Published in final edited form as:

Ann Trop Med Parasitol. 2007 January ; 101(1): 3–14. doi:10.1179/136485907X154638.

Sickle cell disease in Africa: burden and research priorities

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Abstract

Sickle cell disease (SCD) has recently been recognised as a problem of major public-health significance by the World Health Organization. Despite the fact that >70% of sufferers live in Africa, expenditure on the related care and research in the continent is negligible, and most advances in the understanding and management of this condition have been based on research conducted in the North. In order to target limited resources, African countries need to focus research and interventions on areas that will lead to the maximum impact. This review details the epidemiological and clinical background of SCD, with an emphasis on Africa, before identifying the research priorities that will provide the necessary evidence base for improving the management of African patients. Malaria, bacterial and viral infections and cerebrovascular accidents are areas in which further research may lead to a significant improvement in SCD-related morbidity and mortality. As patients with high concentrations of foetal haemoglobin (HbF) appear to be protected from all but mild SCD, the various factors and pharmacological agents that might increase HbF levels need to be assessed in Africa, as options for interventions that would improve quality of life and reduce mortality.

Although the focus of health research in Africa is currently on pandemics such as malaria, tuberculosis and HIV/AIDS, it is anticipated that, over time, non-infectious diseases will assume increased importance. Estimates from developed countries indicate that genetic diseases already constitute up to 40% of the requirements for chronic care in paediatric practice (World Bank, 1993). Sickle cell disease (SCD) still presents a largely unrecognised health problem for millions of Africans, although it is more than a decade since the World Health Organization (WHO) identified it as a problem of major public-health significance (WHO, 1994). In this review, the background to SCD is briefly explored, with an emphasis on its epidemiology in Africa, before the need to establish better evidence, on which to base the most appropriate management of African cases of SCD, is discussed.

Sickle Haemoglobin and Sickle Cell Disease

Sickle haemoglobin (HbS) is one of the most important single gene disorders of humans and results from the substitution of glutamic acid for valine at position 6 on the β -globin molecule ($\beta^{\text{Glu6Val}}/\beta^{\text{s}}$ -gene). When deoxygenated, HbS forms large insoluble polymers that affect the overall structural, functional, and rheological properties of erythrocytes. Sickle cell disease refers to a group of conditions characterised by the presence of HbS, which has three genotypes of major clinical significance (HbSS, HbSC and HbS/ β^{o}). This review will focus on HbSS, the most common genotype leading to SCD in Africa.

Due to the geographical distribution of SCD, it was initially thought that the β^{s} -gene spread by migration of a single mutation (Gelpi, 1973). The results of the analysis of restriction-fragment length polymorphisms (RFLP) have, however, since shown that the β^{s} -gene has actually arisen from mutations occurring at different times at the same locus, resulting in different haplotypes (Kulozik *et al.*, 1986). In West Africa, the predominant haplotypes are Senegal, Benin and Cameroon, whereas the Bantu [also known as the Central African Republic (CAR)] haplotype occurs in East and Central Africa (Ojwang *et al.*, 1987; Oner *et al.*, 1992; Keclard *et al.*, 1996), and the Arab–Indian haplotype in the Middle East and Asia (Daar *et al.*, 2000; Mukherjee *et al.*, 2004).

Between 200,000 and 230,000 children are thought to be born with SCD in Africa every year (WHO, 1994; Diallo and Tchernaia, 2002). These estimates are based on the frequencies of the heterozygous state for the sickle cell gene (AS), which range from 2%–38%, with the highest burden of SCD estimated to be in Tanzania (WHO, 1994; Angastiniotis and Modell, 1998; Weatherall and Clegg, 2001). Although based on the results of surveys that may not be representative of entire populations, these incidences give a sense of the magnitude of the problem. They may now even be under-estimates, as, in their calculation, no allowances were made for changing birth rates.

Although the molecular abnormality leading to the β^{s} -gene is the same in all haplotypes, there is wide variation in the clinical manifestations, pattern and severity of the associated disease. The two main pathological consequences of high levels of HbS in SCD are vaso-occlusive disease (VOD) and increased haemolysis, with patients having increased susceptibility to infections, disturbances of growth and development, and chronic end-organ damage. Among the genetic factors that have been associated with a milder disease phenotype are α -thalassaemia (Higgs *et al.*, 1982; De Ceulaer *et al.*, 1983) and high levels of foetal haemoglobin (HbF; Stevens *et al.*, 1981; Powars *et al.*, 1984). The β^{s} -gene haplotype itself is also associated with differences in disease severity, the Bantu haplotype being associated with a relatively poor prognosis (Nagel and Labie, 1989; Powars *et al.*, 1990; Powars, 1991). Although it seems likely that many other genetic factors that lead to a modification of the phenotypic expression of the β^{s} -gene remain to be discovered, environmental factors such as infections, nutrition and socio-economic status may also influence the course of the disease and the rate of survival. With regard to mortality, evidence from studies conducted in the North, particularly in Jamaica and the U.S.A., has shown that the highest levels of SCD-related mortality occur in children aged between 6 months and 3 years, the commonest causes of death being acute chest syndrome (ACS),

acute splenic sequestration and pneumococcal septicaemia (Rogers *et al.*, 1978; Leikin *et al.*, 1989; Platt *et al.*, 1994). Cerebrovascular accidents (CVA; often called strokes) are also a significant clinical complication and occur predominantly between the ages of 2 and 5 years (Ohene-Frempong *et al.*, 1998).

Despite advances in the understanding of the disease mechanisms and modifying factors, it is only in the past two decades that new interventions have led to significant improvements in the outcome of patients, in resource-rich countries, who have SCD (see Table). Long-term research, particularly in Jamaica and the U.S.A., has shown that interventions such as neonatal screening, programmes of comprehensive care and early detection and treatment of acute events (Vichinsky, 1991) — as well as more complex approaches, such as blood-transfusion therapy (Adams *et al.*, 1998) and hydroxyurea (Charache *et al.*, 1995) — can have a significant, direct and beneficial impact on the clinical course of SCD and the quality of life and survival of patients with the disease. With such interventions, the median survival for males and females with the disease in the U.S.A. is now 42 and 48 years, respectively (Platt *et al.*, 1994).

There is every reason to expect that similar improvements could be achieved in Africa. Despite the fact that 70% of the world's burden of SCD falls on Africa, however, there are still no clear baseline data available on survivorship or the major causes of morbidity and mortality among African cases of SCD.

It is often presumed that SCD in Africa is associated with very high levels of childhood mortality, and historically such mortality has largely been associated with malaria, overwhelming bacterial infections and malnutrition (Fleming, 1989). Given the presumed high mortality in childhood, the prevalence of SCD in older Africans is, however, surprisingly high (Corachan *et al.*, 1979; Elamin, 1980; Knox-Macaulay, 1983).

Clearly there is a need for systematic, prospective studies that document the detailed epidemiology of SCD in different areas of Africa and describe the problems currently facing African patients affected by the disease. Such research assumes an existing ability to detect and manage such patients, and this in itself raises important, operational-research questions about the desirability and implementation of screening programmes, community and patient education, and the integration of national SCD programmes at different levels of the health service. The biological aspects of SCD that are likely to be important in defining approaches to the prevention and treatment of the disease form the focus of the present review. Given the limited resources available, initial research efforts should probably focus on three specific areas: malaria, bacterial and viral infections, and stroke. In addition, as a cross-cutting issue, research on the role of HbF has the potential both to increase our understanding of the mechanisms behind SCD and to provide effective therapeutic options in Africa.

Malaria

It is widely believed that malaria is a major cause of admission and death in patients with SCD in sub-Saharan Africa and, as a result, antimalarial prophylaxis is included in the standard management of patients with the disease in most countries within the region. For

many years, chloroquine provided a cheap, effective, convenient and safe approach. With the spread of chloroquine resistance, however, there has been considerable debate regarding which drugs should now be recommended for long-term prophylaxis among those with SCD. In the light of this ongoing debate, there is a need to review the evidence for the exact role of malaria in SCD.

In their classic study, conducted in the Garki district of Nigeria, Molineaux *et al.* (1979) reported that, although patients with SCD were less likely to have malarial parasitaemias than their neighbours, children with the SS genotype generally died at an early age. Relatively large numbers of older children with SS were found in an area exposed to intensive malaria control but this trend did not reach statistical significance. In a more recent study conducted in Nigeria, Ibidapo and Akinyanju (2000) looked at acute illness in 102 adolescents and adults with SCD and found that the commonest infection among the 64 patients who were admitted with infections was malaria, which was detected in 25 of the patients. Similarly, Ambe *et al.* (2001) found that 66% of Nigerian SCD patients who presented with anaemia had malaria parasitaemias. The results of the studies by Ibidapo and Akinyanju (2000) and Ambe *et al.* (2001) should not be taken as evidence that SCD cases are unusually susceptible to malaria, however, as these investigations were small, hospital-based and did not take into consideration the prevalence of malaria in the communities from which the patients were drawn. In fact, data from several clinico-epidemiological studies indicate that SCD patients may be less susceptible to malaria, at least in terms of the prevalence and intensity of parasitaemia (Okuonghae *et al.*, 1992; Aluoch, 1997; Awotua-Efebo *et al.*, 2004) and the incidence of severe malaria, in particular that of severe malarial anaemia (Aidoo *et al.*, 2002). In two areas of East Africa — an urban area of low and variable transmission (Dar es Salaam, Tanzania) and a rural area of higher stable transmission (Kilifi, Kenya) — SS individuals appear to have relatively low prevalences and intensities of malarial parasitaemia and, in Kilifi, there is no over-representation of SS individuals among patients presenting with *P. falciparum* malaria (unpubl. obs.). Finally, if malaria were a major cause of death in patients with SCD, it might be expected that the advent of wide-spread chloroquine resistance would have been associated with increasing mortality in SCD patients. There seems to be no evidence, either in published reports or anecdotal, indicating that this is the case.

In summary, although it is often stated that malaria is a major cause of morbidity and mortality in patients with SCD living in Africa, the data supporting this are surprisingly limited and, indeed, there is substantial evidence that the SS genotype may confer resistance against malarial infection *per se*. This in itself would not be surprising, given that individuals who are heterozygous for the β^s -gene (AS) enjoy unequivocal protection against malaria, the most striking effect being at the level of the severe and life-threatening forms of the disease. Such protection has been shown in a number of large epidemiological studies (Allison, 1954; Hill *et al.*, 1991; Aidoo *et al.*, 2002; Williams *et al.*, 2005) and is supported by the results of in-vitro studies that indicate a range of potential mechanisms, including reduced invasion of HbAS erythrocytes by malarial parasites, reduced parasite multiplication, and accelerated parasite clearance by the spleen (Luzzatto *et al.*, 1970; Pasvol *et al.*, 1978; Orjih, 1999, 2005). This does raise the question that, if HbS protects the heterozygotes against malaria, shouldn't individuals with SCD, who have even higher levels of HbS, be even better

protected? This is certainly the case in another haemoglobinopathy, HbC, which is commonly found in West Africa; although both heterozygotes (HbAC) and homozygotes (HbCC) are protected against malaria, the degree of protection appears to be considerably greater in the latter (Modiano *et al.*, 2001).

It is important to be cautious in interpreting the data reviewed above because, although it is quite possible that there are significant, major interactions between malaria and SCD, any direct evidence of this is limited by the difficulty of conducting studies with sufficient subjects to make the results statistically significant. In addition, it may be difficult to take certain factors into account, such as the possibilities that severe malaria occurs at much lower parasitaemias in SCD cases than in non-SCD individuals, that malarial infection triggers SCD-related clinical events, or that malarial infection causes many unreported deaths among SCD cases (i.e. deaths that occur in the community and are never detected in hospital). Carefully designed studies to define better the direct and indirect effects of malaria in patients with SCD are clearly required. From a practical point of view, the key questions include: is malaria a major problem in SCD? What are the benefits of antimalarial prophylaxis for SCD cases? What drugs can be recommended for such prophylaxis? Until what age should they be continued? And is there a role for alternative approaches, such as intermittent antimalarial treatment or targeted educational interventions for the home treatment of febrile episodes in patients with SCD?

Bacterial and Viral Infections

World-wide, bacterial infections, particularly those caused by encapsulated organisms, are a common cause of mortality among SCD cases (Craddock, 1973; Overturf *et al.*, 1977). Both functional asplenia, caused by repeated splenic infarction leading to loss of the mechanical function of the splenic vasculature (Pearson *et al.*, 1969), and defective activation of the alternate complement pathway (Johnston *et al.*, 1973) are thought to contribute to a 20-fold increase in the risk of pneumococcal infections in children with SCD (Overturf *et al.*, 1977; Zarkowsky *et al.*, 1986; Gill *et al.*, 1995). Over-whelming evidence from developed countries shows that interventions targeted at SCD cases, such as penicillin prophylaxis, can lead to a significant reduction in the incidence of invasive pneumococcal disease and to improved survival (John *et al.*, 1984; Gaston *et al.*, 1986; Lee *et al.*, 1995). As a result, many countries have adopted antibiotic prophylaxis as national policy for young patients with SCD (i.e. patients aged 4 months–5 years). Prophylaxis for older SCD cases, who carry less risk of invasive disease and greater risk of antibiotic resistance, is recommended less often (Falletta *et al.*, 1995; Woods *et al.*, 1997).

Data regarding the pattern of bacterial infections — particularly the role of pneumococcal disease — in patients with SCD in Africa are limited and conflicting, with studies reporting relatively few pneumococcal isolates and a predominance of organisms such as *Klebsiella* spp., *Staphylococcus aureus* and non-typhoidal *Salmonellae* (Akinyanju and Johnson, 1987; Okuonghae *et al.*, 1993; Athale and Chintu, 1994; Akuse, 1996; Aken'ova *et al.*, 1998; Koko *et al.*, 1998; Etima *et al.*, 2006). It is possible that important differences really do exist, in the epidemiology of invasive bacterial disease in patients with SCD, between Africa and the North. Given compelling evidence from large, systematic studies showing that, overall,

Streptococcus pneumoniae is the commonest cause of childhood bacteraemia in Africa (Lepage *et al.*, 1987; Berkley *et al.*, 2005; Brent *et al.*, 2006), there is, however, no plausible reason to doubt that this pathogen should also be important in patients with SCD. The failure to report *Str. pneumoniae* in African SCD cases probably reflects issues such as the relative lack of good microbiological facilities, the fact that *Str. pneumoniae* is a fastidious organism, and the often high incidence of prior antibiotic treatment among patients recruited in referral hospitals.

In addition to invasive bacterial disease, several viral infections may also be particularly important in SCD. Parvovirus B19, for example, can precipitate erythrocytic aplasia and lead to life-threatening anaemia (Serjeant *et al.*, 1993; Smith-Whitley *et al.*, 2004), although the epidemiology of this virus in Africa is poorly defined (Jones *et al.*, 1990; Teuscher *et al.*, 1991; Yeats *et al.*, 1999). Their frequent need for multiple, and often emergency, blood transfusions means that SCD patients are at high-risk of HIV and other transfusion-transmissible infections (Gumodoka *et al.*, 1993; Tshilolo *et al.*, 1996; Fleming, 1997); this is likely to be particularly important in Africa, given both the massive burden of HIV infection and the operational problems in providing adequate blood-transfusion services.

In summary, evidence for the importance of invasive pneumococcal disease in Africa is sufficiently compelling to indicate that preventative measures, such as antibiotic prophylaxis, should be implemented in patients with SCD whenever possible. Research priorities therefore relate to defining the most effective regimens and to the operational issues in ensuring wide-spread implementation. Against this background, it remains a high priority to define the importance of other bacterial and viral infections in order to design potential, additional interventions.

SCD and Cerebrovascular Accidents

In developed countries, the risk of developing CVA is 250 times higher among children with SCD than in their non-sickle counterparts (Earley *et al.*, 1998). In the U.S.A., approximately 25% of patients with SCD suffer a stroke by the age of 45 years (Ohene-Frempong *et al.*, 1998), the peak incidence being between the ages of 2 and 5 years (Adams *et al.*, 2001). In addition, more subtle neurovascular events are probably responsible for the high rates of developmental disability and poor academic performance observed among SCD cases (DeBaun *et al.*, 1998; Kinney *et al.*, 1999).

Although strokes may result from haemorrhage, embolism or thrombosis, cerebral infarction as the result of an occlusive vasculopathy is the commonest cause in patients with SCD (Stockman *et al.*, 1972). Stenotic lesions, which are predominantly found around the circle of Willis, can be demonstrated by cerebral angiography or magnetic-resonance imaging but transcranial Doppler ultrasonography (TCD) is now widely used as the standard approach to their early detection (DeBaun *et al.*, 1995). TCD measures the time-averaged maximum mean velocity (TAMMV) of the blood flowing in large cerebral vessels. Although a low haematocrit can increase this velocity to 150 cm/s, values greater than this are more likely to be due to stenosis, with velocities of >200 cm/s being associated with a 40% risk of stroke within 3 years (Adams *et al.*, 1992). Other risk factors for infarctive stroke include low HbF

concentration, recent ACS, and hypoxia (Kirkham *et al.*, 2001). These factors are used to identify SCD patients who are at particularly high risk of stroke and therefore require aggressive interventional strategies. Long-term blood-transfusion therapy has been shown to reduce the risk of stroke by 92% (Adams *et al.*, 1998) but, as there are issues with compliance and the risk of alloimmunization, alternative options, such as hydroxyurea, have been explored (Ware *et al.*, 1999).

There are few estimates of the incidence of stroke amongst patients with SCD in Africa. Those that have been published indicate that the incidence in Africa may be higher than in the U.S.A., although the age-group most affected, of children aged 2–5 years, is similar in both regions (Yakubu and Werblinska, 1985; Izuora *et al.*, 1989; Amayo *et al.*, 1992). The relatively high incidence of SCD-associated stroke in Africa may reflect the relatively high prevalence of several factors associated with increased risk, such as low haemoglobin, leucocytosis and Bantu haplotype. It is important to realise, however, that all the evidence for a relatively high incidence of SCD-associated stroke in Africa comes from a few, relatively small studies. A more comprehensive picture of stroke and its associated risk factors in Africa needs to be established. In particular, given that TCD ultrasonography is relatively cheap, safe and well-tolerated, it should be feasible to use this technique to determine the spectrum of cerebral blood-flow velocities in African children with SCD and, subsequently, to define a high-risk group for targeted interventions.

Haemoglobin F

High levels of HbF are associated with amelioration of the severity of SCD because they interfere with HbS polymerization in erythrocytes, resulting in lower rates of haemolysis and fewer irreversibly sickled cells (Ali, 1970; Haghshenass *et al.*, 1977; Stevens *et al.*, 1981; Powars *et al.*, 1984; Miller *et al.*, 1986; Noguchi *et al.*, 1988). Identifying the factors that control HbF production has therefore been a major aim in SCD research for a number of years. In normal subjects, HbF constitutes 60%–80% of the haemoglobin present at birth but its levels gradually decrease, to around 1% of all haemoglobin (or a generally higher percentage in SCD patients), within the first year of life. In adults, HbF is restricted to the F-cells that commonly make up 3%–7% of circulating erythrocytes. The concentration of HbF and the percentage of erythrocytes that are F-cells vary considerably (up to 20-fold) in healthy adults, however, and display a continuous distribution that is substantially positively skewed (Kan and Dozy, 1980). Although factors such as age and gender affect both HbF concentration and the proportion of erythrocytes that are F-cells, genetic effects are also important, with approximately 14% of the variation reported to be linked to the β^S -gene and the rest of the genetic control acting via multifactorial quantitative-trait loci (QTL; Thein and Craig, 1998).

The relationship between HbF and malaria is interesting and may be particularly pertinent in SCD patients who live in malaria-endemic areas. The results of in-vitro studies have shown that HbF reduces the invasion of erythrocytes by malarial parasites and does not support the growth of such parasites (Pasvol *et al.*, 1976; Friedman, 1979; Orjih, 1999). These observations may explain why infants seldom develop severe malaria in the first few months of their lives. Given the tremendous selective force of malaria, high population frequencies

of QTL for high HbF production might be expected, and appear to have been detected, in malaria-endemic regions (Nagel *et al.*, 1987; Fatunde and Scott-Emuakpor, 1992; Green *et al.*, 1993).

The potential importance of HbF levels in conferring protection from the severe manifestations of SCD provides the rationale for the employment of pharmacological agents, including hydroxyurea, as a treatment option for SCD (Veith *et al.*, 1985; Rodgers *et al.*, 1990). Hydroxyurea has been shown to be effective in influencing several clinical features of SCD (Charache *et al.*, 1995; Ware *et al.*, 1995) and the most appropriate approaches to its use (in terms of treatment longevity, duration and dose) and the selection of patients to receive the drug have been studied extensively, albeit, again, outside of Africa (Powars *et al.*, 1984; Steinberg *et al.*, 1997).

Areas of potential research importance in Africa include exploring the relationships between malaria and the genetic factors that control HbF concentration, defining the role and optimum means of employing hydroxyurea in patients with severe SCD, and research into alternative safe drugs that may increase HbF production.

Conclusions

SCD presents a largely unrecognised health problem for millions of Africans, although the WHO has identified it as a condition of increasing public-health significance (WHO, 1994; Angastiniotis and Modell, 1998; Weatherall and Clegg, 2001). African countries need to improve the infrastructure for diagnosing and caring for patients with SCD and, through research, to establish the evidence base to guide policies that ensure the most effective management of such patients in the region. The WHO (1994) recommended a comprehensive approach that involves the establishment of good services for the treatment and prevention of the various complications of SCD. This in itself raises a number of key operational-research questions, such as the most cost-effective way to establish and maintain screening programmes, the relative merits of specialist services compared with integration into general health services, and the optimum approaches to family and community education about SCD. It will be important to conduct systematic studies to define the picture of SCD in Africa better and, in particular, to define age-specific survival and identify the major causes of SCD-associated morbidity and mortality. Such studies do not start in a vacuum and should incorporate insights from research on SCD elsewhere, particularly the investigations in Jamaica and in the U.S.A., which has led to interventions that have improved both the quality of life and survival of patients with SCD (see Table). It should also be realised, however, that there may be important inter-regional differences in the clinical epidemiology of SCD. Particular emphasis should be given to the factors that are already suspected to play a major role in SCD-associated morbidity and mortality, such as malarial, bacterial and viral infection and stroke, for which potential prophylactic and treatment options already exist.

Taking forward a joint care-and-research agenda will require the strengthening of institutions that have the resources (i.e. personnel and laboratory and clinical facilities) to act as national and regional centres of excellence for SCD research, treatment and training. Such

strengthening is essential if the capacity of African countries to provide SCD care at all levels of the health service is to be improved. Unfortunately, current expenditure on both research on, and the clinical care of, SCD patients in Africa is negligible, and there is therefore a need for ministries of health, research organizations and international agencies to work together to develop a clear strategy to achieve this goal (Weatherall *et al.*, 2005).

Acknowledgement

J.M, T.N.W. and K.M. are funded by the Wellcome Trust, U.K.

References

- Adams R, McKie V, Nichols F, Carl E, Zhang D, McKie K, Figueroa R, Litaker M, Thompson W, Hess D. The use of transcranial ultrasonography to predict stroke in sickle cell disease. *New England Journal of Medicine*. 1992; 326:605–610. [PubMed: 1734251]
- Adams RJ, McKie VC, Hsu L, Files B, Vichinsky E, Pegelow C, Abboud M, Gallagher D, Kutlar A, Nichols FT, Bonds DR, et al. Prevention of a first stroke by transfusions in children with sickle cell anemia and abnormal results on transcranial Doppler ultrasonography. *New England Journal of Medicine*. 1998; 339:5–11. [PubMed: 9647873]
- Adams RJ, Ohene-Frempong K, Wang W. Sickle cell and the brain Hematology/Hematology/the Education Program of the American Society of Hematology. *American Society of Hematology. Education Program*. 2001:31–46. Unnumbered.
- Aidoo M, Terlouw DJ, Kolczak M, McElroy PD, ter Kuile FO, Kariuki S, Nahlen BL, Lal AA, Udhayakumar V. Protective effects of the sickle cell gene against malaria morbidity and mortality. *Lancet*. 2002; 359:1311–1312. [PubMed: 11965279]
- Aken'ova YA, Bakare RA, Okunade MA. Septicaemia in sickle cell anaemia patients: the Ibadan experience. *Central African Journal of Medicine*. 1998; 44:102–104. [PubMed: 9810403]
- Akinyanju O, Johnson AO. Acute illness in Nigerian children with sickle cell anaemia. *Annals of Tropical Paediatrics*. 1987; 7:181–186. [PubMed: 2445266]
- Akuse RM. Variation in the pattern of bacterial infection in patients with sickle cell disease requiring admission. *Journal of Tropical Pediatrics*. 1996; 42:318–323. [PubMed: 9009554]
- Ali SA. Milder variant of sickle-cell disease in Arabs in Kuwait associated with unusually high level of foetal haemoglobin. *British Journal of Haematology*. 1970; 19:613–619. [PubMed: 5481506]
- Allison AC. Protection afforded by sickle-cell trait against subtertian malarial infection. *British Medical Journal*. 1954; i:290–294.
- Aluoch JR. Higher resistance to *Plasmodium falciparum* infection in patients with homozygous sickle cell disease in western Kenya. *Tropical Medicine and International Health*. 1997; 2:568–571. [PubMed: 9236824]
- Amayo EO, Owade JN, Aluoch JR, Njeru EK. Neurological complications of sickle cell anaemia at KNH: a five year retrospective study. *East African Medical Journal*. 1992; 69:660–662. [PubMed: 1298628]
- Ambe JP, Fatunde JO, Sodeinde OO. Associated morbidities in children with sickle-cell anaemia presenting with severe anaemia in a malarious area. *Tropical Doctor*. 2001; 31:26–27. [PubMed: 11205596]
- Angastiniotis M, Modell B. Global epidemiology of hemoglobin disorders. *Annals of the New York Academy of Sciences*. 1998; 850:251–269. [PubMed: 9668547]
- Athale UH, Chintu C. Clinical analysis of mortality in hospitalized Zambian children with sickle cell anaemia. *East African Medical Journal*. 1994; 71:388–391. [PubMed: 7835262]
- Awotua-Efebo O, Alikor EA, Nkanginieme KE. Malaria parasite density and splenic status by ultrasonography in stable sickle-cell anaemia (HbSS) children. *Nigerian Journal of Medicine*. 2004; 13:40–43. [PubMed: 15296106]

- Berkley JA, Lowe BS, Mwangi I, Williams T, Bauni E, Mwarumba S, Ngetsa C, Slack MP, Njenga S, Hart CA, Maitland K, et al. Bacteremia among children admitted to a rural hospital in Kenya. *New England Journal of Medicine*. 2005; 352:39–47. [PubMed: 15635111]
- Brent AJ, Ahmed I, Ndiritu M, Lewa P, Ngetsa C, Lowe B, Bauni E, English M, Berkley JA, Scott JA. Incidence of clinically significant bacteraemia in children who present to hospital in Kenya: community-based observational study. *Lancet*. 2006; 367:482–488. [PubMed: 16473125]
- Charache S, Terrin ML, Moore RD, Dover GJ, Barton FB, Eckert SV, McMahon RP, Bonds DR. Effect of hydroxyurea on the frequency of painful crises in sickle cell anemia. Investigators of the Multicenter Study of Hydroxyurea in Sickle Cell Anemia. *New England Journal of Medicine*. 1995; 332:1317–1322. [PubMed: 7715639]
- Claster S, Vichinsky EP. Managing sickle cell disease. *British Medical Journal*. 2003; 327:1151–1155. [PubMed: 14615343]
- Corachan M, Oomen HA Jr, Kigadye FC, Morris H. Sicklers surviving childhood in Tanzania. *Tropical and Geographical Medicine*. 1979; 31:531–535. [PubMed: 542989]
- Craddock PR. Bacterial infection in sickle-cell anemia. *New England Journal of Medicine*. 1973; 288:1301–1302.
- Daar S, Hussain HM, Gravell D, Nagel RL, Krishnamoorthy R. Genetic epidemiology of HbS in Oman: multicentric origin for the betaS gene. *American Journal of Hematology*. 2000; 64:39–46. [PubMed: 10815786]
- De Coulaer K, Higgs DR, Weatherall DJ, Hayes RJ, Serjeant BE, Serjeant GR. α -Thalassemia reduces the hemolytic rate in homozygous sickle-cell disease. *New England Journal of Medicine*. 1983; 309:189–190. [PubMed: 6866027]
- DeBaun MR, Glauser TA, Siegel M, Borders J, Lee B. Noninvasive central nervous system imaging in sickle cell anemia. A preliminary study comparing transcranial Doppler with magnetic resonance angiography. *Journal of Pediatric Hematology/oncology*. 1995; 17:29–33. [PubMed: 7743234]
- DeBaun MR, Schatz J, Siegel MJ, Koby M, Craft S, Resar L, Chu JY, Launius G, Dadash-Zadeh M, Lee RB, Noetzel M. Cognitive screening examinations for silent cerebral infarcts in sickle cell disease. *Neurology*. 1998; 50:1678–1682. [PubMed: 9633710]
- Diallo D, Tchernia G. Sickle cell disease in Africa. *Current Opinion in Hematology*. 2002; 9:111–116. [PubMed: 11844993]
- Earley CJ, Kittner SJ, Feeser BR, Gardner J, Epstein A, Wozniak MA, Wityk R, Stern BJ, Price TR, Macko RF, Johnson C, et al. Stroke in children and sickle-cell disease: Baltimore–Washington Cooperative Young Stroke Study. *Neurology*. 1998; 51:169–176. [PubMed: 9674798]
- Elamin AM. Sickle cell anaemia in adult Zambian Africans. *Central African Journal of Medicine*. 1980; 26:183–186. [PubMed: 7438202]
- Etima M, Mworozzi E, Christopher N, Serjeant GR. Bacteraemia in homozygous sickle cell disease in Africa: is pneumococcal prophylaxis justified? *Archives of Disease in Childhood*. 2006
- Falletta JM, Woods GM, Verter JI, Buchanan GR, Pegelow CH, Iyer RV, Miller ST, Holbrook CT, Kinney TR, Vichinsky E, Becton DL, et al. Discontinuing penicillin prophylaxis in children with sickle cell anemia. Prophylactic Penicillin Study II. *Journal of Pediatrics*. 1995; 127:685–690. [PubMed: 7472817]
- Fatunde OJ, Scott-Emuakpor AB. Foetal haemoglobin in Nigerian children with sickle cell anaemia. Effect on haematological parameters and clinical severity. *Tropical and Geographical Medicine*. 1992; 44:264–266. [PubMed: 1280870]
- Fleming AF. The presentation, management and prevention of crisis in sickle cell disease in Africa. *Blood Reviews*. 1989; 3:18–28. [PubMed: 2650773]
- Fleming AF. HIV and blood transfusion in sub-Saharan Africa. *Transfusion Science*. 1997; 18:167–179. [PubMed: 10174681]
- Friedman MJ. Oxidant damage mediates variant red cell resistance to malaria. *Nature*. 1979; 280:245–247. [PubMed: 377105]
- Gaston MH, Verter JI, Woods G, Pegelow C, Kelleher J, Presbury G, Zarkowsky H, Vichinsky E, Iyer R, Lobel JS, Diamond S, et al. Prophylaxis with oral penicillin in children with sickle cell anemia. A randomized trial. *New England Journal of Medicine*. 1986; 314:1593–1599. [PubMed: 3086721]

- Gelpi AP. Migrant populations and the diffusion of the sickle-cell gene. *Annals of Internal Medicine*. 1973; 79:258–264. [PubMed: 4582014]
- Gill FM, Sleeper LA, Weiner SJ, Brown AK, Bellevue R, Grover R, Pegelow CH, Vichinsky E. Clinical events in the first decade in a cohort of infants with sickle cell disease. Cooperative Study of Sickle Cell Disease. *Blood*. 1995; 86:776–783. [PubMed: 7606007]
- Green NS, Fabry ME, Kaptue-Noche L, Nagel RL. Senegal haplotype is associated with higher HbF than Benin and Cameroon haplotypes in African children with sickle cell anemia. *American Journal of Hematology*. 1993; 44:145–146. [PubMed: 7505527]
- Gumodoka B, Vos J, Kigadye FC, van Asten H, Dolmans WM, Borgdorff MW. Blood transfusion practices in Mwanza region, Tanzania. Bugando Medical Centre. *AIDS*. 1993; 7:387–392. [PubMed: 8471201]
- Haghshenas M, Ismail-Beigi F, Clegg JB, Weatherall DJ. Mild sickle-cell anaemia in Iran associated with high levels of fetal haemoglobin. *Journal of Medical Genetics*. 1977; 14:168–171. [PubMed: 881705]
- Higgs DR, Aldridge BE, Lamb J, Clegg JB, Weatherall DJ, Hayes RJ, Grandison Y, Lowrie Y, Mason KP, Serjeant BE, Serjeant GR. The interaction of alpha-thalassemia and homozygous sickle-cell disease. *New England Journal of Medicine*. 1982; 306:1441–1446. [PubMed: 6176865]
- Hill AV, Allsopp CE, Kwiatkowski D, Anstey NM, Twumasi P, Rowe PA, Bennett S, Brewster D, McMichael AJ, Greenwood BM. Common West African HLA antigens are associated with protection from severe malaria. *Nature*. 1991; 352:595–600. [PubMed: 1865923]
- Ibidapo MO, Akinyanju OO. Acute sickle cell syndromes in Nigerian adults. *Clinical and Laboratory Haematology*. 2000; 22:151–155. [PubMed: 10931163]
- Izuora GI, Kaine WN, Emodi I. Neurological disorders in Nigerian children with homozygous sickle cell anaemia. *East African Medical Journal*. 1989; 66:653–657. [PubMed: 2612404]
- John AB, Ramlal A, Jackson H, Maude GH, Sharma AW, Serjeant GR. Prevention of pneumococcal infection in children with homozygous sickle cell disease. *British Medical Journal (Clinical Research Edition)*. 1984; 288:1567–1570.
- Johnston RB Jr, Newman SL, Struth AG. An abnormality of the alternate pathway of complement activation in sickle-cell disease. *New England Journal of Medicine*. 1973; 288:803–808. [PubMed: 4144343]
- Jones PH, Pickett LC, Anderson MJ, Pasvol G. Human parvovirus infection in children and severe anaemia seen in an area endemic for malaria. *Journal of Tropical Medicine and Hygiene*. 1990; 93:67–70. [PubMed: 2154587]
- Kan YW, Dozy AM. Evolution of the hemoglobin S and C genes in world populations. *Science*. 1980; 209:388–391. [PubMed: 7384810]
- Keclard L, Ollendorf V, Berchel C, Loret H, Merault G. beta S haplotypes, alpha-globin gene status, and hematological data of sickle cell disease patients in Guadeloupe (F.W.I.). *Hemoglobin*. 1996; 20:63–74. [PubMed: 8745433]
- Kinney TR, Sleeper LA, Wang WC, Zimmerman RA, Pegelow CH, Ohene-Frempong K, Wethers DL, Bello JA, Vichinsky EP, Moser FG, Gallagher DM, et al. Silent cerebral infarcts in sickle cell anemia: a risk factor analysis. The Cooperative Study of Sickle Cell Disease. *Pediatrics*. 1999; 103:640–645. [PubMed: 10049969]
- Kirkham FJ, Hewes DK, Prengler M, Wade A, Lane R, Evans JP. Nocturnal hypoxaemia and central-nervous-system events in sickle-cell disease. *Lancet*. 2001; 357:1656–1659. [PubMed: 11425370]
- Knox-Macaulay HH. Sickle cell disease in Sierra Leone: a clinical and haematological analysis in older children and adults. *Annals of Tropical Medicine and Parasitology*. 1983; 77:411–419. [PubMed: 6639186]
- Koko J, Dufillot D, M’Ba-Meyo J, Gahouma D, Kani F. Mortality of children with sickle cell disease in a pediatric department in Central Africa. *Archives of Pediatrics*. 1998; 5:965–969.
- Kulozik AE, Wainscoat JS, Serjeant GR, Kar BC, Al-Awamy B, Essan GJ, Falusi AG, Haque SK, Hilali AM, Kate S, Ranasinghe WAEP, et al. Geographical survey of beta S-globin gene haplotypes: evidence for an independent Asian origin of the sickle-cell mutation. *American Journal of Human Genetics*. 1986; 39:239–244. [PubMed: 3752087]

- Lee A, Thomas P, Cupidore L, Serjeant B, Serjeant G. Improved survival in homozygous sickle cell disease: lessons from a cohort study. *British Medical Journal*. 1995; 311:1600–1590. [PubMed: 8555802]
- Leikin SL, Gallagher D, Kinney TR, Sloane D, Klug P, Rida W. Mortality in children and adolescents with sickle cell disease. Cooperative Study of Sickle Cell Disease. *Pediatrics*. 1989; 84:500–508. [PubMed: 2671914]
- Lepage P, Bogaerts J, Van Goethem C, Ntahurutaba M, Nsengumuremyi F, Hitimana DG, Vandepitte J, Butzler JP, Levy J. Community-acquired bacteraemia in African children. *Lancet*. 1987; i:1458–1461.
- Luzzatto L, Nwachuku-Jarrett ES, Reddy S. Increased sickling of parasitised erythrocytes as mechanism of resistance against malaria in the sickle-cell trait. *Lancet*. 1970; i:319–321.
- Miller BA, Salameh M, Ahmed M, Wainscoat J, Antognetti G, Orkin S, Weatherall D, Nathan DG. High fetal hemoglobin production in sickle cell anemia in the eastern province of Saudi Arabia is genetically determined. *Blood*. 1986; 67:1404–1410. [PubMed: 2421808]
- Modiano D, Luoni G, Sirima BS, Simporé J, Verra F, Konate A, Rastrelli E, Olivieri A, Calissano C, Paganotti GM, D'Urbano L, et al. Haemoglobin C protects against clinical *Plasmodium falciparum* malaria. *Nature*. 2001; 414:305–308. [PubMed: 11713529]
- Molineaux L, Fleming AF, Cornille-Brogger R, Kagan I, Storey J. Abnormal haemoglobins in the Sudan savanna of Nigeria. III. Malaria, immunoglobulins and antimalarial antibodies in sickle cell disease. *Annals of Tropical Medicine and Parasitology*. 1979; 73:301–310. [PubMed: 315213]
- Mukherjee MB, Surve RR, Gangakhedkar RR, Ghosh K, Colah RB, Mohanty D. Beta-globin gene cluster haplotypes linked to the betaS gene in western India. *Hemoglobin*. 2004; 28:157–161. [PubMed: 15182059]
- Nagel RL, Labie D. DNA haplotypes and the beta s globin gene. *Progress in Clinical and Biological Research*. 1989; 316B:371–393. [PubMed: 2575756]
- Nagel RL, Rao SK, Dunda-Belkhodja O, Connolly MM, Fabry ME, Georges A, Krishnamoorthy R, Labie D. The hematologic characteristics of sickle cell anemia bearing the Bantu haplotype: the relationship between G gamma and HbF level. *Blood*. 1987; 69:1026–1030. [PubMed: 2435339]
- Noguchi CT, Rodgers GP, Serjeant G, Schechter AN. Levels of fetal hemoglobin necessary for treatment of sickle cell disease. *New England Journal of Medicine*. 1988; 318:96–99. [PubMed: 2447498]
- Ohene-Frempong K, Weiner SJ, Sleeper LA, Miller ST, Embury S, Moehr JW, Wethers DL, Pegelow CH, Gill FM. Cerebrovascular accidents in sickle cell disease: rates and risk factors. *Blood*. 1998; 91:288–294. [PubMed: 9414296]
- Ojwang PJ, Ogada T, Beris P, Hattori Y, Lanclos KD, Kutlar A, Kutlar F, Huisman TH. Haplotypes and alpha globin gene analyses in sickle cell anaemia patients from Kenya. *British Journal of Haematology*. 1987; 65:211–215. [PubMed: 3828229]
- Okuonghae HO, Nwankwo MU, Offor E. Malarial parasitaemia in febrile children with sickle cell anaemia. *Journal of Tropical Paediatrics*. 1992; 38:83–85.
- Okuonghae HO, Nwankwo MU, Offor EC. Pattern of bacteraemia in febrile children with sickle cell anaemia. *Annals of Tropical Paediatrics*. 1993; 13:55–64. [PubMed: 7681646]
- Oner C, Dimovski AJ, Olivieri NF, Schiliro G, Codrington JF, Fattoum S, Adekile AD, Oner R, Yuregir GT, Altay C, Gurgey A, et al. Beta S haplotypes in various world populations. *Human Genetics*. 1992; 89:99–104. [PubMed: 1577473]
- Orjih AU. Malaria parasite metabolism in sickle cells. *European Journal of Haematology*. 1999; 62:286–292. [PubMed: 10359055]
- Orjih AU. Comparison of *Plasmodium falciparum* growth in sickle cells in low oxygen environment and candle-jar. *Acta Tropica*. 2005; 94:25–34. [PubMed: 15777703]
- Overturf GD, Powars D, Baraff LJ. Bacterial meningitis and septicemia in sickle cell disease. *American Journal of Diseases of Children*. 1977; 131:784–787. [PubMed: 879115]
- Pasvol G, Weatherall DJ, Wilson RJ. Cellular mechanism for the protective effect of haemoglobin S against *P. falciparum* malaria. *Nature*. 1978; 274:701–703. [PubMed: 353566]
- Pasvol G, Weatherall DJ, Wilson RJ, Smith DH, Gilles HM. Fetal haemoglobin and malaria. *Lancet*. 1976; i:1269–1272.

- Pearson HA, Spencer RP, Cornelius EA. Functional asplenia in sickle-cell anemia. *New England Journal of Medicine*. 1969; 281:923–926. [PubMed: 5811425]
- Platt OS, Brambilla DJ, Rosse WF, Milner PF, Castro O, Steinberg MH, Klug PP. Mortality in sickle cell disease. Life expectancy and risk factors for early death. *New England Journal of Medicine*. 1994; 330:1639–1644. [PubMed: 7993409]
- Powars DR. Beta s-gene-cluster haplotypes in sickle cell anemia. Clinical and hematologic features. *Hematology/oncology Clinics of North America*. 1991; 5:475–493. [PubMed: 1713910]
- Powars DR, Weiss JN, Chan LS, Schroeder WA. Is there a threshold level of fetal hemoglobin that ameliorates morbidity in sickle cell anemia? *Blood*. 1984; 63:921–926. [PubMed: 6200161]
- Powars DR, Chan L, Schroeder WA. Beta S-gene-cluster haplotypes in sickle cell anemia: clinical implications. *American Journal of Pediatric Hematology/oncology*. 1990; 12:367–374. [PubMed: 1700639]
- Rodgers GP, Dover GJ, Noguchi CT, Schechter AN, Nienhuis AW. Hematologic responses of patients with sickle cell disease to treatment with hydroxyurea. *New England Journal of Medicine*. 1990; 322:1037–1045. [PubMed: 1690857]
- Rogers D, Clarke J, Cupidore L, Ramlal AM, Sparke BR, Serjeant GR. Early deaths in Jamaican children with sickle cell disease. *British Medical Journal*. 1978; i:1515–1516.
- Serjeant GR, Serjeant BE, Thomas PW, Anderson MJ, Patou G, Pattison JR. Human parvovirus infection in homozygous sickle cell disease. *Lancet*. 1993; 341:1237–1240. [PubMed: 8098391]
- Smith-Whitley K, Zhao H, Hodinka RL, Kwiatkowski J, Cecil R, Cecil T, Cnaan A, Ohene-Frempong K. Epidemiology of human parvovirus B19 in children with sickle cell disease. *Blood*. 2004; 103:422–427. [PubMed: 14525777]
- Steinberg MH, Lu ZH, Barton FB, Terrin ML, Charache S, Dover GJ. Fetal hemoglobin in sickle cell anemia: determinants of response to hydroxyurea. Multicenter Study of Hydroxyurea. *Blood*. 1997; 89:1078–1088. [PubMed: 9028341]
- Stevens MC, Hayes RJ, Vaidya S, Serjeant GR. Fetal hemoglobin and clinical severity of homozygous sickle cell disease in early childhood. *Journal of Pediatrics*. 1981; 98:37–41. [PubMed: 6161241]
- Stockman JA, Nigro MA, Mishkin MM, Oski FA. Occlusion of large cerebral vessels in sickle-cell anemia. *New England Journal of Medicine*. 1972; 287:846–849. [PubMed: 5071963]
- Teuscher T, Baillod B, Holzer BR. Prevalence of human parvovirus B19 in sickle cell disease and healthy controls. *Tropical and Geographical Medicine*. 1991; 43:108–110. [PubMed: 1661040]
- Thein SL, Craig JE. Genetics of Hb F/F cell variance in adults and heterocellular hereditary persistence of fetal hemoglobin. *Hemoglobin*. 1998; 22:401–414. [PubMed: 9859924]
- Tshilolo L, Mukendi R, Girot R. Sickle cell anemia in the south of Zaire. Study of two series of 251 and 340 patients followed-up 1988–1992. *Archives of Pediatrics*. 1996; 3:104–111. (in French).
- Veith R, Galanello R, Papayannopoulou T, Stamatoyannopoulos G. Stimulation of F-cell production in patients with sickle-cell anemia treated with cytarabine or hydroxyurea. *New England Journal of Medicine*. 1985; 313:1571–1575. [PubMed: 2415821]
- Vichinsky EP. Comprehensive care in sickle cell disease: its impact on morbidity and mortality. *Seminars in Hematology*. 1991; 28:220–226. [PubMed: 1887248]
- Ware RE, Steinberg MH, Kinney TR. Hydroxyurea: an alternative to transfusion therapy for stroke in sickle cell anemia. *American Journal of Hematology*. 1995; 50:140–143. [PubMed: 7572993]
- Ware RE, Zimmerman SA, Schultz WH. Hydroxyurea as an alternative to blood transfusions for the prevention of recurrent stroke in children with sickle cell disease. *Blood*. 1999; 94:3022–3026. [PubMed: 10556185]
- Weatherall DJ, Clegg JB. Inherited haemoglobin disorders: an increasing global health problem. *Bulletin of the World Health Organization*. 2001; 79:704–712. [PubMed: 11545326]
- Weatherall D, Hofman K, Rodgers G, Ruffin J, Hrynkow S. A case for developing north–south partnerships for research in sickle cell disease. *Blood*. 2005; 105:921–923. [PubMed: 15466925]
- Williams TN, Mwangi TW, Wambua S, Alexander ND, Kortok M, Snow RW, Marsh K. Sickle cell trait and the risk of *Plasmodium falciparum* malaria and other childhood diseases. *Journal of Infectious Diseases*. 2005; 192:178–186. [PubMed: 15942909]

- Woods GM, Jorgensen JH, Waclawiw MA, Reid C, Wang W, Pegelow CH, Rogers ZR, Iyer RV, Holbrook CT, Kinney TR, Vichinsky E, et al. Influence of penicillin prophylaxis on antimicrobial resistance in nasopharyngeal *S. pneumoniae* among children with sickle cell anemia. The Ancillary Nasopharyngeal Culture Study of Prophylactic Penicillin Study II. *Journal of Pediatric Hematology/oncology*. 1997; 19:327–333. [PubMed: 9256832]
- World Bank. *World Development Report: Investing in Health*. New York, NY: World Bank; 1993.
- World Health Organization. *Guidelines for the Control of Haemoglobin Disorders*. Geneva: WHO; 1994. Document WHO/HDP/HB/GL/94
- Yakubu AM, Werblinska B. Neurological disturbances in sickle cell disease in children in Zaria, Nigeria. *East African Medical Journal*. 1985; 62:129–133. [PubMed: 4042923]
- Yeats J, Daley H, Hardie D. Parvovirus B19 infection does not contribute significantly to severe anaemia in children with malaria in Malawi. *European Journal of Haematology*. 1999; 63:276–277. [PubMed: 10530420]
- Zarkowsky HS, Gallagher D, Gill FM, Wang WC, Falletta JM, Lande WM, Levy PS, Verter JJ, Wethers D. Bacteremia in sickle hemoglobinopathies. *Journal of Pediatrics*. 1986; 109:579–585. [PubMed: 3531449]

Table
Interventions that have reduced the morbidity and mortality associated with sickle cell disease (Claster and Vichinsky, 2003)

Target	Intervention(s)
Newborn screening	Counselling Family education Comprehensive-care programmes
Infection	Oral penicillin prophylaxis Pneumococcal vaccine
Pain	Analgesia Day-care units Hydroxyurea
Stroke	Long term blood transfusion
Surgery/anaesthesia	Pre-operative blood transfusion
Avascular necrosis of the hip	Decompressing coring procedures
Priapism	Adrenergic agonists Antiandrogens