Review Article

Primary Care of Patients with Sickle Cell Disease

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Abstract

In recent decades, advances in the treatment of sickle cell disease have resulted in a longer life span for affected patients. What was once primarily a pediatric disease is now often managed in the adult primary care setting. However, it can be challenging for non-specialists to acquire the detailed knowledge necessary to care for patients with sickle cell disease. Therefore, this review is targeted to primary care physicians. It focuses on the diagnosis and management of the chronic organ system complications seen in adult patients with sickle cell disease, including chronic neuropathic pain, hyposplenism and infection, pulmonary hypertension, asthma, cardiomyopathy, avascular necrosis of bone, osteomyelitis, leg ulceration, stroke, silent cerebral ischemia, cognitive deficits, iron overload, and nephropathy. It addresses recommended prevention and health care maintenance. It provides an overview of treatment options, including hydroxyurea and selectin antagonists, chronic transfusion therapy, bone marrow transplant and gene therapy; with discussion of the risks and benefits of each. Pain management modalities, including appropriate use of opioids, are discussed. We conclude that sickle cell disease is a complex condition affecting multiple organ systems over time. In the current era, patients may survive into their sixties and beyond and often develop chronic complications. Treatments are available to manage specific complications and alter the course of the disease; and curative therapies are on the horizon. Primary care physicians have an essential role in the care of individuals with sickle cell disease.

Keywords: Sickle cell disease, Primary care

Introduction: The Role of Adult Primary Care in Sickle Cell Disease Management

Fifty years ago, sickle cell disease was largely a pediatric condition, since most affected individuals died before reaching adulthood. Since then, treatment advances have extended the average survival in the United States and Europe to 50 or 60 years. It is now a chronic condition, which adult primary care physicians are called upon to co-manage with hematologists and other specialists [1-3].

Sickle cell is considered a rare disease in the general population in the United States, but it has a relatively high prevalence among African-Americans [4,5] - an important target population for efforts to improve care delivery. It
has an enormous impact on the quality of life of affected patients. It involves virtually every organ system. Patients with sickle cell disease often require coordination of care between multiple specialists. Standard preventive measures such as immunizations, counseling on family planning and smoking cessation, and breast and colon cancer screening are easily neglected when care is fragmented and specialist-driven. A strong doctor-patient relationship is the lynchpin of multimodality treatment for these patients [6-9].

The past decade has seen important advances in therapy. Selected patients can be cured with bone marrow transplant. The frequency of painful crises and the incidence of secondary complications can be reduced with disease modifying therapies. Gene therapy, in which the sickle cell gene is replaced in bone marrow cells by a viral vector carrying human DNA, and even germline modification that could eliminate the disease from entire kindred are on the horizon [10,11]. Patients will need informed guidance to access and navigate treatment options.

For all of these reasons, optimal management of sickle cell disease requires the active participation of the primary care physician. In our experience, the care of sickle cell patients is both clinically challenging and highly rewarding. A broad overview of sickle cell disease can be found in several excellent reviews from the past ten years [6,7,12]. We offer this paper to provide primary care physicians with a more in-depth look at specific complications and management options that we hope will be useful in the day-to-day management of their patients with sickle cell disease.

**Etiology and Pathophysiology**

It has long been known that sickle cell disease is caused by a single base pair mutation: alanine is substituted for cytosine at codon 6 of the beta-globin gene, resulting in a defective form of hemoglobin. This hemoglobin tends to polymerize at low oxygen levels, forming long, rigid chains within the red blood cell (which then exhibits a sickled shape if seen under a microscope). This impedes its passage through the capillaries and venules where oxygen is extracted [13].

When explaining this concept to students, we often use the analogy of passing a balloon filled with water through a narrow tube. Under normal circumstances, the balloon can elongate and pass through the tube easily - especially if the inside surface of the tube is lubricated. Imagine, however, that the balloon is filled with pencils (a.k.a. hemoglobin polymers) along with water. Obviously, it would be much more difficult to squeeze a balloon filled with rigid objects pointing in every direction through the tube.

Sickled red blood cells block passage of oxygenated blood into the small vessels. When this process becomes extensive for any given tissue, that tissue becomes ischemic. This usually results in inflammation, which increases oxygen demand. Greater deoxygenation of hemoglobin reaching the tissue causes further sickling in a vicious cycle. Sometimes these events are symptomatic, manifesting as acute organ dysfunction, pain and (if sufficiently widespread or severe) vaso-occlusive crisis. However, it should be noted that many ischemic events are subclinical, leading to gradual organ damage and chronic symptomatology such as heart failure, nephropathy, cognitive decline, arthrosis, and hyposplenism [14-16].

More recent work has exposed the important role of the white cells, platelets, and vascular endothelium in the acute and chronic complications of sickle cell disease [17,18]. Returning to our earlier analogy, consider what would happen to the balloon if the inside of the tube, rather than lubricated, were to become sticky. In a simple sense, this is what happens to the endothelium during sickle cell ischemic events. Rupture of red blood cells releases free radicals and other substances that damage the endothelium. In response, the vessel constricts and procoagulant mediators are expressed. The clotting process, once activated, amplifies the ischemic effect of red blood cell sickling [19]. Of particular importance are the selectin proteins, which mediate adhesion of platelets to the activated endothelium.
The novel therapy, Crizanluzumab, which is a P-selectin inhibitor, is a new therapeutic agent that we will discuss further below.

Acute inflammation and reperfusion disturb the functional integrity of the endothelium, leading to persistent endothelial dysfunction. Returning once more to our balloon and tube analogy, one could think of this as a permanent stickiness or narrowing of the tube. Thus, chronic vascular changes contribute to the end-organ complications of sickle cell disease.

**Vaso-occlusive crisis**

The most widely known complication of sickle cell disease, since it drives most emergency department use and acute admissions of these patients, is vaso-occlusive crisis. Classically, this consists of acute onset of severe pain in one or more body areas. This is also referred to as “sickle crisis” and occurs when the acute vaso-occlusive process described above becomes widespread enough to cause diffuse pain [21].

This threshold varies between individuals. Many patients suffer from varying degrees of daily pain, and attempt to manage pain spikes at home using prescribed analgesics and nonpharmacologic measures such as rest, hydration, avoidance of temperature extremes and the emotional support of caregivers. A recent innovation has been the use of day hospitals, typically operated out of hematology clinics, where patients can come for parenteral hydration and analgesia, thus avoiding a trip to the emergency department. After a few hours, the patient may be discharged home or admitted to the hospital, depending on response [22-24].

For a detailed, stepwise approach to the management of acute vaso-occlusive crisis, we recommend the National Heart, Lung and Blood Institute 2014 Expert Panel Report on Evidence-Based Management of Sickle Cell Disease [9]. A few essential points are emphasized in Table 1.

<table>
<thead>
<tr>
<th>Table 1: Clinical Pearls: Management of Vaso-occlusive Crisis</th>
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<tbody>
<tr>
<td>1. Frequency and timing of vaso-occlusive crisis vary greatly between patients and over the lifespan.</td>
</tr>
<tr>
<td>2. Pain management in vaso-occlusive crisis is based on patient report. There is no biomarker for pain severity.</td>
</tr>
<tr>
<td>3. NSAIDs such as ketorolac and opioids are effective in treating vaso-occlusive pain. Dosing and frequency should take into account outpatient regimen, degree of tolerance to opioids, renal function, and efficacy of prior regimens for acute pain management.</td>
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<tr>
<td>4. Corticosteroids and vasodilators have not been shown to be effective in the setting of acute vaso-occlusive crisis. While corticosteroids may initially appear to help, there is a rebound effect with increase in hospitalizations at taper.</td>
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<tr>
<td>5. Analgesic therapy should be initiated within 30-60 minutes of presentation. Patients should be re-dosed promptly if analgesia begins to wear off, and should be monitored for over-sedation and other side effects.</td>
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<tr>
<td>6. Parenteral hydration at maintenance dose should be administered if the patient is unable to take oral fluids. Hydration should be done at reasonable rates with consideration of cardiac function and of potential fluid overload decrease potential acute chest syndrome.</td>
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<tr>
<td>7. Oxygen is not therapeutic for pain, but should be administered if the patient’s oximetry value is below 95%.</td>
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**Acute chest syndrome**

Acute chest syndrome is a medical emergency that should be recognized and treated expeditiously in an inpatient setting. It is defined as any acute chest or respiratory symptoms (such as chest pain, dyspnea or cough) accompanied by a new infiltrate on chest x-ray. If serial x-rays are obtained, the infiltrate is seen to be rapidly progressive. Acute chest syndrome is most often seen during or within 72 hours after a vaso-occlusive crisis. The etiology may be
infectious, may be due to pulmonary infarction, or may be related to bone marrow infarction, with release of fat that embolizes to the lung, causing an inflammatory reaction [25].

Acute chest syndrome can present more subtly in the outpatient setting. It is important to obtain immediate chest imaging on any patient with sickle cell disease who complains of new onset cough, chest pain or dyspnea. If a new infiltrate is present, the primary care physician should have a low threshold for admitting the patient to the hospital for oxygen, IV fluids and parenteral antibiotics. Blood transfusion and ventilatory support may be necessary in severe cases.

**Chronic pain**

Aside from vaso-occlusive crises, many patients with sickle cell disease suffer from chronic, daily pain. In the Pain in Sickle Cell Epidemiology Study (PISCES) [26], 54% of adult participants reported experiencing pain on more than half of the days in a six-month period, and 30% reported daily pain. Cumulatively, only 12% of days were defined by subjects as sickle cell crisis episodes, and the majority of crisis pain was managed at home.

Chronic pain in sickle cell disease is multifactorial. Some stems from end-organ complications of sickle cell disease, such as aseptic necrosis of bone, arthrosis and skin ulcers. This, like crisis pain, is considered principally nociceptive: caused by activation of peripheral nerve fibers by a potentially damaging stimulus [27]. As sickle cell disease advances, chronic neuropathic pain frequently develops. The pathophysiology of this pain is not well understood, but it probably relates to impaired neural plasticity induced by repeated pain exposure [27-30]. Opioid-induced hyperalgesia may play a role in some patients treated with long-term high-dose opioids [31]. Depression, trauma, emotional and spiritual support and the nature of the patient’s interactions with the health care system are important modifiers of the pain experience [32-34].

The 2014 NHLBI Guidelines provide a clear stepwise approach to pain management in sickle cell disease [9]. Pain should be assessed at regular intervals. Symptomatic management should be guided by the patient’s report of pain. Nonpharmacologic approaches such as massage and relaxation techniques should be tried and may be a part of a multimodal approach [35]. Non-opioid agents such as non-steroidal antiinflammatory drugs, anti-epileptics (i.e gabapentin), tricyclic antidepressants (amitriptyline, nortriptyline, desipramine) and serotonin-norepinephrine reuptake inhibitors (venlafaxine, duloxetine) can be helpful for chronic pain.

Providers should be attuned to functional limitations in patients with musculoskeletal complications of sickle cell disease. Use of adaptive equipment such as canes, walkers, shower chairs and motorized scooters may decrease the pain burden associated with carrying out activities of daily living.

**Avoiding pitfalls in the use of opioids**

Identifying the different types and components of pain for patients with sickle cell disease is important in achieving optimal pain control. Utilizing non-opiate therapies when possible is important for chronic pain, but opioids remain a mainstay in the treatment of more severe chronic pain in patients with sickle cell disease. Patients should be educated on the potential risks of these agents, which should be prescribed at the lowest dose and frequency needed to achieve adequate pain control. By the same token, physicians should not withhold or excessively limit opioids because of unwarranted fear of addiction and abuse.

There is a misperception among many health care providers that patients with sickle cell disease are often drug abusers [36,37]. Aberrant opioid use behavior, such as violation of treatment contracts, obtaining prescriptions from multiple providers, frequent lost prescriptions and early refill requests, is rare in the adult sickle cell population and relatively easy to identify if standard protocols are followed [38,39]. Patients who exhibit such behavior should be
referred for substance abuse treatment. Comorbid psychiatric conditions such as depression and post-traumatic stress disorder that increase the risk of substance abuse should also be addressed [40,41].

It is important not to conflate drug-seeking behavior prompted by uncontrolled pain (pseudoaddiction) with behavior intended to obtain drugs for recreational or non-therapeutic use. Persons with intractable pain may depend quite legitimately on opioids to function. In this setting, the terms "drug dependence" and "drug addiction" are of questionable utility [42,43].

A commonly seen complication of opioid treatment is tolerance, leading to dose escalation and eventual treatment failure. This, too, appears to be relatively rare in patients on chronic opioid therapy [44], though quite problematic when it does arise [45]. Patients requiring more than 120 morphine equivalent dose (MED) units of opioid for chronic pain control should be referred to a pain management specialist.

Providers should not allow the desire to avoid uncommon adverse behavioral outcomes to interfere with effective pain management in the large majority of those with sickle cell disease. Helping the patient to attain adequate pain control is one of the most important contributions providers can make to improved quality of life. In our experience, multimodality pain regimens that include modest doses of opioids (typically 60-90 MED per day) are very effective in sickle cell patients with moderate to severe chronic pain; and many patients remain stable over the course of years on these regimens, which allow them to lead normal and productive lives.

**Hyposplenism and infection risk**

Most patients with sickle cell disease are functionally or actually asplenic. This renders them vulnerable to infection with encapsulated organisms [46-48]. Pneumococcus was the scourge of sickle cell patients until the advent of penicillin prophylaxis in the 1980’s. Universal penicillin prophylaxis from birth to age 5 in the United States (lifelong in some countries) is the principal reason for increased survival of affected children into adulthood. Even so, infection is a major cause of death for sickle cell patients, causing 20% of total adult mortality in this population [49].

The most important means of preventing serious infection in adults with sickle cell disease is vaccination [50]. The benefit of pneumococcal vaccination is well established. There are two primary pneumococcal vaccines, each protecting against different pneumococcal serotypes. The 13-valent conjugate vaccine, sold as Prevnar, produces long-lasting immunity. It should be administered once to patients between age 18 and 64 (the earlier the better) and repeated at age 65. The 23-valent polysaccharide vaccine (Pneumovax) should be administered at or after age 18, repeated 5 years later and repeated at age 65. To maximize immune response, the vaccines should be separated by a minimum of eight weeks. Ideally, the 13-valent vaccine should be given first.

Although meningococcus is not a common pathogen in sickle cell disease, administration of a conjugated meningococcal vaccine is recommended at 5-year intervals [51]. Patients should be vaccinated annually against influenza.

In addition to acute chest syndrome, in which pulmonary infection is often either an initiating or a secondary event, sickle cell patients are susceptible to osteomyelitis (salmonella is the most common pathogen), infected leg ulcers and bacteremia. Patients with a history of unsafe sex or parenteral drug use should be screened for HIV and Hepatitis B and C [52].

Keeping an accurate vaccination and screening record is an important part of the primary care physicians role in the management of sickle cell disease.

**Pulmonary hypertension and asthma**

Pulmonary hypertension is present in about 10% of patient with sickle cell disease [53]. It tends to occur in older patients and confers a worse prognosis [54]. About half of patients demonstrate precapillary hypertension due to
endothelial dysfunction and accumulation of fibrous material in the adventitia, while the other half show elevated pulmonary venous pressures associated with left ventricular hypertrophy [55].

Symptoms and signs include gradually progressive fatigue and dyspnea, loss of exercise tolerance, hypoxemia and edema. The symptoms may be difficult to recognize in patients who are already chronically ill and limited by other complications of sickle cell disease such as avascular necrosis of the femur, which may limit mobility. Thus, primary care physicians should be aware of this complication and have a high index of suspicion. A six-minute walk test and pro-BNP can help to distinguish dyspnea from non-cardiopulmonary causes of increased fatigability such as pain, muscle atrophy and deconditioning [56].

The initial screening test for pulmonary hypertension is transthoracic echocardiography [9,57]. The echocardiographic criterion for further evaluation is a tricuspid regurgitant jet velocity of 2.5 m/s or more. The finding of an elevated n-terminal pro-brain natriuretic peptide (NT-pro-BNP) supports the diagnosis, though it is not always present [57].

Pulmonary hypertension is defined as a resting mean pulmonary artery pressure greater than 25 mm Hg by cardiac catheterization. Echocardiographic screening markedly overestimates the prevalence of pulmonary hypertension. Only 25% of those with a TRV above 2.5 m/s have pulmonary hypertension on catheterization [58]. However, TRV above 2.5 m/s defines a group at higher risk for mortality [56,59]. The combination of TRV greater than 2.5 m/s and the presence of clinical symptoms should warrant a referral for right heart catheterization.

The American Thoracic Society 2014 guideline for management of pulmonary hypertension in sickle cell disease recommends initiating hydroxyurea as first-line treatment for suspected pulmonary hypertension based on echocardiographic criteria, since it has a demonstrated mortality benefit in this setting. If disease-specific therapy is needed, the diagnosis should then be confirmed by catheterization [57]. Chronic transfusion therapy is an alternative to hydroxyurea for diagnosed pulmonary hypertension [60].

Sickle cell disease appears to increase airway responsiveness by mechanisms distinct from those seen in typical asthmatics [61,62]. Complaint of persistent cough and the finding of wheezes on lung exam are relatively common. One or both of these were found in a third of adult sickle cell patients in one study [63]. The presence of asthma increases the incidence of acute chest syndrome and predicts higher mortality [64]. Suspected asthma should be confirmed with pulmonary function testing, including methacholine challenge and should be treated with inhaled bronchodilators and corticosteroids as in the non-sickle cell population [65].

Cardiomyopathy

Anemia in sickle cell disease places increased demands on the heart. Cardiac output increases to meet tissue oxygen needs mainly through dilatation of the left ventricle, with the degree of dilatation corresponding to the severity of the anemia. This leads to an increase in left ventricular stress and a compensatory increase in wall thickness. Left ventricular hypertrophy (LVH) and diastolic dysfunction are seen in children and adults with sickle cell disease, increasing in prevalence with age. LVH and diffuse myocardial fibrosis seen on echocardiogram and MRI respectively is associated with decreased exercise tolerance. If disease-specific therapy is needed, the diagnosis should be confirmed by catheterization [56,66]. Increased left ventricular filling pressure is one contributor to pulmonary hypertension and is an independent predictor of increased mortality [67,68].

Iron overload is another cause of diastolic dysfunction in patients receiving regular transfusions. Overt signs do not appear until later in the course; thus, it should be suspected in patients with lifetime history of more than 10-20 transfusions. It is not necessarily evident on EKG or echocardiogram, but can be detected by cardiac MRI [69].
Skeletal and soft tissue complications

Of all the chronic end-organ complications of sickle cell disease, the one that has the greatest impact on quality of life is avascular necrosis of bone (also known as aseptic necrosis or osteonecrosis) [70]. The total age adjusted prevalence of osteonecrosis of the femoral head is 10% but this skews heavily toward young and middle-aged adults. The prevalence in 25 to 34 year olds is 65%, dropping off gradually in the older age cohorts due to lower survival in affected patients [71]. The humeral head is also often affected, and in both sites osteonecrosis may start unilaterally later affect the contralateral joint [72].

Radiologically, avascular necrosis progresses relentlessly over the course of several years from cysts and sclerosis to subcortical lucency (known on plain films as the “crescent sign”) to subchondral collapse and finally to joint space narrowing and joint degeneration. This corresponds with a clinical progression from asymptomatic disease to steadily increasing joint pain and loss of joint function [73,74]. Occasionally, avascular necrosis can occur abruptly during an episode of acute vasoocclusive crisis and persistent atypical joint pain during an episode of VOC requires further imaging.

Noninvasive management includes physical therapy, analgesics and, in the more advanced stages, adaptive devices such as cane or walker. Surgical options include core decompression in the pre-collapse phase and partial or total arthroplasty once joint collapse has occurred. The aim of core decompression is to alleviate pain and slow the progression to joint collapse [75]. A recent Cochrane review [76] found no difference in outcomes between core decompression and physical therapy but the data for a good quality review were limited and it remains an option for highly symptomatic patients in clinical practice. In the later stages, arthroplasty provides pain relief and restores joint function. Outcomes are generally good despite the higher operative risk for sickle cell patients [77,78].

Although osteonecrosis is usually slowly progressive, it is important to recognize that bone infarcts can arise acutely from sequestration of red blood cells in the marrow [79-82]. This can be diagnosed with plain radiographs or MRI and should be considered in the differential diagnosis of acute facial or limb pain and edema. The duration of symptoms is typically several weeks. The pain responds well to NSAIDs.

Osteomyelitis is less common than acute bone infarct, however it, too, needs to be considered in the differential diagnosis of limb pain. It may overlap with, or be mistaken for, vasoocclusive crisis. Detection is by radionuclide scanning, labeled white blood cell studies or MRI but definitive diagnosis usually requires biopsy [83,84]. Treatment is generally with broad spectrum antibiotics, though there is no evidence supporting specific antibiotic strategies [85].

Leg ulceration appears to occur most commonly in a subset of sickle cell patients who have fewer vasoocclusive crises and are more prone to pulmonary hypertension [86]. Leg ulcers arise most often in the second decade of life. In a minority of patients, these ulcers go on to be chronic and debilitating. Local wound care is similar to that in non-sickle cell patients: application of dressings, treatment of wound infection, mobilization, and action to address predisposing factors such as edema and arterial insufficiency. Treatment of the sickle cell disease itself (with hydroxyurea or transfusions), and of other complications, support wound healing [87]. A wide variety of topical agents has been tested and was the topic of a recent Cochrane Review, which concluded that RGB Protein Matrix has the strongest evidence of efficacy [88].

Stroke

A number of factors render the central nervous system particularly susceptible to damage in sickle cell disease. The brain, which constitutes about 2% of human body weight, accounts for 20% of oxygen consumption [89]. It is highly dependent on a steady oxygen supply to function, and is thus very vulnerable to conditions such as anemia that reduce oxygen delivery. Sickle cell patients are prone to chronic vasculopathy, as described above, and this affects the large cerebral blood vessels. The gradual narrowing of cerebral vessels permits the development of collaterals, which
angiographically resemble a puff of smoke (denoted as moyamoya by the Japanese angiographers who first described it). The collaterals don’t always result in adequate blood flow, and, in regions of these collaterals, blood flow is compromised. In addition, the thin-walled collateral vessels develop aneurysms, increasing the risk of intracerebral and subarachnoid hemorrhage. Aneurysms are present in about 10% of adults with sickle cell disease [90,91].

Several large cohort studies have looked at the incidence and prevalence of stroke in sickle cell patients [92-94]. Ischemic stroke has a threefold higher incidence in persons with homozygous sickle cell disease than in the general African-American population. The highest incidence of ischemic stroke occurs in children aged 2-9, and the next highest occurs in adults ages 20-29. The incidence of hemorrhagic stroke is also increased, and peaks in the 30-40 year age group. Twenty four percent of sickle cell homozygotes have had a stroke by age 45. Importantly, a sickle cell patient who has had a stroke is at high risk for another one. In adults, the recurrence rate after ischemic stroke is 38% and after hemorrhagic stroke 83%.

CNS vasculopathy is the cause of stroke in 82% children and 53% of adults. Other etiologies of stroke in adults include cardioembolism and triggering events such as vasoocclusive crisis, acute chest syndrome and infection. Traditional risk factors such as hypertension, smoking and obesity increase stroke risk in adults. Addressing these risk factors is an important strategy for primary prevention.

Given the high prevalence of stroke in this population, clinicians need to be alert for both typical and atypical stroke presentations. Headache is a common symptom in sickle cell patients, but may also be the first symptom of a CNS event in as many as 58% of patients. Visual changes, vertigo and tinnitus may indicate a bleed in the posterior circulation, where there is a high incidence of aneurysms. In adult patients with history of stroke or TIA presenting with acute onset of suggestive symptoms, a careful exam should be performed looking for focal neurologic signs, and neuroimaging should be strongly considered. Of note, subdural and intracranial hemorrhage can occur without trauma in sickle cell patients [91,95,96].

For suspected stroke, noncontrast head CT is the initial study of choice since it can be performed quickly, and accurately detects intra- and extracranial bleeding. In patients presenting with acute headache, magnetic resonance venogram should be included in the initial workup to rule out central venous thrombosis, which has an increased incidence in sickle cell patients [95]. MRI with diffusion weighted imaging will pick up ischemic stroke, although the findings may lag several days behind the event. MRA of the intra- and extracranial vessels can be used to define the extent of vasculopathy and pinpoint aneurysms at risk of future rupture.

Management of acute stroke is principally supportive. Anticoagulation with heparin should be initiated, in the absence of contraindications, if venous thrombosis is the etiology. Aspirin 325 mg daily is indicated for ischemic stroke. The role of thrombolysis in sickle cell related stroke is not well defined.

For secondary prevention after a first ischemic stroke, the mainstay is transfusion therapy with the aim of maintaining hemoglobin S concentration under 30%. This has been found to reduce the incidence of recurrent stroke by 67%. Most of the data to support this strategy comes from pediatric studies, but it is standard practice in adults, as well [96]. Generally, transfusions are performed every 3-4 weeks indefinitely, or until hemosiderosis (iron overload) develops or the formation of red blood cell antibodies preclude transfusion. The use of exchange transfusions (apheresis) is preferred in order to maintain isovolemia and avoid an excessive rise in hematocrit. Long-term apheresis typically requires implantation of a central venous catheter or port [97].

**Silent cerebral ischemia**

As common as overt stroke is, it may be only the tip of the iceberg of ischemic brain injury in sickle cell patients. Recent work has focused on the high prevalence of silent cerebral ischemia (SCI) in this population. The topic is well covered in two recent reviews [98,99]. MRI findings of damage to brain tissue are seen in as many as 40% of
adolescents and 60% of adults. Controlling for family and sociodemographic factors, King et al found a 5% mean decrease in intelligence quotient associated with the presence of SCI [100]. SCI has been shown to predict poor academic performance in math and reading [101]. This would be expected to have a negative impact on the life trajectory and economic status of affected individuals. Furthermore, SCI is a strong risk factor for progressive neurologic injury and overt stroke.

The problem of SCI has only recently come into focus and no consensus has yet emerged on preventative or management strategies, though there is interest in transcranial Doppler as a tool to screen for cerebral vasculopathy. However, it is important for primary care providers to recognize that some patients with sickle cell disease may have subtle deficits in attention, memory, abstract reasoning and verbal comprehension that may interfere with adherence to complex treatment plans and pose extra challenges in navigating the complexities of the health care system [99]. Active listening, clear communication and requesting feedback during the doctor-patient encounter are helpful tools in caring for patients with mild cognitive impairment. Patients may do better in systems that employ care management and patient navigation for persons with complex chronic illness [102-104].

Urogenital complications

Sickle cell nephropathy is relatively common. In a sample of 98 patients with a mean age of 31.6 years, 29% were found to have chronic kidney disease stage 1 or greater. After 5 years, the prevalence of chronic kidney disease had increased to 41.8%, and 2% of patients had end-stage renal disease [105]. Sickle nephropathy begins with glomerular hyperfiltration in childhood and progresses through normal and then reduced glomerular filtration with histologic findings of hemosiderin deposits, hemorrhage, necrosis and ultimately focal glomerular sclerosis. At the same time, red blood cell sickling in the low oxygen environment of the medulla leads to ischemic injury and microinfarcts [106].

For primary prevention of kidney disease, the target blood pressure for all sickle cell patients should be below 135 systolic and 85 diastolic [9]. Notably, hypertension is rarer in patients with sickle cell disease than in the general population [107].

As with diabetic and hypertensive kidney injury, the earliest urinary finding in sickle cell nephropathy is microalbuminuria, present in 30% of patients aged 15-23 and more than 60% of those above age 35 [108]. Patients without known renal disease should be screened annually for microalbuminuria. If values are above the normal range, a 24-hour urine collection should be obtained. Greater than 300 mg protein loss/24 hours should prompt referral to a nephrologist.

It is recommended, based on experience in diabetic nephropathy, that patients with microalbuminuria and without gross proteinuria be started on an angiotensin converting enzyme inhibitor or angiotensin receptor blocking agent regardless of blood pressure. In addition, it should be noted that the incidence of albuminuria is lower (with an odds ratio of 0.28) in patients treated with hydroxyurea, which suggests a role for that agent in prevention of nephropathy [109]).

Because of medullary kidney damage, hyperkalemia occurs with increased frequency in sickle cell disease. Increased frequency of RTA Type 1 is seen in this patient population. Concentrating defects are also common, leading to polyuria and nocturia. Microscopic hematuria arises from small medullary infarcts and is typically benign and self-limited. However, macroscopic hematuria should prompt evaluation with CT urography for renal papillary necrosis [108].

Priapism - defined as a penile erection that lasts more than 4 hours beyond orgasm or without sexual stimulation - is a widely recognized complication of sickle cell disease. It is similar to compartment syndrome in its effects, resulting, if not treated within 24 hours, in tissue death. Thus, an episode of priapism should be treated as a medical emergency. The term stuttering priapism describes frequent and unwanted painful erections. Treatment for priapism
consists of aspiration of blood from the corpus cavernosum to decompress the penis, followed by intracavernous administration of sympathomimetic drugs [110].

Preventive management of stuttering priapism is under-researched. Hydroxyurea, sildenafil, pseudoephedrine and leuprolide have been ineffective. An important recent study demonstrated the safety and efficacy of chronic transfusion in this condition [111]. Nitrous oxide and adenosine signaling pathways are seen as promising targets [112].

Sensitivity should be used in dealing with this condition, which is not only dangerous but frequently embarrassing. Many of our patients can recount humiliations they have experienced when seeking treatment for priapism.

**Prevention, Screening and Health Care Maintenance**

Health care maintenance recommendations for persons with sickle cell disease are well outlined in the 2014 Expert Panel Report on Evidence Based Management of Sickle Cell Disease from the National Heart, Lung and Blood Institute [9]. Many of the recommendations are mentioned earlier in this paper, but are repeated here for easy reference.

Patients should receive pneumococcal vaccination with the conjugate vaccine before age 18 (or later if neglected in childhood) and again at age 65. The polysaccharide vaccine should be administered every 5 years. Annual influenza vaccination is important, and vaccination against meningococcus should be performed at least once.

Patients without known kidney disease should be screened annually for microalbuminuria.

Patients with suggestive symptoms such as exertional dyspnea, edema or hypoxemia should be evaluated with echocardiography for pulmonary hypertension. Those found to have TRV at or above 2.5 m/s should be started on hydroxyurea. Patients with respiratory symptoms or wheezing should be assessed for asthma with pulmonary function testing.

Patients should be screened every 1-2 years for sickle cell retinopathy with dilated eye exam and referred to a retinal specialist if retinopathy is present.

All patients (male and female) should be counseled on the heritability of sickle cell disease and on reproductive risks. It is recommended that sexual partners of patients with sickle cell disease undergo hemoglobinopathy screening. The aim is not to discourage or encourage particular reproductive choices, but to ensure that individuals make fully informed choices.

Like all sexually active patients, men and women with sickle cell disease should be educated on pregnancy and sexually transmitted disease prevention. For women desiring contraception, combined estrogen-containing agents are less favored than other forms because of the increased thrombotic risk.

Note that hydroxyurea, which is widely used to treat sickle cell disease, is highly teratogenic when used by men or women before conception and by women during pregnancy. Thus, patients on hydroxyurea must be urged to use birth control. Hydroxyurea should be discontinued at least one month prior to any attempt to conceive.

Women who have been transfused and are planning a pregnancy should be screened for red cell alloantibodies; and if the woman is positive, her partner should be screened for corresponding antigens, since this combination can increase the risk of fetal and neonatal hemolysis. Women with sickle cell disease should be counseled on the increased risks associated with pregnancy and, after conception, should be managed in a center that provides high-risk obstetrics.

Standard age- and sex-specific health maintenance measures such as cervical, breast and colon cancer screening should not be neglected in patient with sickle cell disease. Of particular importance is smoking cessation. Smoking has been found to more than double the likelihood of acute chest syndrome and is associated with a significant increased risk of mortality in sickle cell disease [113,114].
### Table 2: Health care maintenance for adults with sickle cell disease

<table>
<thead>
<tr>
<th>Category</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Immunizations</strong></td>
<td>- Pneumococcal: Conjugate vaccine at or after age 18 and again at age 65.</td>
</tr>
<tr>
<td></td>
<td>Polysaccharide vaccine at or after age 18, repeat 5 years later and repeat at age 65 (should follow conjugate vaccine by a minimum of 8 weeks).</td>
</tr>
<tr>
<td></td>
<td>- Meningococcal Vaccine – Adults with actual or functional asplenia should receive 2-dose primary series of MenACWY if not administered in childhood; and a booster every 5 years subsequently.</td>
</tr>
<tr>
<td></td>
<td>- Influenza Vaccination – Annually</td>
</tr>
<tr>
<td></td>
<td>- Other vaccines as per standard recommendations for all adults.</td>
</tr>
<tr>
<td><strong>Renal Screening</strong></td>
<td>- Microalbuminuria annually</td>
</tr>
<tr>
<td></td>
<td>- Referral for potential ACE/ARB if Microalbumin/Creatinine ratio is &gt; 500mg on at least 2 occasions</td>
</tr>
<tr>
<td><strong>Pulmonary Screening</strong></td>
<td>- PFTs, Echo, 6MWT, and proBNP is recommended for patients with shortness of breath, orthopnea, PND, hypoxemia or new onset edema</td>
</tr>
<tr>
<td></td>
<td>- Screening is Controversial for all patient</td>
</tr>
<tr>
<td></td>
<td>- NIH Guidelines recommend screening only for SS/SBo</td>
</tr>
<tr>
<td></td>
<td>- Thoracic Society Recommends annual screening for all genotypes</td>
</tr>
<tr>
<td></td>
<td>- Right Heart Catheterization is recommended for patients with Tricuspid Jet Velocity &gt; 2.5m/s</td>
</tr>
<tr>
<td></td>
<td>- Consideration of either Hydroxyurea or Transfusions for right heart catheterization confirmed pulmonary HTN</td>
</tr>
<tr>
<td><strong>Reproductive Screening</strong></td>
<td>- Screening and counseling for pregnancy and sexually transmitted diseases is recommended as with age matched patients.</td>
</tr>
<tr>
<td></td>
<td>- Additionally, it is recommended for all partners of patients with sickle cell disease for discussion. The aim is not to discourage or encourage particular reproductive choices, but to ensure that individuals make fully informed choices.</td>
</tr>
<tr>
<td></td>
<td>- Oral contraceptive choices should be made with informed consent on potential risk of VTE in patient with sickle cell disease, which is increased with the use of estrogen.</td>
</tr>
<tr>
<td></td>
<td>- Discussion of teratogenic risk of Hydroxyurea and stop this at least one month prior to considering conception.</td>
</tr>
<tr>
<td></td>
<td>- Pregnancy counseling is recommended for patients including potential maternal morbidity and risks. Please obtain screening for red cell antibodies.</td>
</tr>
<tr>
<td><strong>Iron Overload</strong></td>
<td>- Patient with &gt; 20 simple transfusions or chronic transfusion therapy are at risk of iron overload and should have screening annually for iron overload with ferritin. Consider further work up if ferritin is elevated.</td>
</tr>
<tr>
<td><strong>Other Standard Screening</strong></td>
<td>- Smoking Cessation</td>
</tr>
<tr>
<td></td>
<td>- Breast Cancer Screening</td>
</tr>
<tr>
<td></td>
<td>- Colon Cancer Screening</td>
</tr>
<tr>
<td></td>
<td>- Cervical Cancer Screening</td>
</tr>
</tbody>
</table>
Treatment of sickle cell disease

Primary care practitioners should be acquainted with treatment options for sickle cell disease itself. These are normally prescribed or administered by hematologists who specialize in sickle cell disease. However, it is useful for other treating physicians to understand the indications, effects and toxicities of the various treatments. Primary care physicians can play an important role in helping patients with treatment decisions, assessing adherence and monitoring for side effects. Thus, we will provide a brief overview of these options.

**Hydroxyurea:** Hydroxyurea was the first drug found to be effective in treating sickle cell anemia. A landmark study published in 1995 showed a doubling of the time between vasoocclusive crises in adults treated with hydroxyurea and a 50% drop in the incidence of acute chest syndrome [115]. A subsequent study that followed patients out 9 years showed mortality of 6.8 per 100 person-years in subjects who took hydroxyurea for less than a year, compared with 2.7 in those who took it for more than a year [116]. Subsequent work has confirmed the morbidity and mortality benefits [117].

Hydroxyurea works by increasing production of fetal hemoglobin, which does not cause sickling, while reducing the number of red blood cells that carry predominantly hemoglobin S. It is indicated in adults who have frequent vasoocclusive crises (more than 3 per year), those who have experienced acute chest syndrome, those with chronic pain and those with severe symptomatic anemia. It also has a role in secondary prevention of stroke, though transfusion therapy is more often used in that setting [9,118,119].

Toxicities of hydroxyurea are mainly hematological: because of bone marrow suppression, it should not be given to patients with severe leukopenia, thrombocytopenia or anemia, and the reticulocyte count must be monitored at intervals during therapy. Renal and hepatic function are also monitored since toxicity can occur in these organs. Hydroxyurea is teratogenic in animals, and is contraindicated in pregnancy. Response to the drug is assessed by measuring fetal hemoglobin levels.

Not all patients respond to hydroxyurea. The main determinant is the ability to produce fetal hemoglobin, which appears to be genetically determined. As many as 50% of patients do not have a rise in fetal hemoglobin in response to hydroxyurea [120,121]. Others may be unable to take it due to hematologic or other toxicity. Thus, new treatments have been sought.

**Selectin antagonists:** Adhesion of sickle erythrocytes to the vascular endothelium initiates the vasoocclusive process and the ensuing inflammatory cascade that results in vascular damage. Adhesion is mediated by a family of molecules called selectins - principally P-selectin and E-selectin [122]. In early 2007, results were published from the first randomized trial of a P-selectin inhibitor, crizanlizumab. Compared with placebo, high-dose crizanlizumab produced a 45% drop in the rate of vasoocclusive crisis. Adverse effects included arthritis, diarrhea, pruritus, vomiting, and chest pain [123]. Crizanlizumab is expected to be commercially available in the near future and other selectin antagonists are in the pipeline. Currently, there are ongoing trials of Rivapanzel, GMI1070, which has more pan-selectin inhibition in the role of treatment of vaso-occlusive crisis (Clinical Trials.gov NCT02433158, NCT02187003).

**Transfusion therapy:** In most settings, transfusion therapy for sickle cell disease will be administered by a hematologist, but it is important for primary care physicians caring for sickle cell patients to understand the indications for, and limits of, red blood cell transfusion.

In sickle cell disease, transfusion is given, whenever possible, in the form of erythrocytapheresis. “Exchange transfusion” and “red cell exchange” are other terms used for this procedure. The procedure consists of infusing normal red blood cells via one line while removing the patient’s red blood cells via another. It is generally performed...
through a central line with double lumen access, though separate peripheral lines can be used. An implanted catheter is used for chronic transfusion therapy [124].

Erythrocytapheresis has the advantage of rapidly lowering the hemoglobin S concentration to a predetermined level without producing erythrocytosis or volume overload [97]. When multiple transfusions are needed over time, it delays (but does not eliminate) the complication of iron overload [125-128]. It is used acutely for acute chest syndrome, incident stroke, multiorgan failure, severe intrahepatic cholestasis and priapism [129].

There are several indications for chronic transfusions (i.e. regularly scheduled transfusions administered over a long period of time) in sickle cell disease [97,129,130].

In adults who have suffered a clinically overt stroke, erythrocytapheresis is performed regularly for the purpose of preventing subsequent stroke. Hemoglobin S levels are measured at intervals, and patients are transfused to maintain hemoglobin S below 30% of total hemoglobin. This is continued lifelong, or until a contraindication arises. The practice is based on extrapolation from pediatric trials in which chronic transfusion was shown to reduce stroke recurrence [131,132]. It is also supported by the STOP-2 trial, which showed a marked increase in stroke with discontinuation of transfusions [133]. Hydroxyurea seems to be far less effective for secondary prevention of stroke [134].

In children, transfusion has also been shown to reduce recurrent events in patients who have had a silent cerebral infarct [135], but its role in adults with silent ischemia has not been defined.

As noted above, hydroxyurea is the primary agent used to reduce the number and severity of vasoactive crises and to manage chronic sickle cell pain; however, chronic transfusions will sometimes be used for this purpose when hydroxyurea is contraindicated or poorly tolerated. Several studies support a reduction in sickle cell crises and hospitalizations with chronic transfusions [136-138]. Transfusion therapy has a gradual effect on chronic pain and may impact crisis intensity more than frequency [139].

Chronic transfusion is considered a second line therapy for pulmonary hypertension in patients who cannot take hydroxyurea [55,57,140].

One final indication for transfusion is in preoperative management. Complications during and after surgery are common in patients with sickle cell disease, with a rate approaching 40% even for cholecystectomy (a relatively low-risk procedure) [141]. Transfusion before surgery to lower the proportion of hemoglobin S in the circulation reduced the complication rate by more than half [142].

Transfusion is never used to correct chronic anemia. Many patients with sickle cell disease have very low hemoglobin levels, but this is generally well compensated. The risks of transfusion in this setting outweigh the benefits [9].

There are two major complications of chronic transfusion therapy. The development of antibodies to red cell antigens (alloimmunization) occurs frequently and progressively with duration of therapy. The more antibodies are present, the more difficult it is to find matched units for transfusion; and if alloimmunization develops to a very wide range of red blood cell antigens, then transfusion therapy must be discontinued [130].

The second major complication is hemosiderosis (iron overload). Males and non-menstruating females have no way to eliminate iron, which, with repeated transfusions, accumulates in the liver, pancreas, heart, marrow and pituitary gland. If unchecked, this can result in hepatic cirrhosis, diabetes, cardiomyopathy and hypogonadism. The marrow toxicity of iron may also cause ineffective erythropoiesis, exacerbating existing anemia [143,144].

Liver iron concentration is an accurate predictor of complications of transfusional iron overload [145]. In chronically transfused patients, the serum ferritin level may be monitored as an initial indicator of hemosiderosis.
Various ferritin levels ranging from 800 to 2700 micrograms per liter have been suggested as cutoff values to prompt further investigation, but the most useful indicator may be the trend in ferritin over time [144,146,147]. Although biopsy is required for exact quantification of liver iron concentration, the usual practice is to obtain an MRI using an R2 to R2* signal decay protocol, the results of which correlate quite well with biopsy quantification. “Ferriscan” is a widely used proprietary analysis system for obtaining these results [148]. MRI assessment of hepatic iron deposition should be performed at least once in patients at risk of hemosiderosis (i.e. with a lifetime history of more than 10-20 transfusions) and annually in those at ongoing risk due to frequent acute transfusions or chronic transfusion therapy. Those with significant iron deposition are treated with iron chelating agents 9,144.

**Bone marrow transplant:** The first cure of sickle cell anemia occurred in 1984 as an incidental effect of marrow transplantation in an eight year old girl who developed acute myeloblastic anemia [149]. Since then, bone marrow transplantation has been developed as a curative strategy for individuals with sickle cell disease. In adults, it is presently available only on protocol, but may be an option in clinical practice in the near future. In children, work has focused on achieving elimination of sickle cell manifestations with less toxic regimens and with a wider range of donor cells [150]. Nonetheless, the improved prognosis of sickle cell disease in recent decades and the risk of transplant-related morbidity and mortality must be balanced against the benefits of cure in patient decision-making.

**Gene therapy:** As a single-gene mutation, sickle cell disease is a good candidate for gene therapy to replace the sickle hemoglobin gene with a gene to produce normal hemoglobin. The first successful gene transplant in sickle cell disease was reported in March of 2017 [151]. A 13 year old boy with hemoglobin SS in France underwent successful gene transfer using a lentiviral vector. The bone marrow was conditioned with busulfan prior to reimplantation of treated stem cells. At 15 months of follow up, the patient had 48% normal hemoglobin and had experienced no sickle cell complications. Other approaches to in vitro genetic alteration and reimplantation of sickle cell progenitor cells, using the CRISPR gene editing technique, are under study (Mullin 2017).

**Summary and Discussion**

Sickle cell disease, once primarily a pediatric condition, is now encountered with some frequency by adult primary care providers due to the lengthening lifespan of affected patients. Several advances in therapy have contributed to a reduction in mortality. These include the use of antibiotic prophylaxis against pneumococcal pneumonia in childhood, and of hydroxyurea and exchange transfusions to reduce the frequency and severity of sickle crises and to prevent organ system complications.

In spite of these improvements, sickle cell remains a highly disabling condition with significant mortality. In the review, we have provided an overview of the most common chronic sickle cell complications and their management.

In addition to acute vasoocclusive crises, many adult patients with sickle cell disease suffer from chronic neuropathic pain. Chronic pain is a management challenge, since there are relatively few effective pharmacologic agents that are safe and appropriate for long-term use. As first-line treatment, we recommend nonpharmacologic techniques such as mindfulness meditation, exercise, physical therapy, and the use of enabling devices to overcome physical limitations. When pharmacotherapy is required, NSAIDs and pain-modulating agents such as gabapentin may be helpful. If opioids are prescribed, we recommend keeping the dose and frequency as low as possible. We have found that educating patients at the outset about the risks of dependence, tolerance and treatment failure allows them to make prudent decisions about prescription opioid use.

Pulmonary hypertension arises in 10% of individuals with sickle cell disease, with the incidence increasing with age. Signs and symptoms (gradually progressive fatigue and dyspnea, loss of exercise tolerance, hypoxemia and edema) can be subtle, especially in patients who have other comorbidities that impair exercise tolerance. Six-minute
walk test, pro-BNP and echocardiogram can be used to screen for the presence of pulmonary hypertension. Hydroxyurea should be initiated in patients who have a tricuspid regurgitant velocity greater than 2.5 m/s. More aggressive treatment may be warranted for patients with inadequate response to hydroxyurea. In these cases, diagnosis should be confirmed with cardiac catheterization.

A third of persons with sickle cell disease have airway hyperresponsiveness causing intermittent cough and wheezing. These patients can be treated symptomatically with bronchodilators, or a formal diagnosis can be obtained through pulmonary function testing.

Sickle cell disease affects the heart in several ways: anemia increases cardiac output, sometimes producing left ventricular dilatation and subsequently left ventricular hypertrophy. In addition, in patients receiving regular transfusions, iron overload can cause diastolic dysfunction.

Avascular necrosis of bone is a common complication in young adults and middle aged patients with sickle cell disease, and a cause of significant suffering and disability. From onset, lesions enlarge until they lead to collapse of the affected bone. Multiple joints can be affected, often symmetrically, with one side typically preceding the other. In the early phases, analgesia, physical therapy and assistive devices are the recommended treatment modalities. After joint collapse, arthroplasty is an option for patients who can tolerate orthopedic surgery.

Although the chronic presentation is more common, bone infarcts can occur acutely and should be considered in the differential diagnosis of acute limb pain and edema; as should osteomyelitis, which is more common in persons with sickle cell disease than in the general population.

Another musculoskeletal complication is leg ulceration, which occurs in a subset of patients also more prone to pulmonary hypertension. Management is similar to that in non-sickle-cell patients. Treatment with hydroxyurea or transfusion to reduce the proportion of circulating sickle hemoglobin aids healing.

Patients with sickle cell disease are prone to cerebrovascular disease from a young age. Stroke is a recognized indication for red blood cell exchange transfusions, which has demonstrated efficacy for secondary prevention. Stroke can manifest atypically with symptoms such as headache, tinnitus or blurry vision. The threshold for neuroimaging should be low when such symptoms present.

Silent cerebral ischemia may be more common than overt stroke. Treating physicians should be alert to the possibility of subtle cognitive and motor deficits caused by unrecognized ischemic events.

Sickle cell nephropathy has a high prevalence. One study found it in nearly 50% of a prospective cohort by the age of 35. Like diabetics, patients with sickle cell disease should be screened annually with spot urine microalbumin. Angiotensin converting enzyme inhibitors may be beneficial in slowing the progression of renal disease after the onset of microalbuminuria.

Several therapies are effective in ameliorating the impact of sickle cell disease on the various organ systems. Hydroxyurea has been in use since the 1990’s and has been shown to decrease the frequency of vasoocclusive crises and acute chest syndrome. By increasing the proportion of fetal hemoglobin in circulation, hydroxyurea reduces sickling and thus reduces the risk of end-organ complications such as stroke.

In addition to hydroxyurea, the other mainstay of sickle cell management is exchange transfusions. Most patients are treated with one or the other. Like hydroxyurea, the aim of regular transfusion is to reduce the proportion of circulating hemoglobin S and thus decrease sickling events. Indications for chronic transfusion include secondary prevention of stroke, reduction in crisis frequency and intensity, reduction in chronic pain, and treatment for pulmonary hypertension. Transfusion is also used preoperatively to improve postoperative prognosis.

Patients receiving regular transfusions should be screened annually for iron overload with MRI, and treated with chelation if hemosiderosis is present.
A promising new treatment for sickle cell disease is the selectin antagonists. Crizanlizumab is expected to be available commercially in the near future, and Rivapanzel is undergoing clinical trials. These agents reduce vasoocclusive damage through actions on red blood cell and endothelial receptors.

Bone marrow transplant is a potentially curative option, currently available to adults only through clinical trial enrollment. Transplant is limited by the availability of matched donors. Recent trials have shown success with haploidentical (i.e. sibling) donors. The risk of procedure-associated morbidity and mortality is also a significant barrier. Recent work has focused on finding less toxic marrow conditioning regimens. Genetic editing of patients’ own extracted marrow cells to counter or eliminate the sickle mutation, followed by reimplantation in the marrow, is a promising future technology.

**Conclusion**

In conclusion, sickle cell disease is a complex disease with multiple organ system manifestations. As more patients survive into adulthood, it is being managed increasingly by adult primary care providers. This review has surveyed the chronic complications of sickle cell disease, with an emphasis on prevention, identification and management. Knowledgeable primary care practitioners can play an essential role in co-managing sickle cell patients along with hematologists and other specialists.

**References**


86. Ballas SK (1991) Sickle cell anemia with few painful crises is characterized by decreased red cell deformability and increased number of dense cells. Am J Hematol 36: 122-130.


