Sickle Cell Anemia: An Underappreciated and Unaddressed Contributor to Global Childhood Mortality

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Sickle cell disease refers to a heterogeneous group of inherited blood disorders characterized by the predominance of sickle hemoglobin (HbS). The most severe form of sickle cell disease, commonly referred to as sickle cell anemia (SCA), is usually the result of dual inheritance of the HbS allele from both parents (ie, homozygous hemoglobin SS [HbSS] disease) or, less often, as a result of the compound heterozygosity for HbS and β-thalassemia (ie, HbS/β^0 thalassemia). SCA is one of the most common monogenetic diseases in the world, with recent estimates suggesting that more than 312 000 infants are born with HbSS each year.[1] In the US and Europe, early diagnosis by newborn screening (NBS) and comprehensive preventative care has dramatically reduced the early mortality associated with SCA, with published reports from the US and Europe demonstrating that greater than 95% of children screened and enrolled in comprehensive care programs will survive to adulthood.[2,3] Although these published reports are likely overestimates of survival within optimized care programs, the fact remains that death during early childhood from SCA has become a rare event in the developed world. However, these improved mortality rates for children with SCA are most applicable for infants born in the US and Europe, which together represent only 2% of annual SCA births worldwide.

The vast majority of sickle cell births occur in the developing world, with an estimated 230 000 annual HbSS births in sub-Saharan Africa.[1] Without widely available NBS or early access to comprehensive preventative care, the early mortality of SCA in Africa is strikingly high. Although there are no definitive mortality data, various published reports estimate mortality rates between 50% and 90% before the age of 5 years.[4-6] Unfortunately, there is no simple curative treatment to prevent the manifestations of SCA as there is for other screened disorders (eg, congenital hypothyroidism, phenylketonuria), but there are simple and relatively inexpensive interventions that can decrease the risk of acute and life-threatening early complications. SCA affects up to 1%-2% of all births in many sub-Saharan African countries and without early diagnosis and access to care, SCA is likely to contribute significantly to national mortality rates of children younger than 5 years of age, with estimates suggesting that SCA may contribute to 6.4% of all mortalities in children younger than 5 years of age on the African continent.[7] With global efforts focused on the reduction of child mortality from other causes (eg, HIV, tuberculosis), the relative contribution of SCA to global childhood mortality is only going to increase without appropriate intervention. The time for this intervention is now.

Early Mortality and SCA

The presence of high levels of fetal hemoglobin (HbF) in infants with SCA provides relative protection against the development of clinical manifestations of SCA until HbF decreases to levels that do not inhibit sickling or ameliorate clinical symptoms. The decrease in HbF is highly variable, but most infants will lose the protective levels of HbF starting at 4-6 months and most certainly by 2 years of age.[8,9] It is critical that the diagnosis of SCA is made before HbF levels decrease, because the risk of acute and life-threatening complications becomes markedly increased once HbS predominates.

Although many infants will present with symptoms suggesting a diagnosis of SCA (eg, dactylitis), it is not uncommon for a child to die of acute complications before a diagnosis is even made. Early mortality from SCA within the first 5 years is most commonly the result of either acute bacterial infection (most commonly sepsis from *Streptococcus pneumoniae*) or acute anemia from malaria or acute splenic sequestration crisis (ASSC).[4,6,10-16] A recent retrospective analysis of bacteremia among African children demonstrated that patients with invasive pneumococcal infection were 36 times more likely to have sickle cell disease than healthy control patients.[17] Although the sickle cell carrier state confers relative protection against malaria, the baseline anemia among children with SCA results in a very high risk of mortality with coexisting malarial infection.[13,16] These are just a couple of examples indicating that early diagnosis of SCA and associated early recognition and management of acute complications is critical.

Early Mortality Can Be Prevented

Routine NBS for SCA is now performed in all 50 US states. In Europe, NBS for hemoglobinopathies is variable, with few

ASSC	Acute splenic sequestration crisis
HbF	Fetal hemoglobin
HbS	Sickle hemoglobin
HbSS	Hemoglobin SS
NBS	Newborn screening
SCA	Sickle cell anemia

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The author declares no conflicts of interest.

http://dx.doi.org/10.1016/j.jpeds.2014.01.070

regions performing universal screening, many performing targeted screening on the basis of parental ethnicity, and others not screening at all.[18-24] Outside of the US and Europe, NBS is not routine, although there are some countries, such as Jamaica and Brazil, that have recognized the importance of early identification of SCA and implemented screening programs.[25-28] In Africa, it is only during the past decade that several countries have developed small-scale pilot NBS programs.[18,29-32]

NBS is critically important to bring the diagnosis to the attention of both families and health professionals; however, it is also important to recognize that any NBS program (for SCA or any condition) must be closely linked to a clinical care program. Without early access to education and preventive care, there is little utility in screening at all. However, the interventions that can be life-saving are neither difficult nor expensive. Arguably, the most important component of early diagnosis is informing the parents and family of the diagnosis and what it means for the care of their child. Basic sickle cell education with a focus on the early identification of life-threatening symptoms (fever, splenomegaly, lethargy, pallor) is equally as important as any specific medical intervention discussed herein. The well-documented Jamaican cohort provides convincing evidence that teaching parents how to palpate the spleen to enable early access to care significantly reduces the severity and mortality associated with ASSC.[33,34] NBS and closely linked clinical care have been demonstrated to reduce mortality in the US,[35] England,[3] and Jamaica.[27,33]

In addition to NBS and sickle cell education, a number of discoveries and specific interventions have been demonstrated to dramatically reduce infection and mortality for infants and children with SCA. A randomized, double-blind, placebo-controlled trial (Penicillin Prophylaxis in Sickle Cell Disease trial) performed in the US in the 1980s demonstrated that twice-daily prophylactic penicillin resulted in reduced SCA mortality and an 84% reduction in bacterial infections in children younger than 5 years of age.[36] In countries with available early diagnosis, prophylactic penicillin is now the life-saving standard of care for children younger than the age of 5, but its effectiveness is limited by family compliance with this regimen.[37,38] In the developed world, the widespread implementation of vaccines, particularly against encapsulated bacteria (*S pneumoniae*, *Haemophilus influenzae*, and *Neisseria meningitidis*) has further contributed to improved survival rates for children with SCA. Together, NBS, parental education, oral penicillin prophylaxis, and widespread vaccination have resulted in significantly reduced rates of infections and improved survival for children with SCA in the developed world.[39-43]

Early diagnosis and preventative care will not eliminate early SCA mortality. Even with early diagnosis, vaccination, and prophylactic penicillin, children with SCA will remain at risk for acute and potentially deadly complications of SCA (eg, acute malaria, ASSC, stroke). Awareness of the SCA diagnosis is an important first step so that the family seeks timely and appropriate medical care, but there are a number of other systemic health care needs that need to be improved within the developing world to ensure appropriate emergency medical care. Providers across the entire health care system (nurses, doctors, community health workers, etc), particularly those who provide frontline emergency care, must be educated about the appropriate emergency management of sickle cell complications. In addition, simple therapies such as intravenous antibiotics and blood transfusions must be safe and available. These systemic issues (ie, widespread sickle cell education, improvement in transfusion services, and creation of appropriate emergency protocols) will be more challenging to accomplish than simply providing penicillin, but must be considered as approaches are taken to address the global burden of SCA. Systemic efforts such as improvements in the availability and safety of blood transfusions and the quality of emergency care will also provide substantial benefits for the entire population.

The Underappreciated Contribution of SCA to Global Mortality of Children Younger than 5 Years of Age

In discussions of global child health, HIV/AIDS, tuberculosis, malaria, and vaccine-preventable diseases such as pneumococcal infection dominate the discussions and receive most of the global funding from governments and international philanthropy. Despite the high global burden of disease and associated early mortality, it may be surprising that SCA is never listed as a major contributor to mortality in children younger than 5 years of age, even in countries in which 1%-2% of all births may be affected by SCA. This is most commonly due to the lack of awareness of the underlying SCA diagnosis.

Pneumonia, diarrhea, meningitis, malaria, and sepsis are the 5 leading causes of global mortality in children younger than 5 years of age, accounting for more than 60% of deaths outside of the neonatal period in Africa.[44] One could argue that children with SCA are overrepresented within each of these categories. Acute chest syndrome is one of the leading cause of mortality among persons with SCA,[45,46] but without a preexisting diagnosis of SCA, the diagnosis will simply be documented as "pneumonia." Similarly, sepsis with *S pneumoniae*, meningococcal meningitis, and malaria are all conditions for which children with SCA are particularly susceptible. Although diarrheal disease is less of a well-known concern for children with SCA, these children are at increased risk of complicated gastrointestinal infections because of the reduction in defense against invasive salmonella disease[47,48] and the increased sickling induced by dehydration caused by diarrhea. If the diagnosis of SCA was known and documented within these subgroups, there is little question that it would be appropriately included in the leading causes of child mortality. In contrast, if a child with cancer dies of neutropenic infection or a child with HIV dies of pneumonia, these deaths will be included in mortality statistics for cancer or HIV; this does not appear to be the case for SCA. The **Figure** illustrates the causes of mortality in