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AHC Media

Adult Sickle Cell Disease

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The year 2010 marked the 100th anniversary since sickle cell disease was described by Dr. James Herrick in 1910.[1] Worldwide, it is the most commonly encountered genetic disorder. Annually, it afflicts an estimated 100,000 patients in the United States.[2] Currently one 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.

The history of sickle cell disease is a testimonial to the slow, tortuous approach to this public health problem 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]

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]

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] The spectrum of clinical outcomes (stroke, acute chest, avascular necrosis, etc.) cannot be explained by a single gene mutation alone.[7] Studies cited suggest a modulation of inflammation and cell-cell interaction that must be polymorphic in origin. Environment, genetic background, socioeconomic factors, and

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.

psychology all may play a role in phenotypic expression of individual disease activity.[7] Finally, there is a spectrum of disease seen in the various forms of sickle cell disease, sickle-thalassemia vs. homozygous sickle cell, implying 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

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.

Acute Pain Crisis

The most common clinical complication of sickle cell disease is the acute pain crisis. This resulted in an average of 197,000 emergency room visits annually between 1999 and 2007.[14]

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.[15] 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.[16] 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.[17] In addition to this testing, there are no data to support routine use of oxygen, IV hydration,[18] non-narcotic analgesia,[19] piracetam,[20] 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.[21] A recently published article on nitric oxide inhalation did not improve time to crisis resolution.[22] 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

lengths of stay and side effects (nausea and constipation) as well.[23] Many physicians seem hesitant to apply guidelines that support early, aggressive pain control for acute sickle cell crisis pain. 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.[10,11,24]

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.[25]

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.[26,27] The same may be said about phytomedicines (medicines derived from plants in their original states).[28]

The most encouraging work has been with the use of routine administration of hydroxyurea.[29] 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,[30] improve quality of life,[31] and improve overall total amount of narcotics used for pain control.[32] 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.[33] It currently is the only drug approved by the FDA for such use and its approval is only for use in adult patients.

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.[33,34] 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. 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.)

Use of hydroxyurea currently is considered the standard of care for patients with sickle cell anemia.[35,36]

Emergency Medicine Pearl: *The expected CBC and reticulocyte values in a patient with sickle cell anemia seen in the ED may be affected if the patient is on hydroxyurea. Similar to the advance given to asthma patients on ED discharge regarding discussing*

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

with their primary care physician the potential value of "controller" medications, patients with sickle cell disease who are not on hydroxyurea should be encouraged to discuss this potential treatment with the primary care physician.

Chronic Pain

One of the most frustrating and demoralizing struggles in the management of adult sickle cell disease involves the chronic pain so many patients manifest. Lack of information has led to poor management, expensive utilization of health care, and stigmatization of an entire subset of patients.[37]

A recent 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.[38]

Some centers are beginning to approach sickle cell-associated pain utilizing a palliative care approach. 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.[39] 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.

Emergency Medicine Pearl: *Sickle cell disease may result in chronic pain. If present, this should be acknowledged and address similar to other established pain syndromes. Long-acting analgesics may be appropriate in these patients.*

Cardiac

Historically, hematologic and infectious complications were a significant cause of premature death in patients with sickle cell disease. With advances in care, current causes of early death have shifted to cardiopulmonary causes. Nearly 30% of deaths in the five years between 2000 and 2005 were attributed to cardiopulmonary causes, none of which were identified as classic sickle cell-related complications.[40] This has created interest in the use of electrocardiography and echocardiography to identify risk factors for premature cardiac mortality and sudden death. While some risk factors have been identified, current studies do not provide specific treatment recommendations, 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.

Emergency Medicine Pearl: *Routine ECG, chest radiography, and echocardiography have no value in the ED assessment of sickle cell patients with acute painful crisis, but if available, abnormalities can be used to identify patients at increased risk for cardiac complications and sudden death.*

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. Studies note that 70% of patients in the Caribbean with sickle cell disease develop ulcers at some point.[41] 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. Patients with leg ulcers can develop infectious complications and are prone to ankle stiffness. These ulcers can be chronically painful, requiring long-term analgesic treatment. 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. 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.[42] There is no evidence to support hydroxyurea to promote healing, nor does their conclusion support transfusions as part of the approach to management.

Emergency Medicine Pearl: *Leg ulcers should be considered a potential source for localized or disseminated infections. If available, referral to an outpatient wound management program should be considered on ED discharge.*

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 splenic sequestration crises are associated with high mortality and recurrences in sickle cell disease. In homozygous disease, most children are asplenic by early teens. Patients with SC or sickle beta plus thalassemia disease may still experience splenic sequestration and/or infarcts well into adulthood. Splenectomy prevents a recurrence of the acute sequestration episode, but the impact on overall morbidity and mortality is unknown.[43] However, splenectomy 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 revaccinate postoperatively.

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. There is no evidence to support prophylactic cholecystectomy at this time.

The liver can suffer one of several complications in sickle cell 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.

Emergency Medicine Pearl: *Acute cholecystitis should be considered in the differential diagnosis in a sickle cell patient who presents with acute abdominal pain. The presence of other symptoms from an acute pain crisis may mask or mimic this diagnosis.*

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. The mean age of onset was 15 years. Sexual activity was the most common precipitating factor, followed by fever and/or dehydration.[44] 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.[45]

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. While exchange transfusion is frequently performed for priapism in patients with sickle cell disease, there is no good evidence to support its effectiveness.[46]

One group of UK researchers found it to be common for patients to wait to disclose the onset of priapism. The reasons seem fairly

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

Maintenance	Frequency
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	Annually
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, and consider repeating every 5 years
Hepatitis B	Complete series once
Influenza vaccine	Annually

intuitive: embarrassment or, in younger patients, lack of appreciation of what is normal sexual development.[47]

Emergency Medicine Pearl: *Acute priapism in sickle cell patients is treated with alpha agonists, similar to patients without sickle cell disease. Transfusions are often done, but have no proven benefit. Ask patients about symptoms of stuttering priapism, as prophylactic treatment initiated by their primary care physician may reduce recurrences.*

Hematologic

In addition to the transfusion indications discussed elsewhere in this article, it is important to consider the secondary effects of 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.[48] Nonetheless, the majority of homozygous patients receive a significant number of transfusions over their lifetime.

A 2007 narrative review outlined when and where transfusions should be administered.[49] The authors point out that there are indications for both chronic and acute utilization of transfusion. Acute 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.

Finally, any proposed transfusion therapy raises the issue of eventual iron overload. The literature suggests the different hemoglobinopathies carry different complications and degree of iron overload.[50]

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.

Emergency Medicine Pearl: *Emergency blood transfusions in sickle cell patients should be limited to situations with known benefit: 1) acute ischemic stroke, 2) acute chest syndrome, 3) emergency surgery when a patient already has marginal hemoglobin concentration, and 4) symptomatic anemia complicating an acute illness (e.g., myocardial infarction).*

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.

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 vertebrae may be of increased height, a phenomena known as "tower vertebrae."[51] 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,[52] and jaw infarcts are seen more frequently in this population.

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.

Finally, osteomyelitis is a bony complication seen in sickle cell patients. Traditionally uniquely associated with salmonella, 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 had been in tropical regions prior to the infections.[53] 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.[54]

Emergency Medicine Pearl: *Consider the possibility of avascular necrosis or osteomyelitis in sickle cell patients who present with localized joint or bone pain. The pain of an acute pain crisis may mimic or obscure these diagnoses.*

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.[55] 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. Studies of the adult sickle cell population in regard to management of the risk of stroke are

less prevalent. Screening with carotid Doppler, transcranial Doppler, CT angiography, and magnetic resonance angiography may be able to identify patients at risk for stroke. To date, most of these screening studies in sickle cell patients have been performed in children and an appropriate screening approach in adults has not been defined.

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 three-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.[56] 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.

Emergency Medicine Pearl: *Patients with sickle cell disease are at increased risk for stroke and this complication should be considered even in the absence of typical vascular risk factors (e.g., hypertension, diabetes, hyperlipidemia, etc.).*

Obstetric/Gynecologic

Two substantial publications support the use of progesterone for contraception in women with sickle cell disease.[57,58] There is some suggestion that use of depo-medroxyprogesterone acetate may actually reduce pain crises.[57,58] 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. Prophylactic blood transfusions have not been found to negate the effect of the hemoglobinopathy.[59]

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 opioids 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 (oxygen as indicated by hypoxia, IV fluids, analgesic medications).[60] Hydroxyurea use is contraindicated in pregnancy. The management of chronic pain should be balanced with 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.[61] No evidence supports routine use at this time.

Emergency Medicine Pearl: *Patients with sickle cell disease have an increased incidence of pregnancy complications. Standard approaches to treat an acute pain crisis are appropriate in the pregnant patient. If pregnancy is identified in the ED, the patient should be instructed to stop hydroxyurea if she takes that medication.*

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.[62] 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.[63] 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.[64] The primary modality studied has been photocoagulation, as is used in diabetic retinopathy. 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.[65] The complications that currently require surgical intervention are non-clearing vitreous hemorrhage, certain types of retinal detachment, and macular holes or pucker. Indications for surgery include vision loss or a threat to vision.[66]

Emergency Medicine Pearl: *Ophthalmologic complications are common in patients with sickle cell, especially involving the retina. Pharmacologic dilation of the pupil*

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

may be necessary to adequate visualize the patient's retina while in the ED.

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.[67] 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.[68] 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.[67] To date, there is no evidence to support the use of antibiotics, nitric oxide, or brochodilators due to a paucity of studies.[69-72] 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. The mean length of hospitalization is roughly 10 days and overall mortality is 3%.[73] In follow-up, recurrent episodes of acute sickle chest resulted in significant reduction in lung function.[74]

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 nitric oxide at a microvascular level. A recent detailed critical review[75] 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.[76] 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.[77] 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.[78]

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.[79] 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. Once diagnosed, the current NIH guidelines for management, including aggressive control of inflammation that accompanies the disease, should be followed.[80] There also is solid evidence to support administering the polysaccharide pneumococcal vaccines to those with sickle cell disease.[81]

Emergency Medicine Pearl: *Acute chest syndrome is not a typical ED presentation; it usually develops 2-3 days after hospital admission for acute pain crisis. However, some patients may delay seeking medical care until symptoms of shortness of breath develop, and then present to the ED. Shortness of breath, cough, fever, leukocytosis, and a drop in hemoglobin and platelet count from previous baseline ("relative cytopenia") are clues to this complication.*

Renal

Sickle cell disease is associated with a myriad of 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.

The theories underlying sickle renal glomerular disease abound. The current leading thought is that glomerular hyperfiltration develops in the face of chronic hemolysis.

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.[82] 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.

Emergency Medicine Pearl: *Because sickle cell patients have a higher incidence of renal complications, a simple "dipstick urinalysis" is useful when evaluating these patients in the ED.*

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.

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Physician 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. A 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. What is the value of the CBC and reticulocyte count in a sickle cell patient with an acute pain crisis?
   A. to detect the presence of bacterial infection
   B. as a screening tool for aplastic crisis
   C. to differentiate pain crisis from drug-seeking

D. to diagnose acute chest syndrome

5. 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

6. Most studies have found that patients with sickle cell disease have a higher rate of drug addiction than the general population.
   A. true
   B. false

7. Patients with sickle cell disease are at increased risk for sudden cardiac death.
   A. true
   B. false

8. Which of the following statements is *false* regarding biliary disease in sickle cell disease patients?
   A. Homozygous patients have about a 50% incidence of acute cholecystitis in their lifetime.
   B. Cholecystectomy is the most common surgical procedure performed in patients with sickle cell disease.
   C. Prophylactic cholecystectomy is recommended for asymptomatic gallstones in sickle cell patients.
   D. Gallstones in sickle cell patients are formed of bilirubin.

9. Which of the following statements is true regarding priapism associated with sickle cell disease?
   A. Acute priapism is more common than the stuttering variety.
   B. Acute treatment is with beta agonists.
   C. Exchange transfusions are beneficial in treating acute attacks.
   D. The mean age that this complication occurs is 15 years old.

10. Which of the following occurs with increased frequency in patients with sickle cell disease?
    A. asthma
    B. pneumonia
    C. pulmonary hypertension
    D. all of the above

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Adult Sickle Cell Disease

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

Health Maintenance Specific to Adults with Sickle Cell Anemia

Maintenance	Frequency
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	Annually
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, and consider repeating every 5 years
Hepatitis B	Complete series once
Influenza vaccine	Annually

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

Supplement to *Emergency Medicine Reports*, January 30, 2012: "Adult Sickle Cell Disease." *Author:* **Karen Kirkham, MD, FACP**, Associate Professor and Vice-Chair for Undergraduate Medical Education, Department of Internal Medicine, Boonshoft Wright State School of Medicine, Dayton, OH. *Emergency Medicine Reports' "Rapid Access Guidelines."* **Editors:** Sandra M. Schneider, MD, FACEP, and J. Stephan Stapczynski, MD. **Executive Editor:** Shelly Morrow Mark. **Managing Editor:** Leslie Hamlin. For customer service, call: **1-800-688-2421**.