Sickle cell disease: Clinical presentation and management of a global health challenge


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ABSTRACT

Sickle cell disease is an autosomal recessive, multisystem disorder, characterised by chronic haemolytic anaemia, painful episodes of vaso-occlusion, progressive organ failure and a reduced life expectancy. Sickle cell disease is the most common monogenetic disease, with millions affected worldwide. In well-resourced countries, comprehensive care programs have increased life expectancy of sickle cell disease patients, with almost all infants surviving into adulthood. Therapeutic options for sickle cell disease patients are however, still scarce. Predictors of sickle cell disease severity and a better understanding of pathophysiology and (epi)genetic modifiers are warranted and could lead to more precise management and treatment. This review provides an extensive summary of the pathophysiology and management of sickle cell disease and encompasses the characteristics, complications and current and future treatment options of the disease.

1. Introduction

Sickle cell disease is an autosomal recessive, multisystem disorder, characterised by chronic haemolytic anaemia, painful ischaemic episodes of vaso-occlusion, and progressive organ failure. Sickle cell disease is the most common monogenetic disease, with millions affected worldwide. The vast majority of sickle cell disease births occur in sub-Saharan Africa. Due to absence of newborn screening, 50 to 90% of these children will die undiagnosed in the first five years of their life [1–4]. In contrast, in well-resourced countries, comprehensive care programs have increased life expectancy of sickle cell disease patients, with almost all infants surviving into adulthood [5]. Therapeutic options for sickle cell disease patients are however, still scarce. The only clinically available and notably safe disease-modifying treatment

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modalities are hydroxyurea and blood (exchange) transfusions. Haematopoietic stem cell transplantation (HSCT) remains the only curative treatment option. Unfortunately, its use is limited by the lack of suitable donors and concerns about toxicity. Early results of gene therapy trials are promising and may form a potential alternative [6].

2. Classification

Sickle cell disease is a term for a group of conditions resulting from the inheritance of haemoglobin S (HbS). The most prevalent form is HbSS with homozygosity for the S allele in the β-globin gene. Variant syndromes include haemoglobinopathies in which the sickle mutation in the β-globin gene is inherited in combination with another β-globin gene mutation (compound heterozygous sickle cell disease), such as haemoglobin C (HbSC) – the second most common form of sickle cell disease, haemoglobin D (HbSD), haemoglobin E (HbSE), or various forms with a β-thalassaemia mutation (HbSβ0 or HbSβ+ -thalassaemia). The inheritance of both HbA (normal adult haemoglobin) and HbS is defined as sickle cell trait or sickle cell carrier status (HbAS).

3. Epidemiology: Prevalence and burden of disease

The HbS allele was originally distributed throughout sub-Saharan Africa, the Middle East, the Mediterranean area and India. Carrier rates range from 5% to > 40% in these areas [7]. This wide distribution of the HbS allele is indicative of the natural selection of heterozygous HbAS individuals by their relative protection against Plasmodium falciparum malaria. Although the exact mechanism of this protection is yet to be fully understood, several studies have verified the abnormal transportation of malaria parasites and lower parasite densities in HbAS individuals [8–11]. Migration from these malaria-endemic regions to North America, Western Europe and Australia has subsequently led to spreading of the HbS allele far beyond its origins. In addition, with increasing numbers of migrants from countries with HbS allele frequencies higher than 10%, the number of individuals with sickle cell disease in new populations is increasing [12].

The prevalence of sickle cell disease is highest in Nigeria, India and the Democratic Republic of Congo, where half of the world's sickle cell disease population lives. Moreover explicitly, 75% of the global burden of sickle cell disease occurs in sub-Saharan Africa [1,13], where the majority of children with the disease do not reach their fifth birthday. Generally, diagnostic facilities are poor and routine neonatal screening is lacking in these regions. Most infants will therefore die undiagnosed due to acute complications, most notably bacterial sepsis or severe anaemia [14]. In contrast, life expectancy of children with sickle cell disease in well-resourced countries has significantly improved. This has been achieved by the introduction of comprehensive care programs which include neonatal screening, penicillin prophylaxis and hydroxyurea treatment [15]. Recent data from an adult cohort (HbSS and HbSβ0 genotype) in a high-income setting, even reported a median lifespan of sickled erythrocytes in a West Indian student in 1910 [20]. Sickled erythrocytes are rigid, lysis-prone and interact with leucocytes and the vascular endothelium. This results in haemolytic anaemia and recurrent occlusion of the small vessels. Vaso-occlusion leads to ischaemic damage of tissues resulting in severe pain and cumulative organ damage. Subsequent reperfusion of ischaemic tissues promotes chronic inflammation by increased reactive oxygen species (ROS) production [21]. Concomitantly, inflammation amplifies the expression of adhesion molecules, further increasing adherence of sickled erythrocytes to the vascular wall and worsening of vaso-occlusion [22].

Haemolysis in sickle cell disease is also a direct result of HbS polymerisation which damages the sickle cell erythrocyte membrane. The lifespan of sickled erythrocytes is at least six times shorter than that of normal erythrocytes; i.e. 10–20 days versus 120 days. Haemolysis results in the release of haemoglobin and arginase-1 from the erythrocyte into plasma, where they scavenge nitric oxide (NO) and its precursor L-arginine, causing decreased NO bioavailability [23,24]. NO regulates basal vessel tonus by initiating and maintaining vasodilatation. In addition, NO inhibits adhesion molecules and platelet activation and maintains the haemostatic balance [25–27]. Cell free plasma haemoglobin and haem are referred to as erythrocyte damage-associated molecular pattern molecules, which drive oxidative and inflammatory stress. As a consequence persistent intravascular haemolysis promotes vasoconstriction, hypercoagulability and the development of vasculopathy [28,29].

4. Phenotypic heterogeneity

Although a typical Mendelian disease, the clinical expression of sickle cell disease varies significantly. Many studies have investigated genotype- phenotype relationships and it is currently generally accepted that the individual course of disease is influenced by a combination of genetic, epigenetic and environmental factors and their interaction.

4.2.1. Genetic modifiers of disease severity

With the exception of HbSβ0-thalassaemia, the compound heterozygous genotypes of sickle cell disease are generally less severe than the homozygous genotype (HbSS). However, even within identical genotypes, there is a broad range of disease severity. Besides the causative genotype, the clinical phenotype of sickle cell disease is most strongly influenced by two key genetic modifiers: foetal haemoglobin (HbF) expression and co-inheritance of β-thalassaemia [30]. The role of other potential genetic modulators is less clear.

4.2.1.1. β-globin genotypes. The likelihood of sickling is highly dependent on the haemoglobin composition in the erythrocyte, the concentration of HbS, and concentration and type of non-S haemoglobin [31,32]. Hence, it is not surprising that the major primary genetic determinant of disease severity is the specific genotype of sickle cell disease. Homozygous and HbSβ0-thalassaemia
individuals have a haemoglobin composition almost exclusively HbS. The presence of HbA in HbSβ+-thalassaemia has a diluting effect on the individual's haemoglobin.

Abbreviations; HbF: foetal haemoglobin.

Table 1

<table>
<thead>
<tr>
<th>Subphenotype/complication</th>
<th>Gene(s)</th>
<th>Reference(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute vaso-occlusive pain</td>
<td>KIAA1109</td>
<td>Chaturvedi et al., 2017</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>APOB</td>
<td>Zhang et al., 2015</td>
</tr>
<tr>
<td>Acute chest syndrome</td>
<td>COMMD7</td>
<td>Galanneau et al., 2013</td>
</tr>
<tr>
<td>Bilirubin levels and cholelithiasis</td>
<td>UGT1A</td>
<td>Milton et al., 2012</td>
</tr>
<tr>
<td>Nephropathy</td>
<td>MYH9 - APOL1</td>
<td>Kao et al., 2008</td>
</tr>
<tr>
<td>HbF -levels</td>
<td>BCL11A, HBS1L-MYB (HMIP), the 5′HBβ region (i.e. Xmn1-HBG2)</td>
<td>Thein et al., 2007; Uda et al., 2008; Solovieff et al., 2010</td>
</tr>
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4.2.1.2. Foetal haemoglobin. HbF is the major haemoglobin type of the foetus and newborn. By the time a healthy infant reaches the age of 6 months, HbF accounts for < 5% of the total haemoglobin and continues to fall thereafter, reaching adult levels of < 1% by 2 years of age [36]. As both foetal and adult haemoglobin contain α-globin chains, the switch from HbF to HbA is essentially the replacement of γ-globin with β-globin. However, this switch is not complete as it does not lead to a total extinction of HbF in adult life. Mutations that affect β-globin functioning and production (e.g. sickle cell disease and β-thalassaemia) only become clinically apparent as the number of erythrocytes that contain measurable HbF declines [37]. In sickle cell disease patients, persistence of significant HbF levels beyond infancy can ameliorate the severity of the disease [38], including reduced painful vaso-occlusive crises and increased life expectancy [5,39].

The degree of persistent HbF varies greatly between sickle cell disease patients (from 1% up to > 25%) and is largely genetically controlled [40]. The BCL11A gene and ZBTB7A gene (LRF protein) are responsible for the physiological decrease in HbF expression and the switch to adult haemoglobin production [41]. Depending on the population, genetic variations of BLC11A, HBS1L-MYB and HBB loci explain up to 50% of HbF variance in individuals with sickle cell disease [42-44]. See Supplementary Table S1 for an overview of the best established genetic HbF modifiers and their evidence in cells, mice and humans.

Increased HbF levels reduce total HbS concentration, since HbF is excluded from the HbS polymer thereby inhibiting HbS polymerisation [45]. However, the specific HbF level in each individual erythrocyte seems most critical. Patients with high HbF% may exhibit severe disease if HbF is unevenly distributed among F-cells (red blood cells with detectable HbF), with a majority of erythrocytes containing insufficient HbF concentrations to inhibit HbS polymerisation [46].

4.2.1.3. Alpha-thalassaemia. Co-inheritance of α-thalassaemia exists in up to one third of patients of African origin with sickle cell disease, and is present in more than half of the patients in India and Saudi Arabia. Normally, humans have four α-globin genes two on each copy of chromosome 16. The co-inherited α-thalassaemia in sickle cell disease is almost always a result of heterozygosity (−α/αα) or homozygosity (−α/−α) for the α-globin gene deletion [47].

Pathophysiologically, co-inheritance of α-thalassaemia positively influences sickle cell disease phenotype. Due to a decreased presence of α-globin chains, the haemoglobin concentration in the erythrocyte is reduced, which leads to less HbS polymerisation and therefore reduced HbS polymer induced damage. This results in less haemolysis with a higher haematocrit, a lower mean corpuscular volume (MCV) and a lower reticulocyte count [48]. Therefore, patients with sickle cell disease and concomitant α-thalassaemia have a reduced incidence of complications associated with the presence of haemolytic anaemia [49]. This reduction is presumably due to preserved NO bioactivity and reduced chronic inflammation, both as a result of decreased intravascular haemolysis [50]. However, it has also been reported that clinical symptoms associated with microvascular occlusion such as painful vaso-occlusive events, acute chest syndrome and osteonecrosis, may be more common in patients with co-inherited α-thalassaemia, due to increases in haematocrit and therefore blood viscosity [48].

4.2.1.4. Other. Before the development of genome-wide genotyping arrays, molecular genetic research in sickle cell disease was performed with combinations of linkage- and candidate-gene-based approaches [51]. These strategies are complex, since many prior supposed associations between sickle cell disease complications and genetic
aberrations could not be reproduced by genome-wide association studies (GWAS) [52].

Association studies with GWAS-level significance in sickle cell disease are summarised in Table 1.

4.2.1.5. Environmental factors. Environmental factors are likely to play an important role in the phenotypic variability of sickle cell disease. However, studies are limited and results are often inconsistent. Nongenetic factors include socio-economic factors as well as meteorological factors and air quality. Identification of environmental factors that trigger or provoke clinical complications is important. Alteration may lead to improvements in patient care, better quality of life and reduction of hospital admissions and healthcare costs.

4.2.1.6. Socioeconomic factors. Socioeconomic factors are important determinants of health in all individuals. Poverty is associated with higher rates of illness, shorter life expectancy, high stress levels, low birth weight and many other negative health outcomes in general [53]. The ‘Cooperative Study of Sickle Cell Disease (CSSCD)’ suggests that socioeconomic status differs in families with sickle cell disease when compared to matched families in the same country. The study also found a higher percentage of single female heads of household within the sickle cell disease population. Moreover, male sickle cell disease patients had a lower median income compare to healthy black males [54,55]. In addition, low socio-economic status has been reported to be associated with poor academic performance [56]. Another study found lower admission rates for children during weekends, particularly for vaso-occlusive crises. This may arise from the fact that parents are able to stay at home and look after their children at the weekends, whereas this is much more difficult during working days [57].

4.2.1.7. Geography. Geographic location also plays a role in sickle cell disease outcomes. Use of healthcare services is lower in patients living in rural areas, even though they have lower physical functioning and higher socioeconomic distress levels [58,59]. In addition, distance to care has been associated with increases in patient hospitalisations [60].

It has been well documented that exposure to altitude leads to an increased risk of vaso-occlusive crises in children and adults with sickle cell disease [61,62]. Atmospheric pressure and inspired oxygen pressure fall roughly linearly with altitude [63]. Reduced oxygen tension may lead to increased Hbs polymerization and erythrocyte sickling. Therefore, patients living at high, and even moderate altitude, have increased sickle cell-related complication rates [64].

4.2.1.8. Weather and air pollution. An association between acute painful vaso-occlusive events and weather conditions has been recognised for > 80 years, with special note of an increase in vaso-occlusive crises in presence of cold weather [65–68]. Interestingly, a large study in London and Paris recently investigated these associations in young patients with sickle cell disease. The study confirmed previous reports of higher risk of admission in presence of wind and rainfall [57,69]. High wind speed is likely to accelerate skin cooling and to promote vaso-occlusion, possibly as a result of impaired control of vascular tone [70–72]. However, no associations were found with temperature, which may reflect available access to warm clothes and heated building facilities in these countries [57,69].

Patients with sickle cell disease in high-income countries in Europe and the United States predominantly live in capital cities and large urban centres with high concentrations of air pollutants [55]. Air quality is hypothetically an important determinant of complications in patients with sickle cell disease. However, studies have yielded conflicting results. Most pollutants are closely intertwined and correlated with weather conditions, making it difficult to establish the primary cause [55,73].

5. Diagnosis and neonatal screening

Diagnosis of haemoglobinopathies is based on the detection of HbS in relation to HbA and HbF. The most commonly used methods are electrophoresis (gel- or capillary- based), high-pressure liquid chromatography (HPLC), isoelectric focusing and molecular approaches such as PCR [74]. These are relatively cheap techniques and available worldwide. However, all techniques require well-trained staff, reasonable laboratory facilities with special equipment and systems for storage of reagents. As over 80% of the population at risk for sickle cell disease reside in low and middle-income countries, diagnostic facilities for sickle cell disease remain poor globally [75]. In many African settings, the sickle solubility test (Sickledex) is the only available technique, but this test cannot distinguish sickle cell disease from sickle cell trait (HbAS) [76]. Recently, however, promising diagnostic methods for rapid and reliable point-of-care determination of haemoglobin fractions in low-resource settings have been developed, such as HemoTypeSC™ and Sickle SCAN™ [77,78].

A prompt diagnosis is the first step in improving outcomes of individuals with sickle cell disease. Pre-emptive diagnosis allows for parental education on pathophysiology of disease and recognition of specific signs to seek immediate medical care. Moreover, preventive interventions including vaccinations, prophylactic antibiotics and anti-malarial drugs can be discussed and implemented [75]. In developed countries, such as the United States and many European countries, neonatal screening programmes for haemoglobinopathies and subsequent treatment have been established and have decreased childhood mortality significantly [79,80].

In addition to rapid diagnosis followed by adequate prophylactic treatment, an accurate and inexpensive method of determining sickle cell disease carrier status can lead to informed parental choices [77]. Knowledge of sickle cell trait allows for a range of options, including limiting of family size, ensuring that at-risk infants are tested at birth, and consideration of prenatal diagnosis [1]. However, sickle cell disease and its carrier status are still associated with a considerable stigma in many affected communities.

6. Clinical presentation and disease management

6.1. Symptoms of disease

Overall, complications of sickle cell disease can be divided into two main groups: those mainly due to haemolytic disease and functional nitric oxide deficiency which cause large vessel vasculopathy (cerebrovascular disease, pulmonary hypertension, nephropathy, priapism and leg ulcers) and those caused by vaso-occlusive ischaemic events leading to painful episodes and progressive organ damage (hypoalbuminemia, osteonecrosis, retinopathy and liver damage) [28,69].

6.1.1. Acute complications

6.1.1.1. Vaso-occlusive crises. Acute recurrent painful sickle cell crises are caused by vaso-occlusion and ischaemic damage due to obstruction of post-capillary venules, but also due to ischaemia-reperfusion injury [81]. Hypoxia, ischaemia and ultimately tissue damage, leads to the release of inflammatory mediators with concomitant mast cell activation [82,83].

The occurrence of acute vaso-occlusive pain is unpredictable and may be precipitated by triggers such as dehydration, infection and/or fever, cold, stress, acidosis, hypoxia and pain itself [84]. Pain episodes in sickle cell disease are intense and involve peripheral afferent nociceptor activation and hyperalgesia [85]. Overall, most episodes can be successfully managed at home [86]. Treatment is supportive with adequate pain medication (paracetamol, non-steroidal anti-inflammatory drugs and opiate analgesia administered at standard time points), adequate hydration, warmth and rest. Aborting the acute painful crisis at its onset may potentially prevent or minimise tissue
damage [82]. As acute painful vaso-occlusive crises are associated with severe complications, such as acute chest syndrome and multiorgan failure [87], patients and parents/caregivers should be educated as to when to seek medical help. Patients presenting to the emergency department with acute vaso-occlusive pain require rapid triage, evaluation and stringent administration of analgesics. In cases of severe pain unresponsive to standard care, treatment with other medication such as ketamine or clonidine may be necessary [88-90].

Nearly all patients with sickle cell disease will experience vaso-occlusive episodes during their lifetime. The first episode may occur in infancy, often presenting as dactylitis. Classical localisations for vaso-occlusive crises in both children and adults are legs and arms, chest, and back [91,92]. Acute pain is the most important complication from patient's perspective [93,94]. It is also the most common reason for emergency room visits and hospitalisation for both adults and children with sickle cell disease, although it is more prevalent in adolescents and young adults than in young children.

6.1.1.2. Infectious disease. Although comprehensive care programs have dramatically reduced childhood mortality and improved life expectancy [5,15,95], infection remains a significant contributor to morbidity and mortality in sickle cell disease [1,96]. The increased susceptibility to bacterial infections is mainly a result of functional asplenia which is already present at a very young age. Autosplenectomy, but also other factors such as impaired fixation of complement, reduced oxidative burst capacity of chronically activated neutrophils, dysfunctional IgM and IgG antibody responses and defective opsonisation contribute to the increased susceptibility for infectious complications [97–100].

In addition, hypospleninic and asplenic individuals lack IgM memory B cells and therefore cannot mount a rapid specific response to encapsulated organisms. The main pathogen of concern is Streptococcus pneumoniae, though severe and systemic infections with Haemophilus influenzae, Neisseria meningitidis, and salmonellae also occur. Overwhelming sepsis can develop rapidly with no obvious primary source of infection, resulting in shock, disseminated intravascular coagulation, adrenal haemorrhage, and death within 24 to 48 h [101]. Promptly identifying and treating suspected bacterial infections is imperative [88].

Next to being at risk for bacteraemia/sepsis, meningitis and pneumonia, patients with sickle cell disease are predisposed to osteomyelitis. The bone marrow is expanded to accommodate for the increased haematopoiesis and oxygen demand is high. At the same time circulation is sluggish. These factors make bone tissue vulnerable to vaso-occlusive episodes and infarction. Areas of necrotic bone act as foci for infection, which has a high chance of systemic involvement due to haematogenous spread [102,103]. Salmonella is the predominant pathogen in sickle cell disease osteomyelitis [104,105]. This may be a consequence of ischaemia and infarction of the bowel secondary to microvascular occlusion, which in turn allows gut bacteria to invade the intestinal wall and enter the bloodstream [103].

In contrast to the relative resistance of carriers against malaria, patients with sickle cell disease are highly susceptible to the lethal effect of malaria. Co-existence of the two is associated with increased mortality and morbidity [106], and malaria is the most common precipitating cause of vaso-occlusive pain in endemic countries [107]. Patients travelling to endemic countries should therefore be treated with malaria prophylaxis [108].

6.1.1.3. Cerebrovascular accidents. Cerebrovascular accident (CVA) is a devastating complication of sickle cell disease. Complications vary from overt stroke with abrupt onset of neurological deficit to silent cerebral infarcts, which are not clinically apparent but may be associated with cognitive impairment [56,109]. CVA in patients with sickle cell disease often has similar presenting signs and symptoms as in persons without sickle cell disease, including being preceded by transient ischaemic attacks and causing motor, cognitive and psychological deficits. Generally, a sudden onset of neurological symptoms should be presumed as stroke, warranting immediate brain MRI and MRA [110].

Although the underlying pathophysiological mechanisms for CVA remain uncertain, most cases are associated with vasculopathy affecting the distal internal carotid and middle cerebral arteries. Vasculopathy seems to start in infancy and contributing factors include anaemia, leucocytosis, hypoxaemia, endothelial dysfunction, functional NO deficiency, decreased cerebral vascular reserve and impaired regulation of blood flow causing hyperaemia [111-113]. The aetiology of silent cerebral infarcts is less clear [114]. In contrast to overt strokes, they typically occur in the territory of small penetrating arteries [111].

In absence of primary transcranial Doppler (TCD) screening, arterial ischaemic stroke occurs in 5–10% of children with sickle cell disease [115,116]. The cumulative risk for overt stroke is 11% by age 20 years. By age 30 and 45 years, 15% and 24% respectively will have experienced an overt stroke [111,115]. Silent cerebral infarcts occur in approximately one-quarter of children before their sixth birthday and approximately one-third before their 14th birthday [117,118]. Silent infarcts are associated with significant cognitive and academic morbidity [56,119,120], and their presence predicts development of both new silent cerebral infaracts as well as overt strokes [121,122]. Recurrent (secondary) strokes occur in half to two thirds of untreated individuals and are associated with increasing morbidity and mortality [123].

When an acute stroke is diagnosed, immediate exchange transfusion should be performed, followed by regular transfusion therapy to prevent stroke recurrence [124]. During chronic transfusion therapy it is recommended to keep the HbS level below 30% of total haemoglobin [125,126]. The randomised Stroke Prevention Trial in Sickle Cell Anaemia (STOP I trial), showed that long-term blood transfusion therapy given to children with high cerebral artery blood flow velocities reduces the occurrence of a first stroke by 90% [127]. In the STOP II trial, attempts to discontinue transfusions after three years resulted in an increased risk of conversion to abnormal TCD velocities and adverse neurologic events [128,129], suggesting that indefinite therapy is needed for primary stroke prevention. However, chronic transfusion therapy places an intense burden on the patient and their family as monthly transfusions are required. In addition, various medical complications may occur such as alloimmunisation and iron overload [130,131].

The multicentre TCD With Transfusion Changing to Hydroxyurea trial (TWITCH) demonstrated that for a subset of patients with sickle cell disease who have received at least 1 year of transfusions, and have no MRA-defined severe vasculopathy, hydroxyurea is an effective alternative to transfusions [132]. However, long-term follow-up data are needed to define the long-term benefits of hydroxyurea therapy [133,134].

6.1.1.4. Acute chest syndrome. Acute chest syndrome is the second most common cause of hospital admissions in patients with sickle cell disease [39]. It is a form of acute lung injury and is defined as a new pulmonary infiltrate involving at least one lung segment on chest radiograph accompanied by fever and/or respiratory symptoms [87]. Rapid respiratory decline can be life threatening, commonly within 24 h of onset [135].

The underlying cause of acute chest syndrome is unclear, however it is thought to be a combination of infection, fat embolism, hypoventilation and vaso-occlusion of the pulmonary vasculature [87]. Clinical risk factors include higher baseline haemoglobin concentration, leucocytosis and lower HbF concentration [136,137]. Furthermore, several studies have shown that children with sickle cell disease and asthma have a higher rate of acute chest syndrome events than those with sickle cell disease without asthma [135,137-140].

The incidence of acute chest syndrome is lower in older adults compared to children (8.8 events/100 patients’ years in older adults vs...
versus 24.5 events/100 patient years in young children) [136,141]. Severity varies, although acute chest syndrome in children is rarely the primary cause of death (< 1% of episodes); whereas in adults it is a significant cause of mortality. The higher incidence of bone marrow and fat emboli in adults with acute chest syndrome suggests a different aetiology [87,142].

The management of acute chest syndrome is largely similar in children and adults with sickle cell disease and typically includes supportive measures (oxygen, fluids, bronchodilators, pain control). Initial treatment involves antibiotics effective against Streptococcus pneumoniae combined with a macrolide for treatment of Mycoplasma pneumoniae or Chlamydia pneumoniae and should be adjusted according to bacterial cultures [143]. If haemoglobin concentrations decrease or the patient’s clinical condition deteriorates e.g. increasing respiratory rate, increasing oxygen requirement, an erythrocyte transfusion is given to raise the haemoglobin concentration up to 10–11 g/dL (6.2–6.8 mmol/L) [135,144]. In general, it is better to initiate transfusion early as acute respiratory failure can develop rapidly. Exchange transfusion to reduce the HbS level down to 30% should be performed if acute chest syndrome progresses despite simple transfusion, if there are severe clinical features, or if the patient has multi-lobar disease [145]. Lastly, incentive spirometry helps to reduce the risk of acute chest syndrome in patients with chest or rib pain, but has only been proven to be effective in children [146-148].

6.1.1.5. Acute kidney injury. Acute kidney injury, formerly called acute renal failure, is defined as an acute decline in renal function, leading to a rise in serum creatinine and/or a fall in urine output. The aetiology of acute kidney injury in sickle cell disease is not fully known [149]. Vaso-occlusion causes ischaemia in the renal medulla. Contributing factors include volume depletion due to hypothension, frequent and chronic use of non-steroidal anti-inflammatory drugs (NSAIDS), infections, massive haemolysis and rhabdomyolysis [150-152]. Recent studies have established an association between episodes of acute kidney injury and progression to chronic kidney disease [153-157].

Acute kidney injury occurs in 4–10% of hospitalised adult patients with sickle cell disease, and is more frequent in patients with acute chest syndrome (13.6%) [149,158]. In paediatric patients, the incidence may be as high as 17% in children presenting to the hospital emergency room with vaso-occlusive crisis [159].

Management of acute kidney injury involves daily monitoring of renal function, fluid intake and output, and haemodynamic parameters (blood pressure) to avoid hypoperfusion of the kidneys. Potential nephrotoxic drugs and imaging agents should be avoided. The patient should be evaluated for all potential aetiologies [88].

6.1.1.6. Splenic complications. The spleen is one of the first organs to be damaged in sickle cell disease patients, as hypersplenism presents in the majority of children before 12 months of age [160]. The structure and function of the spleen predisposes for ischaemic infarctions as it is characterised by low flow and an open microcirculation leading to deoxygenation and sickling of HbS erythrocytes [161]. These vaso-occlusive events are not painful and clinically silent, but lead to fibrosis and functional asplenia.

There are different manifestations of splenic injury in patients with sickle cell disease which are not mutually exclusive and may coexist. There is no correlation between spleen size and function. Although most spleens rapidly decrease in size, functional hypersplenism and splenomegaly are often combined in young children with sickle cell disease [162]. This is explained by progressive yet moderate trapping of sickled erythrocytes in the red pulp.

Hypersplenism is defined as splenomegaly in combination with anaemia, leucopenia and/or thrombocytopenia. Diagnosis can be difficult as splenomegaly is frequent and anaemia pre-exists. Acute splenic sequestration is defined as an acute splenic enlargement with a ≥ 20% fall in haemoglobin level from baseline level [163]. The rapid sequestration of erythrocytes in the spleen classically causes abdominal pain and distension, with serious haemodynamic symptoms. Severe episodes may lead to hypovolemic shock and death from cardiovascular collapse. Acute splenic sequestration is usually seen in infants and young children with a median age at first episode of 1.4 years [164] and is rarely observed after 6 years of age [165]. To date, no solid predictor of acute splenic sequestration has been identified [161], however a relapse is frequent with 50%–75% of patients experiencing more than one episode [164].

Mild splenomegaly alone warrants no specific management, however along with poor growth, bone marrow hyperplasia or reduced transfusion efficiency, a splenectomy is indicated if age allows [161]. Acute splenic sequestration requires the immediate restoration of blood volume by fluids and blood transfusion. Treatment options to prevent recurrence include watchful waiting, chronic transfusion and splenectomy. There is no clear evidence in favour of splenectomy versus conservative management [166].

6.1.1.7. Hepatobiliary complications. The hepatobiliary system is one of the most common intra-abdominal organs involved in sickle cell disease [167]. Sickle hepatopathy is a term used to describe a wide variety of both acute and chronic causes of liver abnormalities in patients with sickle cell disease, including cholelithiasis, vaso occlusive hypoxic liver injury, hepatic sequestration, venous outflow obstruction, viral hepatitis, sickle cell intrahepatic cholestasis and biliary cirrhosis. The significant clinical heterogeneity and overlap in terms of presentation, investigation and natural history make the use of one descriptive term insufficient [168,169].

Hepatobiliary complications in sickle cell disease occur either directly from the sickling process -which causes microvascular occlusion and ischaemia- or indirectly as a result of chronic haemolysis or iron overload due to multiple blood transfusions. Clinically, diagnosis is confounded by difficulties differentiating abnormal liver enzymes due to intrinsic liver disease from those resulting from haemolysis. In addition, it is important to realise that a spectrum of clinical manifestations may be observed for the same underlying pathophysiology.

Sickle cell intrahepatic cholestasis is a rare, but potentially fatal complication of sickle cell disease. It is characterised by severe right upper quadrant pain, progressive hepatomegaly, extreme hyperbilirubinemia, but mild elevation of liver enzymes, and coagulopathy [170]. The role of liver biopsy in the diagnosis of sickle cell intrahepatic cholestasis is uncertain, due to problems obtaining liver tissue for histologic analysis as this is often contraindicated in the acute setting of critically ill sickle cell disease patients [171].

The management of sickle hepatopathy relies on accurate identification and treatment of any coexisting cause(s) and still remains mainly supportive. Unfortunately, medical management is limited and the role of hydroxyurea or prophylactic cholecystectomy in preventing hepatobiliary manifestations has not been defined [172,173]. Acute hepatic sequestration may lead to hypovolemic shock and therefore prompt treatment with fluids and (exchange) transfusion is warranted [174]. Sickle cell intrahepatic cholestasis in the acute stage requires early and vigorous exchange transfusion to prevent fulminant liver failure. It is not clear which patients will progress to end-stage liver disease and the role of liver transplantation therefore remains controversial [169].

6.1.1.8. Priapism. Priapism is defined as a painful or painless, undesirable and persistent state of penile erection, which may follow in the absence of a sexual stimulus [175]. There are three types of priapism: ischaemic priapism (veno-occlusive, low flow), stuttering priapism (recurrent ischaemic) and non-ischaemic priapism (arterial, high flow). The vast majority of cases in sickle cell disease are ischaemic [176]. Ischaemic priapism is defined by reduced or absent intracorporal blood flow and is characterised by painful rigidity of the corpora cavernosa due to blood stagnation within these structures. This subsequently leads to hypoxia, acidosis and tissue ischaemia. If
priapism, it can lead to permanent local tissue damage with cavernosal fibrosis and permanent erectile dysfunction [177]. Most priapism episodes begin during sleep [178-180] and occurrence is associated with higher HbS levels and inversely correlated to foetal haemoglobin levels [181,182]. The exact pathophysiology of priapism is unclear, however decreased bioavailability of NO most likely plays an important role [183].

The mean age of onset of priapism is 15 years. The calculated actuarial probability of experiencing priapism is 25% by 10 years of age, and 75% by 20 years of age [184]. Medical management is warranted and includes urgent relief of pain with opioids, hydration, and achievement of prompt penile detumescence [185]. Standard treatment involves an oral dose of a vasoactive agent, such as pseudoephedrine to induce smooth muscle contraction and thereby reduce congestion [186]. Corporeal aspiration and phenylephrine intracavernosal injection should only be performed by an urologist and induces rapid detumescence and thus allows oxygenated blood to re-enter the cavernosa [176]. In addition, sickle cell disease patients with priapism may also benefit from hydroxyurea therapy and erythrocyte or exchange transfusions. However these strategies alone cannot be recommended as a standard of care for patients with acute attacks of priapism and in fact, may cause harm by deleterious delaying of timely interventions. Only if conservative measures fail to produce detumescence, penile shunt surgery should be performed [187,188].

Stuttering priapism, also called recurrent priapism, is characterised by multiple self-limited episodes of ischaemic priapism and affects as many as 35% of males with sickle cell disease [189]. Although self-limiting, stuttering priapism may also lead to impotence. Current preventive treatments include the 5a-reductase inhibitor finasteride or short- and long-acting phosphodiesterase type 5 (PDE5) inhibitors, such as sildenafil and tadalafil [190,191]. In addition, hormonal analogues might reduce symptoms, although there is no evidence regarding improvement in functional outcomes [192].

6.1.2. Chronic complications

6.1.2.1. Chronic pain. In addition to intermittent acute vaso-occlusive pain, sickle cell disease patients also experience chronic pain. The aetiology of chronic pain is not clearly understood. Chronic pain in sickle cell disease patients occurs irrespective of a vaso-occlusive crisis and although chronic pain is sometimes secondary to avascular necrosis at various joints, most patients with chronic pain do not have an obvious anatomic source. A number of factors ranging from genetic to behavioural are associated with pain response and are further influenced by interactions between the nervous, endocrine, and immune systems. Patients describe chronic pain using both nociceptive and neuropathic descriptors and sensory testing reveals both peripheral and central nervous system abnormalities [193-197].

Between 17 and 30% of adults with sickle cell disease experience daily pain [86,198]. In addition, 40% of children and adolescents aged 8–18 years have chronic pain with 35% reporting daily pain [199]. The ‘Cooperative Study of Sickle Cell Disease (CSSCD)’ demonstrated that chronic pain impairs health status and quality-of-life more than any other sickle cell disease-related complication [200]. Chronic pain is associated with psychosocial morbidity (e.g., depression, anxiety, despair, loneliness, helplessness), as well as unemployment and school dropout [199,201–204]. The current literature focuses on prevention and management of acute painful episodes, with few data or guidelines on the management of chronic pain. However, early and aggressive treatment of acute sickle cell pain may reduce the development of chronic pain [82]. The purpose of pain control is to maximize quality of life. It is recommended to combine interventions and to include both pharmacological (e.g., acetaminophen, NSAIDs, anticonvulsants, tricyclic antidepressants, judicious use of opioids) and non-pharmacological treatments (e.g., heat, physiotherapy, massage, relaxation therapies, meditation) [205,206]. Cognitive behaviour therapy helps the patient to develop strategies for pain coping and other psychological disturbances caused by sickle cell disease [207]. Because of the complexity of managing sickle cell related pain -and the need to differentiate between acute and chronic pain- ideally a pain management specialist is a member in each sickle cell team.

6.1.2.2. Pulmonary hypertension. Pulmonary hypertension is defined as a mean pulmonary artery pressure of 25 mmHg or more, with a left ventricular end-diastolic pressure of 15 mmHg or lower measured during right heart catheterization [208]. The pathophysiology of pulmonary hypertension in sickle cell disease patients is multifactorial. There is a prominent role for intravascular haemolysis inducing a state of vascular dysfunction, with pulmonary vasculopathy as well as pulmonary hypertension through decreased NO bioavailability and vasoconstriction [209]. In addition, the physiologic response to severe anaemia is a compensatory increase in cardiac output in order to maintain adequate oxygen delivery. This increased cardiac output is generated by increases in blood volume, preload, heart rate, and stroke volume, along with a decrease in afterload [210].

Patients with sickle cell disease develop a high pulse pressure in both the systemic and the pulmonary circulation. About half of sickle cell disease patients with related pulmonary hypertension have pre-capillary pulmonary hypertension with different potential aetiologies, the other half have post capillary pulmonary hypertension secondary to left ventricular and mitral valve dysfunction [211]. It is recognised that the elevation in cardiac output and reduced blood viscosity associated with sickle cell disease results in a lower baseline pulmonary vascular resistance than among healthy individuals. Therefore, the pulmonary artery pressure in sickle cell disease patients is subsequently only moderately elevated [212].

Pulmonary hypertension is associated with increased morbidity and mortality in adult sickle cell disease patients [208,213,214]. Left and right ventricle dilation, diastolic dysfunction, and elevated pulmonary arterial pressures are commonly reported findings. Current interventions include hydroxyurea therapy, and in some cases, chronic transfusions, anticoagulation and oxygen therapy. Specific drugs used in pulmonary hypertension for patients without sickle cell disease may be considered, but these therapies do not have clear evidence of efficacy in sickle cell disease [208,211].

6.1.2.3. Renal dysfunction. Renal dysfunction is almost inevitable in sickle cell disease and starts very early in life with impaired urine concentrating ability and glomerular filtration [215,216]. There is a strong tendency for HbS to polymerise in the renal medulla, due to low partial pressure of oxygen, low pH, and high osmolality. This subsequently causes erythrocyte dehydration and vaso-occlusion [24]. The pathophysiology of glomerular hyperfiltration is mostly attributable to the haemolysis associated vasculopathy [217]. Sickle cell nephropathy is characterised by proteinuria with glomerulosclerosis, decreased glomerular filtration rate and eventual renal failure [218].

A large proportion of children with sickle cell disease have glomerular hyper filtration. The glomerular filtration rate (GFR) seems to start declining after 16 years of age [219]. Proteinuria is age-dependent in sickle cell disease, and occurs in up to 27% of patients in the first three decades and in up to 68% of older patients [220–223]. It can progress to nephrotic proteinuria, with > 3.5 g protein loss in 24 h [224]. Renal involvement contributes substantially to the diminished life expectancy of patients with sickle cell disease, accounting for 5–18% of mortality [39,96,225].

Treatment focuses on screening for microalbuminuria and the early use of hydroxyurea to prevent renal dysfunction [226–231]. In addition, angiotensin converting enzyme (ACE) inhibitors reduce proteinuria and delay the progression of chronic kidney disease [232,233]. In end-stage kidney-failure, renal transplantation has reasonable survival outcomes, comparable with transplant outcomes in patients with
diabetic kidney failure [234].

6.1.2.4. *Avascular necrosis*. Avascular necrosis, also known as osteonecrosis, ischaemic necrosis or aseptic necrosis, is one of the most devastating musculoskeletal manifestations of sickle cell disease. It occurs when vaso-occlusion results in the infarction of the articular surfaces and head of the long bones. Although the exact pathophysiology of this condition in patients with sickle cell disease is unknown, it is suggested that repetitive vaso-occlusion may be associated with tissue hypoxia, reperfusion injury, inflammation, and subsequent bone necrosis and collapse. The most common site of avascular necrosis is the femoral head followed by the head of the humerus, knee and small joints of the hands and feet [104,235,236].

Avascular necrosis affects 50% of the patients by 35 years of age [237,238], and bilateral hip involvement is seen in 40 to 91% of patients [239–242]. Clinical symptoms peak during adolescence, however, patients are frequently asymptomatic during the early stages, delaying diagnosis until it has progressed to advanced stages [243].

Symptomatic patients complain of painful and limited motion of the affected joint, occasionally with pain at rest. Early disease is best diagnosed by MRI, as plain X-rays may not detect early disease [237,244]. If left untreated, osteonecrosis can be extremely debilitating and may lead to severe pain, loss of function, and degenerative joint changes [245,246]. Although several conservative management approaches exist, total joint arthroplasty seems to be the most effective treatment intervention.

6.1.2.5. *Ophthalmologic complications*. Chronic ophthalmological complications of sickle cell disease include proliferative retinopathy and vitreous haemorrhage. Proliferative retinopathy develops due to peripheral retinal arteriolar occlusions. Local ischaemia from repeated episodes of arteriolar closure triggers angiogenesis through the production of vascular endothelial growth factors [247]. Goldberg defined five stages of proliferative retinopathy, with stage I only consisting of arteriolar occlusion and stage V defined by the presence of retinal detachment with or without hole formation in the retina [248].

The prevalence of proliferative retinopathy is higher in the HbSC genotype compared to homozygous sickle cell disease, with reported incidences of 33% and 14% respectively [249–251]. Current research has not yet been able to explain the reason for this profound discrepancy. The peak prevalence of proliferative retinopathy in HbSS patients occurs between 25 and 39 years, whereas in the HbSC genotype it occurs from 15 to 24 years in men and 20–39 years in women [251,252]. Neither gender nor the presence of systemic manifestations is predictive for prevalence or age of onset of retinopathy [253].

Therapeutic intervention is usually recommended in cases of bilateral proliferative disease, spontaneous haemorrhage, large elevated neovascular fronds, and rapid growth of neovascularization. Laser photocoagulation helps in avoiding haemorrhage and sight loss, however it does not significantly lead to the regression of advanced proliferative retinopathy. Innovative therapy includes intravitreal injection of an anti-vascular endothelial growth factor which appears comparatively safe and efficient [254].

6.1.2.6. *Leg ulcers*. Leg ulcers occur in areas with less subcutaneous fat and with decreased blood flow [255]. The skin around both side of the ankle is most often affected, less common sites are the anterior tibia area and the dorsum of the foot [256]. The pathogenesis of chronic ulcers in sickle cell disease is complex. Venographic studies have shown that venous insufficiency is not a primary cause of sickle cell ulcerations. Instead, the arteriovenous shunting is recognised as a decisive factor in ulcer formation. This shunting deprives the skin of oxygen, promoting ulceration [257]. High haemolytic rate and low haemoglobin concentrations have been recognised as risk factors [258].

The prevalence of leg ulcers in sickle cell disease varies geographically, with rates as high as 75% in Jamaica and 25% in the United States [259,260]. However, in the CSSCD, the overall prevalence was 2.5% in persons 10 years of age and older and was higher in patients with HbSS (5%) and HbSβ0 (4%) genotype compared to patients with other genotypes [259]. Regardless, leg ulcers occur ten times more frequently in sickle cell disease than in the general population [261].

The major challenges in management of leg ulcers in patients with sickle cell disease are the prolonged course to recovery and the high recurrence rate of healed or grafted ulcers [262]. The treatment is multidisciplinary with adequate control of sickle cell disease and pain as well as aggressive local therapy including wound care and surgery [263]. The role of hydroxyurea and exchange transfusion is presently unclear, however, there are many potential benefits such as increase in haemoglobin, decrease in haemolysis, increase in oxygen carrying capacity, and improved red blood cell rheology. Lastly, it is crucial to address both the immediate consequences of pain, infection and disability, and long term effects on quality of life, employment and stigma associated with chronic ulceration [264].

6.2. *Comprehensive care*

6.2.1. *Immunisations and infection prophylaxis*

Prior to the initiation of neonatal screening for sickle cell disease, infection due to invasive pneumococcal disease was the leading cause of death in afflicted children [265]. Particularly very young children are at risk, with a reported incidence of invasive pneumococcal disease of 10 per 100 in children aged <3 years and a 30% fatality rate [266,267]. The risk decreases to 1.1 per 100 in those aged 5–9 years, and 0.6 per 100 in those aged over 10 years [268].

The ‘Prophylaxis with Oral Penicillin in Children with Sickle Cell Anaemia’ (PROPS) trial in 1986 demonstrated the significant reduction in morbidity and mortality by penicillin prophylaxis [269]. It was also noted that early initiation of penicillin prophylaxis is most effective as the risk of infection is inversely related to age. Accordingly, most advisory health committees have recommended early diagnosis by neonatal screening in order to commence penicillin prophylaxis in early infancy [270].

To determine the age at which it is safe to stop penicillin prophylaxis, PROPS II was conducted [271]. Infection rate was shown to decrease significantly after the age of five years, whether or not the child received penicillin. Therefore, it was concluded that prophylaxis could be discontinued at five years of age without a clinically important increased risk of infection [271]. However, globally guidelines differ with regard to age at which penicillin prophylaxis is stopped [272].

Additional research has extensively documented the benefit of pneumococcal vaccines next to daily penicillin prophylaxis. There are three main vaccine schedules: polyvalent polysaccharide vaccines (PPV), polysaccharide conjugate vaccines (PCV), and a combination of both. The conventional unconjugated 23-valent PPV (PPV) can only be given to children after 23 months of age. Before this age, which is the period of highest pneumococcal infection risk [273–275], the more recently developed conjugated vaccines in which polysaccharides are covalently linked to protein carriers, should be administered. Two large studies both showed a marked reduction in invasive pneumococcal disease in sickle cell disease patients following PCV introduction [272,276,277].

Finally, it is important to highlight the use of routine courses of immunisations in the care of children with sickle cell disease. These should be administered according to their chronological age regardless of prematurity. In addition children and adult patients should be offered vaccination against influenza annually from the age of six months.

6.2.2. *Screening for complications*

6.2.2.1. *Risk of stroke*. Sickle cell disease has a high incidence of cerebral infarction, primarily occurring in childhood, with a second
peak in adults over the age of 29 years [115]. In children, overt stroke is related to stenosis and occlusion of large cerebral arteries of the Circle of Willis which can be detected by TCD ultrasonography. High maximal mean velocity cerebral artery flow identifies children at high risk of stroke [278,279]. The stroke risk increases in proportion to increasing time-averaged mean of the maximum velocity (TAMV) in the distal internal carotid artery or proximal middle cerebral artery. High flow velocity is an indirect indicator of either increased volume flow or stenosis in the large vessels [280].

Current standard of care includes annual or biannual TCD screening between the ages of 2 and 16 years [88]. Repeated measurements are performed dependent on the result of the prior examination i.e. yearly if the initial TAMV is normal (TAMV < 170 cm/s), every 6 months if low conditional (TAMV 170–184 cm/s), every 3 months if high conditional (TAMV 185–199 cm/s), and within 1 month if abnormal (TAMV ≥ 200 cm/s) [125,126]. If the second TAMV is in the abnormal range, MRI/ MRA imaging is recommended and subsequent transfusion therapy, if cerebral stenosis is confirmed.

Currently, there are no validated methods to screen for increased risk of stroke in adults with sickle cell disease. The velocity criteria used in children cannot be used to stratify risk of stroke in adults, due to an age related decline in TCD velocities and an absence of reference TCD values for adults [281].

6.2.2.2. Retinopathy. Almost all ocular structures can be affected by microvascular occlusions caused by sickle cell disease [282], but the most common complication is proliferative retinopathy. This is characterised by lesions in the areas at the border between the vascular and avascular retina with abnormal arteriovenous communications [251,283,284]. Proliferative retinopathy can lead to visual loss from vitreous haemorrhage, macular lesions and retinal detachment. Until such complications arise, patients are often asymptomatic.

Vision loss from proliferative retinopathy is largely preventable when detected early and if careful follow-up and treatment is initiated. Although the peak prevalence occurs earlier in the HbSC genotype, it is recommended to screen for retinopathy in all sickle cell disease genotypes from the age of 10 years by an ophthalmologist performing diluted fundus examination. Serial examinations may be done biennially for eyes with normal findings, and fluorescein angiography on eyes with abnormal examinations, with follow-up when indicated [88,253].

6.2.2.3. Cardiopulmonary complications. Regular screening for pulmonary and cardiac complications in sickle cell patients is controversial due to the lack of evidence regarding efficacy on clinical outcomes in asymptomatic individuals [88]. However, cardiopulmonary complications are the most common causes of death in adults with sickle cell disease [208,214,285]. In addition, early interventions might reduce severe cardiac disease development.

A non-invasive method for screening of patients to determine the presence of pulmonary hypertension uses Doppler echocardiography to measure tricuspid valve regurgitation velocity (TRV). Approximately one-third of adult patients with sickle cell disease have an elevated tricuspid valve regurgitant jet velocity (TRV) of 2.5 m/s or higher, a threshold that is associated with an increased risk of having a mean artery systolic pressure of at least 30 mmHg measured with right heart catheterisation [214,286,287]. Although pulmonary hypertension is only found in about 10% of patients with elevated TRV [288], patients with a TRV above 2.5 m/s have a 9- to 10-fold higher risk for early mortality than those with a lower TRV [214,286,289]. Abnormal echocardiography should therefore instigate referral to a cardiologist or pulmonologist with expertise in pulmonary hypertension. Regardless of the echocardiographic findings, right heart catheterization is the golden standard for diagnosis of pulmonary hypertension [290].

NT-proBNP (N-terminal prohormone brain natriuretic peptide) is a hormone released from the cardiac ventricles in response to cardiomyocyte stretching. High levels reflect cardiac chamber volume and pressure overload. NT-proBNP gives systemic vasodilatation, inhibits the sympathetic nervous system and the renin-angiotensin-aldosterone system while promoting natriuresis [291,292]. Elevated plasma concentrations of NT-proBNP (> 160 pg/mL) are an independent risk factor for mortality in sickle cell disease [214,293–296]. The prevalence of a high NT-proBNP level increases with age in adults. This is not the case for paediatric patients given the physiologically higher normal NT-proBNP levels in children, especially during the first year of life [292].

To screen for pulmonary hypertension, the American Thoracic Society recommends annual echocardiography and NT-proBNP concentrations for adult patients [212]. The prevalence and consequences of increased TRV and signs of pulmonary hypertension in children with sickle cell disease are less clear as there are no large data sets of children with this condition. Neither have reports been published in children on associations of elevated TRV with increased mortality [297–300]. This may be due to the overall low mortality rate in children with sickle cell disease in high income countries [15]. Routine echocardiographical screening for paediatric patients is therefore not recommended [88]. Given the lack of data, it may be possible that patients are underdiagnosed and therefore under treated [297,301]. See Table 2 for rationale for (not) screening for pulmonary hypertension in adult and paediatric patients with sickle cell disease according to the principles for screening proposed by Wilson and Junger [302]. These principles give guidance in the selection of conditions that would be suitable for screening.

6.2.3. Treatment

6.2.3.1. Hydroxyurea. The primary benefits of hydroxyurea for sickle cell disease relate to its ability to increase HbF levels, first described in the 1980s [303]. The exact mechanisms by which hydroxyurea induces HbF remain incompletely understood [304]. In addition, the full benefits of hydroxyurea therapy in sickle cell disease are multifactorial, extending beyond HbF induction. Other mechanisms of action include decreased neutrophil and reticulocyte counts due to cytotoxic effects of hydroxyurea, a reduced expression of surface molecules that adhere to the endothelium and increased levels of NO as a consequence of hydroxyurea metabolism that may contribute to local vaso-dilatation [305,306].

Several prospective clinical trials have consistently shown both clinical efficacy (e.g. less frequent vaso-occlusive pain- and acute chest episodes, fewer hospitalisations and blood transfusions) as well as effects on laboratory values (e.g. increased total haemoglobin and foetal haemoglobin, decreased lactate dehydrogenase and bilirubin) of hydroxyurea in both paediatric and adult sickle cell disease patients [307–310]. Importantly, the BABY HUG trial allowed the enrolment of clinically asymptomatic infants, and proved the benefits of hydroxyurea treatment in both children with and without sickle cell disease-related symptoms and complications [311]. Additional effects of hydroxyurea on organ function also included decreases in urine albumin to creatinine ratio (ACR) and decreased glomerular hyperfiltration [229,231,312], normalised microvascular blood flow [313], less airway hyper-reactivity [314], higher oxygen saturations [315–317], improved cognitive functioning [318] and lower transcranial Doppler (TCD) velocities [231,319–322]. In addition, observational studies have confirmed safety and long-term clinical efficacy and reduction of mortality in both adults and children on hydroxyurea treatment [323–328].

Side effects of hydroxyurea are usually mild and include dose-dependent myelosuppression, cutaneous effects including nail- and skin hyperpigmentation and gastrointestinal symptoms [307]. Consequently, recent National Heart, Lung, and Blood Institute (NHLBI) guidelines and the British Society for Haematology Guideline recommend offering hydroxyurea to all children of 9 months of age and older with sickle cell disease (HbSS or HbSß0 genotype), regardless of their symptoms in order to reduce and prevent complications [88,329].
Table 2
Rationale for (not) screening for pulmonary hypertension (echocardiography) in patients with sickle cell disease.

<table>
<thead>
<tr>
<th>Characteristic of disease appropriate for screening</th>
<th>Supporting evidence in adults</th>
<th>Supporting evidence in children (&lt; 18 y)</th>
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| Disease is relatively common.                       | Prevalence elevated TRV: 24.4% (95% CI 18.4–30.4) 
\( ^{a} \), of which 6–11% have PH confirmed on RHC 
\( ^{l} \). Both elevated TRV and PH are associated with an increased mortality 
\( ^{l} \). Patients with PH are frequently asymptomatic early on; cases of PH are often identified late in the course of disease 
\( ^{l} \). Treatment before symptoms occur is more effective than if treatment is delayed. 
\( ^{l} \). No data, however highly plausible as a number of studies on PH in the general population indicate that early therapeutic intervention positively influences disease progression when compared to delayed treatment 
\( ^{l} \). The positive predictive value of echocardiography for detection of PH in SCD is 25% 
\( ^{l} \). | Prevalence elevated TRV: 20.7% (95% CI 15.7–25.6) 
\( ^{a} \), no data on prevalence PH. No association between TRV, mortality and clinically relevant morbidity 
\( ^{a} \). No data. 
\( ^{l} \). Different clinical associations with PH in adults vs. children with sickle cell disease suggests alternative mechanisms of disease pathogenesis. So far there are no data if paediatric PH persists into adulthood 
\( ^{l} \). No data, however patients with elevated TRV should undergo a RHC. RHC is associated with a low risk of complications, but is invasive. Doppler echocardiography is simple and non-invasive. |

Abbreviations; y: year, TRV: tricuspid valve regurgitant jet velocity, pH: pulmonary hypertension, RHC: right heart catheterisation, vs: versus, SCD: sickle cell disease

* According to the principles for screening proposed by Wilson and Junger 


\( ^{m} \) World Health Organization; Wilson JMGJ. G. The principles and practice of screening for disease. 1966.

Despite the accumulating evidence on the safety, efficacy and cost-effectiveness, hydroxyurea in sickle cell disease patients is still underutilised in clinical practice [330]. This is partly due to concerns about side effects and uncertainties about long term effects of hydroxyurea. As treatment duration currently approaches 15 to 20 years in some children [331,332,333], the main indication for an emergency top-up red blood cell transfusion is severe anaemia in particular due to red cell aplasia caused by parvovirus B19 infection or acute splenic sequestration. The aim is to correct the anaemia and to improve the oxygen carrying capacity of blood. The main indications for an acute exchange transfusion are clinical complications which require an immediate and significant decrease in HbS percentage, i.e. acute stroke, acute multiorgan failure, acute chest syndrome, severe sepsis and intrahepatic cholestasis [338,339]. Indications for chronic (exchange) transfusion most often relate to stroke prevention, either to prevent secondary stroke or as primary prevention in children with a raised TCD velocity over 200 cm/s [88]. Preoperatively, transfusions are administered to prevent postoperative complications related to sickle cell disease [339]. There is insufficient evidence to determine whether simple top-up preoperative transfusion is as effective as exchange transfusion [340].

Red blood cell transfusions are associated with severe side effects and patients must therefore be carefully monitored. Main risks are red blood cell alloimmunization, delayed haemolytic transfusion reactions, hyperhaemolysis, iron overload and risk of transmission of infectious diseases [341,342]. In addition, transfusions raise the haematocrit of circulating blood, resulting in an increased viscosity which may overload the heart. However, its use is limited by difficulties with venous access and the need for increased volumes of donor red blood cells [337].
promote sickling and trigger vaso-occlusion [343]. Red blood cell al-
loimmunisation occurs in approximately 30% of transfused sickle cell disease patients compared to 2–5% of all transfusion recipients [344]. This is partly due to the differences in non-ABO red blood cell antigen expression frequencies between Caucasian blood donors and the mostly African-American recipients with sickle cell disease [345]. Although antibody titres may be low or even undetectable, alloantibodies are known to persist for many years and can result in clinically significant delayed haemolytic transfusion reactions. Alloimmunisation therefore limits the ability to identify compatible blood units for transfusions when life threatening situations occur [346]. Lastly, iron overload due to frequent transfusions can cause cardiac, liver and endocrine dys-
fuction. Chelation therapy should be initiated to remove excess iron in patients with secondary iron overload [342].

Although red blood cell transfusions can help ameliorate many sickle cell disease complications, more research is indicated, and risks and benefits of transfusion should be fully discussed with patients and their families before a (long-term) transfusion program is commenced [347].

6.2.3.3. Haematopoietic stem cell transplantation. At this moment, HSCT is the only curative treatment for patients with sickle cell disease. Worldwide, over 1000 patients with sickle cell disease have received HSCT [348,349]. Most HSCTs in sickle cell disease patients have been performed in children with human leucocyte antigen (HLA)-compatible sibling donors. HSCT is effective in preventing clinical complications, such as vaso-occlusive crises, acute chest syndrome, stroke and progression of cerebrovascular disease [350,351]. With declining incidences of rejection, graft-versus-host disease (GvHD) and transplant-related mortality, overall survival and disease free survival in paediatric patients are now approaching 90% [349,350,352–354]. In adult patients, remarkable data have recently been published showing that reduced intensity conditioning in HLA-matched siblings transplantations results in a successful engraftment in > 85% of the patients [355,355,356].

Unfortunately, overall only 10–20% sickle cell disease patients have an HLA-identical sibling [357]. The outcomes of unrelated donor HSCT are often complicated by delayed engraftment and/or GvHD. Especially chronic GvHD is associated with an unacceptable morbidity and mor-
tality, especially in a non-malignant disease such as sickle cell disease [354,358]. Substantial efforts are ongoing to increase availability of HSCT by expansion of the donor pool. These include alternative stem cell sources such as HSCT with HLA-haploidentical donors, use of cord blood cells and CD34+ selection [359,360]. To date, however, the outcome of patients with sickle cell disease undergoing unrelated donor HSCT has shown disappointing results [361–363].

Although HSCT is potentially curative, there is much debate about the eligibility criteria for HSCT as substantial concerns remain with regard to the transplant-related mortality and long-term toxicities, particularly infertility [326,360]. In a recent review, Fitzhugh et al. suggested that HSCT should be considered for all patients with HbSS or HbSβ0 patients who have a HLA-matched sibling donor, regardless of symptomatology [364]. In contrast, DeBaun argued that HSCT should only be offered in multicentre peer-reviewed clinical trials to children with sickle cell disease that have progressive decline in organ function [365]. With current supportive care and increasing data on long-term hydroxyurea therapy, which appears to be safe and effective, survival is likely to increase significantly. A Belgium cohort study showed that patients treated with hydroxyurea had a better 15-year survival rate than those treated with HSCT [326]. Similarly, the most recent NHLBI guidelines do not offer recommendations regarding HSCT in sickle cell disease, claiming that more research is needed to implement it widely in this population [88].

The challenges faced by patients, parents, and health care providers considering HSCT for sickle cell disease will likely evolve over time. Besides improvements in the clinical management of sickle cell disease and HSCT, identification of (bio) markers may be helpful to predict disease severity and risk of complications in HSCT [366]. Meanwhile, patients and families should be educated on disease severity, the like-
lihood of reduced life expectancy and the advantages, limitations and adverse events associated with HSCT, so that they are able to make an informed decision together with treating physicians [367].

6.2.3.4. Emerging therapies

6.2.3.4.1. Gene therapy. Gene therapy studies to modify or cure sickle cell disease have been ongoing for many years [368]. Gene therapy involves the therapeutic ex vivo modification of autologous haematopoietic stem cells to treat and hopefully cure sickle cell disease. As gene therapy does not necessitate the identification of a HLA-matched donor and avoids the risk of GvHD and graft rejection, this is potentially a valuable alternative to allogeneic HSCT [369].

Various gene therapy approaches have been developed. In gene modification, the most commonly used method, a lentiviral vector is used to transfer a modified gene into haematopoietic stem cells [370]. The rationale behind γ-globin gene addition is based on the observation that high levels of foetal haemoglobin (α2;2) positively influence sickle cell disease phenotype (α2β2).

Recently, a 13 year old boy with HbSS genotype was reported who received treatment with a self-inactivating lentiviral vector. Once the transduced stem cells had engrafted, normal blood cell counts were attained in all lineages, haemolysis was corrected as well as other hallmark clinical features [6]. So far, five clinical trials are ongoing to evaluate gene therapy for sickle cell disease (Table 3) [371,372]. In addition, one study focuses on the long-term safety and efficacy for individuals with haemoglobinopathies (including sickle cell disease) who have been treated with gene therapy in clinical studies [373].

It is important to consider however, that although gene therapy is certainly a potential therapy for sickle cell disease in well-developed parts of the world, it will not be available for several decades for millions of patients in sub-Saharan Africa and elsewhere [14].

6.2.3.4.2. Other. After a lack of drug development trials in the last 20 years, new pharmacotherapeutic approaches to sickle cell disease are being explored as indicated by a large number of clinical trials [374,375]. The most promising interventions are the oral pharmaceutical-grade γ-glutamine treatment, the intravenously antiadhesives agent crizanlizumab and rivipansel, and the oral haemoglobin modifier voxelotor. A γ-glutamine treatment has recently been approved by the FDA for preventing acute painful crises in children and adults with sickle cell disease [376]. Although the mechanism of action of the drug is not fully understood, it is thought to be effective by its antioxidant characteristics.

Rivipansel is a pan-selectin antagonist that inhibits selectin mediated vaso-occlusion and has demonstrated to reduce the use of opioid analgesics during vaso-occlusive crises [377]. Crizanlizumab is a monoclonal antibody against P-selectin. In the SUSTAIN study, which compared two different doses of crizanlizumab with placebo, crizanli-
zumab significantly reduced the frequency of sickle cell pain crises versus placebo [378]. However, more definitive answers are required regarding short and long term benefits as well as potential risks of this novel therapy [379].

Voxelotor (previously called GBT440) is an anti-polymisation agent which increases haemoglobin oxygen affinity. A recent randomised phase 1/2 placebo-controlled trial in patients with sickle cell disease demonstrated haematologic improvements including increased haemoglobin levels and a reduction in haemolysis and HbS levels [380].

Other non-genetic approaches currently being assessed mostly aim to ameliorate the downstream sequelae of HbS polymerisation. Given the wide phenotypic variety of sickle cell disease, it is likely that the most optimal therapy will only be achieved by a multitargeted approach in which hydroxyurea and new pharmacotherapeutic approaches will be combined.
### 6.2.4. Reproductive care

#### 6.2.4.1. Contraception

Contraceptive use is an important strategy for reducing the risk of unintended pregnancy. However, provision of various contraceptive options, especially those containing hormones, is controversial in women with sickle cell disease due to lack of compiled evidence on safety. The principal concern is the potential for an increased risk of venous thromboembolism (VTE), due to a chronically activated coagulation system in sickle cell disease patients [381–383]. However, there is no clear evidence to suggest that hormonal contraceptive use is associated with an increased risk of complications in women with sickle cell disease [384,385]. Therefore, the WHO currently classifies sickle cell disease as a Category 2 for combined oral contraceptives, meaning that the benefits of combined oral contraceptives use among women with this condition generally outweigh the theoretical or proven risks [386].

#### 6.2.4.2. Preconceptional care

Premarital and preconceptional screening programs have been established in some high income countries and programs are starting to be developed in areas with a very high prevalence of sickle cell disease, including India and some African countries [69]. However, voluntary premarital screening relies upon recognition of the high risk groups and a proper organisation to screen patients. [387]. Especially in Western countries, where the sickle cell gene is less common, awareness of carriership of the disease is relatively low.

In countries with comprehensive sickle cell care, the majority of women with the disease are seen regularly in a haematology outpatient clinic where they are monitored for chronic complications. However, many of these having implications in pregnancy. Conception and contraception should be discussed during regular outpatient visits once the woman reaches child bearing age [388]. Education of women regarding the inheritance of sickle cell disease, including genetic screening of partners and the possibility of preimplantation genetic diagnosis, is an essential part of preconceptional care. In addition, couples should be aware of the risks of pregnancy in sickle cell disease.

Women on chronic blood transfusion regimes should be fully assessed for the complications of iron overload before embarking on pregnancy. This includes a cardiac and hepatic MRI scan. Patients should undergo aggressive iron chelation in case of iron overload before trying to conceive [388]. In addition, it is advised to stop taking hydroxyurea before conceiving due to teratogenic effects in animals [389,390]. However, ‘the Multicenter Study of Hydroxyurea in Sickle Cell Anemia (MSH)’ trial followed parents who, although advised to use contraceptives, became pregnant during hydroxyurea use and they found no teratogenic changes in those pregnancies, indicating that pregnancy termination because of the use of hydroxyurea during pregnancy is not needed [391].

#### 6.2.4.3. Pregnancy

Pregnancy in women with sickle cell disease is complicated by the maternal condition characterised by years of chronic organ damage, as well as by the physiologic changes and adaptations that are inherent to pregnancy. For example, plasma volume begins to expand between 6 and 8 weeks of gestation, ultimately achieving a 45% increase over non-pregnancy volume [392]. Adaptation required by the haematologic, cardiovascular, respiratory and renal systems are problematic in patients with sickle cell disease [393], while those physiologic changes are generally well tolerated in healthy pregnant women [394].

Pregnancy in women with sickle cell disease is associated with an increased risk of adverse perinatal outcomes, including spontaneous abortion, intra uterine growth retardation (IUGR), pre-eclampsia, severe foetal anaemia, stillbirth, the risk of caesarean delivery and neonatal mortality [395–398]. Those increased risks are regardless whether these women live in low- or high-income countries. However, the risk of maternal mortality is significantly higher for low income countries [399].

### Table 3

| ClinicalTrials.gov Identifier or European clinical trials database number | Group | Cellular product | Conditioning Disease Status | NCT02430554 Bluebird Bio Autologous BM CD34+ cells transduced by the βA-T87Q | Ages (years) | Disease Status | Conditioning | Status |
|---|---|---|---|---|---|---|---|---|---|
| NCT02140554 Bluebird Bio, Necker Children’s Hospital Paris | | | | | | | | | Recruiting |
| NCT02151526 University of Southern California | | | | | | | | | Recruiting |
| NCT02186418 University of Cincinnati Medical Center | | | | | | | | | Recruiting |

**Abbreviations:** BM: bone marrow.
Antenatal care is provided by a multidisciplinary team, including an obstetrician with experience in high risk antenatal care and a sickle cell disease specialised haematologist [398]. Screening of the partner for carrier status is important if this has not been done preconceptionally. If both parents are carrier of, or affected by, sickle cell disease the couple should receive appropriate counselling regarding the risk of having affected offspring. In addition, they should be informed about the methods and risk of prenatal diagnosis and termination of pregnancy, ideally by ten weeks gestation [388].

7. Conclusion and future considerations

There has been a significant increase in our understanding of the pathophysiology and factors contributing to the severity of sickle cell disease over the past decade. Comprehensive care programs including neonatal screening, infection prophylaxis, prevention of neurological complications and early hydroxyurea therapy will hopefully further increase life expectancy and quality of life of sickle cell disease patients. Allogeneic stem cell transplantation is becoming more safe and more widely available, although its use is limited to developed countries. In the near future HSCT may be superseded by the gene addition and editing approaches with the first patients having received gene therapy now showing complete clinical remission.

Establishing national, and ultimately international, databases for sickle cell disease will be of great importance to understand the natural history and diverse heterogeneity of the disease and to improve symptom management. However, many healthcare providers do not have the comprehensive knowledge and expertise to care for people with sickle cell disease. Therefore, ensuring implementation of existing standard-of-care guidelines and best practices is essential.

The global burden of sickle cell disease is enormous and there is a lack of knowledge and information among the wider population regarding sickle cell disease, indicating the need for more awareness initiatives for the public. In countries with poor public health systems, sickle cell disease remains a major killer of infants and children, similar to other diseases like malaria and HIV/AIDS. Governments and philanthropic groups should be educated about the importance of screening and caring for people with this disease. Hopefully, with growing public and governmental awareness together with global multidisciplinary partnerships, sickle cell disease can emerge from its neglected stage.

Practice Points

- Sickle cell disease is the most common monogenic disorder worldwide and has been declared a global health problem by the World Health Organisation.
- High quality evidence is limited in most areas of sickle cell disease management; most recommendations are solely expert-opinions.
- Patients with sickle cell disease should be treated in a multi-disciplinary setting before they develop chronic, irreversibly and ultimately fatal organ damage.
- Patient and family support is crucial in order to practice optimal comprehensive care.

Research Agenda

- Establishment of international databases to determine the natural course of sickle cell disease and to identify disease modifying factors.
- Insight into the genetic modifiers and non-genetic risk factors of sickle cell disease and treatment outcome.
- Prospective, ethical research focussing on improvement of survival and quality of life for individuals with sickle cell disease in low-resource settings.
- Development of new, affordable pharmacological therapies.

Conflict of interest statement

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bjre.2019.05.004.

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