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Adult Sickle Cell Anemia

Sickle cell disease celebrated its 100th anniversary last year, prompting consideration of what has transpired for those with the disease since its description by Dr. James Herrick in 1910.[1] Worldwide, it is the most commonly encountered genetic disorder. Annually, it afflicts a quarter of a million newborns in Sub-Saharan Africa and an estimated 100,000 patients in the United States.[2] Currently 1 in 350 African American newborns are diagnosed yearly in the United States.[3] The life span of patients with sickle cell disease in the United States has lengthened appreciably in the last several decades. As survival has improved, it has become a disease seen in the adult primary care office more and more frequently.

For those taking care of the patient with sickle cell disease, it can be a daunting task. The history of sickle cell disease is a testimonial to the slow, tortuous approach to this public health problem. For the first 40 years after identification, the underlying pathophysiology of the pain and anemia of sickle cell was unknown and predominantly supportive care was available. It wasn't until Linus Pauling's work in 1949 that it became recognized as a molecular derangement. Ingram and Hunt went on to identify the substitution of valine for glutamic acid at position 6 in 1956.[4] It was understood that it was an autosomal recessive gene and that its most severe expression is in those who are homozygous. Following this, there was another prolonged period of growth in interest and acceptance culminating in the early 1970s, with the establishment of national programs for study and treatment: the National Sickle Cell Disease Program, the National Sickle Cell Anemia Control Act, the Comprehensive Sickle Cell Centers under the NIH, and the Cooperative Study of Sickle Cell Disease.[4] Since the 1980s, the number of clinical interventions and studies have begun to flourish. This has led to the beginning of a substantive management approach for a far too common disease.

What Is Happening in Active Sickle Cell Anemia?

Sickle cell disease has been characterized by some as simply a disruption of the delivery of blood at a microvascular level due to mechanical obstruction by sickle-shaped cells. The substitution of valine for glutamic acid at a molecular level predisposes to mechanical changes in the red cell when exposed to such triggers as dehydration, low oxygen tension, pH changes, and others still being identified. The result of this structural alteration is a dehydration of the red cell and distortion of its shape, via polymerization. This creates not only mechanical flow issues, but also marked hemolysis and inflammatory mediator release. It is the latter that is gradually being acknowledged as a more substantive issue. The presence of free heme is thought to liberate inflammatory mediators that initiate a complicated cascade of injury. Microvascular occlusion coupled with the concomitant inflammatory process results in widespread multisystem damage. Its clinical presentation results in a triad of signs and symptoms, summarized as: (1) hemolytic anemia and its sequelae; (2) pain syndromes and related issues; and (3) complications affecting major organs and their function.[5]

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Executive Summary

Sickle cell disease just celebrated its 100th anniversary of discovery and it remains the most commonly encountered genetic disorder worldwide. It affects one in 350 African American newborns each year.

- The most common clinical complication of sickle cell disease is the acute pain crisis.
- Chronic pain in sickle cell disease is quite common; although there is no proven best approach to management, the condition should be addressed as any other established pain syndrome.
- Common complications of sickle cell disease involve cardiac, dermatologic, gastrointestinal, genitourinary, musculoskeletal, pulmonary, and hematological systems.
- The developments of stem cell transplantation, chelation therapy, stimulants of fetal hemoglobin production, and small molecule anti-inflammatory therapies all hold promise in the future management of this chronic disease.

There is a growing awareness that the phenotype of a patient with sickle cell disease seems to predict the disease course. For example, studies have shown that the percentage of circulating fetal hemoglobin is directly proportional to clinical severity. In addition, as hemolysis proceeds unabated, it leads to not only anemia and fatigue, but progressive vasculopathy. Recent research suggests that, for example, patients with low hemoglobin concentrations and high hemolytic rates develop pulmonary hypertension while those with a higher hemoglobin concentration tend to suffer from acute chest syndromes.[6] In addition, a recent report from the National Heart, Blood, and Lung Institute suggests that steady-state LDH levels can identify patients who do not suffer frequent pain crisis but, nonetheless, have earlier mortality due to vasculopathy. A 2009 article discusses the perplexing phenotypic heterogeneity of sickle cell disease.[7] The authors reflect that the spectrum of clinical outcomes (stroke, acute chest, avascular necrosis, etc.) cannot be explained by a single gene mutation alone. Studies cited suggest a modulation of inflammation and cell-cell interaction that must be polymorphic in origin. They also note that environment, genetic background, socioeconomic factors, and psychology all may play a role in phenotypic expression of individual disease activity.[7] Finally, the fact that there is a spectrum of disease seen in the various forms of sickle cell disease, sickle-thalassemia vs homozygous sickle cell implies there is some impact of the presence of other hemoglobin types in modifying disease activity.

How Does This Impact Management?

Increasingly, there has been a shift in how sickle cell anemia is viewed. Beyond the recognition of its complicated pathophysiologic impact is a growing awareness of its spectrum of clinical phenotypes and the specific organ system impact.[8] Just as diabetes has different presentations and courses in individual patients, it is becoming clear that this is also the behavior of sickle cell disease, which significantly impacts nearly every organ system over time.

Sickle cell disease is unique because currently there are limited objective measures of disease activity that provide either validation to patients or "evidence" to providers. This, along with likely socioeconomic factors, has resulted in sickle cell, specifically pain crisis, being stigmatized in a significant number of adult settings,[9] even leading to delays in care compared to patients with pain as the presenting complaint.[10,11] Sickle cell disease in pediatric care settings most often involves well-organized care teams, whereas adult patients often struggle to have their disease understood[12] and, thus, often find themselves under treated and distrustful of health care.[13] Even more powerful is the concept that those patients with the least pain actually may have the most significant clinical progression of disease. This creates a potpourri of care issues both in regard to care process and knowledge of management.

Clinical Impact of Sickle Cell Disease

As appreciation for this disease has grown, it is helpful to think of sickle cell disease in the same was as other chronic diseases: consider and manage specific organ system impact. The widespread impact of sickle cell disease is summarized in Table 1. Clinicians should take a two-pronged approach to patient care: consistently apply and modify therapies/interventions that control acute disease activity and focus on prevention or delay of disease progression. Again, they should take a markedly similar approach as that taken for the multitude of other chronic diseases managed in clinical practice. The literature is expanding with studies of the various organ system impact and management approaches.

Acute Pain Crisis

The most common clinical complication of sickle cell disease is the acute pain crisis. Acute care encounters and rehospitalizations are high for people with sickle cell disease, particularly for those ages 18-30 years old.[14] This resulted in an average of 197,000 emergency room visits annually between 1999 and 2007.[15] In several administrative

Table 1: Multi-organ System Complications Associated with Adult Sickle Cell Disease

Cardiac
Arrythmias, diastolic dysfunction, high output failure
Dermatologic
Leg ulcers, left ventricular hypertrophy
Gastrointestinal
Functional asplenia, gallstones, hepatic sequestration, intrahepatic cholestasis, ischemic colitis, splenic infarct
Genitourinary
Priapism
Hematologic
Acute hyperhemolysis, alloimmunization, aplastic crisis, chronic anemia, splenic sequestration, thrombosis
Mental Health
Anxiety, chronic pain, depression
Musculoskeletal
Avascular necrosism, compartment syndrome, dental caries, dental pulp necrosis, meniscus tears, osteoarthritis, osteonecrosis, tendonopathies
Multisystem
Acute pain crisis
Neurologic
Carpal tunnel syndrome, cognitive Impairment, hemorrhagic stroke, ischemic stroke, neuropathy (mono or poly)
Obstetrics/Gynecology
Caesarean delivery, low birth weight infants, miscarriage, pre-eclampsia, preterm delivery
Ophthalmologic
Glaucoma, proliferative sickle cell retinopathy, retinal detachment, traumatic hyphema, vitreous hemorrhage
Pulmonary
Acute chest syndrome, pulmonary hypertension, worsened course of asthma
Renal
Chronic renal insufficiency, hematuria, nephrotic syndrome, papillary necrosis, proteinuria, pylenephrosis

data sets, the vast majority of the roughly 60,000-75,000 annual hospitalizations in those with sickle cell disease were for vaso-occlusive crisis. The average charge for hospitalizations was $18,000 in 2006.[16] This substantial resource outlay pales in comparison to the impact these episodes have on patient lives.

The sickle cell acute pain crisis is defined as generalized pain occurring in the back, chest, or extremities for which no other identifiable cause can be found. Frequent sites of sickle cell pain include the back, knee/shin, hip, shoulders, long bones, sternum, and chest.[17] Initial assessment to rule out a precipitating cause of the pain crisis is appropriate, much as one would do for exacerbation of asthma, congestive heart failure, or diabetic ketoacidosis. The routine use of a complete blood and reticulocyte count in assessing "legitimacy" or severity of an acute pain crisis is not supported by any evidence. They have not been shown to alter the treatment or outcome of care in any substantial way.[18] Unfortunately treating providers often refer to this as "evidence" that a patient is more drug-seeking than in acute pain. There is, literally, no evidence to support reticulocyte count or complete blood counts in the diagnosis of sickle cell pain crisis. It should only be viewed as a screening tool to evaluate for aplastic crisis or worsening anemia. A concensus statement predominantly from Saudia Arabian hematologists (where 5% of the population has sickle cell trait) encourages measurement of pulse oximetry at admission as well as a chest x-ray, urine, and serum chemistries.[19] In addition to this testing, there are no data to support routine use of oxygen, IV hydration,[20] non-narcotic analgesia,[21] piracetam,[22] or bed rest. There is evidence that corticosteroid use along with narcotics may shorten the length and severity of crisis pain, but its use is not recommended due to the long-term side effects.[23] A recently published article on nitric oxide inhalation did not improve time to crisis resolution.[24] Non-narcotic analgesia is generally used and recommended, as it has additional analgesic effect with opioids (for example, nonsteroidal anti-inflammatory drugs [NSAIDS]).

However, studies do suggest that patient-controlled analgesia (PCA pump) results in better pain control at a lower narcotic consumption rate. There is a suggestion of shorter length of stays and side effects (nausea and constipation) as well.[25] Many physicians seem hesitant to apply guidelines that support early, aggressive pain control for acute sickle cell

crisis pain. A recent article in *Blood* noted the disturbing discrepancy between published guidelines (some in place since 1999) and available medical textbooks in 2008.[26] Only 21% of textbooks presented pain treatment regimens consistent with recommendations, and only 37% of textbooks noted the infrequency of addiction as a problem in this patient population. Of note, 92% of the same textbooks provide such reassurance in regards to cancer patients.[26] Studies in the emergency medicine literature are replete with reports of delay of analgesia as well as discharge home without achievement of acceptable pain control.[10,11,27]

Currently, the practicing clinician must operate with the limited evidence and focus treatment predominantly on pain management via parenteral narcotics and IV hydration — the standard of care in most locations. There are some suggestions of average ranges of hospital stays for crisis pain resolution, but individual variance can be quite substantial.[28] The full clinical picture of any individual patient should be considered when managing sickle cell disease and its associated complications in the hospital setting.

Prevention of acute pain crisis continues to be a main focus of sickle cell anemia research efforts. Drugs to prevent red cell dehydration (zinc, gardos channel blockers) have shown promise but no substantive clinical benefit.[29,30] The same may be said about phytomedicines (medicines derived from plants in their original states).[31]

The most encouraging work has been with the use of routine administration of hydroxyurea.[32] Hydroxyurea works by increasing the production of fetal hemoglobin-containing red cells, effectively diluting the sickled cells in the circulation. There is strong evidence that regular use of hydroxyurea modifies the number and severity of sickle pain crisis episodes and may decrease mortality,[33] improve quality of life,[34] and improve overall total amount of narcotics used for pain control.[35] A 2008 NIH concensus statement also relates that there is high-grade evidence that hydroxyurea also reduces the incidence of acute chest syndrome, decreases the number and severity of pain crisis episodes, and decreases the need for transfusion support via increasing hemoglobin (specifically fetal hemoglobin) levels.[36] It currently is the only drug approved by the FDA for such use and its approval is only for use in adult patients.

Although it has been used in trials for nearly 25 years, studies have not demonstrated long-term toxicity with hydroxyurea use in sickle cell disease. Known short-term side effects (supported by evidence) include leukopenia, thrombocytopenia, anemia, decreased reticulocyte count, pneumonitis, and skin rash. These short-term issues resolve with discontinuation of the medication. Long-term, there is the risk of hyperpigmentation. Unproven associations have been suggested with nausea, increased incidence of superficial skin cancers, and decreased sperm count.[36,37] Its use in pregnancy is discouraged at this time, although there is no definitive evidence implicating hydroxyurea in miscarriages, birth defects, or fetal/infant developmental delay.

Dosing is achieved by starting with a 15 mg/kg daily dose and titrating by 5 mg/kg/day for 12 weeks to a maximum dose of 35 mg/kg/day. This requires monitoring of blood counts frequently at first and then intermittently as time goes on. The decreased hematologic counts should be expected and are dose related. This is easily managed with temporary discontinuation of hydroxyurea for 1-2 weeks. Following that, treatment should be reinstituted with dosing adjustments dependent on circumstances. (For example, following concomitant viral illness the medication may be restarted at the previous dose once counts have recovered.)

Of note, some studies suggest that there may be different genetic subtypes of sickle cell that are less responsive to the beneficial effects of hydroxyurea.[38] This has not been definitively proven, but studies currently suggest that patients with mild clinical disease experience a better response to hydroxyurea.[33,39] Use of hydroxyurea currently is considered the standard of care for patients with sickle cell anemia.[40,41]

PRIMARY CARE PEARL: Hydroxyurea should be prescribed for adult sickle cell patients with hemoglobin SS or sickle beta zero thalassemia. For those with "milder" genotypes, for example SC, sickle beta plus thalassemia, the use is usually limited to those with complications. Hydroxyurea is the only evidence-based preventive intervention available for this disease.

Chronic Pain

One of the most frustrating and demoralizing struggles in the management of adult sickle cell disease involves the chronic backdrop of pain so many patients manifest. A 2006 Cochrane review found no studies of methodology befitting a meta-analysis to make any comments on what helps in the management of chronic pain in this population.[23] A second study of psychological therapies by the Cochrane group, updated last in 2009, also concluded insufficient evidence to espouse adding these approaches.[42] In 2004, a research group in Virginia designed a study to look at the ways of identifying and managing sickle cell pain. The initial commentary on the problems managing this complication included the very real conclusion that there simply has not been a detailed attempt to define pain in this population. This lack of information has led to poor management, expensive utilization of health care, and stigmatization of an entire subset of patients.[43]

A recent discussion of the resulting cohort study, which appeared in the *Annals of Internal Medicine*, reported on 6 months and 31,000 patient days that captured the daily experience of pain by 232 distinct patients suffering from sickle cell disease. This group (ages 16 years and older) provided the data that many who care for this population already knew: Sickle cell disease is a

chronic pain syndrome. The authors concluded that there was little relationship between utilization of health care, even though 54.4% of patient days reported pain. A striking 29.3% of patients reported pain in greater than 95% of their diary days. Frequency of home opioid use was an independent predictor of pain, crisis, and health care utilization. Pain days that were not associated with a crisis occurred 10 times more often as pain days associated with health care utilization.[44] A recent letter in a leading hematology journal highlighted the findings of the Comprehensive Sickle Cell Centers Clinical Trial Consortium Sites regarding quality of life scores. It is no surprise that the findings conclude effective treatment of chronic pain and related depression would be most beneficial to quality of life.[45]

Some centers are beginning to approach sickle cell-associated pain utilizing a palliative care approach. A sickle cell pain clinic at Beth Israel published its observation that patients required significantly less acute care for pain crisis once they were maintained in this manner. The clinic observed dramatic improvements in several patients' admission rates and noted no significant side effects with long-term narcotic therapy.[46] A review article published in 2010 found a paucity of literature available to allow any conclusions about approach to the management of sickle cell-affected patients with chronic pain. The authors found that the majority of attention to pain management has been focused on the "crisis" pain traditionally associated with this disease. Of the studies that did have some relevance, narcotics were the most frequently utilized agents.[47] An Italian review also drew the same conclusion that many patients with sickle cell disease are poorly treated for their pain.[48] The generalization that sickle cell patients suffer a high rate of addiction is not based in fact. In reality their rate of addiction is less than the general population in most studies.

PRIMARY CARE PEARL: Sickle cell disease may result in daily chronic pain, but there is no proven "best approach" to management. The chronic pain should be acknowledged and addressed as it is in other established pain syndromes.

Cardiac

Although throughout history hematologic and infectious complications greatly contributed to early death in sickle cell disease, current causes of death have shifted to cardiopulmonary etiologies. One autopsy series reported deaths as sudden and unexpected up to 40% of the time.[49] In data recently reported from Duke, the overall median survival was 40 years of age. Pulseless electrical activity arrest, pulmonary emboli, multi-organ system failure, and stroke were the most frequent causes of death. Nearly 30% of deaths in the five years between 2000 and 2005 were attributed to cardiopulmonary causes, none of which were identified as classical sickle cell-related complications.[50] This has created interest in pursuing more defined cardiac parameters in sickle cell patients. Ideally, this would allow researchers to expand treatment of identified cardiac disorders to impact some of the increasing cardiac mortality. Unfortunately, current studies have not led to significant progress in this area. Diastolic dysfunction (as reflected by a low E/A ratio) when found in association with pulmonary hypertension in sickle cell disease was noted to contribute independently to mortality risk.[51] Another group conducted a retrospective review of hospital records of adult patients with sickle cell disease. They found elevated tricuspid regurgitation velocity, mitral valve regurgitation, and pulmonary valve regurgitation to be common findings. Investigators noted that elevated tricuspid regurgitation velocity was associated with elevated serum lactate dehydrogenase concentration and lower hemoglobin levels. There was definite selection bias in their cohort, so no further conclusions could be drawn at the end of the study.[52] Electrocardiographic findings in a study of adult Nigerians with sickle cell anemia revealed higher mean heart rates, P-wave duration, P-wave dispersion, PR interval, QRS duration, QRS dispersion, QTc interval, and QTc dispersion than non-sickle cell patients. In addition, left ventricular hypertrophy was noted in 75% of patients, left atrial enlargement in 40%, biventricular hypertrophy in 11%, and ST segment elevation in 10% (vs essentially 0% in age-/sex-matched controls).[53] Currently, the studies do not give the primary care provider specific direction as to which treatment interventions to apply in which subset of patients, but the literature does suggest that primary care physicians begin to more actively consider these important long-term complications in patients. If discovered, current management applies standard recommendations for systolic or diastolic dysfunction. If iron overload is determined to be a contributor, chelation therapy should be instituted.

PRIMARY CARE PEARL: There are no standard recommendations for cardiac screening, but it may be appropriate to perform electrocardiograms and/or echocardiography in adult sickle cell disease patients to establish baselines.

Dermatologic

Leg ulcers are a long-recognized complication of sickle cell disease, yet their treatment has evolved little over the last 100 years. Leg ulcers occur much more frequently in those with homozygous disease and male gender. They can be excruciating and unrelenting, lasting from weeks to years. Leg ulcers are another complication that is believed to be associated with severity of hemolysis and concomitant lower hemoglobin levels, especially that of fetal hemoglobin. They seem to be more common in those with other markers of vasculopathy, such as priapism and pulmonary hypertension. A study of 88 patients in Turkey found a significant increase incidence of pulmonary hypertension in patients presenting with leg ulcers, even without overt symptoms of pulmonary involvement.[54] A group in Jamaica looked at

the incidence of venous insufficiency in a cohort of homozygous sickle cell patients and they found evidence to suggest a positive association.[55] They also note that 70% of patients in the Caribbean with sickle cell disease develop ulcers at some point. This is a markedly higher incidence than in the United States, where roughly 10% of homozygous patients are affected. This seems to suggest a genetic, environmental, or infectious component may be contributing.

The impact of leg ulcers on an individual patient can be simply devastating. A series of 20 patients with a history of sickle cell-associated ulcers in France were followed and found to develop regional infections 85% of the time, ankle stiffness in 50%, and mood disorders in 85%. Ninety percent of patients needed analgesics, 20% being opioids. Median loss of time from work was 12.5 months. The Short Form 36 Health Survey showed physical and mental component summary scores of 41.5 and 40.7, respectively, indicating severe alteration close to that found in lung cancer or hemodialysis.[56] This small study highlights the magnitude of impact of this disabling condition on the affected patient.

Regardless of the predisposition of the patient, once ulcers are present management currently differs little from non-sickle cell-associated lower extremity ulcerations. Ulcers are difficult to resolve effectively and the best therapeutic approach is currently unknown. Focus tends to be on antibiotic treatment of concomitant infections, protections from direct trauma/extreme temperatures, elevation, wet-to-dry dressings, debridement as needed, or the use of an Unna boot. An article published in 2010 reported on a small trial utilizing weekly arginine butyrate infusions that suggested improved healing of even quite chronic ulcers. Its use requires central venous access, which limited its use in some patients. Its proposed mechanism of action was theorized to be predominantly via the butyrate component via its stimulation of angiogenesis.[57] Recent advances were summarized in a review of the topic and include use of opioids for pain control, topical application of a platelet-derived growth factor, and the use of cultured skin grafts.[58] The same group reports no evidence to support hydroxyurea to promote healing, nor does their conclusion support transfusions as part of the approach to management.

PRIMARY CARE PEARL: The management of leg ulcers currently utilizes the same approach as other lower extremity ulcers: local wound care, avoidance of trauma, elevation, pain control, and treatment of infection.

Table 2: Health Maintenance Specific to Adults with Sickle Cell Anemia

Pharmacotherapy	
Prophylactic hydroxyurea	ongoing, if SS, S beta 0 thal, & symptomatic "milder" forms
Chelation therapy	ongoing, if elevated Ferritin
Ace inhibitor	ongoing, if microalbuminuria
Laboratory Monitoring	
On hydroxyurea: complete blood count, reticulocyte count	quarterly to semiannually, once stable
Liver function tests	semiannually
BUN/creatitine test	semiannually
Urine analysis and spot microalbumin	annual
Serum ferritin	annually
Exams/Studies:	
Dilated eye exams	annually
Routine dental care	semiannually
Pulmonary function testing	baseline, then as indicated
2D echo, EKG	baseline, then as indicated
Urology, if priapism present	ongoing
Vaccinations:	
Pneumococcal, meningococcal vaccines	once, repeat every 5 years?
Hepatitis B	complete series once
Influenza vaccine	annually

Gastrointestinal

The major gastrointestinal organs impacted in sickle cell disease are the spleen, gall bladder, and liver, in order of typical disorder presentation. There are rare reports of ischemic bowel problems but this is uncommon.

Acute spelenic sequestration crises are associated with high mortality and recurrences in sickle cell disease. In homozygous disease, most children are aspenic by early teens. Patients with SC or sickle beta plus thalassemia disease may still experience splenic sequestration and/or infarcts well into adulthood. A systematic review attempted to find reports in the literature on the impact of splenectomy on morbidity and mortality. Unfortunately, there were no trials to include in their study. The authors concluded that splenectomy prevented a reoccurrence of the acute sequestration episode, but the impact on overall morbidity and mortality is unknown.[59] Nonetheless, not performing a splenectomy increases the risk of mortality if further sequestration episodes occur. It certainly raises concerns for increased risk of infection with encapsulated bacteria in this population of patients. This

leads to the mandate to maintain immunizations and to re-vaccinate postoperatively. A specific interval of recommended boosters has not been determined.

Cholecystectomy is the most common surgical procedure in patients with sickle cell disease. Nearly half of homozygous patients, by some reports, develop actute cholelithiasis associated with bilirubin stones. The incidence is closer to one-fifth of sickle cell disease patients.[60] In either case, it was associated with a 70% greater length of stay and costs were 12% higher than for those without sickle cell disease by one study's report.[61] There is no evidence to support prophylactic cholecystectomy at this time.

The liver can suffer one of several complications in sickle cell disease. A descriptive review article in 2007 suggested that there are distinct patterns of disease including: hepatocellular necrosis, acute sequestration and cholestasis in the presence of sepsis, cirrhosis, chronic cholestasis, mechanical biliary obstruction, generalized cholangiopathy, and venous outflow obstruction. The authors found, with the use of biopsy-confirmed histology, that their patients' clinical pictures conformed poorly to the published descriptions of sickle cell-associated liver disease. Currently, clinicians mainly are left with supportive care of acute infarctions, acute hepatic sequestration crisis, and acute crisis associated cholestasis. The long-term management of sickle cell complications has yet to be determined.

PRIMARY CARE PEARL: Gastrointestinal involvement with sickle cell disease primarily involves supportive management of episodes of sequestration or cholestasis due to accelerated hemolysis. The may require transfusion support in collaboration with a hematologist. Surgical interventions are warranted in severe, recurrent splenic sequestration or infarct and in the case of cholecystitis.

Genitourinary

Priapism, prolonged painful erections, affects between one-third to one-half of all men with sickle cell disease. It is defined as acute fulminant if lasting longer than 6 hours or stuttering if occurring in repeated short episodes. A questionnaire of patients in five centers in the United Kingdom and Nigeria found 35% of 130 patients reported a history of priapism. The mean age of onset was 15 years. Sexual activity was the most common precipitating factor, followed by fever and/or dehydration. Twenty-one percent reported a concomitant history of erectile dysfunction and dissatisfaction with intercourse.[62] The most recent Cochrane evidence-based review found no studies to support alpha agonist use in acute, fulminant priapism although it is the current treatment of choice.[63] A 2008 review of stuttering priapism, the more common of the two types in sickle cell disease, summarizes mostly anecdotal reports regarding treatment. The main approach taken in the studies was prophylactic treatment in patients with frequent episodes that impacted quality of life. The studies mainly employed means to reduce circulating testosterone — oral bicalutamide, cyproterone acetate, and leuprolide acetate, all of which effectively "medically castrate" patients. Probably the most commonly utilized approach is administration of estrogens, commonly at stilboestrol or low-dose ethynyl estradiol. Both reported success in small trials. The authors comment that a surprising number of patients maintain their libido and erectile function while maintained on these agents.

Another approach has been to increase corpus cavernosum smooth muscle tone with digoxin, procyclidine (a muscarinic antagonist), pseudoephedrine, terbutalin, etilefrine (an alpha-adrenergic agonist), and phosphodiesterase type 5 inhibitors. All suggest benefits in very small series of patients. More invasive approaches discussed include intracorporal phehylephrine delivery systems, arterial embolisation if high velocity flow fistula are identified, or penile prosthesis implantation. The authors conclude that the first-line agents currently are either the antiandrogens or LH-RH analogues.[64] Another group reviewed the indication for blood transfusion therapy in the face of priapism and found no support for this approach.[65] The earlier cited questionnaire-based study found exchange transfusion the most frequently implemented therapy by hematologists at their centers.[62]

It seems prudent for the primary care physician to take a proactive approach to priapism in the sickle cell patient. One group of UK researchers found it to be common for patients to wait to disclose the onset of priapism. The reasons seem fairly intuitive: embarrassment or, in younger patients, lack of appreciation of what is normal sexual development.[66] This would imply that a conversation about the possibility of its occurrence may be of benefit, much at discussing sexual side effects of anti-hypertensives in the effective management of hypertension.

PRIMARY CARE PEARL: Talk with the patient openly about possibility of priapism, especially in teens and young adults. Approach to therapy is not evidence supported, but focuses on prophylactic alpha-blockers or anti-testosterone agents in those with recurrent symptoms.

Hematologic

In addition to the transfusion indications discussed elsewhere in this article, it is important to consider the general management of the anemia associated with sickle cell disease. It is also imperative to monitor and manage the secondary effects of its main therapy, transfusions.

A systematic review from the Cochrane Collaboration found no evidence to support the routine use of transfusions perioperatively, although well-done trials were lacking.[67] Nonetheless, the majority of homozygous patients receive a significant number of transfusions over their lifetime.

At a hospital in London, it was noted that 88% of red cell transfusions in sickle cell went to patients with this genotype.[68] Over that same

time period, 8171 units of blood were give, predominantly via the format of exchange transfusions.

A 2007 narrative review outlined when and where transfusions should be administered.[69] The authors point out that there are indications for both chronic and acute utilization of transfusion. Acute chapters of illness, stroke, or surgical intervention in which the patient is hospitalized or symptomatic would be indications for acute transfusions. Chronic indications in adults are all fairly controversial and include frequent pain crisis, acute pain crisis, recurrent acute chest syndrome, prevention/treatment of symptomatic pulmonary hypertension, priapism, pregnancy, chronic renal failure, and leg ulcers.

The decision of whether to provide simple transfusions of whole blood vs delivering the red cells through exchange transfusion is an area with little evidence to guide the practitioner. The basic theory is that when volume expansion would be detrimental to the clinic situation (for example cardiac dysfunction, acute chest syndrome, or high viscosity such as with high normal starting hematocrit), exchange transfusion is the recommended approach. It involves more support and blood products, even when utilizing an apheresis instrument, and, thus, is more costly. This tends to limit its frequent application in clinical practice. Again, the literature provides little evidence to guide therapy in this area, thus a hematologist should be consulted prior to determining appropriate application.

Finally, in the face of any proposed transfusion therapy flies the issue of eventual iron overload. The literature suggests the different hemoglobinopathies carry different complications and degree of iron overload. One multicenter study found that patients with thalassemia had a significantly higher rate of fractures than sickle cell disease patients with similar iron loads.[70] In a separate paper, the same group of investigators note that patients receiving transfusions are hospitalized more frequently. However, this does not confirm a relationship between these two factors, as disease severity may be greater in some aspect, which may be why the patient required the transfusion support originally.[71]

The medications available to manage iron overload include both oral (deferasirox) and intravenous (deferoxamine) chelation agents. A Cochran review found evidence to support equal short-term efficacy and safety of both agents. Long-term safety and efficacy of deferasirox were not available.[72] Numerous other studies in the literature reach similar conclusions and note the patients' preferences for the oral rather than IV delivery.[73-75] The literature provides no solid evidence on interval screening, target ferritin, or interval treatment monitoring (beyond those provided by the manufacturers).

PRIMARY CARE PEARL: When first confronted with a new comorbidity that may benefit from transfusions or iron chelation, consultation with a hematologist should be sought. Evidence to guide therapy in both this and the initiation of chelation are lacking at this juncture.

Musculoskeletal

During acute pain crisis, the most frequent patient complaint is bone pain. The marrow hyperplasia in sickle cell is a persistence of red marrow in response to the severe anemia unbuffered by fetal hemoglobin after infancy. Red marrow hyperplasia leaves this patient population at increased susceptibility to osteomyelitis and marrow infarcts. At a histopathological level, sickle cell-related osteonecrosis is characterized by diffuse necrotic lesions of bone trabeculae and marrow. Further, it is associated with inflammation and new bone formation. These changes are a direct consequence of chronic ischemia with ostoblastic activity overlay.[76]

Spinal vertebrae are a common site of infarction due to local microvascular occlusion of the vertebral arteries. This is coupled with marrow hyperplasia that displaces trabecular bone leaving the central vertebral body structurally weak. These in combination lead to the classic "fish-mouth" or "H-shaped" vertebra seen on plain x-rays. Accompanying the "H-shaped" deformities, adjacent vertebra may be of increased height, a phenomena known as "tower vertebra."[77] In addition, sickle cell anemia patients suffer a disproportionately high incidence of osteopenia, osteoporosis, and vitamin D deficiency. Finally, microvascular infarct of bone, dental caries,[78] and jaw infarcts are seen more frequently in this population. Jaw pain is known to be part of acute pain crisis, but its diagnosis is one of exclusion.

Although the vertebral bodies frequently are affected in acute pain crisis, the proximal femur or proximal humerus is the site of avascular necrosis. This is a frequent and severe complication of sickle cell anemia, but there are very limited data to guide therapy. Current literature found little evidence to support hip core decompression over physical therapy alone, but studies were extremely limited.[79-81] Duration of study follow-up ranged from 3 years in one study to 18 years in another. The longer study suggested that the eventual outcome is hip replacement, but that is frought with significant perioperative complications compared with the non-sickle cell patient.[82] Should surgical intervention be required, length of stay tended to be twice as long and expenses were 40% higher than for patients without sickle cell disease.[61] The main treatment goal is to maintain large joint mobility in the face of severe pain.

Finally, osteomyelitis is a bony complication seen in sickle cell patients. Traditionally found to be uniquely associated with salmonella, this infectious complication has extremely limited literature to guide the clinician's approach.[83] A recent prospective record review in the United Kingdom reported that one-third of the bacteremia cases in sickle cell patients were due to salmonella, and 60% of these developed joint involvement, most commonly osteomyelitis. The numbers were quite small, however, and some patients

Table 3: Current Evidence-based Sickle Cell Interventions in Adults

Recommended
• Polysaccharide pneumococcal vaccination
• Hydroxyurea
• Malaria chemoprophylaxis where endemic
Consider
• Zinc sulfate
• Patient-controlled analgesia
Unknown Benefit
• Penicillin prophylaxis over the age of 5 years
• Piracetam

had been in tropical regions prior to the infections.[84] Suggestions that sickle cell patients should be vaccinated against salmonella is not currently supported by any evidence.[85] There exist no specific guidelines on management of osteomyelitis in this patient population. The incidence of septic joint in patients with sickle cell anemia appears to be low and, if present, to be associated with osteomyelitis or osteonecrosis.[86]

PRIMARY CARE PEARL: Remain alert to the common complications of osteopenia/osteoporosis and accompanying vitamin D deficiency. No recommendations regarding routine screening exist at this time. Attention to persistent hip/joint pain (especially in hips and proximal humerus) is indicated to rule out avascular necrosis or osteomyelitis. Evidence in support of surgical interventions over physical therapy in large joint disease is difficult to find.

Neurologic

The neurologic complications of sickle cell disease range from stroke to peripheral neuropathy. Stroke is a particularly devastating complication in children, occurring at a rate of 1.02% per year between ages 2 and 5 years. Eleven percent of patients suffer clinically apparent strokes by age 20 and 24% by the age of 45.[87] Little has been defined in well-done studies regarding the specific pathophysiology or prevention of stroke in adult sickle cell patients. The traditional view is that vessels are narrowed, in this case, as a result of large vessel vasculopathy. A recent study involving 45 consecutive Amsterdam clinic patients with no vascular disease were studied regarding cerebrovascular CO2 vascular responsiveness. They found that there was a lower CO2 responsiveness in sickle cell disease patients regardless of degree of anemia or hemoglobin F level. The authors concluded that the vasodilatory capacity of the cerebral vasculature is impaired independent of markers of hemolysis.[88] The profound impact of stroke on this patient population has led to a significant amount of research in the pediatric population regarding treatment and prevention. Currently identification of high-risk patients rests on transcranial Doppler flow studies and treatment rests in overlapping transfusions and hydroxyurea treatment in children.[89] Studies of the adult sickle cell population in regard to management of the risk of stroke are less prevalent. A recently published study of asymptomatic adults with homozygous sickle cell disease and hemoglobin ≤ 10 mg/dL concluded that they had poorer cognitive performance than community-matched controls. This decline was associated with anemia and age. MRI could not explain the clinically observed difference, despite the fact that lacunar infarcts were more prevalent in those with sickle cell anemia.[90] A small retrospective review of a unit in the UK from 1995-2005 found 10 cases of vascular intracranial complications. Such occurrences were found only in homozygous sickle cell disease and were related to poor outpatient follow-up. The most common pathology was vaso-occlusive disease, followed by aneurismal subarachnoid hemorrhage. Seventy percent of patients had a previous cerebral infarct with residual deficit. The authors suggest screening with carotid dopplers and CT angiogram in their conclusions.[91] One recently published study looked at brain imaging results in 50 sickle cell disease patients; approximately half complained of headache and an additional one-fourth complained of hemiparesis/hypoesthesia. The findings revealed predominantly ischemic lesions as a clinically relevant finding. An additional 50% demonstrated low marrow signal intensity and thickness of the diploic space or cerebral atrophy.[92] A 2009 study conducted in Brazil examined the value of transcranial Doppler screening paired with MRI in adults with sickle cell disease. The authors evaluated 50 patients at their clinic and found more abnormalities on imaging than expected. Though lower than those described in children with sickle cell, transcranial Doppler velocities in adult patients with intracranial stenosis were consistently abnormal on screening. The authors conclude screening transcranial dopplers, paired with MRI screening, may help identify sickle cell patients at high risk for stroke.[93] To date, studies have not defined a good screening approach for for stroke for adults with sickle cell disease. Studies in children are ongoing and may provide some guidance in this area.

The most recent recommendations for prevention of stroke in sickle cell disease from the American Heart Association do not provide much stronger evidence or specific guidance. Again, recommendations made are based almost entirely on studies in children and relate to transfusions to maintain a percentage of hemoglobin S to < 30-50%. Additionally, they endorse the use of hydroxyurea and suggest a 3-year window for the transfusion therapy post-stroke. The guidelines recommend the general approach to strokes in non-sickle cell patients that focus on risk reduction (reduction of blood pressure, use of antiplatelet agents) and reflect an increasing interest in the possible benefit of statins in this population. They support bypass surgery in the case of advanced occlusive disease, as in the non-sickle cell population.[94] The current general clinical approach is to acknowledge the increased risk of stroke in adult patients with

sickle cell disease and to continue transfusions indefinitely post-stroke with the addition of hydroxyurea for stroke prevention remaining unproven. Utilization of bypass procedures, for example in the case of sickle-cell related Moyamoya disease, is considered. Again, most studies are ongoing regarding effectiveness of these approaches, and the majority are being conducted in children.

PRIMARY CARE PEARL: Sickle cell disease is a risk factor for stroke and many who have stroke do not have the constellation of typical vascular risk factors (for example, hypertension or dyslipidemia). Thus, the applicability of the American Heart Association guidelines is limited and the main therapy is chronic transfusions. The role of hydroxyurea in recurrent vasculopathy-driven stroke is not established.

Obstetric/Gynecologic

Although an important topic for the adult woman with sickle cell disease, the complete literature on gynecology and pregnancy was not reviewed for this article. Highlights relevant to the general practice of adult medicine will be reviewed.

Literature regarding contraception was notable for two substantial publications in support of progesterone for contraception in women with sickle cell disease. There is some suggestion that use of depo-medroxyprogesterone acetate may actually reduce pain crises.[95,96] Sickle cell disease is a known identifier for high risk in pregnancy. Miscarriages, pre-eclampsia, preterm delivery, low birth weight infants, and caesarean delivery are all more common in this group of mothers. A study of 500 patients prospectively followed at Duke, the University of North Carolina, and Emory over 5 years found nearly 30% risk of stillbirth, miscarriage, or ectopic implantation.[97] Prophylactic blood transfusions have not been found to negate the effect of the hemoglobinopathy.[98] In counseling adult women in primary care, it is helpful to be aware that adjusted odds of fetal death among deliveries to women with sickle cell disease is 2.2 times those among women without sickle cell disease.[99]

There is no current evidence on the best approach to management of acute pain crisis in the pregnant sickle cell patient and, thus, the usual approach is to treat as in the non-pregnant patient. Trials are limited because pregnant women are excluded from clinical trials studying narcotics as a treatment. The fact that morphine constricts the blood vessels in the placenta raises concerns of harm to the fetus with its use. Again, no studies are available, so conventional approaches usually are utilized (transfusions, oxygen as indicated by hypoxia, IV fluids, analgesic medications).[100] Hydroxyurea use is contraindicated in pregnancy. The management of chronic pain should be balanced with respect to well-being of the fetus in light of prolonged pain crisis vs narcotic withdrawal at birth. The use of prophylactic transfusions in one study seemed to decrease vaso-occlusive crisis but may have increased intrauterine growth retardation.[101] No evidence supports routine use at this time.

PRIMARY CARE PEARL: Pregnancy is a high-risk undertaking in the patient with sickle cell disease. The primary care physician should work collaboratively and early with a high-risk obstetrician and hematologist to maximize outcomes. Genetic counseling should be offered and encouraged so that patients are fully informed of the likelihood of sickle cell disease-affected children.

Ophthalmologic

Eye manifestations become more of a concern in the adult patient with sickle cell disease than they are in the pediatric population. Of interest, ophthalmologic complications are more common in the non-homozygous forms of sickle cell than in sickle cell disease.[102] The most discussed complication is proliferative sickle retinopathy. It is currently characterized as occurring in five stages: peripheral arterial occlusion, peripheral arteriovenous anastomoses, neovascular and fibrous proliferations, intravitreal hemorrhage, and retinal detachment.[103] Visual loss has been reported in up to 10% of patients, but few remain permanent. It remains unclear how to approach the sickle cell disease patient with proliferative retinopathy because up to a third of the time spontaneous regression occurs.[104] The primary modality studied has been photocoagulation, as is used in diabetic retinopathy. Some centers are exploring the use of scatter photocoagulation with promising results.[105] It is currently the standard approach to sickle cell retinopathy management. A recent review of traumatic hyphema concluded that patients with traumatic hyphema who receive aminocaproic acid or tranexamic acid are less likely to experience secondary hemorrhaging. However, hyphema in patients on aminocaproic acid took longer to clear and the evidence was limited.[106] While these approaches are being studied, the important role of annual eye exams for screening remains unchallenged. In light of the variety of ophthalmologic comorbid conditions, it is also prudent for the primary care physician to inquire about and refer any visual symptoms in adults with sickle cell disease. The complications that currently require surgical intervention are nonclearing vitreous hemorrhage, certain types of retinal detachment, and macular holes or pucker. Indications for surgery include vision loss or a threat to vision.[107]

PRIMARY CARE PEARL: Referral for annual screening for retinopathy by an ophthalmologist is standard of care in sickle cell disease.

Pulmonary

The pulmonary system is host to frequent complications of sickle cell, encompassing a range of problems from acute chest syndrome to pulmonary hypertension. Acute chest syndrome is the most common form of lung injury in sickle cell disease, occurring in one-third of all patients at some point. It is defined as the development of new pulmonary infiltrates involving at least one lobe that

is associated most frequently with fever and/or cough. It is the second most common cause of admission to the hospital in sickle cell patients and the second leading cause of death. The major causes of acute sickle chest syndrome are pulmonary infection, fat emboli, and acute sickling in the pulmonary vasculature, essentially pulmonary infarction. Its clinical course and presentation is quite similar to acute respiratory distress syndrome.[108] As noted earlier, certain phenotypes of patients are more likely to develop specific complications. There is an association of asthma with the development of acute chest syndrome. The adult patient with sickle cell disease with higher steady-state hemoglobin is more likely to develop acute chest syndrome, and the only proven preventive intervention to this date has been hydroxyurea.

Acute chest syndrome presents clinically with fever, leukocytosis, and cough, and typically occurs 2-3 days into the hospital stay for acute pain crisis. It can be subtle at onset and progress over the span of a few days. Its course is characterized by worsening shortness of breath, abrupt drop in previously higher hemoglobin, and a drop in platelet count to less than 200,000. Radiographically, lower lobe infiltrates develop in 92% of patients and exudative pleural effusions are present roughly one-fourth of the time. Hypoxemia may or may not be present and use of pulse oximetry is not an effective screening tool. Sputum cultures and blood cultures should be obtained, but brochoalveolar lavage usually is not indicated.[109] Infectious agents implicated include atypical bacteria, typical community-acquired bacteria, and viruses. *Chlamydia pneumoniae*, *mycoplasma pneumoniae*, and respiratory syncytial virus have been the most frequently isolated organisms. However, acute chest syndrome is a clinical diagnosis and cultures are usually negative. Clinical management includes cautious hydration to avoid worsening pulmonary edema, analgesia, oxygen therapy, antibiotic coverage, mechanical ventilation, and rapid simple or exchange transfusions.[108] To date, there is no evidence to support the use of transfusions, antibiotics, nitric oxide, or brochodilators due to a paucity of studies.[110-113] Steroids currently are not employed in its management. Transfusion or exchange transfusion tends to be employed in the face of a significant drop in hemoglobin or progressive worsening of the patient's condition. Again, no specific evidence-based guidelines exist regarding their use in acute sickle cell chest syndrome. Pulmonary and hematology consultants should be actively involved in their management. The mean length of hospitalization is roughly 10 days and overall mortality is 3%.[114] In follow-up, recurrent episodes of acute sickle chest resulted in significant reduction in lung function.[115] There is some discussion of the value of incentive spirometry in the prevention of acute chest syndrome.

A second pulmonary complication of sickle cell disease is pulmonary hypertension, which currently is believed to occur as a result of arteriopathy that complicates a chronic hemolytic state. The working hypothesis in the literature is that chronic hemolysis leads to depletion of nitic oxide at a microvascular level. A recent detailed critical review[116] raises many concerns with this theory and points out that evidence of this mechanism of injury is still just theory. Nonetheless, the adult patients most at risk for developing pulmonary hypertension in the face of sickle cell disease seem to be those with chronically high level hemolysis, age, renal and lung disease, hepatitis C, and chronic transfusions.[117] Risk also seems unrelated to acute chest syndrome episodes or acute pain crisis frequency. Studies suggest that up to 30% of adult sickle cell syndrome patients have pulmonary hypertension, the presence of which significantly increases their mortality rate.[118] Recent reviews suggest that the prudent clinician screen adult sickle cell disease patients with a transthoracic echo for possible pulmonary hypertension.[118,119] There is some disagreement as to what should be the true cutoff for tricuspid regurgitant jet pressure to define the disorder in adult sickle cell disease patients. It generally has been agreed upon to be a velocity of at least 2.5 m per second on a transthoracic echocadiography. In cases where there are questions, a pulmonary angiography remains the gold standard. Screening for possible contributing causes and/or aggravating factors is usual clinical care. In the sickle cell population, however, clear-cut contributors were not identified in recent study of 90 patients in the Netherlands. The researchers found no difference between sickle cell disease patients with and without pulmonary hypertension (diagnosed by transthoracic echocardiography). The screening tests included general laboratory testing, plain chest radiography, electrocardiography, high-resolution computer tomography of the thorax, pulmonary function testing, and plasma N-terminal brain natriuretic peptide and brain natriuretic peptide. These findings led the authors to conclude that other avenues of defining this condition must be pursued.[120] Nonetheless, various therapeutic interventions for this common disorder are actively discussed in the literature. In a recent update in *Chest*, the authors said it requires a multi-faceted approach including optimizing SCD therapy (hydroxyurea, transfusion therapy), treating hypoxemia and thromboembolic disease, identifying and treating comorbid cardiopulmonary disease, and consideration of pulmonary vasodilators/anti-remodeling agents.[118] Recent studies continue to define baseline alterations in these patients that pharmacologic approaches could modify. One recent study of 76 patients noted that inflammatory markers are elevated in patients with pulmonary hypertension compared with sickle cell disease adults without pulmonary hypertension. Their suggestion was to pursue consideration of anti-inflammatories or anticoagulants.[121] There are ongoing trials of endothelin receptor antagonists that aim to decrease the

levels of this potent vasoconstrictor.[122,123] A group of researchers is studying the association between pulmonary hypertension and renal disease in these patients. The presence of either condition made the other much more likely in most studies. The fact that pulmonary hypertension in sickle cell disease is associated with a 40% 40-month mortality in the United States confers great significance to aggressive pursuit of treatment modalities.[124]

Finally, asthma must be mentioned as a common comorbidity with sickle cell disease. A group of researchers at Washington University found that asthma confers a two-fold higher risk of mortality to the patient with sickle cell anemia.[125] In a recent review article, the authors state that although the prevalence of asthma is 30-70% in sickle cell disease, there are no specific trials of management in this population. They suggest that given this prevalence, annual pulmonary function tests should be paired with an asthma questionnaire to facilitate earlier diagnosis. Once diagnosed, the current NIH guidelines for management, including aggressive control of inflammation that accompanies the disease, should be followed.[126] There also is solid evidence to support administering the polysaccharide pneumococcal vaccines to those with sickle cell disease. It has been shown to be safe and effective, although the follow-up immunization frequency still needs to be established in well-designed trials.[127]

PRIMARY CARE PEARL: Pulmonary complications are one of the top two systems leading to mortality. It is key to suspect acute chest syndrome early on and aggressively treat it with the help of pulmonary or critical care. Pulmonary hypertension and asthma both significantly add to morbidity and mortality. Some suggest routine PFTs, but at a minimum, active inquiry about worsening dyspnea or fatigue should cue further studies and referral if determined to be present.

Renal

Sickle cell disease has a myriad of expressions with regard to renal complications. The potential complications range from microhematuria to gross hematuria with papillary necrosis, microalbuminuria to frank nephrotic syndrome, recurrent urinary tract infections to pylenophritis, and acute to chronic renal failure. Hyposthenuria is also an identified complication. A database review in the mid-1990s revealed that 0.11% of patients in ESRD therapy suffered from sickle cell disease.[128] Their mean age at presentation was 40.68 $\pm$ 14 years. A patient with sickle cell disease and ESRD had a higher mortality risk than a patient with diabetes and renal failure. Interestingly, the authors discovered that when the models were adjusted for the disproportionate rate of renal transplantation in sickle cell, the increased risk did not persist. The majority of current studies are focused on understanding the evolution and management of nephrotic sydrome, as uniquely related to this disorder. The other listed complications are managed supportively at this juncture.

The theories underlying sickle renal glomerular disease abound. The current leading thought is that glomerular hyperfiltration develops in the face of chronic hemolysis. One example of this theory is a study of 280 patients with homozygous sickle cell disease at a center in Paris, which revealed a 50% prevalence of hyperfiltration. Half of those demonstrated either micro- or macroalbuminuria. The authors also noted that patients with lone hyperfiltration had lower than average hemoglobin and fetal hemoglobin levels. They conclude that this suggests hyperfiltration is attributable to hemolysis-associated vasculopathy, as opposed to vacosocclusive mechanism.[128] A separate set of authors studied patients with nephrotic syndrome and found an increasing risk with a decrease in red cell survival reflected by a ratio of mature red cells to reticulocytes.[129]

Two separate studies in the Jamaican population examined renal disease in sickle cell patients. In one study, glomerular renal disease was found to be more severe in homozygous sickle cell disease than in HbSC disease. The authors found lower hemoglobin and higher white cell counts coupled with hypertension suggested imminent renal disease. Hemolysis did not appear to play a role.[130] The second study further described the concept that since GFR is higher in sickle cell patients with renal disease, a lower normative creatinine should be established for these patients. A retrospective study involving MRI evaluation of the kidneys in 73 patients with thalassemia compared with 75 sickle cell patients revealed that iron was only present in the renal cortex of sickle cell patients and was unrelated to iron overload states. The authors conclude that this suggests renal iron is a marker for chronic hemolysis and not iron overload, as some had previously hypothesized.[131] Also, that renal disease in sickle cell is unrelated to transfusion history.

From a primary care point of view, there are only general recommendations in the literature, none of which have evidence of any rigor regarding screening or treatment of renal disease. The general commentary seems to be to monitor urine for albumin and to treat with an ace inhibitor when present. It seems prudent to seek nephrology collaboration in patients with nephrotic syndrome or elevated creatinine, especially adults older than 30.

PRIMARY CARE PEARL: There are no hard and fast rules for screening or management. Routine urine analysis and treatment with an ace inhibitor when albuminuria is present seems prudent. Involvement of nephrology, as with other patients with chronic renal disease, is appropriate.

Future Directions

The sickle cell story has been unfolding in its own unique way over the last 100 years. The hope is that those suffering with sickle cell will begin to have options that make a significant impact on improving quality of life. The developments in stem cell transplantation, chelation therapy, stimulants of fetal hemoglobin production, and small molecule

anti-inflammatory therapies all hold promise. The patients with this disabling, chronic disease have waited patiently to capture our attention, and it is very exciting to anticipate making a substantive impact on their disease and their suffering.

References

1. Serjeant GR. One hundred years of sickle cell disease. *Br J Haematol* 2010;151:425-429.
2. Hassell KL. Population estimates of sickle cell disease in the U.S. *Am J Prev Med* 2010;38(4 Suppl):S512-21.
3. Bonds DR. Three decades of innovation in the management of sickle cell disease: The road to understanding the sickle cell disease clinical phenotype. *Blood Rev* 2005;19:99-110.
4. Prabhakar H, et al. Sickle cell disease in the United States: Looking back and forward at 100 years of progress in management and survival. *Am J Hematol* 2010;85:346-353.
5. Ballas SK, et al. Definitions of the phenotypic manifestations of sickle cell disease. *Am J Hematol* 2010;85:6-13.
6. Rees DC, et al. Sickle-cell disease. *Lancet* 2010;376:2018-2031.
7. Driss A, et al. Sickle cell disease in the post genomic era: A monogenic disease with a polygenic phenotype. *Genomics Insights* 2009;2009:23-48.
8. Steinberg MH. Predicting clinical severity in sickle cell anaemia. *Br J Haematol* 2005;129:465-481.
9. Aisiku IP, et al. Comparisons of high versus low emergency department utilizers in sickle cell disease. *Ann Emerg Med* 2009;53:587-593.
10. Tanabe P, et al. Emergency department management of acute pain episodes in sickle cell disease. *Acad Emerg Med* 2007;14:419-425.
11. Lazio MP, et al. A comparison of analgesic management for emergency department patients with sickle cell disease and renal colic. *Clin J Pain* 2010;26:199-205.
12. Okumura MJ, et al. Comfort of general internists and general pediatricians in providing care for young adults with chronic illnesses of childhood. *J Gen Intern Med* 2008;23:1621-1627.
13. Aisiku IP, et al. Patient satisfaction in specialized versus nonspecialized adult sickle cell care centers: The PiSCES study. *J Natl Med Assoc* 2007;99:886-890.
14. Brousseau DC, et al. Acute care utilization and rehospitalizations for sickle cell disease. *JAMA* 2010;303:1288-1294.
15. Yusuf HR, et al. Emergency department visits made by patients with sickle cell disease: A descriptive study, 1999-2007. *Am J Prev Med* 2010;38(4 Suppl):S536-41.
16. Grosse SD, et al. Administrative data sets and health services research on hemoglobinopathies: A review of the literature. *Am J Prev Med* 2010;38(4 Suppl):S557-67.
17. McClish DK, et al. Pain site frequency and location in sickle cell disease: The PiSCES project. *Pain* 2009;145:246-251.
18. Bernard AW, et al. Best evidence topic report. Full blood count and reticulocyte count in painful sickle crisis. *Emerg Med J* 2006;23:302-303.
19. Mousa SA, et al. Management of painful vaso-occlusive crisis of sickle-cell anemia: Consensus opinion. *Clin Appl Thromb Hemost* 2010;16:365-376.
20. Okomo U, Meremikwu MM. Fluid replacement therapy for acute episodes of pain in people with sickle cell disease. *Cochrane Database Syst Rev* 2007;(2):CD005406.
21. Bartolucci P, et al. A randomized, controlled clinical trial of ketoprofen for sickle-cell disease vaso-occlusive crises in adults. *Blood* 2009;114:3742-3747.
22. Al Hajeri AA, et al. Piracetam for reducing the incidence of painful sickle cell disease crises. *Cochrane Database Syst Rev* 2007;(2)(2):CD006111.
23. Dunlop RJ, Bennett KC. Pain management for sickle cell disease. *Cochrane Database Syst Rev* 2006;(2):CD003350.
24. Gladwin MT, et al. Nitric oxide for inhalation in the acute treatment of sickle cell pain crisis: A randomized controlled trial. *JAMA* 2011;305:893-902.
25. van Beers EJ, et al. Patient-controlled analgesia versus continuous infusion of morphine during vaso-occlusive crisis in sickle cell disease, a randomized controlled trial. *Am J Hematol* 2007;82:955-960.
26. Solomon LR. Treatment and prevention of pain due to vaso-occlusive crises in adults with sickle cell disease: An educational void. *Blood* 2008;111:997-1003.
27. Tanabe P, et al. Adult emergency department patients with sickle cell pain crisis: A learning collaborative model to improve analgesic management. *Acad Emerg Med* 2010;17:399-407.
28. Smith WR, Scherer M. Sickle-cell pain: Advances in epidemiology and etiology. *Hematology Am Soc Hematol Educ Program* 2010;2010:409-415.
29. Nagalla S, Ballas SK. Drugs for preventing red blood cell dehydration in people with sickle cell disease. *Cochrane Database Syst Rev* 2010;(1):CD003426.
30. Bao B, et al. Zinc supplementation decreases oxidative stress, incidence of infection, and generation of inflammatory cytokines in sickle cell disease patients. *Transl Res* 2008;152:67-80.
31. Oniyangi O, Cohall DH. Phytomedicines (medicines derived from plants) for sickle cell disease. *Cochrane Database Syst Rev* 2010;(10):CD004448.
32. Davies S, Olujohungbe A. Hydroxyurea for sickle cell disease. *Cochrane Database Syst Rev* 2001;(2):CD002202.
33. Steinberg MH, et al. The risks and benefits of long-term use of hydroxyurea in sickle cell anemia: A 17.5 year follow-up. *Am J Hematol* 2010;85:403-408.
34. Ballas SK, et al. Hydroxyurea and sickle cell anemia: Effect on quality of life. *Health Qual Life Outcomes* 2006;4:59.
35. Ballas SK, et al. Hydroxyurea and acute painful crises in sickle cell anemia: Effects on hospital length of stay and opioid utilization during hospitalization, outpatient acute care contacts, and at home. *J Pain Symptom Manage* 2010;40:870-882.
36. Brawley OW, et al. National Institutes of Health Consensus Development Conference statement: Hydroxyurea treatment for sickle cell disease. *Ann Intern Med* 2008;148:932-938.
37. Berthaut I, et al. Influence of sickle cell disease and treatment with hydroxyurea on sperm parameters and fertility of human males. *Haematologica* 2008;93:988-993.
38. Ma Q, et al. Fetal hemoglobin in sickle cell anemia: Genetic determinants of response to hydroxyurea. *Pharmacogenomics J* 2007;7:386-394.
39. Lanzkron S, et al. Systematic review: Hydroxyurea for the treatment of adults with sickle cell disease. *Ann Intern Med* 2008;148:939-955.
40. Brawley OW, et al. National Institutes of Health Consensus Development Conference statement: Hydroxyurea treatment for sickle cell disease. *Ann Intern Med* 2008;148:932-938.
41. McGann PT, Ware RE. Hydroxyurea for sickle cell anemia: What have we learned and what questions still remain? *Curr Opin Hematol* 2011;18:158-165.
42. Anie KA, Green J. Psychological therapies for sickle cell disease and pain. *Cochrane Database Syst Rev* 2002;(2):CD001916.
43. Smith WR, et al. Understanding pain and improving management of sickle cell disease: The PiSCES study. *J Natl Med Assoc* 2005;97:183-193.
44. Smith WR, et al. Daily assessment of pain in adults with sickle cell disease. *Ann Intern Med* 2008;148:94-101.
45. Dampier C, et al. Health-related quality of life in adults with sickle cell disease (SCD): A report from the comprehensive sickle cell centers clinical trial consortium. *Am J Hematol* 2011;86:203-205.
46. Shaiova L, Wallenstein D. Outpatient management of sickle cell pain with chronic opioid pharmacotherapy. *J Natl Med Assoc* 2004;96:984-986.
47. Taylor LE, et al. A review of the literature on the multiple dimensions of chronic pain in adults with sickle cell disease. *J Pain Symptom Manage* 2010;40:416-435.
48. Niscola P, et al. Pain syndromes in sickle cell disease: An update. *Pain Med* 2009;10:470-480.
49. Manci EA, et al. Causes of death in sickle cell disease: An autopsy study. *Br J Haematol* 2003;123:359-365.
50. Fitzhugh CD, et al. Cardiopulmonary complications leading to premature

deaths in adult patients with sickle cell disease. *Am J Hematol* 2010;85:36-40.
51. Sachdev V, et al. Diastolic dysfunction is an independent risk factor for death in patients with sickle cell disease. *J Am Coll Cardiol* 2007;49:472-479.
52. Naoman SG, et al. Echocardiographic findings in patients with sickle cell disease. *Ann Hematol* 2009 Jun 2 [Epub ahead of print].
53. Oguanobi NI, et al. Electocardiographic findings in adult Nigerians with sickle cell anaemia. *Afr Health Sci* 2010;10:235-241.
54. Serarslan G, et al. High prevalence of pulmonary hypertension in homozygous sickle cell patients with leg ulceration. *Clin Exp Hypertens* 2009;31:44-48.
55. Clare A, et al. Chronic leg ulceration in homozygous sickle cell disease: The role of venous incompetence. *Br J Haematol* 2002;119:567-571.
56. Halabi-Tawil M, et al. Sickle cell leg ulcers: A frequently disabling complication and a marker of severity. *Br J Dermatol* 2008;158:339-344.
57. McMahon L, et al. A randomized phase II trial of arginine butyrate with standard local therapy in refractory sickle cell leg ulcers. *Br J Haematol* 2010;151:516-524.
58. Minniti CP, et al. Leg ulcers in sickle cell disease. *Am J Hematol* 2010;85:831-833.
59. Owusu-Ofori S, Riddington C. Splenectomy versus conservative management for acute sequestration crises in people with sickle cell disease. *Cochrane Database Syst Rev* 2002;(4):CD003425.
60. Ebert EC, et al. Gastrointestinal and hepatic complications of sickle cell disease. *Clin Gastroenterol Hepatol* 2010;8:483-489; quiz e70.
61. Dinan MA, et al. Outcomes of inpatients with and without sickle cell disease after high-volume surgical procedures. *Am J Hematol* 2009;84:703-709.
62. Adeyoju AB, et al. Priapism in sickle-cell disease; incidence, risk factors and complications — an international multicentre study. *BJU Int* 2002;90:898-902.
63. Chinegwundoh F, Anie KA. Treatments for priapism in boys and men with sickle cell disease. *Cochrane Database Syst Rev* 2004;(4):CD004198.
64. Muneer A, et al. Stuttering priapism — a review of the therapeutic options. *Int J Clin Pract* 2008;62:1265-1270.
65. Merritt AL, et al. Myth: Blood transfusion is effective for sickle cell anemia-associated priapism. *CJEM* 2006;8:119-122.
66. Addis G, et al. The physical, social and psychological impact of priapism on adult males with sickle cell disorder. *Chronic Illn* 2007;3:145-154.
67. Riddington C, Williamson L. Preoperative blood transfusions for sickle cell disease. *Cochrane Database Syst Rev* 2001;(3):CD003149.
68. Drasar E, et al. Blood transfusion usage among adults with sickle cell disease — a single institution experience over ten years. *Br J Haematol* 2011;152:766-770.
69. Josephson CD, et al. Transfusion in the patient with sickle cell disease: A critical review of the literature and transfusion guidelines. *Transfus Med Rev* 2007;21:118-133.
70. Fung EB, et al. Fracture prevalence and relationship to endocrinopathy in iron overloaded patients with sickle cell disease and thalassemia. *Bone* 2008;43:162-168.
71. Fung EB, et al. Morbidity and mortality in chronically transfused subjects with thalassemia and sickle cell disease: A report from the multicenter study of iron overload. *Am J Hematol* 2007;82:255-265.
72. Meerpohl JJ, et al. Deferasirox for managing transfusional iron overload in people with sickle cell disease. *Cochrane Database Syst Rev* 2010;(8):CD007477.
73. Vichinsky E, et al. Patient-reported outcomes of deferasirox (Exjade, ICL670) versus deferoxamine in sickle cell disease patients with transfusional hemosiderosis. Substudy of a randomized open-label phase II trial. *Acta Haematol* 2008;119:133-141.
74. McLeod C, et al. Deferasirox for the treatment of iron overload associated with regular blood transfusions (transfusional haemosiderosis) in patients suffering with chronic anaemia: A systematic review and economic evaluation. *Health Technol Assess* 2009;13:iii-iv, ix-xi, 1-121.
75. Taher A, et al. Efficacy and safety of deferasirox doses of > 30 mg/kg per d in patients with transfusion-dependent anaemia and iron overload. *Br J Haematol* 2009;147:752-759.
76. Mukisi-Mukaza M, et al. Histopathology of aseptic necrosis of the femoral head in sickle cell disease. *Int Orthop* 2011;35:1145-1150.
77. Serarslan Y, et al. Morphometry of the thoracolumbar vertebrae in sickle cell disease. *J Clin Neurosci* 2010;17:182-186.
78. Laurence B, et al. Sickle cell anemia and dental caries: A literature review and pilot study. *Spec Care Dentist* 2002;22:70-74.
79. Marti-Carvajal AJ, et al. Treatment for avascular necrosis of bone in people with sickle cell disease. *Cochrane Database Syst Rev* 2009;(3):CD004344.
80. Hernigou P, et al. The natural history of symptomatic osteonecrosis in adults with sickle-cell disease. *J Bone Joint Surg Am* 2003;85-A:500-504.
81. Neumayr LD, et al. Physical therapy alone compared with core decompression and physical therapy for femoral head osteonecrosis in sickle cell disease. Results of a multicenter study at a mean of three years after treatment. *J Bone Joint Surg Am* 2006;88:2573-2582.
82. Al-Mousawi FR, Malki AA. Managing femoral head osteonecrosis in patients with sickle cell disease. *Surgeon* 2007;5:282-289.
83. Marti-Carvajal AJ, et al. Antibiotics for treating osteomyelitis in people with sickle cell disease. *Cochrane Database Syst Rev* 2009;(2):CD007175.
84. Richards LH, et al. Community-acquired Salmonella bacteraemia in patients with sickle-cell disease 1969-2008: A single centre study. *Scand J Infect Dis* 2011;43:89-94.
85. Odey F, et al. Vaccines for preventing invasive salmonella infections in people with sickle cell disease. *Cochrane Database Syst Rev* 2009;(4)(4):CD006975.
86. Hernigou P, et al. Septic arthritis in adults with sickle cell disease often is associated with osteomyelitis or osteonecrosis. *Clin Orthop Relat Res* 2010;468:1676-1681.
87. Ohene-Frempong K, et al. Cerebrovascular accidents in sickle cell disease: Rates and risk factors. *Blood* 1998;91:288-294.
88. Nur E, et al. Cerebrovascular reserve capacity is impaired in patients with sickle cell disease. Blood 2009;114:3473-3478.
89. Verduzco LA, Nathan DG. Sickle cell disease and stroke. *Blood* 2009;114:5117-5125.
90. Vichinsky EP, et al. Neuropsychological dysfunction and neuroimaging abnormalities in neurologically intact adults with sickle cell anemia. *JAMA* 2010;303:1823-1831.
91. Liaquat I, et al. Paediatric and adult vascular intracranial complications of sickle-cell disease. *Acta Neurochir (Wien)* 2010;152:1175-1179.
92. Alkan O, et al. Cranial involvement in sickle cell disease. *Eur J Radiol* 2010;76:151-156.
93. Silva GS, et al. Brain magnetic resonance imaging abnormalities in adult patients with sickle cell disease: Correlation with transcranial Doppler findings. *Stroke* 2009;40:2408-2412.
94. Furie KL, et al. Guidelines for the prevention of stroke in patients with stroke or transient ischemic attack: A guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2011;42:227-276.
95. Legardy JK, Curtis KM. Progestogen-only contraceptive use among women with sickle cell anemia: A systematic review. *Contraception* 2006;73:195-204.
96. Manchikanti A, et al. Steroid hormones for contraception in women with sickle cell disease. *Cochrane Database Syst Rev* 2007;(2)(2):CD006261.
97. Adam S, et al. Surgical and obstetric outcomes in adults with sickle cell disease. *Am J Med* 2008;121:916-921.
98. Ngo C, et al. Pregnancy in sickle cell disease: Maternal and fetal outcomes in a population receiving prophylactic partial exchange transfusions. *Eur J Obstet Gynecol Reprod Biol* 2010;152:138-142.
99. Barfield WD, et al. Sickle cell disease and pregnancy outcomes: Women of African

descent. *Am J Prev Med* 2010;38(4 Suppl):S542-549.
100. Marti-Carvajal AJ, et al. Interventions for treating painful sickle cell crisis during pregnancy. *Cochrane Database Syst Rev* 2009;(1):CD006786.
101. Grossetti E, et al. Selective prophylactic transfusion in sickle cell disease. *Acta Obstet Gynecol Scand* 2009;88:1090-1094.
102. Fadugbagbe AO, et al. Ocular manifestations of sickle cell disease. *Ann Trop Paediatr* 2010;30:19-26.
103. Goldberg MF. Classification and pathogenesis of proliferative sickle retinopathy. *Am J Ophthalmol* 1971;71:649-665.
104. Downes SM, et al. Incidence and natural history of proliferative sickle cell retinopathy: Observations from a cohort study. *Ophthalmology* 2005;112:1869-1875.
105. Sayag D, et al. Retinal photocoagulation for proliferative sickle cell retinopathy: A prospective clinical trial with new sea fan classification. *Eur J Ophthalmol* 2008;18:248-254.
106. Gharaibeh A, et al. Medical interventions for traumatic hyphema. *Cochrane Database Syst Rev* 2011;(1):CD005431.
107. Elagouz M, et al. Sickle cell disease and the eye: Old and new concepts. *Surv Ophthalmol* 2010;55:359-377.
108. Gladwin MT, Vichinsky E. Pulmonary complications of sickle cell disease. *N Engl J Med* 2008;359:2254-2265.
109. Melton CW, Haynes J Jr. Sickle acute lung injury: Role of prevention and early aggressive intervention strategies on outcome. *Clin Chest Med* 2006;27:487-502, vii.
110. Alhashimi D, et al. Blood transfusions for treating acute chest syndrome in people with sickle cell disease. *Cochrane Database Syst Rev* 2010;(1):CD007843.
111. Al Hajeri A, et al. Inhaled nitric oxide for acute chest syndrome in people with sickle cell disease. *Cochrane Database Syst Rev* 2008;(1):CD006957.
112 Knight-Madden JA, Hambleton IR. Inhaled bronchodilators for acute chest syndrome in people with sickle cell disease. *Cochrane Database Syst Rev* 2003;(3):CD003733.
113. Marti-Carvajal AJ, et al. Antibiotics for treating acute chest syndrome in people with sickle cell disease. *Cochrane Database Syst Rev* 2007;(2):CD006110.
114. Vichinsky EP, et al. Causes and outcomes of the acute chest syndrome in sickle cell disease. National Acute Chest Syndrome Study Group. *N Engl J Med* 2000;342:1855-1865.
115. Knight-Madden JM, et al. The impact of recurrent acute chest syndrome on the lung function of young adults with sickle cell disease. *Lung* 2010;188:499-504.
116. Hebbel RP. Reconstructing sickle cell disease: A data-based analysis of the "hyperhemolysis paradigm" for pulmonary hypertension from the perspective of evidence-based medicine. *Am J Hematol* 2011;86:123-154.
117. Hagar RW, et al. Clinical differences between children and adults with pulmonary hypertension and sickle cell disease. *Br J Haematol* 2008;140:104-112.
118. Vij R, Machado RF. Pulmonary complications of hemoglobinopathies. *Chest* 2010;138:973-983.
119. Gladwin MT. Current and future therapies of sickle cell anemia: An historical perspective. *Hematology Am Soc Hematol Educ Program* 2008:176.
120. van Beers EJ, et al. Cardiopulmonary imaging, functional and laboratory studies in sickle cell disease associated pulmonary hypertension. *Am J Hematol* 2008;83:850-854.
121. Ataga KI, et al. Coagulation activation and inflammation in sickle cell disease-associated pulmonary hypertension. *Haematologica* 2008;93:20-26.
122. Minniti CP, et al. Endothelin receptor antagonists for pulmonary hypertension in adult patients with sickle cell disease. *Br J Haematol* 2009;147:737-743.
123. Barst RJ, et al. Exercise capacity and haemodynamics in patients with sickle cell disease with pulmonary hypertension treated with bosentan: Results of the ASSET studies. *Br J Haematol* 2010;149:426-435.
124. Klings ES. Pulmonary hypertension of sickle cell disease: more than just another lung disease. *Am J Hematol* 2008;83:4-5.
125. Boyd JH, et al. Asthma is associated with increased mortality in individuals with sickle cell anemia. *Haematologica* 2007;92:1115-1118.
126. Morris CR. Asthma management: Reinventing the wheel in sickle cell disease. *Am J Hematol* 2009;84:234-241.
127. Davies EG, et al. Pneumococcal vaccines for sickle cell disease. *Cochrane Database Syst Rev* 2004;(1):CD003885.
128. Haymann JP, et al. Glomerular hyperfiltration in adult sickle cell anemia: A frequent hemolysis associated feature. *Clin J Am Soc Nephrol* 2010;5:756-761.
129. Maier-Redelsperger M, et al. Strong association between a new marker of hemolysis and glomerulopathy in sickle cell anemia. *Blood Cells Mol Dis* 2010;45:289-292.
130. Asnani MR, et al. Higher rates of hemolysis are not associated with albuminuria in Jamaicans with sickle cell disease. *PLoS One* 2011;6:e18863.
131. Schein A, et a;. Magnetic resonance detection of kidney iron deposition in sickle cell disease: A marker of chronic hemolysis. *J Magn Reson Imaging* 2008;28:698-704.

CME Questions

1. The complications of sickle cell disease are primarily a result of:
   a. a genetic defect coupled with inflammatory mediators.
   b. high output cardiac failure.
   c. severe anemia.
   d. toxicity of medications used to manage pain.

2. The leading cause of death in sickle cell disease is:
   a. acute chest syndrome.
   b. hepatic failure due to iron overload.
   c. nephrotic syndrome.
   d. stroke.

3. The only evidence-based intervention in sickle cell disease is:
   a. chelation therapy in iron overload.
   b. early, aggressive treatment of pulmonary hypertension.
   c. hydroxyurea.
   d. prophylactic transfusion.

4. The largest impact on quality of life in sickle cell disease comes from:
   a. anemia-associated fatigue.
   b. inability to perform activities of daily living.
   c. medication side effects.
   d. poor control of chronic pain.

5. An important intervention to delay expression of eye disease in sickle cell disease is:
   a. annual dilated eye exam.
   b. control of blood pressure.
   c. screening for concomitant glaucoma.
   d. use of an ace inhibitor if concomitant renal disease.

6. Renal disease can be detected by:
   a. edema.
   b. muscle cramps.
   c. proteinuria.
   d. worsening hypertension.

7. Chelation therapy is primarily important in iron overload to:
   a. avoid early dementia.
   b. decrease acute pain crisis frequency.
   c. decrease the risk of end organ failure due to iron deposition.
   d. eliminate the risk for cardiomyopathy.

Primary Care Reports CME Objectives

Upon completion of this activity, participants should be able to:

1. Summarize recent, significant studies related to the practice of primary care medicine;
2. Evaluate the credibility of published data and recommendations related to primary care medicine;
3. Discuss advantages and disadvantages of new diagnostic and therapeutic procedures in the primary care setting.

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