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REVIEW

Management of sickle cell disease from childhood through adulthood

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ABSTRACT

Sickle cell disease (SCD) is a genetic disorder characterised by anaemia and "sickling" of red blood cells, leading to chronic haemolytic anaemia, vascular injury, and organ dysfunction. Although children and adults experience many similar symptoms and problems, complications increase with age, leading to early mortality. Hydroxyurea (hydroxycarbamide), the only US Food and Drug Administration-approved treatment, continues to be under-utilised and other treatments available to children are often inaccessible for adults. Haematopoietic stem-cell transplantation is a curative option, but is limited by a lack of donors and concerns for transplant-related toxicities. Although comprehensive programs exist in paediatrics, affected adults may not have access to preventative and comprehensive healthcare because of a lack of providers or care coordination. They are often forced to rely on urgent care, leading to increased healthcare utilisation costs and inappropriate treatment. This problem highlights the importance of primary care during the transition from paediatrics to adulthood.

1. Introduction

Sickle cell disease (SCD), the most common inherited red blood cell (RBC) disorder, affects individuals of African, Mediterranean, and Asian descent and manifests as haemolysis and vaso-occlusion [1]. Patients experience a spectrum of disease symptoms and complications, including periods of acute pain (vaso-occlusive episodes [VOE]), chronic pain, multi-organ injury, reduced quality of life, and a shortened lifespan [1,2]. Worldwide it is estimated that over 200,000 children affected with SCD are born every year, primarily in sub-Saharan Africa (180,000 births per year) [3,4]. Approximately 2000 children in the US [5] are born with SCD each year, with a disease incidence of 1 in 2474 live births (newborn screening data 1990–1999) [6]; the estimated US prevalence ranges from 70,000–140,000 [7,8].

Among individuals with the homozygous sickle haemoglobin mutation (HbSS) living in first-world countries, the estimated mean life expectancy is 39 years [8], which has improved significantly over the last few decades. Increased overall survival of paediatric patients with SCD [9] (Fig. 1) can be attributed to the landmark Prophylactic Penicillin Study (PROPS; 1986), [10] which demonstrated that the use of prophylactic penicillin could prevent life-threatening infections in affected children. Thus, universal newborn screening became standard practice in the US in the late 1990s and in the United Kingdom in the early 2000's [10–12], enabling early diagnosis and patient management. The introduction of a pneumococcal conjugate vaccine also significantly contributes to decreased SCD mortality in children younger than 10 years of age [12,13]. However, in low-resource countries, more than 50% of children younger than 5 years of age die due to complications of SCD [14].

Because more than 98% of children with milder forms of SCD in high-resource countries are living into adulthood, SCD is now a chronic condition requiring comprehensive, life-long management [9]. Specific challenges for this emerging adult population include difficulty in managing the transition from paediatric to adult care because of a lack of available healthcare providers for adults with SCD. Thus, adults with SCD often rely on emergency department (ED) physicians and inpatient treatment for their care. The aim of this review is to familiarize primary care physicians, inpatient hospitalists, and ED physicians with the current understanding and management of SCD.

2. Pathophysiology of SCD

SCD is the result of a single-point mutation (replacement of glutamic acid with valine in position 6) on the β-globin subunit of haemoglobin [1], resulting in a mutant form of haemoglobin known as sickle haemoglobin (HbS). People who inherit two copies of the HbS mutation are homozygous (HbSS) and have the disease phenotype, whereas heterozygous carriers (HbAS) do not exhibit clinical disease (known as sickle cell trait). Other forms of SCD occur when mutations responsible for other aberrant types of haemoglobin (C or E) or for β-thalassemia combine with HbS as a compound heterozygous mutation (haemoglobin genotypes SC, SE, $S\beta^+$, or $S\beta^0$). Persons with HbSS and $HbS\beta^0$ have the most severe forms of SCD.

HbS polymerizes under low oxygen conditions (e.g. stress, hypoxia, or acidosis), resulting in deformed and fragile RBCs that have a characteristic sickle (half-moon) shape and a reduced lifespan (from 120 days

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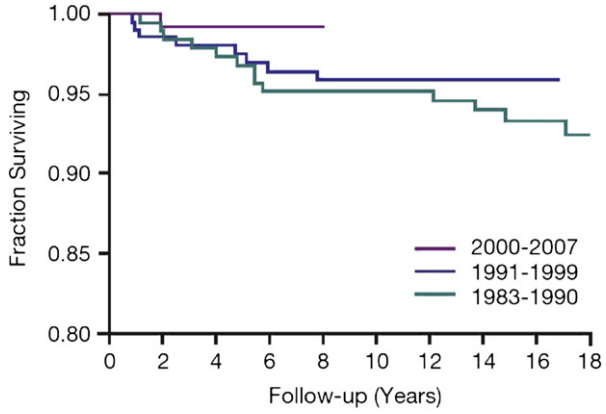

Fig. 1. Improvements in survival of children with sickle cell disease (SCD). Trends in overall survival for children with sickle cell anaemia and sickle β^0-thalassemia by cohort era. *Note*: Cohort eras are defined by year of birth (1983–1990, 1991–1999, and 2000–2007). Republished with permission of American Society of Hematology, from Improved survival of children and adolescents with sickle cell disease. Quinn CT, Rogers ZR, McCavit TL, Buchanan GR. [Blood 2010;115:3447-52]; permission conveyed through Copyright Clearance Center, Inc.

to 10–20 days) [15]. These sickle RBCs occlude the microvascular circulation, leading to tissue ischaemia, infarction, and chronic haemolytic anaemia (Fig. 2) [15]. In addition to vaso-occlusion, breakdown of the sickle RBC results in chronic haemolytic anaemia, which increases free haemoglobin production. This pathophysiologic process results in inflammation, platelet activation, increased adhesion of RBCs to the vascular endothelium, and abnormal nitric oxide metabolism [16]. Platelet activation yields alpha granule excretion of inflammatory markers, such as P-selectin, that further increases adhesion of RBCs and platelets to the vascular endothelium. Sequestered neutrophils also interact with the endothelium mediated by E-selectin ligand-1 [17], which exacerbates tissue damage (Fig. 3). These abnormalities combine to produce a multi-system disorder of chronic inflammation, blood vessel damage, and anaemia. As the pathophysiologic abnormalities in SCD are better understood, newer targets for treatment have been identified.

3. Clinical manifestations of SCD

SCD shows considerable phenotypic heterogeneity resulting from both genetic and environmental factors. It is a multi-organ disease in which patients experience a range of symptoms and complications that worsens with age (Table 1) [1,2,18–20].

Pain (acute or chronic) is the hallmark feature of SCD [15]. It can result from small vessel blockage/constriction and subsequent tissue infarction, organ impairment, or be idiopathic. VOEs are severe, acute painful episodes that result from vaso-occlusion with inflammatory and ischaemic consequences [21]. VOEs can occur throughout the body, including bones, muscles, mesentery, and other organs [1,2,18–20]. Chronic pain, which is poorly understood, can be debilitating and may result from leg ulcers, avascular necrosis, and/or neuropathic complications.

Other defined sickle cell crises include sequestration crisis (pooling of blood in an organ), aplastic crisis (reduced function of bone marrow), haemolytic crisis (a rapid breakdown of blood cells causing a drop in haemoglobin levels), acute chest syndrome (ACS), or other acute organ damage (including myocardial infarction), and stroke [1,15]. In

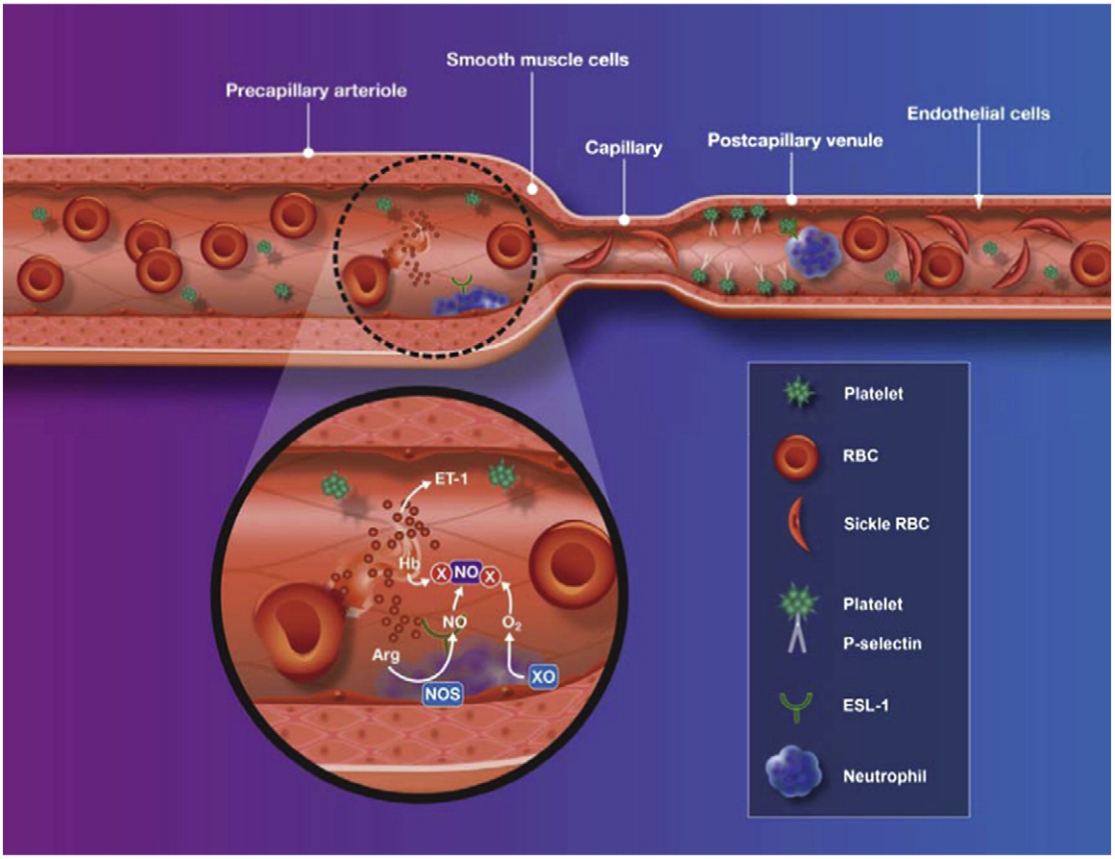

Fig. 2. Pathophysiology of vaso-occlusion in SCD. Arg, arginine; ESL-1, E-selectin ligand-1; ET-1, endothelin-1; Hb, haemoglobin; NO, nitric oxide; NOS, nitric oxide synthase; O_2^-, superoxide; RBC, red blood cell; SCD, sickle cell disease; XO, xanthine oxidase.
Adapted from Brown [15], Hebbel et al. [75], Tailor et al. [76], Looney et al. [17], and Gladwin et al. [77].

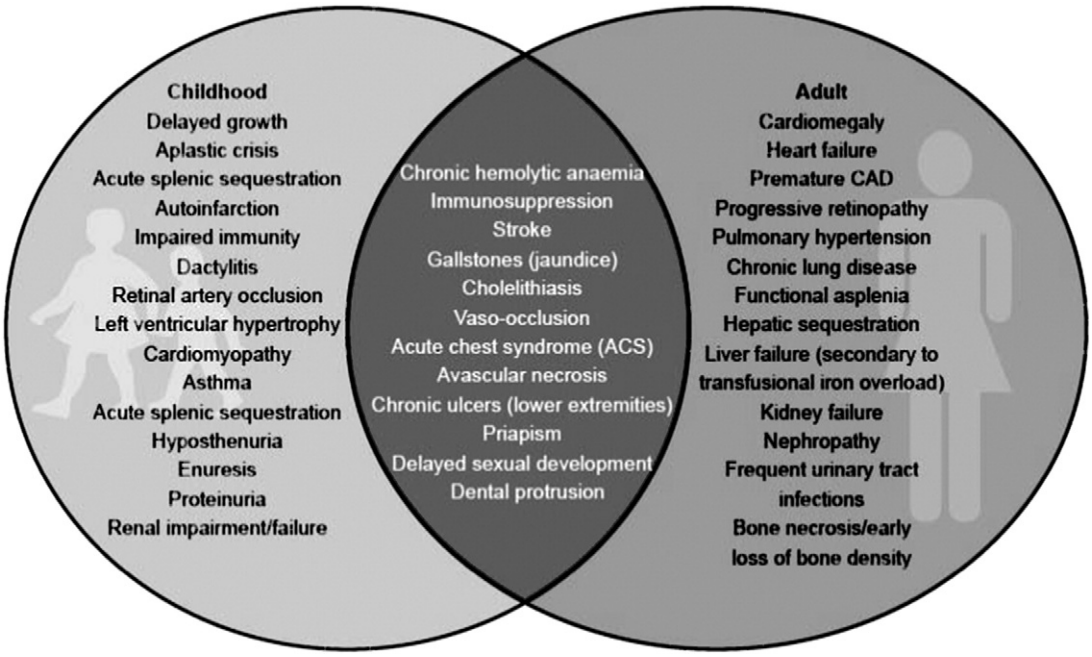

Fig. 3. Complications of SCD: childhood and adulthood [18]. CAD, coronary artery disease; SCD, sickle cell disease.

addition, patients with SCD have an increased susceptibility to infection and are at risk for numerous life-threatening complications, such as sepsis, stroke, ACS, multi-organ injury progressing to end-organ damage, pulmonary embolism, pulmonary hypertension, cardiomyopathy, and hepatic disease [1]. In addition to the above complications, patients often have a shortened lifespan, a reduced quality of life, and significant anxiety and depression as well [22].

4. Symptoms and complications

4.1. Infants/children

Infants with SCD can present with symptoms beginning at 6 months of age (as foetal haemoglobin dissipates) with dactylitis (painful swelling of the hands or feet), anaemia, mild jaundice, or an enlarged spleen

Table 1
Clinical manifestations of paediatric and adult SCD [1,2,18–20].

	Paediatric SCD		Adult SCD (additional symptoms and complications)
Symptoms			
	Infants	Children	
	Pain in chest, abdomen, and limbs/joints	Pain (acute or chronic)	Severe joint pain
	Dactylitis	Acute anaemia	Chronic leg ulcers
	Anaemia	Infections	Retinopathy
	Mild jaundice	Jaundice	Thromboembolic complications
	Enlarged spleen	Poor nutritional status and growth	Neurocognitive impairments
	Fever	Academic failure	Narcotic dependence/tolerance
	Frequent upper respiratory infections	Delayed puberty	
Complications			
CNS	Stroke		Recurrent ischemic stroke, haemorrhagic stroke
Eye	Retinal artery occlusion/retinopathy		Progressive retinopathy
Lung	ACS		Recurrent ACS
	Asthma		Pulmonary hypertension
			Chronic lung disease
Heart	Left ventricular hypertrophy		Premature coronary artery disease
	Cardiomyopathy		Heart failure
Spleen	Acute splenic sequestration		Functional asplaenia
	Auto-infarction		
	Impaired immunity (e.g. bacterial infection, sepsis)		
Liver			Hepatic sequestration
			Liver failure secondary to transfusional iron overload
Kidney	Hyposthenuria		Nephropathy
	Proteinuria		Frequent urinary tract infections
	Renal impairment/failure		
Gall bladder	Cholelithiasis		Cholelithiasis
Genitals	Priapism		Priapism
Bones/joints	Avascular necrosis		Avascular necrosis
	Aplastic crisis		Early loss of bone density
Skin	Chronic ulcers, typically on the ankles		Chronic leg ulcers

SCD, sickle cell disease; CNS, central nervous system; ACS, acute chest syndrome.

(Table 1; Fig. 3) [1,2,18–20]. The most frequent problems seen in paediatric SCD are pain, infection, acute splenic sequestration, ACS, and stroke. Poor splenic function results in a compromised immune system and increased susceptibility to infection (including sepsis), which is the primary cause of mortality in paediatric patients [1]. Penicillin prophylaxis and anti-pneumococcal vaccination have significantly decreased the incidence of life-threatening infections in children with SCD in regions in which these treatments are utilised [23,24]. Newborn screening programs are slowly being initiated in parts of Africa, including Ghana, but many affected individuals are still without access to these necessary prevention measures [14].

4.2. Acute chest syndrome

ACS often presents with clinical symptoms similar to pneumonia. In high-resource countries, ACS is the greatest cause of mortality after 2 years of age in patients with SCD, the leading cause of admissions to the paediatric intensive care unit, and the second-most common cause of hospital admission after VOE [9,17]. ACS is caused by vaso-occlusion in the pulmonary vasculature and is clinically described as the combination of hypoxia, fever, and a new infiltrate identified on chest X-ray. However, the clinical symptoms of hypoxia and fever often coincide with symptoms of VOE (especially in patients who receive narcotic medications) and may precede the radiographic changes, resulting in delayed diagnosis and treatment. When patients admitted with VOE develop these symptoms, chest X-ray and blood counts are recommended to assess for new infiltrates or an abrupt decrease in haemoglobin. Although blood transfusions should be avoided for the treatment of VOE, they should be considered in patients with ACS.

4.3. Stroke

Stroke is also a significant complication in SCD, with the potential for major morbidity and mortality [25]. In HbSS disease, the incidence of overt stroke is 11% by age <20 years [26], and silent cerebral infarcts are more frequent (up to 30%) [27]. A silent infarct (SI) is defined as a lesion on magnetic resonance imaging (MRI) consistent with an infarction, but without focal neurologic deficit lasting longer than 24 h. Despite the terminology, these lesions are not clinically silent. SIs are associated with cognitive impairment, decrement in intellectual abilities, poor academic attainment, and increased risk for subsequent infarction [28]. Importantly, Transcranial Doppler (TCD) testing can predict patients' risk for stroke (shown in the Stroke Prevention in Sickle Cell Anaemia [STOP] study [29]), enabling preventative treatment with simple and exchange transfusion therapy. Unfortunately, TCD remains limited both in low-resource areas as well as in regions of first-world countries in which patients with SCD are remotely located or not seen in large numbers [30,31].

4.4. Asthma

Asthma is also common in children with SCD, with a prevalence of 8–53% [20]. The pulmonary complications, which cannot be attributed to genetic predisposition alone, likely reflect overlapping pathophysiologic mechanisms between SCD and asthma [32]. The presence of asthma in SCD patients increases the risk of hospitalisation for both VOE and ACS [32]. Furthermore, asthma is an independent predictor of mortality in patients with SCD. However, effective asthma management may help prevent SCD-related complications [33]. In addition, patients with SCD and asthma who are hospitalised for VOE should be treated with bronchodilators to prevent a concurrent asthma exacerbation.

4.5. Adult SCD

Adults with SCD experience many of the same symptoms as children. However, additional disease manifestations may present or worsen as patients age, including leg ulcers, sickle retinopathy, nephropathy, decreased bone density, thromboembolic complications, pulmonary hypertension, cardiac failure, transfusional iron overload, and avascular necrosis (Table 1) [1,2]. Causes of death in adults with SCD are more variable than in children and include infection, ACS, pulmonary emboli, liver failure (due to iron overload), stroke, and heart failure [34–36]. For adults with SCD, VOE is the leading admission diagnosis and the main reason for ED visits [34,35]. Acute pain episodes peak at age 20–29 years [37], and, in one study [38], adults reported pain on more than 50% of days, with severe SCD-related pain reducing quality of life [1]. Adult patients who report more than three pain crises per year have a predicted decreased survival [37]. Strokes in adults with SCD tend to be severe, with ischaemic stroke (most frequent between 35 and 65 years of age) often causing physical and cognitive disability, and haemorrhagic stroke (most frequent in young adults) having a high mortality rate [39].

5. Disease management of SCD

Pain is the most common reason for patients with SCD to seek treatment. However, although most pain experienced by SCD patients is likely due to vaso-occlusion, there are also other mechanisms of pain that are poorly understood. A schema for the differential diagnosis of SCD-related pain as well as systematic approach to the treatment of SCD-related pain are presented in Fig. 4 [40]. In addition, there is a paucity of specialised resources available for patients aged >18 years seeking treatment for SCD-related pain. For patients presenting with acute VOE, rapid and aggressive treatment is needed. Traditional treatments include opioids, non-steroidal anti-inflammatory drugs, and hydration [40]. Hydroxyurea (discussed below), although not helpful for acute relief, can decrease the number of painful episodes when taken chronically. Relaxation techniques, warmth, massage, and psychological pain management (e.g. cognitive behavioural therapy) should be considered. It is essential to examine all patients presenting with VOE for signs of infection [41], ACS, pulmonary embolism, splenic or hepatic sequestration, cholecystitis, stroke, or other underlying etiologies.

Many high-risk complications may also present as VOE, and thus careful evaluation of patients with pain is critical. One study of SCD patients aged >21 years demonstrated that more than 50% of patients who died in the hospital were admitted with the diagnosis of seemingly uncomplicated VOE [42]. Transfusion therapy is not recommended for patients with isolated pain crisis because of the significant risk of iron overload in patients who receive more than 20 lifetime blood transfusions, as well as the propensity for allo-antibody formation.

5.1. Hydroxyurea

Hydroxyurea (HU) is currently the only established preventative pharmacologic treatment for both paediatric and adult patients with recurrent VOEs [43,44]. The mechanism of action is partly a result of the increased production of foetal haemoglobin, as well as decreased production of leukocytes and reticulocytes that may contribute to vaso-occlusion [43,44]. The Multi-Centre Study of Hydroxyurea in Sickle Cell Anaemia (MSH) confirmed its efficacy in adults with SCD by reducing the number of acute VOEs and hospitalisations [45]. There are also significant cumulative data from several multicentre, randomised, placebo-controlled studies in paediatric patients that demonstrate the safety and efficacy of HU in children [46–49]. Paediatric patients maintained on the maximum tolerated dose of HU over several years showed significant reductions in VOEs, hospitalisations, end-organ damage, chronic hypoxemia, and stroke without significant neutropenia, growth reduction, documented carcinogenesis, or end-organ damage. HU is grossly under-utilised in high-resource countries, likely in part because of a lack of physicians comfortable with prescribing the medication, as well as the current recommendations for periodic laboratory testing. In resource-poor environments, HU is often unavailable or prohibited by lack of laboratory testing capabilities. However, it is

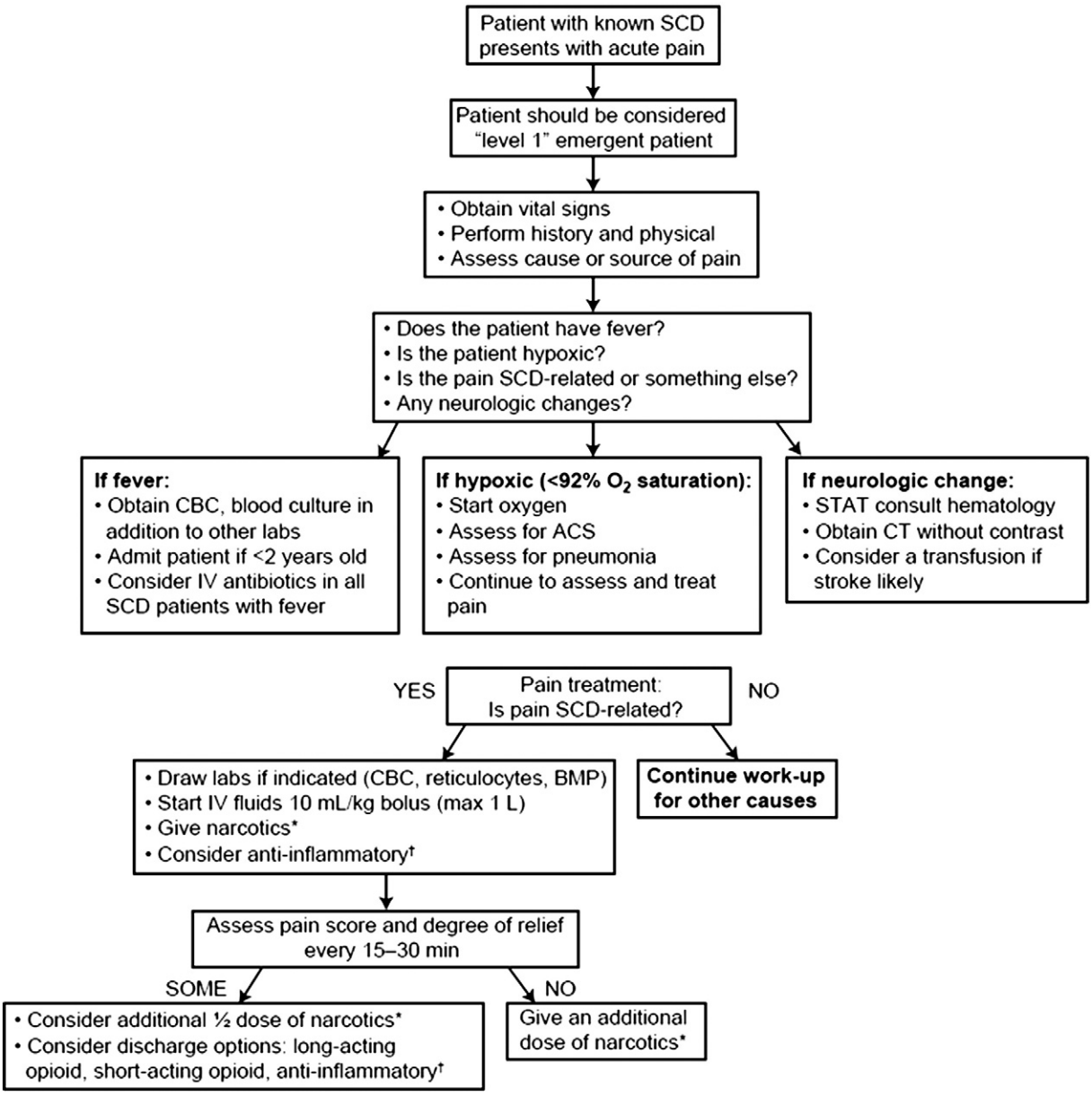

Fig. 4. Clinical management of pain and other aspects of SCD.* Morphine 0.1 mg/kg or hydromorphone 0.015–0.02 mg/kg.† Ketorolac (Toradol®) 0.5 mg/kg (max of 30 mg) or ibuprofen (10 mg/kg). ACS, acute chest syndrome; BMP, basic metabolic panel; CBC, complete blood count; CT, computed tomography; i.v., intravenous; SCD, sickle cell disease; STAT, immediate.

unclear if rigorous monitoring is necessary in SCD patients. Recent studies have not demonstrated significant bone marrow suppression [46]. Therefore, it is reasonable that HU could be prescribed and monitored by primary care physicians with the use of pre-set practice guidelines and consultation with a haematologist.

5.2. Transfusion therapy

Chronic blood transfusions have been demonstrated to reduce the risk of both primary and secondary stroke and prevent repeated ACS [28,33,50]. Blood transfusions can be given as simple or exchange transfusions in which patients' RBCs are removed by pheresis or by manual exchange and replaced with healthy RBCs. The aim of exchange transfusion therapy is to reduce HbS to below 30%, which effectively prevents stroke and SIs [29]. However, chronic transfusions and exchange transfusions may lead to iron overload and iron deposition in organs (liver, heart, pituitary, and pancreas), with end-organ damage potentially occurring before the onset of symptoms. Thus, although blood transfusions may shorten VOE, it is important to reserve transfusion therapy only for life-threatening complications such as ACS, splenic sequestration, aplastic crisis, and cerebral infarction. Patients with SCD should be treated with permissive anaemia (even when the haemoglobin level is below an individual's baseline) to prevent the detrimental effects of iron toxicity. All patients requiring long-term transfusion therapy or those who have received multiple lifetime transfusions should be started on iron chelation therapy early and monitored closely for the deleterious effects of iron overload [51]. Iron chelators, which form a complex with iron to promote its excretion, include deferoxamine, deferiprone, and deferasirox, with oral deferasirox currently being the most frequently used [52]. The gold standard for assessing iron overload has shifted in the last decade from liver biopsies, which are sample-dependent and invasive, to specialized T2* MRI assessments of liver iron concentration [51]. Other options for monitoring transfusional iron overload include serial laboratory evaluations (ferritin levels), which are much less accurate.

TCD ultrasonography screening should be performed annually in patients aged 2–26 years to predict stroke risk and initiate preventative therapies. TCDs measure abnormal blood flow velocity in large intracranial arteries. The STOP study conclusively demonstrated that patients with flow velocity ≥200 cm/s time-averaged mean of the maximum (TAMM) had a 10% increased risk of stroke, which can be reduced by simple or exchange transfusions [29]. Studies have also demonstrated that in patients who have suffered a stroke, subsequent stroke can be prevented with monthly transfusion therapy [42,53,54]. HU is not effective to reduce repeat stroke outside of transfusion therapy (as shown in the Stroke With Transfusions Changing to Hydroxyurea [SWiTCH] study) [55]. Current studies are ongoing to evaluate the ability of HU to prevent primary stroke in patients with abnormal TCDs (TCD With Transfusions Changing to Hydroxyurea [TWiTCH] study).

5.3. Disease management specific to paediatrics

Management programs for paediatric patients with SCD in high-resource areas are comprehensive and include acute care, routine prevention (e.g. childhood vaccinations and monitoring of growth and development [19]), and the treatment of complications (e.g. cardiac, respiratory, and renal) [56]. Annual monitoring with TCDs, transfusion therapy with iron-chelation therapy (if indicated), HU therapy, and/or aggressive asthma management have also become standard of care in most comprehensive centres, with evidence-based treatments initiated early to prevent disease progression [57]. Careful attention is paid to the academic achievement of children with SCD in order to screen for possible SI, which would warrant MRI evaluation.

Haematopoietic stem cell transplantation (HSCT) is the only recognised cure for SCD [58,59], and has been shown to have an 85–90% success rate in certain paediatric patient groups [59]. The use of HSCT is restricted by the lack of fully matched sibling donors for many potentially eligible patients [58]. Thus, newer studies are examining the use of unrelated donors, including umbilical cord blood donors, for this patient population. Although HSCT is associated with an increased risk of morbidity (e.g. infertility, gonadal failure, and graft-versus-host disease) and mortality, it has been conclusively shown to improve quality of life in high-risk patients with SCD [55]. Unfortunately, the use of HSCT also remains highly limited to resource-rich environments, although people living in Africa and other areas often travel great distances for this treatment.

5.4. Disease management specific to adults

The management of SCD is more complex in adult patients because of additional co-morbidities, increased multi-organ involvement due to SCD, chronic pain, psychosocial and socioeconomic factors, potential neurocognitive impairments, and (often misguided) concerns for narcotic dependence and tolerance. The lack of available specialised providers leads to difficulty in transitioning adolescents to adult care, which further complicates SCD management. Adult patients require multi-disciplinary management of chronic conditions, such as stroke, cardiovascular complications (e.g. pulmonary hypertension), pulmonary complications, kidney failure, retinopathy, bone necrosis, and leg ulcers, by subspecialist providers. It is therefore imperative that adults with SCD receive coordinated care led by a primary care physician in coordination with a provider experienced in SCD, as well as other adult subspecialty providers (i.e. neurology, ophthalmology, pulmonology, cardiology, nephrology, pain management, and orthopaedics).

As in paediatrics, treatment options for SCD remain limited in adults, with HU being the only approved treatment [60]. HU has been shown to decrease pain, reduce transfusions and hospitalisations, and decrease mortality; however, it is under-utilised. Transfusion therapy remains efficacious for SCD adults who have suffered strokes or severe ACS, but is limited because of a lack of qualified providers comfortable with RBC exchange therapy. Moreover, the use of transfusion therapy in adults is complicated by iron overload and allo-immunization. Thus, many patients successfully treated with transfusion therapy in childhood are unable to continue that therapy as adults.

On the other hand, acute care and inpatient providers may over-utilise transfusion for baseline anaemia or vaso-occlusive pain in adults because of a lack of SCD management experience [61]. Patients with SCD have a physiological adaptation to their anaemia; thus, it is crucial to know a patient's baseline haemoglobin and transfuse only for life- or organ-threatening complications. Iron overload is a frequent complication in adult patients with SCD and requires chelation therapy and monitoring. Up to 10% of adult patients with SCD are noted to have complications of iron toxicity at the time of death [54].

HSCT is also curative in adults with SCD but is more difficult because of the increased risk of treatment-related complications. Newer studies have demonstrated effective transplantation with reduced-intensity conditioning, which may increase the options for adult patients [58,59]. Additional complications for HSCT in adults include the lack of available donors and lack of available adult transplantation centres with expertise in SCD.

Regardless of treatment, pain is the most-common presenting symptom of SCD in adults. VOEs are often under-treated, which may cause excessive hospital utilisation, including ED visits and inpatient hospitalisations, as well as lost work productivity [62]. Concerns regarding addiction, dependence, and tolerance to pain medication are often unfounded, but add an important layer of complexity to patient care. Pain contracts between patients and providers, as well as drug-monitoring, can be beneficial, but require outpatient follow-up. The manifestations of VOE in conjunction with a lack of preventative care and insufficient insurance coverage in this population can make it difficult to provide effective management in adults [63]. Primary and secondary prevention are also essential and are best addressed in a comprehensive setting. Some key points are presented in Table 2.

6. Access to healthcare: transition from paediatric to adult healthcare

Although many more children with SCD are living into adulthood, there has not been a corresponding increase in medical haematologists trained to treat older patients.

Accessing adequate health and medical services for the young adult with SCD can be a challenge, and usually involves a change in the physician and location of care. Furthermore, the transition from paediatric to adult care may be mired by additional issues of poor communication between healthcare providers, lack of early disease education, limited availability of qualified adult providers, and a lack of information or understanding about the complexity of SCD in aging patients [64–68].

Refining continuity of care during transition is essential to improving patient outcomes, with a successful transition completed when the young adult has attained medical maturity and is receiving care in an adult healthcare setting [68]. In contrast, the lack of a transition care plan may have a negative impact on outcomes in young adults with SCD. Without a designated provider, affected adults become dependent on acute care services without the necessary ancillary support services [68]. There is a higher re-admission and acute care utilisation rate in patients aged 18–30 years, with dramatic increases in 30-day rates of return to any acute care facility from 27.4% (patients aged 10–17 years) to 48.9% (patients aged 18–30 years) [69]. This increase is especially concerning since early rehospitalisation is associated with increased mortality. In the US, these issues are compounded by financial constraints, including the loss of medical insurance and/or decreased financial reimbursement from public insurance plans [34]. Adults who were transitioned without a concrete plan reported feeling ill-prepared and that their transition was based on age rather than readiness or needs. These adult patients also reported that their follow-up care had declined since the transfer [70].

Thus, transition programs that prepare paediatric patients with SCD for the adult healthcare environment promote self-advocacy and self-

Table 2
Primary and secondary preventative measures in adult SCD [60,62,63].

Measure	Management regimen
Vaccinations to prevent complications for encapsulated organisms, especially in patients with HbSS disease who likely do not have a functional spleen	• Patients should receive a flu vaccine every year, a pneumococcal vaccine every 5 years, and a meningococcal vaccine series (2-dose primary series administered 2 months apart for persons > 2 years • Since most patients are exposed to blood products, they should also undergo the hepatitis A and B vaccine series
Routine screening for sickle cell retinopathy	• Should be done once a year
Routine screening for hypertension	• Should be done at least annually • Patients should be started on antihypertensive treatment with a goal to lower blood pressure to ≤140/90 mm Hg
Urine assessment for proteinuria	• Urine should be checked for proteinuria periodically and, in case of persistent proteinuria, patients should be referred to a renal specialist • The use of an ACE inhibitor should be considered
Routine screening for pulmonary hypertension	• Currently not indicated in asymptomatic individuals, but should be done if symptomatic • Individuals with pulmonary hypertension have a higher risk of mortality when presenting with VOC and should be monitored more carefully
Patients with a life-time transfusion history of 10–20 units of blood	• Are at high risk for iron overload • Although ferritin is not an accurate measure of iron overload (and could be markedly elevated during acute pain as an acute phase reactant), levels of >1000 ng/mL could indicate an overloaded state; further transfusions in those individuals should be avoided whenever possible and iron chelation should be initiated • Further assessment with liver biopsy or FerriScan® (Resonance Health, Australia) to quantitate iron toxicity should be performed • Patients with evidence of iron overload should be referred for outpatient management of chelation therapy
Ischaemic stroke	• The etiology of ischaemic stroke in older adults with SCD is poorly understood and may have similar risk factors as non-SCD patients in this age group • The role of acute and chronic transfusion in adults has not been defined; therefore, treatment for stroke in adult patients with SCD is based on paediatric patients with SCD and patients should undergo exchange transfusion for acute stroke in consultation with a haematologist • Patients with SCD and stroke may have cognitive deficits that cause difficulty in understanding discharge instructions and remembering to keep follow-up appointments

SCD, sickle cell disease; HbSS, homozygous sickle haemoglobin mutation; ACE, angiotensin converting enzyme; VOC, vaso-occlusive crisis.

management. Model transition programs use interdisciplinary teams to help adolescents develop this independence and knowledge [68,71,72]. This approach links them with adult healthcare providers prior to transition in order to optimise communication, continuity of care, and collaboration, as well as decrease anxiety during this process.

7. Future directions in the management of SCD

This review highlights several gaps in the current understanding of SCD management throughout the patient's lifespan. Further research should include prevalence studies in SCD, randomised-controlled assessments of novel medical therapies, and improvements in transition of care. Additional quality improvement should focus on cost-effective preventative, comprehensive care programs for adults with SCD; research on methods to increase HU utilisation; and cooperative trials in alternative-donor HSCT for patients with SCD.

A better understanding of SCD, including the identification of genetic polymorphisms and clinical characteristics that can predict disease severity in childhood, would also improve preventative management. Continued studies on pharmacotherapies to reduce the occurrence of VOE and prevent organ dysfunction/failure are also warranted.

Current knowledge about the pathophysiology of SCD provides multiple loci for novel potential therapeutic interventions (Table 3) [73]. Increasing the opportunity for HSCT of at-risk paediatric patients before the development of organ dysfunction will also be instrumental to improving survival. Gene therapy offers another potential cure for SCD, but concerns over the safety of random genomic insertion need to be resolved [74].

8. Conclusions

SCD is a complex disorder with considerable variability among individuals and accumulating morbidities associated with aging, which challenge its management. Furthermore, few treatments exist for SCD, and the primary treatment (HU) is significantly underused. Internationally, focus needs to continue on instituting newborn screening in low-resource countries, point-of-care testing, and early childhood care to prevent early morbidity. Additionally, although comprehensive management programs exist for paediatric patients with SCD, there is a need for improved transition of care to reduce early mortality in young adults and to reduce hospital utilisation costs by preventing over-reliance on acute care facilities. Although curative options with HSCT exist for SCD, they still remain limited due to a lack of appropriate donors and concerns with procedural toxicities. In high-resource countries, comprehensive coordinated care for adults with SCD remains a priority. Until adult patients with SCD have access to acceptable preventative care services and specialised management centres, they will continue to receive suboptimal care at unnecessarily high cost.

Table 3
Potential new medications for SCD.

- Novel low-molecular-weight compounds that can alter key aspects of SCD, such as haemoglobin polymerization, expression of HbF, and leukocyte adhesion
- Calcium-sensitive Gardos channel inhibitors (such as ICA-17043), with or without hydroxyurea, to prevent the dehydration of RBCs
- Statins to increase NO production and reduce leukocyte adhesion
- Anti-inflammatory drugs that inhibit NF-kB and upregulate adhesion molecules
- Intravenous γ-globulins to reduce leukocyte adhesion and the number of interactions between RBCs and white blood cells, and to improve microcirculatory blood flow and survival
- Anti-platelet agents for preventing SCD-related platelet activation leading to vaso-occlusion and acute chest syndrome

SCD, sickle cell disease; HbF, foetal haemoglobin; RBC, red blood cell; NO, nitric oxide; NF-kB, nuclear factor kappa B. Compiled from Frenette, et al. [73].

9. Practice points

- The model of care of patients with sickle cell disease (SCD) should be preventative and comprehensive in addition to acute care management.
- Adults with SCD need coordinated care led by a primary care physician in coordination with a provider experienced in SCD, as well as other adult subspecialty providers.
- SCD shows considerable phenotypic heterogeneity resulting from both genetic and environmental factors and different patients (with the same genotype) may have very different symptomatology that worsens with age.
- Patients with SCD and asthma who are hospitalised for vaso-occlusive episodes should be treated with bronchodilators to prevent a concurrent asthma exacerbation.
- Hydroxyurea can be prescribed and monitored by primary care physicians with the use of pre-set practice guidelines.

10. Research agenda

- Identification and application of biomarkers of disease severity in sickle cell disease
- Identification and implementation of new disease-modifying medications to prevent or reduce vascular and endothelial damage
- Increase understanding and utilization of stem-cell transplant with reduced-intensity preparative regimens and/or the use of novel donors
- Projects dedicated to improving the health resources available for this at-risk global patient population

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Conflict of interest statement

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