudes and beliefs about blood donation and transfusion.[75] Educational materials such as pamphlets, posters and videos may be employed effectively in this regard.[76] Finally, robust infectious screening, both of donors as well as recipients, is imperative. In one such programme, the National Heart, Lung, and Blood Institute has approved funding for a research initiative termed 'BLOODSAFE', which aims to support projects that improve access, safety and sufficiency of the blood supply in low-resource settings.[71]

CONCLUSION

Cure remains the overarching goal for SCD, irrespective of geographic location or socioeconomic status. Blood transfusion is a major treatment for SCD; it is also integral to curative therapies given the need for transfusion support during periods of myelosuppression. Disparity in transfusion access and safety between HICs and LMICs merits attention if SCD is to be tackled effectively.

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JWJ and EMB performed the research and drafted the manuscript. LA, FP, CT, IA, LHP, AART, JC, JM, MTG, MD, DJT

and IO critically revised the manuscript. EMB provided supervision. All authors approved the final version.

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DATA AVAILABILITY STATEMENT

All data are presented in the manuscript.

DISCLAIMERS

EMB is a member of the U.S. Food and Drug Administration (FDA) Blood Products Advisory Committee. Any views or opinions expressed in this manuscript are his and are based on his own scientific expertise and professional judgment; they do not necessarily represent the views of the Blood Products Advisory Committee or the formal position of the FDA and do not bind or otherwise obligate or commit either the Advisory Committee or the FDA to the views expressed.

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