REVIEW ARTICLE

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Sickle Cell Disease

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Sickle cell disease is an increasing global health problem. Estimates suggest that every year approximately 300,000 infants are born with sickle cell anemia, which is defined as homozygosity for the sickle hemoglobin (HbS) gene (i.e., for a missense mutation [Glu6Val, rs334] in the β-globin gene [*HBB*]) and that this number could rise to 400,000 by 2050.[1] Although early diagnosis, penicillin prophylaxis, blood transfusion, transcranial Doppler imaging, hydroxyurea, and hematopoietic stem-cell transplantation can dramatically improve survival and quality of life for patients with sickle cell disease, our understanding of the role of genetic and nongenetic factors in explaining the remarkable phenotypic diversity of this mendelian disease is still limited. Better prediction of the severity of sickle cell disease could lead to more precise treatment and management. Beyond well-known modifiers of disease severity, such as fetal hemoglobin (HbF) levels and α-thalassemia, other genetic variants might affect specific subphenotypes. Similarly, although the influence of altitude and temperature has long been reflected in advice to patients with sickle cell disease, recent studies of nongenetic factors, including climate and air quality, suggest more complex associations between environmental factors and clinical complications.[2] New treatments and management strategies accounting for these genetic and nongenetic factors could substantially and rapidly improve the quality of life and reduce health care costs for patients with sickle cell disease.

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DISTRIBUTION AND BURDEN OF DISEASE

Sickle cell disease is the most common monogenic disorder.[3] The prevalence of the disease is high throughout large areas in sub-Saharan Africa, the Mediterranean basin, the Middle East, and India because of the remarkable level of protection that the sickle cell trait (i.e., heterozygosity for the sickle cell mutation in *HBB*) provides against severe malaria.[4] Although the exact role of several mechanisms of protection that have been identified is still being debated, the "malaria hypothesis" formulated by Haldane in 1949 and by Allison in 1954 is a textbook example of natural selection and balanced polymorphism, a process that is ongoing.[5] Because of slave trading and contemporary population movements, the distribution of sickle cell disease has spread far beyond its origins.[6] Population estimates in the United States suggest that a total of approximately 100,000 persons have the disease.[7] There is neither a reliable, all-age estimate for any other country nor a global estimate, but newborn estimates consistently suggest that approximately 300,000 babies per year are born with sickle cell anemia.[8] The vast majority of these births occur in three countries: Nigeria, the Democratic Republic of the Congo, and India (Fig. 1).

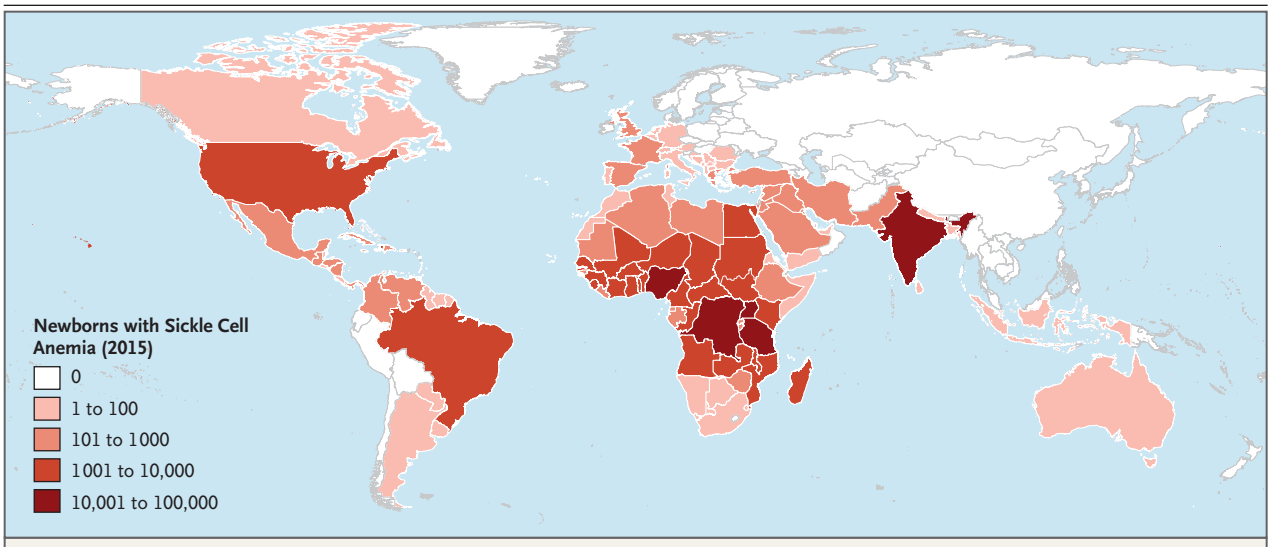

Figure 1. Number of Newborns with Sickle Cell Anemia in Each Country in 2015.
Data are based on estimates from Piel et al.[1] Alaska is shown separately from the rest of the United States.

The number of patients with sickle cell disease is expected to increase, both in high-income and lower-income countries.[1,9] In high-income countries, this increase largely reflects gains in life expectancy among affected persons as a result of interventions such as newborn screening, penicillin prophylaxis, primary stroke prevention, and hydroxyurea treatment (Table 1).[14] Life expectancy has improved significantly in high-income countries over the past 40 years, with childhood mortality now close to that in the general population[15] and an observed median survival of more than 60 years.[16]

Despite these remarkable achievements, life expectancy for patients with sickle cell disease is reduced by about 30 years, even with the best medical care, and the quality of life is often poor. Hydroxyurea treatment — the sole approved pharmacologic therapy for sickle cell disease — is increasingly used in both adults and children.[17] However, treatment and management of the disease remain costly,[18] making full access to care available only for the most privileged; otherwise, access is very limited because of increasing pressures on public health services.[19] New developments in the management of sickle cell disease are highlighted by many recent and ongoing phase 3 clinical trials (Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org) and by the increasing numbers of patients who are benefiting from hematopoietic stem-cell transplantation (Table S2 in the Supplementary Appendix).

In lower-income countries, where childhood mortality from all causes has been substantially reduced in the past two decades,[20] increased numbers of affected babies and young children now survive to adulthood, requiring diagnosis and treatment. In Africa, where there is a lack of newborn screening and routine childhood vaccinations and where malaria, malnutrition, and poverty remain important challenges, the mortality among children with sickle cell disease who are younger than 5 years of age can be as high as 90%.[21] Although a few large-scale screening programs have been successfully launched relatively recently (Table S3 in the Supplementary Appendix), the lack of a basic health care infrastructure in many regions makes the prevention and management of sickle cell disease extremely difficult.

PATHOPHYSIOLOGY

Sickle cell disease is a multisystem disorder that is caused by a single gene mutation. Nearly every organ in the body can be affected (Fig. 2). Characterized by the presence of abnormal erythrocytes damaged by HbS, this variant of normal adult hemoglobin (HbA) is inherited either from both parents (homozygosity for the HbS gene) or from one parent, along with another hemoglobin

Table 1. Summary of Recommended Treatment Approaches for Sickle Cell Disease.*

Treatment Approach	Dose and Frequency	Duration	Recommendation	Evidence Quality	Availability in Low-Resource Areas
Prevention of infection					
Penicillin V	62.5–250 mg, twice daily	At least until 5 yr of age	Strong	Moderate	Available
Pneumococcal vaccines	Every 5 yr, starting at 2 yr of age	Lifelong	Strong	Moderate	Limited availability
Malarial prophylaxis when appropriate	Daily (e.g., proguanil), weekly (e.g., pyrimethamine), or intermittent (e.g., mefloquine–artesunate or sulfadoxine–pyrimethamine plus amodiaquine)	Lifelong (in malarious area)	Strong	Low	Available
Blood transfusion					
Acute care					
Treatment of anemia	Simple transfusion; target hemoglobin level, 10 g/dl	Limited	Strong	Low	Limited availability
Preoperative transfusion (if hemoglobin <8.5 g/dl)	Simple transfusion, performed once; target hemoglobin level, 10 g/dl		Strong	Moderate	Limited availability
Ongoing care					
Primary stroke prevention	Target HbS, <30%; transfusions every 3–6 wk	Indefinite	Strong	High	Very limited availability
Secondary stroke prevention	Target HbS, <30% or <50%; transfusions every 3–6 wk	Indefinite	Moderate	Low	Very limited availability
Prevention of additional silent cerebral infarctions	Target HbS, <30%; transfusions every 3–6 wk	Indefinite	Moderate	Moderate	Very limited availability
Hydroxyurea					
Universal use	20–35 mg/kg/day	Indefinite	Moderate	Moderate	Limited availability
Prevention of acute complications	15–35 mg/kg/day	Indefinite	Strong	High	Limited availability
Primary stroke prevention	15–35 mg/kg/day	Indefinite	Strong	Moderate	Limited availability

* Data on recommended treatments, the strength of the recommendation, and the quality of the evidence are from DeBaun et al.,[10] Ware et al.,[11] and Yawn et al.[12] Data on availability in low-resource areas are from Bello-Manga et al.[13] HbS denotes sickle hemoglobin.

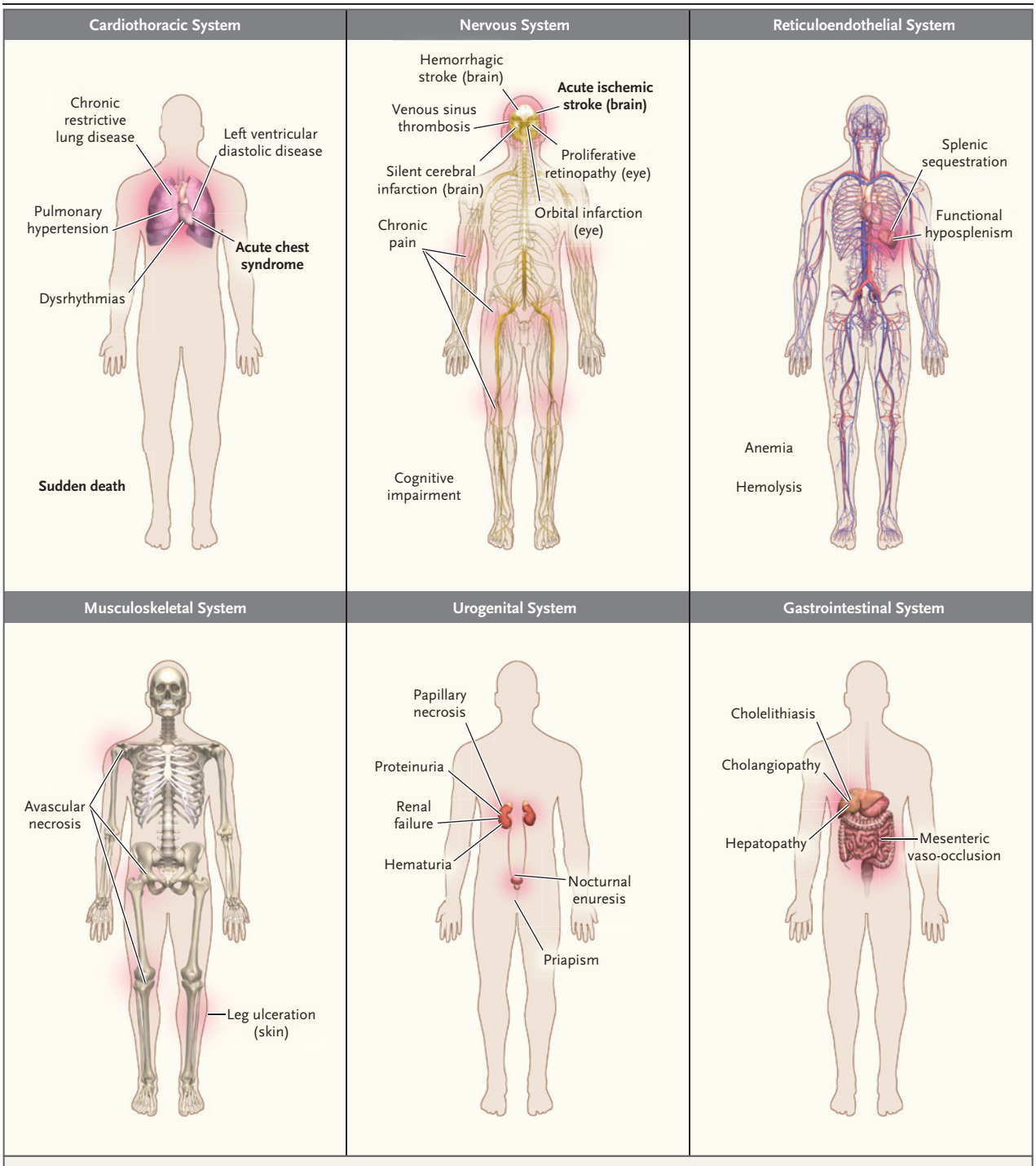

Figure 2. Common Clinical Complications of Sickle Cell Disease.

Data are from Rees et al.[3] and Serjeant.[22] Acute complications are shown in boldface type.

variant, such as hemoglobin C (HbC), or with β-thalassemia (compound heterozygosity). When deoxygenated, HbS polymerizes, damaging the erythrocyte and causing it to lose cations and water. These damaged cells have abnormalities in rheologic features and in the expression of adhesion molecules, resulting in hemolytic anemia and a likelihood of blocked small blood vessels, which in turn cause vaso-occlusion (Fig. S1 in the Supplementary Appendix). Vaso-occlusion typically causes acute complications, including ischemic damage to tissues, resulting in severe pain or organ failure. The acute chest syndrome is a typical example of organ failure in sickle cell disease and one of the leading causes of hospitalization and death among patients.[23]

Although HbS polymerization, vaso-occlusion, and hemolytic anemia are central to the pathophysiology of sickle cell disease, they precipitate a cascade of pathologic events, which in turn lead to a wide range of complications. These processes include vascular–endothelial dysfunction, functional nitric oxide deficiency, inflammation, oxidative stress and reperfusion injury, hypercoagulability, increased neutrophil adhesiveness, and platelet activation.[3] The interaction and relative importance of these disorders are poorly understood and probably differ according to the particular complication. Chronic complications fall into two main groups: those related to large-vessel vasculopathy (cerebrovascular disease, pulmonary hypertension, priapism, and retinopathy) and those caused by progressive ischemic organ damage (hyposplenism, renal failure, bone disease, and liver damage). Hyposplenism is a particularly important cause of illness and death in young children because of the increased risk of infection.

Patients with sickle cell disease may have any of a number of hemoglobin genotypes. Nearly all genetic studies of sickle cell disease have concentrated on the genotype of sickle cell anemia (i.e., *HBB* Glu6Val, rs334). Other genotypes of sickle cell disease are due to compound heterozygosity for the HbS gene and other hemoglobin (Hb) variants such as HbC, HbE, and HbD or to the many varieties of HbS–β-thalassemia. With the exception of HbS–β^0-thalassemia (β^0 denotes no HbA), the compound heterozygous genotypes of sickle cell disease are usually less clinically severe than is the genotype of sickle cell anemia. Nevertheless, within each sickle cell disease genotype there is substantial phenotypic heterogeneity.

Many studies have investigated phenotype–genotype relationships in sickle cell disease. Early evidence from studies of patients with sickle cell disease who were exposed to high altitude highlighted the influence of environmental factors on disease complications.[24] Later, the genetic identification of several haplotypes of the HbS gene (Bantu, Benin, Cameroon, Senegal, and Arab–Indian), suggesting different origins of the HbS mutation across areas of high prevalence, led to speculation that the HbS gene haplotype could explain phenotypic differences.[25] A pilot study, looking at nine identical twin pairs, tried to disentangle the roles of genetic and nongenetic factors, with interesting but limited results because of the small sample.[26] The following sections summarize current knowledge of the role of genetic and nongenetic modifiers (Fig. 3).

GENETIC MODIFIERS OF DISEASE SEVERITY

The phenotypic diversity of sickle cell anemia is partially explained by genetic variants controlling the expression of the HbF genes and coinheritance of the α-thalassemia gene. The role of other potential genetic modifiers is less clear.

α-THALASSEMIA

Polymerization of deoxygenated HbS initiates the pathologic changes that characterize sickle cell disease. The rate of HbS polymerization is highly dependent on the erythrocyte hemoglobin level, with lower levels of HbS leading to less cellular damage; α-thalassemia reduces the level of hemoglobin in the cell, indirectly mitigating HbS polymer–induced erythrocyte damage.[27] Caused most often by the deletion of one or two of the four α-globin genes, α-thalassemia is present in a third of patients of African origin and up to half of patients of Middle Eastern or Indian descent.[28] The coinheritance of α-thalassemia and

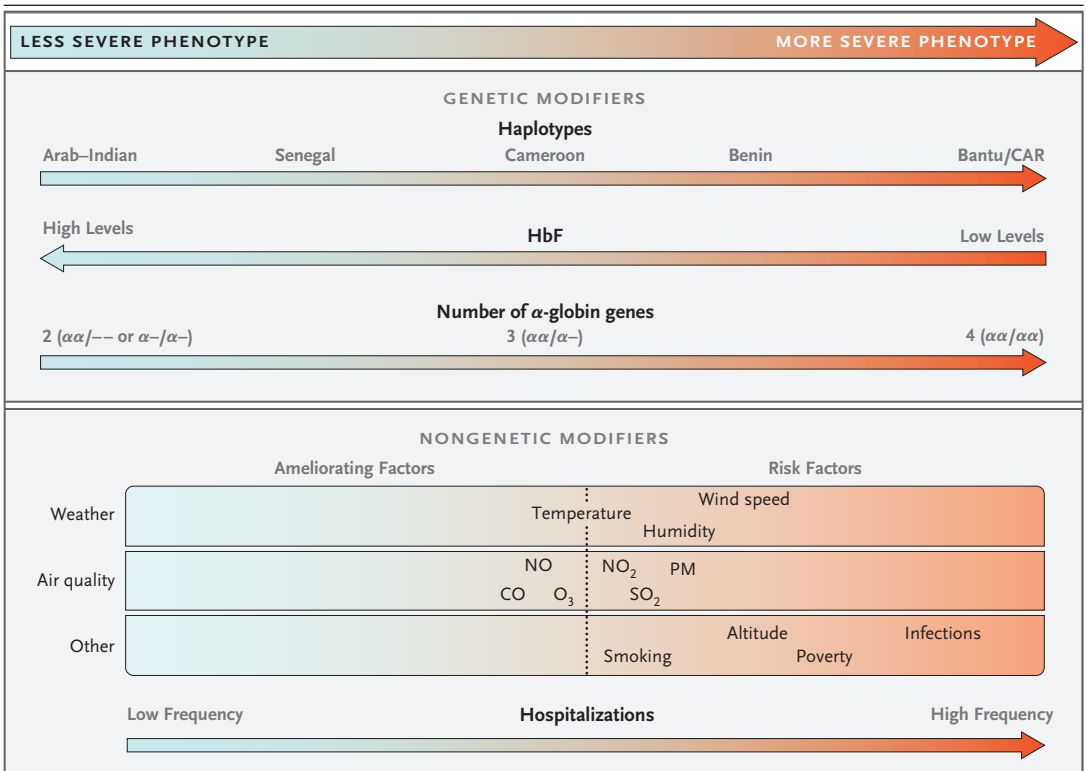

Figure 3. Current Evidence for Genetic and Nongenetic Modifiers of Phenotypic Severity in Sickle Cell Disease.

Arrows indicate whether the factor is usually associated with a milder or a more severe phenotype. The scale for nongenetic biomarkers is only indicative, since much of the evidence is inconsistent. CAR denotes Central African Republic, CO carbon monoxide, HbF fetal hemoglobin, NO nitric oxide, NO_2 nitrogen dioxide, O_3 ozone, PM particulate matter, and SO_2 sulfur dioxide.

sickle cell anemia is characterized by higher hemoglobin levels than the inheritance of sickle cell anemia alone, as well as by a lower mean corpuscular volume, less hemolysis, and fewer complications that have been associated with hemolysis epidemiologically (Table 2). Conversely, some features of disease associated with sickle cell vaso-occlusion, such as acute painful episodes, are more common in coinherited sickle cell anemia and α-thalassemia (Table 2), perhaps because of a higher packed-cell volume.[30,31]

Vascular homeostasis is maintained by endothelial nitric oxide, which relaxes perivascular smooth muscle.[32-34] The reduction in some hemolysis-associated complications in patients with both sickle cell anemia and α-thalassemia was hypothesized to result in part from preserved nitric oxide bioavailability that is compromised by intravascular hemolysis of sickle erythrocytes. During hemolysis, hemoglobin released into the plasma reacts with nitric oxide, forming inert nitrate, and erythrocyte arginase metabolizes arginine, the substrate for nitric oxide synthases. Nitric oxide activity is also inhibited by reaction with asymmetric dimethylarginine.[35,36] Nitric oxide bioavailability contributes to the phenotypic variability of sickle cell disease beyond coinheritance of α-thalassemias.[37]

FETAL HEMOGLOBIN

HbF interrupts polymerization of deoxygenated HbS, since HbF is excluded from the HbS polymer.[38] HbF levels peak in midgestation; by the time an unaffected, healthy infant reaches the age of 6 months, HbF accounts for less than 1% of the total hemoglobin, but the levels are higher in most adults with sickle cell disease (Table S4 in the Supplementary Appendix).

The first genetic variant associated with increased HbF in sickle cell anemia, which was a marker of the Senegal haplotype of the *HBB* cluster, was a single-nucleotide polymorphism

Table 2. The Effects of α-Thalassemia and Fetal Hemoglobin on Common Complications of Sickle Cell Anemia.*

Complication	α-Thalassemia	Fetal Hemoglobin
Stroke, silent infarction	Reduces risk	Little evidence of protection in childhood, when stroke is most common; possibly some protection in adulthood
Painful episodes	Increases risk	High level reduces risk
Acute chest syndrome	Is associated with little evidence of an effect	High level reduces risk
Osteonecrosis	Increases risk	Equivocal evidence of protection
Priapism	Reduces risk	Little evidence of protection
Leg ulcers	Reduces risk	High level provides protective effect
Cholelithiasis	Reduces risk	High level provides protective effect
Renal complications	Reduces risk	Little evidence of protection
Elevated tricuspid regurgitant velocity	Provides equivocal evidence of an effect	Little evidence of an effect
Reduced erythrocyte survival and hemoglobin level	Increases erythrocyte lifespan and hemoglobin level	Increases erythrocyte lifespan and hemoglobin level
Reduced survival	Probably has little effect on survival	Prolongs survival

* Data are based on studies that differed with respect to the experimental design and the demographic characteristics of the study participants. The findings were derived in part from Steinberg and Sebastiani.[29]

(SNP) (rs7482144) in the promoter region of *HBG2*, one of the paired HbF genes.[39] Carriers of this haplotype had HbF levels of about 10%, as compared with 5 to 6% in carriers of the two other common African haplotypes (Table S4 in the Supplementary Appendix). The silencing of the HbF genes from fetal development to adulthood is accounted for by the activity of *BCL11A* and *ZBTB7A*.[40] Genetic variation of an erythroid-specific enhancer of *BCL11A*, along with polymorphisms in an enhancer of *MYB*, explains 10 to 50% of the observed HbF variance among persons with sickle cell anemia, depending on the population examined.[41-43]

In the Eastern Province of Saudi Arabia and in India, the HbS gene is often on an autochthonous Arab–Indian *HBB* haplotype. In these cases, HbF levels in adults are nearly twice those found in the Senegalese haplotype. Consequently, the disease, especially in childhood, when HbF levels are about 30%, is usually milder.[44-46] The genetic basis of high HbF levels in these persons might in part lie in haplotype-specific polymorphisms of the superenhancer of the *HBB* cluster and other variants exclusive to this haplotype[47-49] (Table S4 in the Supplementary Appendix). Saudi patients with the Benin haplotype have HbF levels that are nearly twice as high as the levels in African patients with the same haplotype. The reason for this difference is unknown.

HbF does not ameliorate all subphenotypes of disease to the same extent (Table 2). The critical determinant of the effect of HbF on the phenotype of sickle cell disease is its level in each erythrocyte.[50] In compound heterozygotes for HbS and hereditary persistence of HbF where *HBB* is deleted, HbF makes up approximately 30% of total hemoglobin and is homogeneously distributed in the red-cell population, with each cell containing about 10 pg. This level is sufficient to thwart polymerization of deoxygenated HbS so that persons with this genotype have nearly normal hemoglobin levels and are mostly asymptomatic. Although hydroxyurea increases HbF levels in most patients, its distribution in sickle erythrocytes is heterogeneous. Cells with lower HbF levels are afforded less protection from polymer-induced damage, hemolytic anemia persists, and most patients remain symptomatic, albeit with a reduced rate of complications and perhaps improved survival. Alongside hydroxyurea, several new treatments based on HbF induction (e.g., histone deacetylase inhibitors, lysine-specific histone demethylase 1 [LSD1] inhibitors, and immunomodulatory drugs) are currently in various phases of investigation.[51]

OTHER GENETIC MODIFIERS

The biologic complexity of sickle cell disease provides numerous sites for its genetic modula-

tion by genes whose primary actions are extraerythrocytic. Many genetic polymorphisms have been associated with specific subphenotypes, with either a protective or a permissive effect on the biologic feature of interest. The clearest association markers have been found for stroke. Thirty-eight SNPs in 22 genes were genotyped in 130 patients with sickle cell anemia and stroke and in 103 patients who had sickle cell anemia without stroke (controls).[52] In addition to the known association of α-thalassemia with a reduced risk of stroke, SNPs in *ANXA2*, *TEK*, *ADCY9*, and *TGFBR3* were associated with an increased or a decreased risk of stroke. These results partially confirmed the results of a study that tested 108 SNPs in 39 candidate genes and showed that 31 SNPs in 12 genes modulated the risk of stroke.[53] Other genetic markers include polymorphisms in the genes for the bacteremia, osteonecrosis, and priapism subphenotypes (*CCL5*, *BMP6*, and *KL*, respectively).[29]

A consistent result of studies that preselected candidate genes to test the association of their variants with multiple subphenotypes was the detection of associations with several genes of the transforming growth factor β–SMAD–bone morphogenetic protein pathway.[29] This pathway regulates diverse cellular processes that are important in the pathophysiology of sickle cell disease, including inflammation, fibrosis, cell proliferation and hematopoiesis, osteogenesis, angiogenesis, wound healing, and the immune response. Genomewide association studies, which provide an unbiased assessment of the genetic association with a phenotype, have not replicated these candidate gene–based results. Such studies require thousands of participants and careful phenotypic analysis to achieve statistical significance if the contribution of a genetic variant to a phenotype is small. For sickle cell disease, obtaining such a large sample has not been possible. Other than the results of studies using the HbF level as a subphenotype, genomewide association studies have so far contributed little to an understanding of the genetic basis of phenotypic heterogeneity in sickle cell disease.

NONGENETIC MODIFIERS OF DISEASE SEVERITY

Research has mostly focused on genetic variants that account for the phenotypic variability of sickle cell disease, and the role of nongenetic factors has been relatively neglected. However, nongenetic factors may explain much of the clinical variability. Most dramatically, the survival of children with sickle cell disease in high-income countries approaches that of unaffected children,[54] whereas in most of sub-Saharan Africa, up to 90% of children with sickle cell disease die,[55] even though these are genetically very similar populations. Nongenetic factors include climate and air quality, as well as socioeconomic factors, which are assessed, for example, on the basis of access to medical care, safe blood transfusions, and treatment of infections.

CLIMATIC AND METEOROLOGIC FACTORS

A link between cold weather and acute complications of sickle cell disease was first described in the United States in 1924.[56] Proposed mechanisms include cold weather causing increased infections and peripheral vasoconstriction causing higher deoxygenation, decreasing shear flow[57] and vascular steal effects.[58] However, the link between cold weather and acute pain has been identified inconsistently in larger time-series analyses. Studies conducted in Ghana,[59] New York,[54] Virginia,[60,61] Jamaica,[62] Kuwait,[63] and Canada[64] suggest a link between cold and pain across a range of climates. Conversely, no effects of cold weather were found in Chicago[65] and Atlanta[66] and in two separate studies conducted in London.[67,68] A large study in Paris recently showed that both hot and cold weather were associated with increased episodes of pain.[69] These inconsistent findings may reflect differences in the methods and analyses used in these studies, which were all limited to analyzing the number of hospital admissions, which is a very indirect surrogate for pathophysiological changes associated with temperature variations. Some of the inconsistencies may also reflect the influence of location-specific features, including housing, clothing, and social and geographic factors, on the effects of temperature.[2]

Although not usually noted by patients, wind speed has emerged as a factor that is consistently associated with pain in sickle cell disease, and higher wind speeds have been associated with increased hospital admissions for pain in England,[68] France,[69] Canada,[64] and the United States.[70] It is unclear how high wind speeds might precipitate episodes of acute pain, although there is evidence that skin cooling can provoke vaso-occlu-

sion,[71] possibly as a result of impaired control of vascular tone.[71]

Both high and low humidity have been associated with increased hospital admissions for pain,[2] and higher pain scores were associated with increased humidity in a study in Canada.[64] Increased episodes of acute pain are reported during the rainy season in regions with tropical climates, such as Jamaica[62] and Nigeria,[59] although no consistent effects of rain emerge where the climate is temperate, such as France[69] and England.[68] Again, the inconsistencies may be due to differences in housing and social factors.

AIR QUALITY

Air pollution is emerging as an important cause of illness, although its role in sickle cell disease is poorly understood. In Europe and the United States, patients with sickle cell disease live predominantly in urban areas,[2] where they are exposed to high concentrations of pollutants, including several with bioactivity. As discussed above, sickle cell disease is associated with functional nitric oxide deficiency.[72] Small, retrospective studies in London suggested that short-term exposure to higher atmospheric nitric oxide levels was associated with fewer hospital admissions[73] and that prolonged exposure was associated with decreased markers of hemolysis.[74]

Carbon monoxide is another bioactive, gaseous pollutant, which in theory may be of therapeutic benefit in sickle cell disease, since carboxyhemoglobin is locked in the R (relaxed) form and cannot polymerize. The therapeutic role of carbon monoxide is currently being explored in a trial of pegylated bovine carboxyhemoglobin.[75] Studies in both Paris and London showed that higher atmospheric levels of carbon monoxide were associated with decreased hospital admissions for acute pain,[73] although the opposite effect was found in São Paulo.[76]

Other potentially important pollutants include ozone (O_3), nitrogen oxides (NO and NO_2), sulfur oxides (SO and SO_2), and particulate matter (PM_{10} and $PM_{2.5}$ [i.e., particulate matter with an aerodynamic diameter of 10 μm and 2.5 μm, respectively]), which have all been associated to varying degrees with complications in patients with sickle cell disease, without a coherent picture emerging.[73,74,76] There is good evidence that asthma is exacerbated by air pollutants, particularly ozone,[77] and there is a strong association between asthma and acute complications of sickle cell disease.[78]

The analysis and interpretation of climatic and air-quality effects are complicated by the close correlations among the various factors and the lack of consistency in methodologic and statistical approaches. Furthermore, all studies so far have looked at associations at the population level. The hope is that increasing use of mobile sensors to assess individual exposure will lead to clearer results.

OTHER ENVIRONMENTAL FACTORS

The home environment is likely to be a major determinant of health in patients with sickle cell disease, although this factor remains largely unexplored other than in a few studies suggesting that exposure to firsthand or secondhand tobacco smoke influences clinical outcomes and complications of sickle cell disease.[79] In addition, high altitude has been linked to various complications in sickle cell disease, presumably because of lower oxygen levels. However, the evidence for this association comes primarily from small studies performed before hydroxyurea was widely used, and the true effects of altitude are unclear. Splenic infarction occurs in sickle cell trait,[80] and splenic sequestration in patients with sickle hemoglobin C disease.[81] Acute vaso-occlusive pain also seems to be more common in patients living at high altitude.[82]

INFECTIOUS DISEASES

Infection is a major determinant of the outcome in patients with sickle cell disease, particularly children in Africa. Infection is probably the most important cause of premature deaths among these children. Splenic dysfunction has a key role in the increased susceptibility to bacterial infections seen in children with sickle cell disease,[83] and pneumococcal and haemophilus infections seem to be important both in the northern and southern hemispheres, suggesting that basic interventions, including penicillin prophylaxis and vaccinations, could lead to substantial improvement in survival among patients with sickle cell disease in lower-income countries, just as such interventions have done in high-income countries.[84] Malaria is the other infection that is widely believed to contribute to excess mortality among patients with sickle cell disease in Africa, although data supporting this belief are scant. Studies in

Kenya and Tanzania showed that the incidence of malaria was not increased among patients with sickle cell disease but that the risk of death was higher once malaria developed.[55,85]

In high-income countries, infection also contributes significantly to morbidity and mortality among patients with sickle cell disease, particularly as a cause of death in children (*Streptococcus pneumoniae*) and as a cause of osteomyelitis (salmonella, *Staphylococcus aureus,* gram-negative bacilli, and *Mycobacterium tuberculosis*)[86] and the acute chest syndrome (chlamydia, mycoplasma, and viruses) in all patients, regardless of age.[23] Although the spectrum of infections may vary across environments, the effect is greatly modified by the availability of facilities for prophylaxis and treatment, including access to antibiotics and safe blood transfusion.

PREVENTION AND MANAGEMENT

Premarital, antenatal, and neonatal screening programs have been established in some high-income countries, including parts of the Middle East and the United States, but more important, such programs are starting to be developed in areas with a very high prevalence of sickle cell disease, including India and some African countries (Table S3 in the Supplementary Appendix). The development of cheap and reliable point-of-care diagnostic tests with high sensitivity and specificity could hugely facilitate screening for sickle cell disease in these lower-income countries, particularly in rural areas across sub-Saharan Africa and India.[87] Nevertheless, if diagnosis is not followed by preventive interventions and treatment with an inexpensive oral agent to prevent complications of acute disease, genotypic identification is almost meaningless.

Clinical outcomes have gradually improved over the years, mostly as a result of developments in supportive care and treatment with hydroxyurea. Relatively few interventions have a strong evidence base, but those that do include penicillin prophylaxis in children,[88] primary stroke prevention with the use of transcranial Doppler screening and blood transfusion,[89] regular blood transfusions to prevent the progression of silent cerebral infarction,[10] and hydroxyurea to prevent acute pain and the acute chest syndrome[90] as well as primary stroke[11] (Table 1). With growing evidence of the safety and efficacy of hydroxyurea in both adults and children, its use is increasing in high- and lower-income countries, but it continues to be underused.[11,91] Various other small-molecule therapies are undergoing clinical trials; recent phase 3 trials are listed in Table S1 in the Supplementary Appendix. In addition, a New Drug Application has been submitted to the Food and Drug Administration for an oral, pharmaceutical-grade L-glutamine treatment to reduce the frequency of acute pain and hospitalizations among patients with sickle cell disease. Also, a recent report on a multicenter, phase 2, randomized, placebo-controlled, double-blind study showed that a monoclonal antibody inhibiting P-selectin[92] reduced the frequency of acute pain in adults with sickle cell disease. This is an exciting result, given that hydroxyurea is still the only drug with established efficacy for this indication.

Hematopoietic stem-cell transplantation is potentially curative, although its use is restricted by the high cost, toxicity, and limited availability of suitable donors. This is becoming potentially more applicable with the development of less toxic conditioning regimens and the use of alternative sources of donor cells,[93] although allogeneic stem-cell donation may be superseded by gene therapy and gene editing approaches (Table S2 in the Supplementary Appendix).[94] A recent case report describing the use of a self-inactivating lentiviral vector to inhibit HbS polymerization as a proof of concept of complete clinical remission with correction of hemolysis and biologic hallmarks of the disease certainly reflects the fast pace of current developments in gene therapy for sickle cell disease.[95] In view of the technical, economic, and ethical challenges, however, it seems very unlikely that these novel therapies will be widely used in the short term; in the longer term, high costs are likely to remain a major barrier to their availability, particularly in sub-Saharan Africa.

Some of the interventions currently used for the prevention and treatment of sickle cell disease in high-income countries would be cost-effective[96] and could save the lives of millions of children in sub-Saharan Africa if implemented now.[1] Other interventions, such as transcranial Doppler scanning or blood transfusion, could be much harder to scale up in areas with a high prevalence of sickle cell disease and limited availability of or access to health care (Table 1).

A better understanding of genetic modifiers is essential for advances in gene therapy and drug development. However, the identification of nongenetic risk factors would allow for the tailoring of advice given to patients, and this could potentially have an immediate effect in preventing clinical complications and improving the quality of life for hundreds of thousands of patients worldwide who have sickle cell disease.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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REFERENCES

1. Piel FB, Hay SI, Gupta S, Weatherall DJ, Williams TN. Global burden of sickle cell anaemia in children under five, 2010-2050: modelling based on demographics, excess mortality, and interventions. PLoS Med 2013;10(7):e1001484.
2. Tewari S, Brousse V, Piel FB, Menzel S, Rees DC. Environmental determinants of severity in sickle cell disease. Haematologica 2015;100:1108-16.
3. Rees DC, Williams TN, Gladwin MT. Sickle-cell disease. Lancet 2010;376:2018-31.
4. Piel FB, Patil AP, Howes RE, et al. Global distribution of the sickle cell gene and geographical confirmation of the malaria hypothesis. Nat Commun 2010;1:104.
5. Elguero E, Délicat-Loembet LM, Rougeron V, et al. Malaria continues to select for sickle cell trait in Central Africa. Proc Natl Acad Sci U S A 2015;112:7051-4.
6. Piel FB, Tatem AJ, Huang Z, Gupta S, Williams TN, Weatherall DJ. Global migration and the changing distribution of sickle haemoglobin: a quantitative study of temporal trends between 1960 and 2000. Lancet Glob Health 2014;2(2):e80-e89.
7. Hassell KL. Population estimates of sickle cell disease in the U.S. Am J Prev Med 2010;38:Suppl:S512-S521.
8. Piel FB, Patil AP, Howes RE, et al. Global epidemiology of sickle haemoglobin in neonates: a contemporary geostatistical model-based map and population estimates. Lancet 2013;381:142-51.
9. Weatherall DJ. The inherited diseases of hemoglobin are an emerging global health burden. Blood 2010;115:4331-6.
10. DeBaun MR, Gordon M, McKinstry RC, et al. Controlled trial of transfusions for silent cerebral infarcts in sickle cell anemia. N Engl J Med 2014;371:699-710.
11. Ware RE, Davis BR, Schultz WH, et al. Hydroxycarbamide versus chronic transfusion for maintenance of transcranial doppler flow velocities in children with sickle cell anaemia — TCD With Transfusions Changing to Hydroxyurea (TWiTCH): a multicentre, open-label, phase 3, non-inferiority trial. Lancet 2016;387:661-70.
12. Yawn BP, Buchanan GR, Afenyi-Annan AN, et al. Management of sickle cell disease: summary of the 2014 evidence-based report by expert panel members. JAMA 2014;312:1033-48.
13. Bello-Manga H, DeBaun MR, Kassim AA. Epidemiology and treatment of relative anemia in children with sickle cell disease in sub-Saharan Africa. Expert Rev Hematol 2016;9:1031-42.
14. Quinn CT, Rogers ZR, McCavit TL, Buchanan GR. Improved survival of children and adolescents with sickle cell disease. Blood 2010;115:3447-52.
15. Lê PQ, Gulbis B, Dedeken L, et al. Survival among children and adults with sickle cell disease in Belgium: benefit from hydroxyurea treatment. Pediatr Blood Cancer 2015;62:1956-61.
16. Gardner K, Douiri A, Drasar E, et al. Survival in adults with sickle cell disease in a high-income setting. Blood 2016;128:1436-8.
17. Wong TE, Brandow AM, Lim W, Lottenberg R. Update on the use of hydroxyurea therapy in sickle cell disease. Blood 2014;124:3850-3857, quiz 4004.
18. Kauf TL, Coates TD, Huazhi L, Mody-Patel N, Hartzema AG. The cost of health care for children and adults with sickle cell disease. Am J Hematol 2009;84:323-7.
19. Shortell SM, Addicott R, Walsh N, Ham C. The NHS Five Year Forward View: lessons from the United States in developing new care models. BMJ 2015;350:h2005.
20. Kyu HH, Pinho C, Wagner JA, et al. Global and national burden of diseases and injuries among children and adolescents between 1990 and 2013: findings from the Global Burden of Disease 2013 study. JAMA Pediatr 2016;170:267-87.
21. Grosse SD, Odame I, Atrash HK, Amendah DD, Piel FB, Williams TN. Sickle cell disease in Africa: a neglected cause of early childhood mortality. Am J Prev Med 2011;41:Suppl 4:S398-S405.
22. Serjeant GR. The role of preventive medicine in sickle cell disease: the Watson Smith lecture. J R Coll Physicians Lond 1996;30:37-41.
23. Vichinsky EP, Neumayr LD, Earles AN, et al. Causes and outcomes of the acute chest syndrome in sickle cell disease. N Engl J Med 2000;342:1855-65.
24. Ware M, Tyghter D, Staniforth S, Serjeant G. Airline travel in sickle-cell disease. Lancet 1998;352:652.
25. Bitoungui VJ, Pule GD, Hanchard N, Ngogang J, Wonkam A. Beta-globin gene haplotypes among cameroonians and review of the global distribution: is there a case for a single sickle mutation origin in Africa? OMICS 2015;19:171-9.
26. Weatherall MW, Higgs DR, Weiss H, Weatherall DJ, Serjeant GR. Phenotype/genotype relationships in sickle cell disease: a pilot twin study. Clin Lab Haematol 2005;27:384-90.
27. Hofrichter J, Ross PD, Eaton WA. Kinetics and mechanism of deoxyhemoglobin S gelation: a new approach to understanding sickle cell disease. Proc Natl Acad Sci U S A 1974;71:4864-8.
28. Steinberg MH, Embury SH. Alpha-thalassemia in blacks: genetic and clinical aspects and interactions with the sickle hemoglobin gene. Blood 1986;68:985-90.
29. Steinberg MH, Sebastiani P. Genetic modifiers of sickle cell disease. Am J Hematol 2012;87:795-803.
30. Kato GJ, Gladwin MT, Steinberg MH. Deconstructing sickle cell disease: reappraisal of the role of hemolysis in the development of clinical subphenotypes. Blood Rev 2007;21:37-47.
31. Taylor JG VI, Nolan VG, Mendelsohn L, Kato GJ, Gladwin MT, Steinberg MH. Chronic hyper-hemolysis in sickle cell anemia: association of vascular complications and mortality with less frequent vasoocclusive pain. PLoS One 2008;3(5):e2095.
32. Cannon RO III, Schechter AN, Panza JA, et al. Effects of inhaled nitric oxide on regional blood flow are consistent with intravascular nitric oxide delivery. J Clin Invest 2001;108:279-87.
33. Dejam A, Hunter CJ, Schechter AN, Gladwin MT. Emerging role of nitrite in human biology. Blood Cells Mol Dis 2004;32:423-9.
34. Kim-Shapiro DB, Schechter AN, Gladwin MT. Unraveling the reactions of nitric oxide, nitrite, and hemoglobin in physiology and therapeutics. Arterioscler Thromb Vasc Biol 2006;26:697-705.
35. Morris CR, Kato GJ, Poljakovic M, et al. Dysregulated arginine metabolism, hemolysis-associated pulmonary hypertension, and mortality in sickle cell disease. JAMA 2005;294:81-90.
36. Landburg PP, Teerlink T, Biemond BJ, et al. Plasma asymmetric dimethylarginine concentrations in sickle cell disease are related to the hemolytic phenotype. Blood Cells Mol Dis 2010;44:229-32.
37. Kato GJ. Defective nitric oxide metabolism in sickle cell disease. Pediatr Blood Cancer 2015;62:373-4.
38. Akinsheye I, Alsultan A, Solovieff N, et al. Fetal hemoglobin in sickle cell anemia. Blood 2011;118:19-27.
39. Nagel RL, Fabry ME, Pagnier J, et al.

Hematologically and genetically distinct forms of sickle cell anemia in Africa — the Senegal type and the Benin type. N Engl J Med 1985;312:880-4.
40. Masuda T, Wang X, Maeda M, et al. Transcription factors LRF and BCL11A independently repress expression of fetal hemoglobin. Science 2016;351:285-9.
41. Bae HT, Baldwin CT, Sebastiani P, et al. Meta-analysis of 2040 sickle cell anemia patients: BCL11A and HBS1L-MYB are the major modifiers of HbF in African Americans. Blood 2012;120:1961-2.
42. Bauer DE, Kamran SC, Lessard S, et al. An erythroid enhancer of BCL11A subject to genetic variation determines fetal hemoglobin level. Science 2013;342:253-7.
43. Lettre G, Sankaran VG, Bezerra MA, et al. DNA polymorphisms at the BCL11A, HBS1L-MYB, and beta-globin loci associate with fetal hemoglobin levels and pain crises in sickle cell disease. Proc Natl Acad Sci U S A 2008;105:11869-74.
44. Alsultan A, Alabdulaali MK, Griffin PJ, et al. Sickle cell disease in Saudi Arabia: the phenotype in adults with the Arab-Indian haplotype is not benign. Br J Haematol 2014;164:597-604.
45. Perrine RP, John P, Pembrey M, Perrine S. Sickle cell disease in Saudi Arabs in early childhood. Arch Dis Child 1981; 56:187-92.
46. Perrine RP, Pembrey ME, John P, Perrine S, Shoup F. Natural history of sickle cell anemia in Saudi Arabs: a study of 270 subjects. Ann Intern Med 1978;88:1-6.
47. Dean A. On a chromosome far, far away: LCRs and gene expression. Trends Genet 2006;22:38-45.
48. Vathipadiekal V, Alsultan A, Baltrusaitis K, et al. Homozygosity for a haplotype in the HBG2-OR51B4 region is exclusive to Arab-Indian haplotype sickle cell anemia. Am J Hematol 2016;91(6):E308-E311.
49. Shaikho EM, Habara AH, Alsultan A, et al. Variants of *ZBTB7A* (LRF) and its β-globin gene cluster binding motifs in sickle cell anemia. Blood Cells Mol Dis 2016;59:49-51.
50. Steinberg MH, Chui DH, Dover GJ, Sebastiani P, Alsultan A. Fetal hemoglobin in sickle cell anemia: a glass half full? Blood 2014;123:481-5.
51. Telen MJ. Beyond hydroxyurea: new and old drugs in the pipeline for sickle cell disease. Blood 2016;127:810-9.
52. Flanagan JM, Frohlich DM, Howard TA, et al. Genetic predictors for stroke in children with sickle cell anemia. Blood 2011;117:6681-4.
53. Sebastiani P, Ramoni MF, Nolan V, Baldwin CT, Steinberg MH. Genetic dissection and prognostic modeling of overt stroke in sickle cell anemia. Nat Genet 2005;37:435-40.
54. Telfer P, Coen P, Chakravorty S, et al. Clinical outcomes in children with sickle cell disease living in England: a neonatal cohort in East London. Haematologica 2007;92:905-12.
55. Makani J, Komba AN, Cox SE, et al. Malaria in patients with sickle cell anemia: burden, risk factors, and outcome at the outpatient clinic and during hospitalization. Blood 2010;115:215-20.
56. Graham GS. A case of sickle cell anemia with necropsy. Arch Intern Med 1924; 34:778-800.
57. Lipowsky HH, Williams ME. Shear rate dependency of red cell sequestration in skin capillaries in sickle cell disease and its variation with vasoocclusive crisis. Microcirculation 1997;4:289-301.
58. Serjeant GR, Chalmers RM. Current concerns in haematology. 1. Is the painful crisis of sickle cell disease a "steal" syndrome? J Clin Pathol 1990;43:789-91.
59. Konotey-Ahulu FI. Sicklaemic human hygrometers. Lancet 1965;1:1003-4.
60. Amjad H, Bannerman RM, Judisch JM. Sickling pain and season. Br Med J 1974;2:54.
61. Smith WR, Coyne P, Smith VS, Mercier B. Temperature changes, temperature extremes, and their relationship to emergency department visits and hospitalizations for sickle cell crisis. Pain Manag Nurs 2003;4:106-11.
62. Redwood AM, Williams EM, Desal P, Serjeant GR. Climate and painful crisis of sickle-cell disease in Jamaica. Br Med J 1976;1:66-8.
63. Ibrahim AS. Relationship between meteorological changes and occurrence of painful sickle cell crises in Kuwait. Trans R Soc Trop Med Hyg 1980;74:159-61.
64. Rogovik AL, Persaud J, Friedman JN, Kirby MA, Goldman RD. Pediatric vasoocclusive crisis and weather conditions. J Emerg Med 2011;41:559-65.
65. Seeler RA. Non-seasonality of sickle-cell crisis. Lancet 1973;2:743.
66. Slovis CM, Talley JD, Pitts RB. Non relationship of climatologic factors and painful sickle cell anemia crisis. J Chronic Dis 1986;39:121-6.
67. Kehinde MO, Marsh JCW, Marsh GW. Sickle cell disease in North London. Br J Haematol 1987;66:543-7.
68. Jones S, Duncan ER, Thomas N, et al. Windy weather and low humidity are associated with an increased number of hospital admissions for acute pain and sickle cell disease in an urban environment with a maritime temperate climate. Br J Haematol 2005;131:530-3.
69. Mekontso Dessap A, Contou D, Dandine-Roulland C, et al. Environmental influences on daily emergency admissions in sickle-cell disease patients. Medicine (Baltimore) 2014;93(29):e280.
70. Nolan VG, Zhang Y, Lash T, Sebastiani P, Steinberg MH. Association between wind speed and the occurrence of sickle cell acute painful episodes: results of a case-crossover study. Br J Haematol 2008;143:433-8.
71. Mohan J, Marshall JM, Reid HL, Thomas PW, Hambleton I, Serjeant GR. Peripheral vascular response to mild indirect cooling in patients with homozygous sickle cell (SS) disease and the frequency of painful crisis. Clin Sci (Lond) 1998;94: 111-20.
72. Kato GJ, Hebbel RP, Steinberg MH, Gladwin MT. Vasculopathy in sickle cell disease: biology, pathophysiology, genetics, translational medicine, and new research directions. Am J Hematol 2009;84:618-25.
73. Yallop D, Duncan ER, Norris E, et al. The associations between air quality and the number of hospital admissions for acute pain and sickle-cell disease in an urban environment. Br J Haematol 2007; 136:844-8.
74. Mittal H, Roberts L, Fuller GW, et al. The effects of air quality on haematological and clinical parameters in children with sickle cell anaemia. Ann Hematol 2009;88:529-33.
75. Abuchowski A. PEGylated bovine carboxyhemoglobin (SANGUINATE): results of clinical safety testing and use in patients. Adv Exp Med Biol 2016;876:461-7.
76. Barbosa SMD, Farhat SCL, Martins LC, et al. Air pollution and children's health: sickle cell disease. Cad Saude Publica 2015;31:265-75.
77. Friedman MS, Powell KE, Hutwagner L, Graham LM, Teague WG. Impact of changes in transportation and commuting behaviors during the 1996 Summer Olympic Games in Atlanta on air quality and childhood asthma. JAMA 2001;285: 897-905.
78. DeBaun MR, Strunk RC. The intersection between asthma and acute chest syndrome in children with sickle-cell anaemia. Lancet 2016;387:2545-53.
79. Sadreameli SC, Eakin MN, Robinson KT, Alade RO, Strouse JJ. Secondhand smoke is associated with more frequent hospitalizations in children with sickle cell disease. Am J Hematol 2016;91:313-7.
80. Goodman J, Hassell K, Irwin D, Witkowski EH, Nuss R. The splenic syndrome in individuals with sickle cell trait. High Alt Med Biol 2014;15:468-71.
81. Githens JH, Gross GP, Eife RF, Wallner SF. Splenic sequestration syndrome at mountain altitudes in sickle/hemoglobin C disease. J Pediatr 1977;90:203-6.
82. Mahony BS, Githens JH. Sickling crises and altitude: occurrence in the Colorado patient population. Clin Pediatr (Phila) 1979;18:431-8.
83. Brousse V, Buffet P, Rees D. The spleen and sickle cell disease: the sick(led) spleen. Br J Haematol 2014;166:165-76.
84. Williams TN, Uyoga S, Macharia A, et al. Bacteraemia in Kenyan children with sickle-cell anaemia: a retrospective cohort and case-control study. Lancet 2009;374: 1364-70.
85. McAuley CF, Webb C, Makani J, et al. High mortality from Plasmodium falci-

parum malaria in children living with sickle cell anemia on the coast of Kenya. Blood 2010;116:1663-8.
86. Hughes M, Akram Q, Rees DC, Jones AK. Haemoglobinopathies and the rheumatologist. Rheumatology (Oxford) 2016; 55:2109-18.
87. Kanter J, Telen MJ, Hoppe C, Roberts CL, Kim JS, Yang X. Validation of a novel point of care testing device for sickle cell disease. BMC Med 2015;13:225.
88. Gaston MH, Verter JI, Woods G, et al. Prophylaxis with oral penicillin in children with sickle cell anemia — a randomized trial. N Engl J Med 1986;314:1593-9.
89. Adams RJ, McKie VC, Hsu L, et al. Prevention of a first stroke by transfusions in children with sickle cell anemia and abnormal results on transcranial Doppler ultrasonography. N Engl J Med 1998;339:5-11.
90. Charache S, Terrin ML, Moore RD, et al. Effect of hydroxyurea on the frequency of painful crises in sickle cell anemia. N Engl J Med 1995;332:1317-22.
91. Mulaku M, Opiyo N, Karumbi J, Kitonyi G, Thoithi G, English M. Evidence review of hydroxyurea for the prevention of sickle cell complications in low-income countries. Arch Dis Child 2013;98:908-14.
92. Ataga KI, Kutlar A, Kanter J, et al. Crizanlizumab for the prevention of pain crises in sickle cell disease. N Engl J Med 2017;376:429-39.
93. Hsieh MM, Fitzhugh CD, Weitzel RP, et al. Nonmyeloablative HLA-matched sibling allogeneic hematopoietic stem cell transplantation for severe sickle cell phenotype. JAMA 2014;312:48-56.
94. Hoban MD, Orkin SH, Bauer DE. Genetic treatment of a molecular disorder: gene therapy approaches to sickle cell disease. Blood 2016;127:839-48.
95. Ribeil JA, Hacein-Bey-Abina S, Payen E, et al. Gene therapy in a patient with sickle cell disease. N Engl J Med 2017;376: 848-55.
96. Kuznik A, Habib AG, Munube D, Lamorde M. Newborn screening and prophylactic interventions for sickle cell disease in 47 countries in sub-Saharan Africa: a cost-effectiveness analysis. BMC Health Serv Res 2016;16:304.