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Sickle cell anemia in sub-Saharan Africa: advancing the clinical paradigm through partnerships and research

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Introduction

Sickle cell anemia (SCA) carries orphan disease designation in the United States, with ~2000 affected infants born annually and fewer than 100 000 persons living with this condition.[1] Patients with SCA have numerous acute and chronic medical problems, which collectively contribute to life-threatening morbidity, early mortality, and annual domestic medical costs exceeding $1.1 billion.[2-6] Worldwide, >300 000 infants are born with SCA each year,[7] but <1% of sickle cell births occur in North America and the United Kingdom/Europe, where nearly all SCA research and health care dollars are spent. Millions of persons throughout the world are living with, and unfortunately dying from, this inherited blood disorder without the benefits of proper diagnosis and appropriate clinical care. Although the burden of SCA is truly global, with the highest incidence in Africa, India, the Caribbean, Central America, and South America, the focus of this editorial perspective is SCA within Africa.

More than 75% of the global burden of SCA occurs in sub-Saharan Africa,[8] where scarce health resources and inadequate awareness among health care providers and the general public contribute to shocking rates of early mortality. With few data from neonatal screening programs, and virtually no prospective natural history studies, true mortality rates are unknown, but an estimated 50% to 90% of infants born with SCA in sub-Saharan Africa die before their fifth birthday.[9,10] Without early diagnosis, which allows early preventive treatments including pneumococcal vaccination, penicillin prophylaxis, and parental education, most infants will die of acute complications, most notably bacterial sepsis or severe anemia. Regrettably, death attributed to SCA is missing completely from recent global summaries,[11] presumably because of a lack of accurate data, making SCA at best a neglected and, more accurately, an invisible killer of children.[12,13]

Over the past 40 years, beginning with the landmark US Cooperative Study of Sickle Cell Disease[14-16] and Jamaican Cohort Study,[17] substantial evidence has accumulated from well-designed prospective research trials. Together, these studies document the life-threatening severity of untreated SCA, but demonstrate unquestionable benefits of penicillin prophylaxis, pneumococcal vaccinations, transcranial Doppler (TCD) screening for primary stroke prevention, safe transfusions for acute and chronic complications, and hydroxyurea as a safe and potent disease-modifying therapy. Unfortunately, the status of SCA in Africa remains stagnant, with most affected persons lacking access to basic diagnostics and clinical care. As SCA finally begins to be addressed in Africa, we must ask whether proven evidence from well-resourced countries is directly transferable, or must additional studies be replicated and verified in the African setting? Are new National Heart, Lung, and Blood Institute (NHLBI) evidence-based guidelines for SCA[18] feasible or even appropriate for limited-resource settings? How do we augment these guidelines to be clinically and economically feasible, while remaining effective across sub-Saharan Africa?

Acknowledging the unjustifiable disparity in clinical care and outcomes between well-resourced and limited-resource settings for persons with SCA, some institutions that lead and fund sickle cell care and research have begun to take action. Both the NHLBI and American Society of Hematology (ASH) are committing financial and programmatic efforts to address the global burden of SCA in limited-resource settings, particularly in sub-Saharan Africa.[19-21] We must think carefully about what is needed to improve outcomes, and how these needs can be met safely and effectively within the clinical and financial contexts of limited-resource settings. Although the HbS mutation is the same worldwide, the environment, infectious exposures, and general health care infrastructure faced by persons living with SCA in Africa are quite different from those in well-resourced settings. With our admittedly Western bias, we suggest that plans to shift our clinical care and treatment paradigms automatically to Africa are neither logical nor likely to succeed. Instead, we advocate for the formation of multidisciplinary partnerships and research collaborations with a shared vision and mutual benefits, with short-term goals of obtaining high-quality data while emphasizing local capacity building and health system strengthening, and long-term goals of helping to develop national (and global) strategies for SCA that are impactful and sustainable. Herein, we offer our subjective summary of opportunities by which sickle cell capacity and outcomes can be improved, based upon our own experiences with African partnerships and research collaborations. Each high burden country should carefully assess its own needs to develop national sickle cell strategies that are in line with their own resources, and offer a plan for sustainability.

Improving diagnostics

When faced with unsettling mortality statistics for children with SCA in Africa, it is natural to think about improving the availability and reducing the costs of disease-modifying therapies such as hydroxyurea, blood transfusions, and even stem cell transplantation. Although these are important considerations, with some potentially feasible, the reality

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is that most deaths from SCA in Africa occur before the diagnosis is ever made. Children die of pneumonia, bacterial sepsis, and acute anemia without anyone knowing that SCA was the critical underlying diagnosis. It is impossible to properly treat children whose true underlying disease remains unknown, until technological capacities allow early and accurate diagnosis.

Currently, the diagnostic capacity for SCA in Africa is severely limited. In many African settings, the sickle solubility test (Sickledex) is the only available technique, but this test cannot distinguish sickle cell disease (HbSS or HbSC) from sickle cell trait (HbAS), which affects 10% to 25% of African populations.[22] Positive solubility tests can be misinterpreted, which exacerbates confusion and limits awareness and understanding of SCA. Definitive hemoglobin-based diagnostic techniques, including isoelectric focusing (IEF), high-performance liquid chromatography (HPLC), or capillary zone electrophoresis (CZE) are sometimes available, usually at costly private clinics or large central hospitals. These methodologies, although reliable, require substantial investment in expensive equipment, plus ongoing costs to maintain an adequate reagent supply, plus training and support for local laboratory expertise. Initial investments fail when financial support and technical expertise are not maintained for the inevitable repairs of expensive equipment.[23] Based on our experience in numerous countries across sub-Saharan Africa, IEF is suitable for large-scale screening, but expensive diagnostic equipment frequently malfunctions and reagents run dry; without local capacity for training and repairs, the value of such unsustained investments is questionable.

To improve awareness of the global importance of SCA, methods for simple and accurate diagnosis are sorely needed. IEF is robust and time-honored, but requires technical training and time to batch samples before results are available, whereas HPLC and CZE are expensive (Table 1). Fortunately, development has begun for inexpensive, rapid, and accurate point-of-care (POC) diagnostic devices. The NHLBI Small Business Innovation Research grant program[24] has stimulated development of POC diagnostics for SCA, and several devices have encouraging preliminary results.[25-29] Beyond reported successes and accuracy in controlled laboratory settings, these preliminary findings must be validated in "real world" African settings, to confirm that the devices produce reliable results in the hands of those who will use them. Such efforts are ongoing through partnered research, and we predict that within 3 years, several accurate POC devices will be validated and ready for widespread use across sub-Saharan Africa.

With rapid and affordable diagnostics imminently available, critical questions will then be whom, when, and how to screen? In North America and Europe, the concept of screening typically refers to newborn screening, either targeted or universal. In Africa, where many infants are not born in hospital or spend only hours in overcrowded and under-staffed maternity wards, traditional screening before leaving the birth hospital will not always be practical. But with childhood vaccination rates improving across Africa and a "grace period" of several months before clinical complications of SCA develop, testing early in life at the time of immunizations offers a more practical and efficient screening option.

Early diagnosis is necessary but not sufficient, and no single solution will be applicable for all African countries. The critical benefits obtained through early accurate diagnosis cannot be overstated, however, especially if results can be stored electronically and documented in the patient's medical record or vaccination card. Arguably, it is equally important to screen adolescents and young adults for HbAS, to allow informed reproductive decisions toward reducing the number of affected children. Because of the importance of diagnostics and their likelihood of transforming the SCA diagnostic landscape in Africa, international research and philanthropic communities must support these efforts and subsidize their cost. Successful models of communicable disease control and prevention for malaria and HIV, which feature substantial financial support by government, foundations, and industry, must now be expanded to include SCA, recognizing that each country's health care system is responsible for achieving the effective implementation and integration of these diagnostic approaches. For any diagnostic test, it is critical that screening be introduced carefully, and with specific regard for social and cultural norms; this will help avoid stigmatization, family unrest, or even paternity concerns as a result of incomplete understanding of the inheritance patterns. Screening results should always be confirmed with accurate diagnostic testing.

Implementing preventive care

Fever and infections

Children with SCA have a well-documented increased risk of invasive bacterial infections, particularly from encapsulated organisms like *Streptococcus pneumoniae* and *Haemophilus influenzae* type b.[30] Before routine use of penicillin prophylaxis, morbidity and mortality from invasive pneumococcal disease among US children with SCA was very high.[31,32] The prospective phase 3, placebo-controlled Prophylactic Penicillin Study (PROPS) demonstrated the benefits of penicillin in reducing the morbidity and mortality of pneumococcal infection for children under age 5 years.[33] The subsequent PROPS II study failed to demonstrate sustained benefits,[34] so current recommendations include penicillin prophylaxis through age 5. New NHLBI guidelines also encourage both protein-conjugated and polysaccharide pneumococcal vaccines as added protection for infants and toddlers.[18]

In Africa, the rarity of isolating *S pneumoniae* was not properly attributed to inadequate culture techniques, which led to inappropriate skepticism regarding the risks of fatal bacterial infections.[35] This issue was settled by a landmark case-control study from Kenya documenting remarkably elevated risks of bacteremia in children with SCA, including *S pneumoniae*, non-typhus *Salmonella*, and *H influenzae*.[36] By confirming that the etiologies of invasive bacterial infection are similar for children with SCA in Africa, this study provided the rationale for adopting both penicillin prophylaxis and pneumococcal immunization. We argue against further randomized clinical trials to justify protection against bacterial sepsis, but note that the optimal duration of penicillin and appropriate acute evaluation and management of fever remain undetermined (Table 1).

Malaria prevention and treatment

Although the HbS mutation protects against severe malaria in the heterozygous (HbAS) state, the risks of malaria for persons with SCA are not fully elucidated.[37,38] Currently, there is variable practice based on scant data regarding effective malaria prevention and treatment regimens for SCA patients living in malaria-endemic settings. Some programs recommend daily or intermittent oral chemoprophylaxis, whereas others opt for intermittent treatment regimens or insecticide-treated bed nets alone. Without data demonstrating the clear consequences of malaria for children with SCA, local providers should assess their local malaria burden, seasonal prevalence, and resistance patterns before determining if and when to provide malaria chemoprophylaxis. Determining the risks and optimizing management of malaria in sub-Saharan Africa are critically important areas that need further prospective research. A multinational clinical trial comparing available treatment strategies would help establish evidence-based

Table 1. Sickle cell guidelines and recommendations with relevance for sub-Saharan Africa

Topic	Goal	Age range	Applicable to Africa	Feasible for Africa	Need for more testing	Current trials
Screening	Diagnosis					
Electrophoresis by IEF, HPLC, CZE		Neonates, teens, young adults	Yes	Yes	No	No
Point-of-care testing		Neonates, teens, young adults	Yes	Yes	Yes	Yes
Education	Early recognition					
Splenic sequestration		<2 y	Yes	Yes	No	No
Fever management		All ages	Yes	Yes	No	No
Preventive care	Prophylaxis					
Antimalarials		All ages	Yes	Yes	Yes	Yes
Insecticide-treated bed nets		All Ages	Yes	Yes	No	No
Penicillin		<5 y	Yes	Yes	No	No
Vaccination		<5 y	Yes	Yes	No	No
Antibiotics for fever		All ages	Yes	Yes	No	No
Blood culture with fever		All ages	Yes	No	No	No
Screening	Early identification					
TCD ultrasound		2-16 y	Yes	Yes	Yes	Yes
Proteinuria		All ages	Yes	Yes	Yes	Yes
Cardiac function (TR Jet velocity)		Adults	Possibly	Possibly	Yes	No
Treatment	Therapeutic					
Transfusions		All ages	Yes	Yes	Yes	No
Hydroxyurea		All ages	Yes	Yes	Yes	Yes
Transplantation		All ages	No	No	No	No

guidelines and reduce the morbidity and mortality of severe malarial infection.[39]

Transcranial Doppler screening

Previous studies have documented a high stroke incidence in SCA, especially among children.[40,41] The emergence of TCD ultrasonography as a screening tool to identify patients at highest risk of stroke, coupled with prophylactic monthly blood transfusions, represents an important advance toward the NHLBI goal of a stroke-free generation.[42] The STOP trial demonstrated the efficacy of transfusions to reduce stroke in children with abnormal TCD velocities,[43] but the follow-on STOP 2 trial documented that transfusions were required indefinitely.[44] Despite the documented effectiveness of universal TCD screening programs,[45-47] these findings do not translate easily to sub-Saharan Africa, where blood transfusions are not readily available, safe, or affordable (Table 1).

The true stroke risk for SCA patients in Africa is unknown, because published data may be skewed as a result of early mortality from other complications. However, stroke rates and complications are documented from Nigeria, Benin, Cameroon, Uganda, and Tanzania.[48-52] TCD screening is realistic in sub-Saharan Africa for primary stroke screening,[53] but indefinite transfusion therapy for thousands of children is an insurmountable challenge. Hydroxyurea represents an alternative to transfusions for stroke prevention, but its safety and feasibility for sub-Saharan Africa are not yet established.

Other health maintenance

The grim prognosis for children with SCA in Africa forces us to focus on early diagnosis and prevention of early morbidity and mortality, but many adolescents and adults also live with SCA. These older patients suffer from complications such as leg ulcers and chronic renal, cardiac, and lung disease. Women with SCA face the significant challenges of pregnancy and its perinatal complications.[54-58] The NHLBI guidelines include recommendations for selected screening of renal, infectious, ophthalmologic, cardiac, and neurologic complications.[18] With limited resources, such routine screening may not be feasible or warranted in Africa at this time, because of the unknown prevalence and lack of clear management plans. However, a recent publication from the West African CADRE cohort documenting albuminuria in children with SCA supports early screening for renal disease.[59] Although chronic complications and management of adults should not be ignored, priority should be placed on basic diagnostic and treatment capacities.

Choosing treatment options

The availability of accurate diagnostics plus increased infection prophylaxis will undoubtedly decrease the early mortality associated with SCA, but will not reduce overall morbidity. Vaso-occlusive crises, including life-threatening complications like acute chest syndrome and stroke, cause pain and suffering, and portend chronic damage to nearly every organ system. Recreating natural history studies of SCA in Africa in the absence of disease-modifying therapy is unnecessary and unethical, and we believe therapeutic interventions must be included in all plans to address the sickle cell burden. Three treatments used in well-resourced countries are potentially available to prevent or reduce the morbidity and mortality of SCA: transfusions, hydroxyurea, and stem cell transplantation (Table 1).

Transfusions

Some acute complications of SCA, including splenic sequestration and aplastic crisis, require immediate blood transfusion as life-saving therapy. Other complications like stroke and acute chest syndrome benefit from chronic transfusions to prevent recurrent events. Unfortunately, blood transfusions in Africa represent an enormous medical and public health challenge for many reasons and clear,

Table 2. Therapeutic options for SCA with potential relevance for sub-Saharan Africa

Treatment	Advantages and indications	Disadvantages and challenges
Erythrocyte transfusions	• Treatment of severe anemia due to splenic sequestration, parvovirus infection, or malaria	• Lack of sufficient blood donors
	• Additional oxygen-carrying capacity for life-threatening acute vaso-occlusion and organ damage	• Infection transmission (HIV, hepatitis B and C, syphilis)
	• Effective treatment option for stroke and other neurologic complications	• Erythrocyte alloimmunization
		• Inability to prepare blood components
		• Eventual need for iron chelation
Hydroxyurea	• Reduction of acute vaso-occlusive complications (pain, acute chest syndrome)	• Limited drug availability
	• Oral administration	• High cost relative to daily wages
	• Once-daily dosing	• Optimal dosing not yet determined
	• Documented laboratory and clinical efficacy and efficacy	• Cost and feasibility of routine laboratory monitoring, including WBC differential and reticulocytes
	• Low cost compared with alternatives	• Inability to measure quantitative %HbF
Stem cell transplantation	• Potential cure	• Lack of facilities and clinical expertise
	• Availability of full siblings, which increases the chance of HLA matching	• Limited technology for HLA typing, cell processing, and preparation
		• Inadequate supportive care (antibiotics, transfusions, isolation rooms)
		• High risk of morbidity (graft versus host disease) and mortality
		• Extremely high cost

HLA, human leukocyte antigen; WBC, white blood cell.

country-specific data of blood safety are limited (Table 2).[60] First, a high incidence of hepatitis B and C, as well as HIV, exists in the general population and the blood supply,[61,62] and not all donors are fully screened for blood-borne viral infections. In countries without voluntary blood donation, replacement or paid donors are not always properly screened, which results in an increased number of transfusion-transmitted infections.[62] Further, the donation rate and blood supply in Africa are insufficient to meet the demand. The World Health Organization (WHO) estimates only 20% to 50% of transfusion requirements are met by current donation rates across Africa.[63] In many settings, individual blood components are unavailable and transfusions use whole blood, raising additional safety concerns regarding transfusion volume and reactions.

Despite a more homogenous genetic background, erythrocyte alloimmunization can still develop and pose serious challenges to safe and effective transfusions.[64,65] Even if chronic transfusions were feasible in Africa, patients would inevitably develop iron overload and face unaffordable costs of iron chelation. The need to improve safety and access of the blood supply in Africa is unquestionable, but represents a significant global health problem extending beyond SCA. Currently we believe chronic transfusion is not a practical long-term option for management of SCA in sub-Saharan Africa.

Hydroxyurea

With more than 30 years of published evidence, hydroxyurea has emerged as the primary disease-modifying therapy for both adults and children with SCA. The phase 3 placebo-controlled Multicenter Study of Hydroxyurea and BABY HUG trials demonstrated hydroxyurea has many salutary laboratory and clinical benefits across the lifespan of patients, from asymptomatic infants to severely affected adults.[66,67] Several publications even document prolonged survival with hydroxyurea therapy.[68-71] Clinical indications for hydroxyurea therapy are expanding as providers and patients gain experience, and NHLBI guidelines offer recommendations for treatment of all ages.[18]

Unfortunately, hydroxyurea remains largely unknown and unavailable throughout sub-Saharan Africa to both providers and patients, and is available in few pharmacies and hospitals, but with prohibitive costs. Limited experience exists with hydroxyurea in the setting of malnutrition with unique environmental and infectious exposures, and assumptions about dosing and toxicities based on published data are not necessarily valid. Before hydroxyurea is offered widely in Africa, it is essential to demonstrate that treatment is safe and feasible, and to establish locally appropriate dosing and monitoring guidelines. One important question is whether fixed low-dose therapy (10-20 mg/kg per day) is more practical than escalation to maximum tolerated dose (20-30 mg/kg per day), because medication optimization requires frequent monitoring, dose adjustments, and clinical expertise.[72,73]

Small retrospective studies suggest hydroxyurea will have beneficial effects on both primary and secondary stroke prevention in Africa,[74,75] similar to earlier findings from Jamaica.[76] Prospective research regarding hydroxyurea therapy is now underway in Africa, and Table 3 highlights currently registered clinical trials. When the feasibility, dosing, and safety of hydroxyurea treatment are known, practical dosing and monitoring guidelines can be established. Finally, it is critical to increase availability of hydroxyurea by reducing its cost, so all patients have access. The current cost (typically $0.50-2.00 USD per 500-mg capsule) is prohibitive as a lifelong medication for families earning less than $2 per day. Because hydroxyurea is on the WHO Model List of Essential Medicines for Children with a specific indication for SCA,[77] we recommend that treatment be subsidized to allow universal access to hydroxyurea, similar to the model in African countries for treatment of HIV, malaria, and tuberculosis.

Transplantation

As the only currently available curative therapy, stem cell transplantation is an enticing option and frequent topic of discussion among African patients and providers. A widely publicized successful transplant in Nigeria has led to increasing interest about its wider applicability to sub-Saharan Africa.[78,79] However, the risks and benefits of transplantation extend beyond individual patients, because high costs and resources required for this procedure would almost surely divert funding from highly effective and inexpensive

Table 3. Current prospective research trials using hydroxyurea therapy for SCA in sub-Saharan Africa

Clinical trial	ClinicalTrials.gov and status	Performance sites	No. of participants	Study end points
Sickle Cell Disease–Stroke Prevention in Nigeria Trial (SPIN)	NCT01801423 Active, not recruiting	Kano, Nigeria	40	TCD velocity
Realizing Effectiveness of Hydroxyurea Across Continents (REACH)	NCT01966731 Recruiting	Luanda, Angola; Kinshasa, DRC; Kilifi, Kenya; Mbale Uganda	600	Adherence, toxicity, dosing
Novel use Of Hydroxyurea in an African Region with Malaria (NOHARM)	NCT01976416 Active, not recruiting	Kampala, Uganda	200	Malaria events
Risk Clinical Stratification of Sickle Cell Disease in Nigeria: Assessment of Efficacy/ Safety of Hydroxyurea Treatment	NCT02149537 Enrolling by invitation	Ibadan, Nigeria	40	Cytopenia
Primary Prevention of Stroke in Children With SCD in Sub-Saharan Africa II (SPRING)	NCT02560935 Recruiting	Kano, Nigeria	440	Stroke occurrence
Low Dose Hydroxyurea for Secondary Stroke Prevention in Children With Sickle Cell Disease in Sub-Saharan Africa (SPRINT)	NCT02675790 Not yet recruiting	Kano, Nigeria	60	Stroke recurrence

The ClinicalTrials.gov Web site was last accessed September 29, 2016.

interventions like neonatal screening, penicillin, transfusions, and hydroxyurea. We believe that transplantation and other potentially curative therapies are currently impractical solutions for SCA in most African settings. With improved health care infrastructure and additional therapies, treatments for SCA in Africa may eventually expand to include transplantation and other novel agents currently in development.

Moving forward, together

When acknowledging the enormous global burden of disease from SCA, it is tempting to recommend that strategies working in well-resourced countries be quickly transferred to low-resource settings. Such an attitude is presumptuous and fallacious, however, and we posit that such recommendations need to be reconsidered. Multidisciplinary partnerships involving not only academia and government, but also the private sector and civil society, can facilitate critical and integrated research, build local capacity, and contribute to national health care strategies. Research questions must be developed in the context of local settings, with input and guidance from local investigators and from community stakeholders and leaders as well.

Our experiences in sub-Saharan Africa suggest that partnerships should be inclusive and based on mutual agreement and benefit, and must rely on the trust and good will of the collaborating parties to enable transparency, dialogue, creativity, flexibility, and respect to establish a truly balanced partnership. We have participated in several successful prospective sickle cell research and capacity-building programs using this philosophy: a newborn screening program in Angola through formal agreements among government, academia, and industry[80]; a large surveillance study in Uganda between academia and the Ministry of Health[81]; and prospective clinical trials with hydroxyurea generously donated by pharmaceutical industries.[82,83] Through these partnerships, we recognized the striking lack of sickle cell education and clinical training in most African countries for doctors, nurses, and other frontline health care providers. Training is a critical need and should be a tangible addition to all international partnerships, to improve local awareness and knowledge about the diagnosis and treatment of SCA.

ASH deserves approbation for making public commitments to SCA, not only to assist with training and education, but also to forge strategies for advancing clinical care.[20,21] The newly developed ASH Newborn Screening and Early Intervention in Africa Initiative proposes a prospective registry for newborn screening and early intervention across Africa. This program could provide critical prospective data regarding the feasibility and benefits of early screening, but will require partnerships to be successful. Based on our own experiences, we offer practical recommendations about the best approaches to SCA partnerships and research opportunities in sub-Saharan Africa (Table 4).

There are no easy solutions to the crushing global burden of SCA. But with increased public, governmental, and philanthropic awareness of noncommunicable diseases, coupled with an overdue intellectual and financial pivot from communicable diseases, SCA can emerge from its current neglected state.[12,13] We suggest prioritization of partnerships to create visible collaborations that feature local capacity building, with emphasis on prospective ethical research. We predict that successful partnerships will improve the diagnostic and therapeutic landscape, and ultimately lead to improved survival and quality of life for persons with SCA in Africa and around the world.

Table 4. Recommended approaches to partnerships and research opportunities in sub-Saharan Africa

1. Involve local leaders as collaborators, especially from academia and government.
2. Create partnerships that emphasize training and local capacity building.
3. Conduct prospective research to ensure results are evidence-based.
4. Follow rigorous ethical and research standards, to protect the rights of potentially vulnerable study participants.
5. Train and use local personnel whenever possible, increasing in-country expertise and limiting exportation of samples and data.

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