Knowledge Insufficient: The Management of Haemoglobin SC Disease

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Abstract

Although haemoglobin SC (HbSC) accounts for 30% of sickle cell disease (SCD) in the United States and United Kingdom, evidence-based guidelines for genotype specific management are lacking. The unique pathology of HbSC disease is complex, characterized by erythrocyte dehydration, intracellular sickling and increased blood viscosity. The evaluation and treatment of patients with HbSC is largely inferred from studies of SCD consisting mostly of haemoglobin SS (HbSS) patients. These studies are underpowered to allow definitive conclusions about HbSC. We review the pathophysiology of HbSC disease, including known and potential differences between HbSS and HbSC, and highlight knowledge gaps in HbSC disease management. Clinical and translational research is needed to develop targeted treatments and to validate management recommendations for efficacy, safety and impact on quality of life for people with HbSC.

Keywords

Haemoglobin SC; Haemoglobin Sickle C; sickle cell disease; sickle cell anaemia

Background

Co-inheritance of the haemoglobin S (HbS) and haemoglobin C (HbC) beta globin gene (*HBB*) mutations causes haemoglobin SC (HbSC) disease. Valine replaces glutamic acid at position 6 (Glu6Val) in HbS, while lysine is substituted for glutamic acid (Glu6Lys) in HbC. Haemoglobin AC and haemoglobin AS (HbC and HbS trait, respectively) are largely asymptomatic carrier states, whereas HbSC has a unique pathological phenotype (Nagel *et al*, 2003; Steinberg & Nagel, 2009). Although considered a milder sickle cell disease (SCD)

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variant, HbSC is associated with potentially severe morbidities that warrant surveillance and intervention (Nagel *et al*, 2003; Steinberg & Nagel, 2009).

In 2014, the National Heart, Lung and Blood Institute (NHLBI) of the US National Institutes of Health released treatment guidelines, Evidence-Based Management of Sickle Cell Disease (Yawn *et al*, 2014), based on available scientific evidence and expert consensus. This report provides recommendations for clinical management of all patients with either SCD or sickle cell anaemia (SCA). The largest multi-centre study of HbSC, the 1,000+ HbSC cohort enrolled in the Cooperative Study of Sickle Cell Disease (CSSCD), is nearly 40 years old, and like most subsequent studies of patients with HbSC, this rich dataset was non-interventional and non-randomized. The lack of high quality disease-specific evidence precludes publication of evidence-based guidelines for optimal management of HbSC disease (Yawn *et al*, 2014). Here, we review the epidemiology, pathophysiology, clinical complications and treatment of HbSC, highlighting important knowledge gaps and research opportunities.

DISTRIBUTION & PATHOPHYSIOLOGY

Epidemiology

In the UK and US, HbSC accounts for nearly 30% of SCD. In the UK, 1:2000 babies are born with SCD and 1:7174 has HbSC (Streetly *et al*, 2008). Similarly, in the US, 1:941 babies are born with SCD, while 1:6173 newborns has HbSC (Therrell *et al*, 2015). In parts of West Africa, where HbC originated, HbSC accounts for more than 50% of SCD (Saraf *et al*, 2014). The allelic frequency of HbC is a consequence of the survival advantage against severe malaria conferred through inheritance of one *HBB* (beta globin gene) mutation (Modiano *et al*, 2001; Piel *et al*, 2013). Emigration from West Africa, forced and voluntary, spread HbC to Europe and the Americas. Worldwide, at least 55,000 children are born with HbSC annually (Weatherall, 2010).

Survival of patients with HbSC is superior to SCA, probably reflecting delayed onset of irreversible organ injury (Powars *et al*, 2002; Hassell, 2010; Steinberg & Nagel, 2009). In the decades-old CSSCD, median survival of patients with HbSC was 60 years for men (n = 417) and 68 years for women (n=427) (Platt *et al*, 1994). A recent single-centre study reported median survival of patients with HbSC and HbSβ$^+$ patients (n = 93) to be 66 years (Elmariah *et al*, 2014). In these data sets, US patients received care at designated sickle cell centres. Older longitudinal studies from the US report median survival of 37 years (n = 248) (Powars *et al*, 2002) and 50 years (n =106) (Koduri *et al*, 2001). Life expectancy in HbSC, as for all SCD, remains context-dependent, with patients in high-income countries benefiting from access to newborn screening and to preventive, emergency and intensive care (Streetly *et al*, 2008; Chaturvedi & DeBaun, 2016).

Pathophysiology

HbSC red blood cells (RBCs) contain roughly equal amounts of HbC and HbS and low (1-3%) levels of HbF (Nagel *et al*, 2003; Gualandro *et al*, 2015). HbSC disease pathogenesis is modulated by interactions between HbS and HbC as well as RBC dehydration from

altered membrane transporter function. When RBCs are dehydrated, the HbS concentration increases (Mozzarelli *et al*, 1987). At moderate to high intra-erythrocyte concentrations, HbS subunits polymerize, forming long, rigid molecules that persist as RBCs enter and obstruct the microcirculation (Nagel *et al*, 2003). At high concentrations of oxygenated HbC, tetragon crystals form, but in the deoxygenated state they dissolve rapidly (Nagel *et al*, 2003). HbF impedes HbC crystallization and HbS polymerization (Nagel *et al*, 2003). Increasing HbF is of therapeutic interest in HbSC, as it is for haemoglobin SS (HbSS) disease. Other potential sites of therapeutic intervention include the three pathways that cause RBC dehydration and cation loss: (1) deoxy-dependent, nonselective P-sickle pathway calcium ion permeability (Gallagher, 2015) (2) calcium-activated Gardos potassium channels (Gallagher, 2015); and (3) increased K-Cl cotransport that leads to potassium, chloride and water loss (Nagel *et al*, 2003; Rees *et al*, 2015). Erythrocyte water and solute transport is incompletely understood and has not yet been successfully therapeutically exploited (Gallagher, 2015). Initial trials of magnesium, a modulator of K-Cl cotransport in HbSS and HbSC, were disappointing (Rees *et al*, 2015; Nottage *et al*, 2016; Wang *et al*, 2011).

Alpha thalassaemia trait

Inheritance of alpha thalassaemia gene deletions decrease HbS polymerization (Steinberg & Embury, 1986) and modulate HbSC disease severity (Embury *et al*, 1982, 1984; Powars *et al*, 2002,). In a seminal observational cohort study of 248 patients with HbSC, Powars et al (2002) reported that patients with two *HBA1/2* (alpha globin gene) deletions had less (17% vs. 32%) and later (48 vs. 33 years) osteonecrosis, later onset gallbladder disease (55 vs. 34 years), less retinopathy (26% vs. 41%) and fewer painful crises (48% vs. 80%). These patients also had favourable clinical outcomes measured by composite scores of major organ failure (Powars *et al*, 2002). Iron deficiency mimics alpha thalassaemia trait by decreasing alpha globin production (Bunn, 1994). This is one rationale for therapeutic phlebotomy in HbSC (Lionnet *et al*, 2016).

Laboratory findings in HbSC

People with HbSC have a higher mean Hb and lower absolute reticulocyte count (ARC) than people with HbSS disease (Table I). Erythrocyte lifespan is twice that of HbSS (29 vs. 15 days) (McCurdy & Sherman, 1978; McCurdy *et al*, 1975). Over 70% of people with HbSC have anaemia, but only 10% have Hb lower than 100 g/l. Mean corpuscular volume (MCV) is low, and inheritance of alpha thalassaemia trait further reduces MCV (Embury *et al*, 1984). Leucocytosis is less pronounced or absent in HbSC compared to HbSS. Platelet counts may be normal, but mild to moderate thrombocytopenia occurs in patients with splenomegaly and hypersplenism. The abundance of target cells on the peripheral blood smear results from the relatively increased surface area secondary to RBC dehydration (Figure 1A). Distorted tri-concave or elongated erythrocytes containing Hb crystals occur infrequently. Irreversibly sickled cells are rare. Blood viscosity is increased even compared to HbSS (Nagel *et al*, 2003).

Diagnosis

In newborn screening programmes for SCD in the US and the UK, screening and confirmatory testing is performed using high-performance liquid chromatography and isoelectric focusing. Newborn screening reduces SCD morbidity and mortality by facilitating implementation of early preventive medical care (Streetly *et al*, 2008). Because many people with HbSC emigrate from countries without newborn screening, patients may only be diagnosed when a disease-related complication arises. Primary care and emergency department clinicians should consider undiagnosed HbSC disease in children or adult patients presenting with complications such as priapism, hypersplenism and painful crises.

Identifying couples at risk for having a child with HbSC enables pre-conception counselling and diagnostic strategies, including pre-implantation genetic testing, and post-conception chorionic villus sampling or amniocentesis (Mason *et al*, 2016; Kuliev *et al*, 2011). Non-invasive analysis of cell-free fetal DNA extracted from maternal blood samples is an emerging technology for prenatal SCD diagnosis (Perlado *et al*, 2016; Barrett *et al*, 2012).

Penicillin Prophylaxis and Vaccination

Reducing the risk of life threatening complications, such as infection, provides one rationale for newborn screening for SCD. Unfortunately, the efficacy and timing of penicillin prophylaxis in HbSC are debated because of a lack of evidence (Lane *et al*, 1995; Yawn *et al*, 2014). In the CSSCD, bacterial sepsis in HbSC children (n=177, 339 patient years) occurred mostly before age 2 years (Zarkowsky *et al*, 1986); however, in the Dallas Newborn Cohort, the rate of bacterial sepsis in non-prophylaxed children with HbSC (n=242, 842 patient years) was similar to that of age-matched controls (Rogers & Buchanan, 1995), perhaps because of a later loss of splenic function in HbSC (Buchanan *et al*, 1983). Faced with uncertainty about the timing and extent of splenic function loss in HbSC and the efficacy of prophylactic measures, we prescribe penicillin prophylaxis to children with HbSC as for all with SCD. Our patients also receive multi-valent vaccination against encapsulated organisms (meningococcus, pneumococcus and Haemophilus influenza) and immunizations against hepatitis A and B (Yawn *et al*, 2014; Gaston 1986). We urgently evaluate and empirically treat febrile patients, regardless of vaccination status (Yawn *et al*, 2014).

SYSTEMIC COMPLICATIONS

Ocular Manifestations

Proliferative sickle retinopathy, or retinitis proliferans (RP), is the most common complication of HbSC disease, occurring in 30-70% of patients with HbSC compared to 3% in HbSS (Lutty *et al*, 2001; Lemonne *et al*, 2014; Gualandro *et al*, 2015; Myint *et al*, 2015). RP is caused by excessive retinal blood vessel growth. It may occur late in the first decade of life, and incidence peaks in the third and fourth decades (Leveziel *et al*, 2012). The retinal neovascularization of RP is classically described as "black sea fan", "black sunburst" and "salmon patch" (Welch & Goldberg 1966). One hypothesis explaining the higher incidence of RP is that in HbSC, peripheral retinal vessels are occluded but the minimal oxygen delivery needed for neovascularization is maintained, while in HbSS, frank retinal ischaemia

inhibits neovascularization (Nagel *et al*, 2003). Co-inheritance of alpha thalassaemia trait is associated with decreased rates of retinopathy (Powars *et al*, 2002). RP may be more directly associated with hyperviscosity in HbSC, reflecting RBC rheology and Hbconcentration, rather than Hbor RBC density alone (Lemonne *et al*, 2014). Proliferative neovascularization causes vision loss by vitreous haemorrhage and tractional retinal detachment.

Non-proliferative damage occurs via occlusion of ocular structures (conjunctiva, anterior segment, choroid, retina or optic nerve) and typically presents as acute vision loss. Central retinal artery occlusion is rare in HbSC (Fine *et al*, 2000). Acute vision loss in SCD patients requires emergent evaluation to optimize preservation of function (Myint *et al*, 2015; Yawn *et al*, 2014).

Early detection and intervention are effective in preventing vision loss. NHLBI guidelines recommend annual ophthalmological screening for SCD patients beginning at age 10 years and prompt referral for expert management of complications. Given the higher incidence of RP in HbSC, we recommend annual ophthalmological examinations. Treatment options include diathermy, cryotherapy and transpupillary or transscleral diode laser photocoagulation. The preferred intervention is transpupillary laser photocoagulation. Other laser therapies merit ongoing investigation (Myint *et al*, 2015). High-grade evidence for treatment with simple or exchange transfusions is lacking.

Pain

Painful crises are a hallmark of HbSC disease. At least 50% of people with HbSC report a painful episode requiring a hospital visit (Powars *et al*, 2002) and about 5% of HbSC patients may have frequent debilitating painful events (Luchtman-Jones *et al*, 2016). Prevention and treatment strategies for painful crises in HbSC include hydration, analgesia and adequate oxygenation. Rehydration of HbSC erythrocytes *in vitro* normalizes the mean corpuscular haemoglobin concentration (MCHC), increases Hb oxygen affinity, lowers the viscosity of deoxygenated RBC suspensions, reduces the rate of sickling and improves the deoxygenation-induced potassium efflux (Nagel *et al*, 2003). Acute treatment recommendations include prompt and aggressive pain management, using non-steroidal anti-inflammatory drugs (NSAIDs) with the addition of opiates, depending upon renal function and pain severity. Mechanism-specific medications, like the K-Cl cotransporter inhibitor magnesium, have not demonstrated efficacy in modulating acute painful crises (Rees *et al*, 2015; Nottage *et al*, 2016).

Health-related quality of life (HRQL) measurements in SCD are not genotype-specific. Pain negatively impacts the quality of life in people with SCD. A systematic review of HRQL in SCD concluded that adults and children have significantly impaired HRQL similar or worse than in other chronic diseases (Panepinto & Bonner, 2012). Physical functioning domains are especially affected, probably due to pain. Other factors that modify HRQL are age, socioeconomic status, medical or neurobehavioural comorbidities, and disease-modifying therapies (Panepinto & Bonner, 2012). Future clinical trials for HbSC should include validated HRQL measures.

Splenic complications

Splenic acidosis and relative hypoxia can precipitate RBC sickling. Aging and damaged RBCs are removed by the spleen (Crary & Buchanan, 2009). Functional asplenia is reported in 45% of HbSC patients by age 12 years (Lane *et al*, 1995). Chronic splenomegaly is associated with thrombocytopenia in 35% of children and 50% of adults with HbSC and may cause recurrent abdominal pain. Hypersplenism may impede optimal treatment with transfusion or hydroxycarbamide (Zimmerman & Ware, 2000; Aquino *et al*, 1997).

Acute splenic sequestration crisis (ASSC), precipitated by obstruction of splenic outflow with sickled erythrocytes, causes massive pooling of blood within the splenic sinusoids. ASSC occurs in 6-12% of children with HbSC. Affected patients present with rapid, progressive and, especially in older patients, painful splenomegaly (Aquino *et al*, 1997). Platelet counts fall with worsening anaemia, typically 20 g/l or more below baseline. Splenic infarction, characterized by moderate splenomegaly, left upper quadrant pain and wedge-shaped defects on liver-spleen scan, occurs spontaneously or is triggered by high-altitude exposure. Splenic infarcts may mimic pain crises and are likely under diagnosed (Aquino *et al*, 1997; Githens *et al*, 1977). Primary treatment for ASSC is RBC transfusion, with cautious hydration due to the risk of high output congestive heart failure. Anticipating that Hb will increase as RBCs are released from the enlarged spleen ("auto-transfusion"), conservative simple RBC transfusions of 5 ml/kg are advised. Splenomegaly improves within hours to days after transfusion (Koduri & Nathan, 2006). Recurrent sequestration is common and may require complete or partial splenectomy, although strong evidence in HbSC is lacking (Englum *et al*, 2016).

The incidence and optimal management of HbSC splenic sequestration is unknown (Koduri & Nathan, 2006). Splenectomy improves anaemia and thrombocytopenia. Whether this causes an injurious increase in viscosity for HbSC patients is unclear (Subbannan *et al*, 2009). Splenectomy is ideally performed at least two weeks after vaccination against encapsulated organisms, and post-splenectomy antibiotic prophylaxis is recommended. Caregivers and patients should learn splenic palpation and recognition of the signs of sequestration (Aquino *et al*, 1997; Zimmerman & Ware, 2000).

Osteonecrosis

Osteonecrosis, or avascular necrosis (AVN), is common, occurring in 12 - 24% of HbSC patients (Lionnet *et al*, 2012; Mukisi-Mukaza *et al*, 2009). AVN typically affects large joints, such as hips and shoulders, but can occur in other joints, including the spine. Bilateral hip disease is more common in HbSS than in HbSC. Hyperviscosity may contribute to the development of AVN, though high-grade evidence is lacking (Milner *et al*, 1991; Lemonne *et al*, 2013). Alpha thalassaemia trait, while a risk factor for AVN in HbSS, is less strongly associated in HbSC, and may even be protective (Powars *et al*, 2002; Milner *et al*, 1991; Ballas *et al*, 1989). Evidence does not support surveillance x-rays in asymptomatic patients.

AVN usually presents as focal pain, but it can precipitate diffuse pain crisis and should be considered when diffuse pain resolves, but focal pain persists (Almeida & Roberts, 2005). Initial evaluation in symptomatic patients is with plain radiographs; however, magnetic

resonance imaging (MRI) is the most sensitive diagnostic modality and delineates the extent of joint damage. Original AVN scoring systems, developed prior to the availability of MRI, have been adapted (Steinberg & Steinberg, 2004).

Reducing pain and disability are the primary management goals of AVN. Unfortunately, high-level evidence about timing or type of joint intervention is lacking (Almeida & Roberts, 2005; Stoica *et al*, 2009). Depending upon the extent and progression of joint injury, management may include analgesia, physical therapy and surgery. Localized lidocaine- or opiate-eluting patches may decrease systemic opiate intake. Patients with progressive AVN should be referred to orthopaedics for evaluation. Core decompression may alleviate pain and delay arthroplasty (Mukisi-Mukaza *et al*, 2009). When femoral head damage progresses to collapse, total hip arthroplasty may be indicated. Several recent studies investigated the optimal type and timing of joint repair or replacement without definitive conclusions (Almeida & Roberts, 2005; Stoica *et al*, 2009).

Central Nervous System Complications

Neurological complications, including headache, overt ischaemic stroke, haemorrhagic stroke, and silent cerebral infarcts (SCI), are common in SCD (DeBaun & Kirkham, 2016). Risk factors for ischaemic stroke include hypertension (adults and children), hyperlipidaemia, renal disease and atrial fibrillation. Risk factors for haemorrhagic stroke include hypertension (all ages), kidney disease, and coagulopathy (Strouse *et al*, 2009). Stroke rates for HbSC, while much lower than in SCA, peak in older adults, in whom haemorrhagic stroke is more common (Strouse *et al*, 2009; DeBaun & Kirkham, 2016).

Few data distinguish the neurological sequelae of HbSC from all SCD. However patients with HbSC are known to suffer overt stroke (2%) and SCI (8 – 13.5%) (Wang *et al*, 2001; Guilliams *et al*, 2015) at higher rates than in the general population. Baseline transcranial Doppler (TCD) values are reportedly lower in children with HbSC (Deane *et al*, 2008). Children with HbSS and HbSC without evidence of stroke on brain MRI scored slightly lower, but within the population means, on neurocognitive testing (Gold *et al*, 2008), whereas HbSS and HbSC patients with SCI scored 9-10 points lower on neuropsychological testing. Impairment was associated mostly with frontal lobe tasks requiring attention and concentration. Children also had problems with hyperactivity, cognitive and academic performance, and executive functioning (Gold *et al*, 2008). Although annual TCD screening and intervention with chronic RBC transfusions have reduced ischaemic stroke rates in children with SCA, neither is validated in HbSC disease.

Little is known about headaches in HbSC disease, as most studies do not report genotype-specific outcomes. Up to 36% of children and adolescents with SCD experience chronic headaches; in adults with SCD, chronic headache is associated with opioid use and vaso-occlusive events (DeBaun & Kirkham, 2016). Neurology consultation may help guide chronic headache treatment with therapies, such as pizotifen, propranolol, topiramate or valproic acid. Tryptans are avoided because of concerns about exacerbating cerebral ischaemia (DeBaun & Kirkham, 2016).

Increased incidence of sensorineural hearing loss, sometimes associated with retinopathy, is reported in HbSC (Leveziel *et al*, 2012; Onakoya *et al*, 2010; Lionnet *et al*, 2012). We maintain a high index of suspicion for hearing loss or vestibular problems, especially in patients with retinopathy, and in the absence of high-level evidence, support a low threshold for audiological testing in these patients.

Sexual development and Pregnancy

Young women with HbSC may have marginally delayed menarche compared to unaffected controls (median age 13.7 vs. 13 years) (Serjeant *et al*, 2005). The CSSCD found comparable onset of menarche across sickle cell genotypes consistent with constitutional growth delay (Platt *et al*, 1984). In women with HbSS, menses may precipitate painful crises and infertility rates are increased (Stimpson *et al*, 2016; Yoong & Tuck, 2002; Smith-Whitley, 2014). These complications are unexplored in HbSC. Koduri (2003) hypothesizes that menstrual blood losses lower iron stores and reduce blood viscosity thereby improving HbSC disease severity.

Women with HbSC, like all women with SCD, are at increased risk of maternal and fetal morbidity and mortality. They may experience sickle and non-sickle related complications during pregnancy including acute pain, pre-eclampsia, acute chest syndrome (ACS) and urinary tract infections (Oteng-Ntim *et al*, 2015a, 2015b). Babies born to mothers with HbSC are more often born at term, with fewer fetal complications than those born to mothers with HbSS (Oteng-Ntim *et al*, 2015b; Wilson *et al*, 2012; Serjeant *et al*, 2005). In a cohort of Brazilian women with HbSC, erythrocytapheresis or manual exchange in the third trimester reduced maternal and fetal complications (Benites *et al*, 2016), but high-level evidence for transfusion during pregnancy is lacking (Okusanya & Oladapo, 2013).

Education about the heritability of HbSC, contraception options and the need for high-risk obstetrics care should begin in early adolescence (Stimpson *et al*, 2016). A 2010 survey of women with HbSS in the UK found that 53% experienced an unintended pregnancy (Eissa *et al*, 2015). High quality evidence to identify the optimal forms of contraception in women with SCD is needed, particularly given the risk of venous thromboembolism (VTE) with oestrogen-containing contraception. Depot medroxyprogesterone-acetate use is associated with decreased rates of pain crises in SCD (Manchikanti *et al*, 2007), but whether reversible changes in bone mineral density exacerbate disease related complications is unknown (Kaunitz *et al*, 2008).

Priapism

Priapism, an unwanted erection lasting four hours or more, occurs in 20% of men with HbSC and is a clinical emergency (Lionnet *et al*, 2012). Priapism often occurs as young men reach sexual maturity (Adeyoju *et al*, 2002), and may be the presenting sign of HbSC disease in previously undiagnosed men (Anele *et al*, 2015). Typically caused by acute ischaemic injury, priapism may be continuous, intermittent or recurrent (stuttering priapism). Treatment goals are detumescence and pain reduction to prevent future erectile dysfunction and impotence. If conservative management with aggressive hydration and analgesia is unsuccessful, treatments include oral alpha-adrenergic agonists, phosphodiesterase-5

inhibitors and urological consultation for penile aspiration or corporeal irrigation with alpha-adrenergic agonists. Transfusion has no demonstrated efficacy for management of priapism and in HbSS, there may be an association between priapism, exchange transfusion and neurological complications (Merritt *et al*, 2006).

Cardiovascular and Pulmonary Complications

Cardiovascular complications of SCD arise from complex interactions between blood and vascular endothelium and from the systemic response to anaemia (Pecker & Ackerman, 2016). Blood pressure (BP) in patients with HbSC is similar to healthy controls whereas in HbSS it is lower (Pegelow *et al*, 1997; Lionnet *et al*, 2012). Near normal BP might be expected in HbSC, where milder anaemia probably improves vascular tone. Patients with all sickle cell genotypes require monitoring and treatment of hypertension due to stroke risk (Pegelow *et al*, 1997; Yawn *et al*, 2014; James *et al*, 2014). SCD-related changes in cardiac function may reflect intrinsic myocardial injury, the sequelae of chronic high-output demand or elevated tricuspid valve regurgitant jet velocity (TRJV) (Voskaridou *et al*, 2012; Niss *et al*, *2016*). Echocardiogram, electrocardiogram (EKG) and serum markers, such as brain natriuretic peptide (BNP) and troponins are difficult to interpret in the setting of SCD, and clinical condition dictates management (Voskaridou *et al*, 2012). Routine EKGs, echocardiograms and TRJV are not recommended for asymptomatic patients (Yawn *et al*, 2014).

Acute and chronic pulmonary complications contribute to morbidity and mortality in SCD (Saraf *et al*, 2014; Mehari & Klings, 2016). Hyper-reactive airways, asthma, ACS, pulmonary embolism (PE), pulmonary hypertension, sleep disordered breathing, obstructive sleep apnoea, reduced Hboxygen saturation and compromised pulmonary function are described more commonly in SCA cohorts (Saraf *et al*, 2014; Mehari & Klings, 2016). In a prospective evaluation of pulmonary hypertension in SCA, Gladwin *et al.* (2004), reported statistically significantly lower TRJV in subjects with HbSC, presumably due to relatively reduced haemolysis. ACS occurs in HbSC at similar or lower rates than in HbSS (Waltz *et al*, 2013; Lionnet *et al*, 2012; Vichinsky *et al*, 1997). In a study examining resting and exercise-induced oxygen desaturation, 50% of HbSS subjects, but none with HbSC, had baseline oxygen saturation <98%. After a six-minute walk test, baseline oxygen saturation fell 3% in children with HbSC and HbSS (18% vs. 34%) (Waltz *et al*, 2013). Lower oxygen saturation in children with HbSC correlated with reduced RBC deformability, but not blood viscosity, Hb, ACS rates or vaso-occlusive events. Severe ACS is an indication for blood transfusion, and hydroxycarbamide reduces the recurrence of ACS in patients with SCA, but these disease-modifying treatments are unstudied for HbSC disease (Yawn *et al*, 2014). Research is needed to establish optimal diagnostic, prognostic, and therapeutic approaches for lung disorders in SCD, particularly in HbSC.

Thrombosis

HbSC is a hypercoagulable state associated with arterial thrombosis and VTE complications and elevations in fibrinogen (Ajuwon *et al*, 2014), tissue factor expression, D-dimer and thrombin-antithrombin complexes (Colella *et al*, 2015). Alterations in protein C, protein S, nitric oxide, microparticles and markers of endothelial activation at steady state and in crisis

may contribute to a prothrombotic state in SCD and in HbSC (Piccin *et al*, 2015). Deep vein thrombosis (DVT) and PE, which constitute VTE, are increased in HbSC, as are AVN, stroke and pregnancy-related complications (Colella *et al*, 2015). Retrospective cohort studies identify higher rates of non-catheter-related VTE in HbSC than HbSS (Lionnet *et al*, 2012; Naik *et al*, 2014a). In an autopsy study of 44 HbSC patients, PE was the second leading cause of death (Manci *et al*, 2003). Risk factors for VTE in HbSC include higher Hb and splenectomy (Yu *et al*, 2016). Therapeutic phlebotomy is used at some centres to reduce disease complications associated with increased blood viscosity and higher Hb in HbSC (Lionnet *et al*, 2012; Yu *et al*, 2016), but whether this reduces thrombotic complications is unknown. Oestrogen-based hormone therapy generally increases baseline thrombosis risk, but there is no SCD-specific data (Manchikanti *et al*, 2007).

Clinicians should have a high index of suspicion for thrombosis in HbSC and follow general expert guidelines for prevention and detection of thromboembolic disease, recognizing that D-dimer cannot be reliably interpreted due to chronic and fluctuating activation of coagulation (Naik *et al*, 2014a; Kearon *et al*, 2016). Patient education includes VTE prevention strategies and recognizing signs and symptoms of venous and arterial thrombosis. SCD-specific VTE prophylaxis guidelines do not exist and no known disease-modifying interventions alter the risk of thrombosis in patients with HbSC disease.

Renal

Renal complications in HbSC occur later, more gradually, and less commonly than in HbSS and include hyposthenuria, acute papillary necrosis and microalbuminuria. The sickle nephropathy of HbSC is distinct from HbSS in that it occurs later in life and rarely leads to end-stage-renal-disease (ESRD) (Aygun *et al*, 2011; Lionnet *et al*, 2012). Microalbuminuria occurs in 30% of patients with HbSC, and ESRD develops in 2-3% by their 5th decade (Powars *et al*, 1991, 2002; Lionnet *et al*, 2012; Drawz *et al*, 2016). Children with HbSC typically develop irreversible hyposthenuria at 10 - 15 years of age and have evidence of glomerular damage and medullary injury (Iyer *et al*, 2000; Drawz *et al*, 2016). Acute HbSC renal complications include renal papillary necrosis and renal infarction. Renal medullary carcinoma, associated with HbAS, but not HbSS, is also reported in HbSC (Davis *et al*, 1995; Dimashkieh *et al*, 2003), raising intriguing questions that are beginning to be explored about mechanisms of renal injury in people with one HbS gene (Naik *et al*, 2014b).

The management of renal complications is not HbSC-specific (Sasongko *et al*, 2015). Annual screening for proteinuria starts at age 10 years for all children with SCD. Rapid deterioration in renal function is inconsistent with the natural history of HbSC disease and should prompt investigation of another aetiology (Sharpe & Thein, 2014). Hydroxycarbamide may improve the concentrating defect in children with SCA (Aygun *et al*, 2011), but its effects in HbSC are unclear (Iyer *et al*, 2000).

Hepatobiliary disease

Gallbladder-related complications are less common in HbSC (15-20%) than in HbSS (50%), probably because of lower haemolytic rates (Walker *et al*, 2000; Powars *et al*, 2002). The incidence of cholelithiasis increases with age, occurring in 3% of HbSC children under age

14 years, and in nearly 20% by age 20 years (Walker *et al*, 2000). Inheritance of alpha thalassaemia trait is associated with lower rates and later onset of symptomatic gallbladder disease (Powars *et al*, 2002).

DISEASE MODIFYING THERAPIES

Hydroxycarbamide and RBC transfusion are currently the most available and under-utilized disease modifying therapies in SCD (Yawn *et al*, 2014). For people with HbSC, the use of disease modifying RBC transfusions (Estcourt *et al*, 2016a), phlebotomy (Lionnet *et al*, 2012) and hydroxycarbamide are supported by low-level evidence of safety and efficacy (Luchtman-Jones *et al*, 2016). Haematopoietic stem cell transplant (HSCT) for HbSC is described for patients with an additional diagnosis like cancer, but has not been reported in patients with isolated HbSC disease, probably because the risks of HSCT are thought to outweigh potential benefits (Kamble *et al*, 2006).

Red Cell Transfusion

Most adults with HbSC receive a RBC transfusion in their lifetime, but the efficacy of transfusions is not well demonstrated for prevention or treatment of disease complications (Estcourt *et al*, 2016a, 2016b). A retrospective analysis of HbSC patients in the CSSCD showed benefit for preoperative RBC transfusions (Koshy *et al*, 1995); however a prospective nonrandomized clinical trial of 75 HbSC patients transfused at the discretion of their physician did not show benefit, except in moderate risk procedures (such as abdominal surgery) (Neumayr *et al*, 1998). Low quality evidence reviewed in a recent meta-analysis prevented conclusions about perioperative transfusions in HbSC disease (Estcourt *et al*, 2016b). The use of empiric transfusion in the UK is inconsistent (Buck *et al*, 2005). Higher potential risk has been attributed to certain surgeries where acidosis, dehydration and tissue hypoxia seem likely, such as cardiac bypass surgery. Case reports detail preoperative or intraoperative exchange transfusion procedures, usually to reduce HbS + C to less than 30% (Marchant *et al*, 2001; Law *et al*, 2007)

Acute and chronic RBC transfusion modalities are important in HbSC, where higher Hb and hyperviscosity are concerns. Simple transfusion raises Hb and blood viscosity. Exchange transfusions remove sickled RBCs and replace them with allogeneic RBCs, lowering or minimally increasing blood viscosity. Partial volume exchange, performed manually or by apheresis, facilitates rapid reduction in the %HbS while maintaining a stable Hb concentration. Therapeutic targets for RBC transfusion in HbSC are derived from HbSS, where the goals are Hb of 100 g/l and HbS < 30%. Higher baseline Hb in HbSC may unacceptably increase blood viscosity and Hb after simple transfusion, while marginally reducing the HbS%. Exchange transfusion is favoured, often with a goal of reaching a HbS % of 15 - 25, so that HbS + C% is 30 or 50, respectively.

Risks of RBC transfusion include infection, transfusion reactions, alloimmunization, iron overload and vascular access problems. Exchange transfusion and apheresis procedures are associated with vascular access issues and higher donor exposure rates because more RBC units are required. A knowledge gap exists about alloimmunization rates in transfused HbSC

patients (Chou & Fasano, 2016). RBC transfusion in HbSC for management of refractory pain, ACS or other vaso-occlusive complications remains empiric.

Decisions about preoperative transfusion should include consideration of the type of procedure and published complications rates, the severity of the patient's HbSC disease in general and a frank discussion with the patient and family about the risks and benefits of preoperative transfusion. Given that hypoxia and acidosis are predicted to precipitate sickling, reduction of HbS + C to < 30% will probably remain usual practice for high risk surgical procedures until better evidence is available.

Phlebotomy

Because of a possible association between higher Hb concentration and sickle complications, phlebotomy targeting a reduction in Hb to 95 - 100 g/l has been empirically implemented for some HbSC patients. Phlebotomy reduces blood viscosity and iron stores. In a retrospective, nonrandomized study of 64 HbSC patients with clinical complications including pain, ACS, priapism and thrombosis, Lionnet *et al* (2012) reported clinical improvement in 71% after serial phlebotomy procedures. Whether this benefit is attributable to hyperviscosity is unclear because actual measured blood viscosity may not correlate with hyperviscosity predicted by using factors like haemoglobin, RBC deformability and aggregation. Lemonne *et al* (2015) measured blood viscosity directly in a cohort of 90 HbSC patients and found no significant association between the direct measurement of hyperviscosity and hyperviscosity as predicted by high Hb values). Venesection-induced iron restriction could decrease blood viscosity by decreasing Hb, MCV and MCHC, but compensatory thrombocytosis might at least partially counteract the positive benefits. Iron restriction in paediatric SCD patients, who have an increased risk of neurocognitive impairment at baseline, limits the study of this intervention in children (Lukowski *et al*, 2010). Phlebotomy and vascular access are often technically challenging. Randomized, controlled clinical trials are needed to determine the safety, tolerability and efficacy of phlebotomy in the management of acute and chronic complications in HbSC disease.

Hydroxycarbamide

NHLBI guidelines strongly recommend hydroxycarbamide use for adults with SCA and severe or recurrent ACS, frequent sickle cell pain or chronic anaemia and make a moderate-strength recommendation in asymptomatic infants, children and adolescents with SCA. A paucity of safety and efficacy data in HbSC prevented recommendations for its use (Yawn *et al*, 2014). Before 2014, five retrospective and prospective publications described the effects of hydroxycarbamide in 71 adult and paediatric patients with HbSC. Hydroxycarbamide was well tolerated, but the dose, treatment duration and laboratory and clinical efficacy varied. Concerns remained about whether treatment could dangerously increase blood viscosity, Hb and/or MCV, and whether increased HbF and clinical efficacy were possible in HbSC. Hydroxycarbamide may improve RBC rheology despite higher MCV, reduce circulating microparticles and inflammation, lower absolute neutrophil count (ANC) and ARC and enhance nitric oxide release in the vasculature (Luchtman-Jones *et al*, 2016).

In 2016, investigators from 18 US sickle cell centres reported retrospective data on 133 paediatric and young adult patients with HbSC taking a median hydroxycarbamide dose of 20mg/kg/day. Luchtman-Jones et al (2016) found laboratory changes and potential efficacy in reducing painful events in treated patients. Laboratory results included stable Hb concentration, increased HbF and MCV and reductions in white blood cell counts, ANC and ARC (Table I). Subtle changes in RBC morphology can be seen on peripheral blood smear (Figure 1B). Overall, hydroxycarbamide was well tolerated, with reversible cytopenias (neutropenia and thrombocytopenia) occurring in 22% of patients, similar to published rates in HbSS (Luchtman-Jones *et al*, 2016). Hydroxycarbamide treatment for the subset of HbSC patients with severe or refractory painful events or, less commonly, ACS remains common but empiric (Luchtman-Jones *et al*, 2016; Summarell & Sheehan, 2016). Summarell & Sheehan (2016) reported a series of 14 paediatric HbSC patients with clinically severe disease treated with hydroxycarbamide. Four patients who did not respond were treated with a combination of daily hydroxycarbamide, monthly phlebotomy and iron supplementation with positive clinical effect (Summarell & Sheehan, 2016). A prospective single-centre study of hydroxycarbamide in children with HbSC is ongoing (NCT02336373).

There is a knowledge gap about the safety of hydroxycarbamide in pregnant or lactating women. Hydroxycarbamide use is not recommended for these women. Counselling regarding contraception use is necessary for men and women while they are taking hydroxycarbamide (Yawn *et al*, 2014).

Conclusions

Considered a milder SCD variant, HbSC is associated with significant comorbidities, including high rates of retinopathy, AVN, pain and priapism. Although 30% of patients with SCD in the US and UK have HbSC, disease-specific data are lacking. In the era of precision medicine, studies that combine HbSC patients with other types of SCD obfuscate genotypic differences among the sickle haemoglobinopathies. There is an urgent need for HbSC-specific baseline data, followed by high quality clinical trials that include efficacy, safety and HRQL outcomes to define best practices and treatment options. Research funding should prompt validation of currently used disease modifying therapies, but also serve as a catalyst for discovery of novel therapeutics targeting disease-specific mechanisms.

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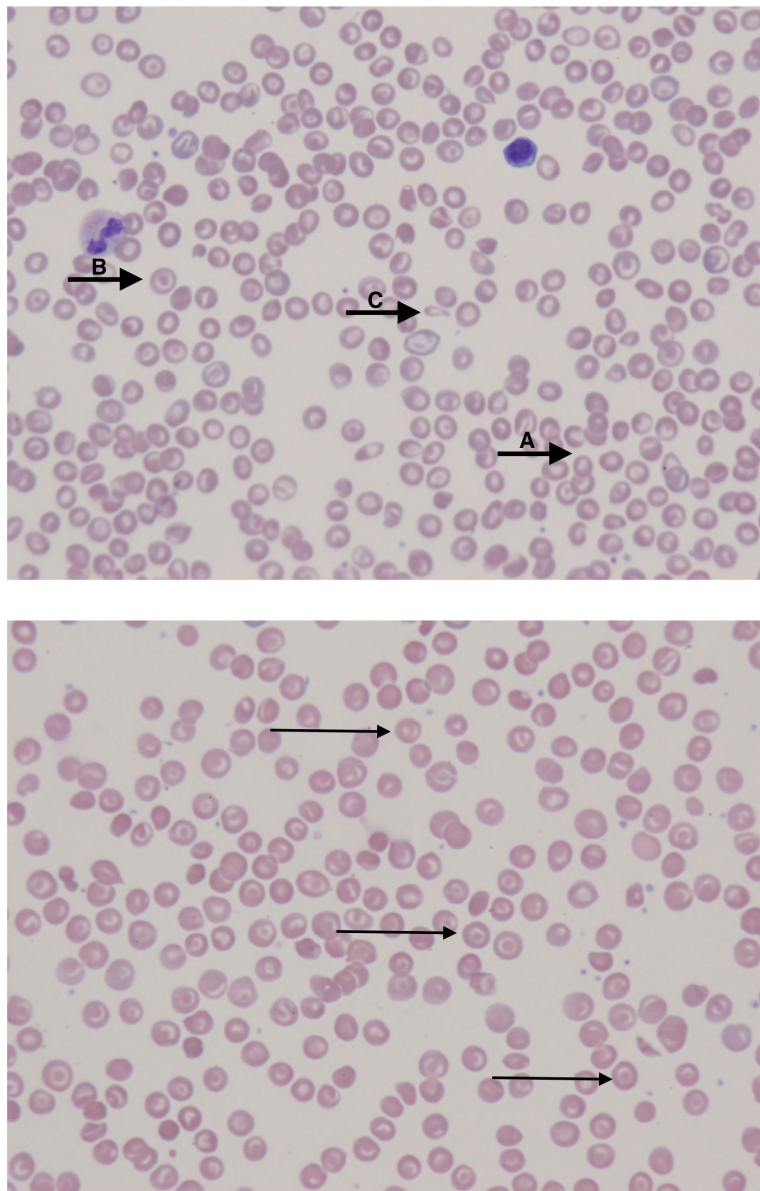
FIGURE 1.

The peripheral blood smear from a patient with HbSC **(A)** shows abundant red blood cell (RBC) polychromasia (A) as well as target cells with relatively increased surface area secondary to RBC dehydration (B). Distorted tri-concave or elongated erythrocytes containing haemoglobin crystals occur infrequently (C). Irreversibly sickled cells are rare. With hydroxycarbamide exposure, the peripheral blood smear **(B)** demonstrates more uniformity in the RBC target cell population (arrows) with an increase in mean corpuscular volume and less polychromasia.

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Table I

Laboratory Results at Baseline and After 12 Months of Hydroxycarbamide Therapy in Patients with HbSC Disease

	Hb (g/l)	MCV (fl)	ARC (×10⁹/l)	WBC count (×10⁹/l)	Platelet count (×10⁹/l)	ANC (×10⁹/l)	%HbA	%HbS	%HbC	%HbF	%HbA2
HbSC[1]	108 ± 12	75.7 ± 7	161 ± 97	9.6 ± 3.8	329 ± 155	4.88 ± 2.72	0	50	45	2.8 ± 2.9	<3.5
HbSC treated with HC[1]	111 ± 12	87 ± 12	129 ± 88	7.5 ± 2.8	273 ± 145	3.58 ± 2.08	NR	NR	NR	5.7 ± 4.7	NR

[1]Values taken from Luchtman-Jones *et al* (2016)

ANC, absolute neutrophil count; ARC, absolute reticulocyte count; Hb, haemoglobin; HbSC, haemoglobin SC; HC, hydroxycarbamide; MCV, mean corpuscular volume; NR, not reported; WBC, white blood cell.