EMERGENCY MEDICINE PRACTICE

AN EVIDENCE-BASED APPROACH TO EMERGENCY MEDICINE

Sickle Cell Disease And Other Hemoglobinopathies: Approaches To Emergency Diagnosis And Treatment

December 2001
Volume 3, Number 12

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CME Objectives

Upon completing this article, you should be able to:
1. explain the basic pathophysiology of sickle cell anemia and some of the more common variant hemoglobinopathies, with emphasis on the development of complications;
2. discuss current and developing treatments for the various complications of sickle cell disease;
3. discuss proper pain management strategies for patients with vaso-occlusive crises; and
4. describe the most common complications of sickle cell disease and their presentations.

Date of original release: December 1, 2001.
Date of most recent review: November 28, 2001.
See "Physician CME Information" on back page.

A 5-year-old boy is brought to the ED with joint pain and fever. His mom tells you he has sickle cell disease, and for the past few days the boy has had a cough and runny nose. The child looks well but has a temperature of 101˚F. You wonder, "Do I need a CBC with diff, chest x-ray, and UA? Or does this child just need some Tylenol?"

A 27-year-old man with frequent visits to the ED complains of his usual sickle pain in both knees. He is afebrile and non-toxic-appearing. Again, you wonder, "Is a shot of pain meds enough? Or do I 'round up the usual suspects' and get bloodwork (including a reticulocyte count) and start an IV?"

A 2-year-old boy with sickle cell disease presents pale and shocky. What's the next step?

SICKLE cell anemia (SCA) refers to a family of genetic disorders that results in the production of hemoglobin S. Thalassemia is a mutation that impairs the synthesis of hemoglobin but not its structure. Variants of both diseases exist, depending on the genotype. The most common hemoglobinopathies, in descending order of frequency, are sickle cell disease (SCD), hemoglobin S/C disease, sickle-beta$^+$thalassemia and sickle-beta^{0}thalassemia.[1]

While there are over 350 types of abnormal hemoglobins,[2] the most clinically important of these disorders is SCD. In the United States, one of every 600 people of African descent has SCD.[3]

The costs of caring for patients with SCD are significant. There were 75,000 hospitalizations per year between 1989 and 1993 for patients with

SCD, representing an annual cost of $470 million.[4] Patients with SCD are frequent users of the ED, as well. In one study of patients who came to the ED five or more times in a 12-month period, those with SCD had the highest likelihood of return visits of any group with chronic conditions—even more than those with renal failure or COPD.[5]

As a result of improved treatment, most patients with SCD survive long into adulthood, but they still encounter a lifetime of complications, including chronic hemolytic anemia, recurring bouts of pain, and other sequelae of vascular occlusion.[1] Children still die from the complications of SCD—mostly from infection, complications of acute splenic sequestration, or acute chest syndrome (ACS).

Patients who present to the ED with SCD offer several challenges to the treating physician. First and foremost is offering sufficient treatment for the patient's pain. Equally important, though, is determining the cause of the patient's pain. A diagnosis of SCD does not rule out other conditions; moreover, SCD predisposes its victims to certain complications that demand prompt and effective treatment. Finally, patient disposition must be handled carefully on a case-by-case basis. Despite the many challenges inherent in treating SCD patients, one thing is certain: As ED crowding increases, emergency physicians will play an ever-expanding role in the care of SCD patients.

This issue of *Emergency Medicine Practice* explains the basic terminology, pathophysiology, natural progression, and expected complications of SCA. Appropriately, the article emphasizes the ED evaluation and management of SCD.

Terminology

The hemoglobin molecule contains four heme units and four globin chains. There are four different types of globin chains: alpha, beta, gamma, and delta. Of the four globin chains, two are always alpha, and the other two are either beta (in normal adult hemoglobin—HbA), gamma (in fetal hemoglobin—HbF), or delta (in minor adult hemoglobin—HbA_2).[1]

SCD is a molecular disease. It results from a mutation that substitutes valine for glutamic acid at position 6 of the beta subunit to produce HbS. People who inherit the abnormal gene from both parents have the homozygous SS genotype and the most severe form of SCA. These patients produce no normal hemoglobin A, but instead produce mostly HbS and small amounts of HbF and HbA_2.[1,6] Those who inherit the gene from only one parent are heterozygous and have sickle cell trait. These patients usually have more than 80% normal hemoglobin, produce insignificant amounts of HbS, and usually remain asymptomatic.[7]

Hemoglobin C differs from HbS in the substitution of lysine rather than valine in place of glutamic acid at position 6. When it is combined with the HbS gene, it produces HbSC disease.[1] SCD may co-exist with various thalassemias. HbSC disease and the sickle-thalassemia variants are clinically less severe than SCA.

Historical Background And Prevalence

Though SCA and its variants have existed for a long time, it was not until 1910 that the first description of SCD was published, when James Herrick described a case in a 20-year-old dental student.[8] The sickle mutation is believed to have evolved due to the selective advantage afforded to the heterozygote carrier (the patient with sickle cell trait) to falciparum malaria. As mentioned, one of every 600 people of African descent in the United States has SCD.[3] Additionally, the disease is also found in people of Middle Eastern, Mediterranean, and Indian heritage.[6] Interestingly, the combined incidence of all sickle cell variants approximately equals that of SCD.[6]

Pathophysiology

When deoxygenated, the sickle hemoglobin forms polymers. This polymerization damages the erythrocyte cell membrane, causes premature cell death, and ultimately leads to accelerated removal of the red blood cell from the circulation.[9] Vaso-occlusion is the hallmark of SCD and is responsible for most of its significant complications. Due to the altered cell membrane and reduced deformability, the sickled cells coalesce and react with other blood cells and the vascular endothelium. This causes the characteristic "sludging" in the end-arterioles, resulting in microvascular occlusion and subsequent ischemia and acidosis. The acid environment promotes sickling of additional red cells and incites a worsening spiral. Other hemoglobins, specifically HbF, interfere with the polymerization of sickled cells, which helps terminate the cycle.[6]

Pain occurs when the inflexible sickled erythrocytes become trapped in the capillaries. This slows blood flow, which leads to hypoxemia and more sickling, creating a vicious cycle of infarction, tissue necrosis, and inflammation.[10] Infants younger than 6 months are typically spared because fetal hemoglobin (HbF) prevents the polymerization of HbS. When the level of HbF decreases (by 6 months of age), clinical complications begin.[10]

The other hematologic complications seen in SCD include acute splenic sequestration, chronic anemia, hyperhemolytic crisis, and aplastic crisis. The anemia of SCD is typically due to chronic hemolysis. The erythrocytes usually have a normal volume and hemoglobin concentration (normocytic and normochromic), but the plasma hemoglobin concentration is low (usually 7-8 g/dL). Most patients tolerate this degree of anemia well.

The immune defect in SCD appears to be specific for encapsulated organisms. This may be secondary to the loss of specific antibodies that normally are produced by the spleen.[11] Children with sickle cell have functional asplenia (> 90% by age 5) and can easily succumb to

septicemia from encapsulated organisms such as *Streptococcus pneumoniae*. As the person ages, the cause of bacterial infections changes from pneumococcus to gram-negative organisms such as *Escherichia coli*, *Klebsiella* sp., and *Salmonella* sp.[12]

Sickle Cell Trait And Other Hemoglobinopathies

Sickle Cell Trait

Nearly 2 million people in the United States have sickle cell trait (SCT).[13] SCT has little impact on overall morbidity and mortality, and patients who have it do not develop pain crises.[13] The most significant conditions include hematuria and hyposthenuria (inability to concentrate urine). While hematuria occurs more frequently in SCT patients compared to the general population, it is sufficiently rare that when it occurs, another cause should always be sought.[13] Hyposthenuria may lead to dehydration but is otherwise not clinically significant. The hypoxia of altitude exposure, as occurs with flights in un-pressurized airplanes, may result intravascular sickling.[13]

Hemoglobin SC Disease

HbC is a structural variant in which the normal glutamic acid at position 6 of the beta chain is replaced by lysine. When combined with the HbS gene, it is known as HbSC disease.[1] This condition is found in one out of 833 people of African descent.[6] Because the presence of HbC accentuates the deleterious effects of HbS, this makes HbSC disease a clinically significant disorder.[6] Red blood cell indices typically demonstrate a microcytic and hyperchromic picture.[14] When viewed under the microscope, these abnormal hemoglobins cause the red cells to fold over (resembling a taco).

All of the complications seen in SCD occur in patients with HbSC disease. Most of these complications are less frequent, less severe, and occur later in life when compared to SCA. The one exception is proliferative retinopathy, which is more common in those with HbSC disease.[6]

Thalassemias

Thalassemia refers to a group of conditions that result from a deficiency in the production of the alpha globin chain (alpha thalassemia) or beta globin chain (beta thalassemia). Several syndromes exist, with varying clinical severities. The superscript 0 indicates that no globin chains are produced, while the superscript + indicates that globin chains are produced, but at a reduced rate.[1]

The imbalance caused by decreased production of the affected chain leads to insoluble, nonfunctioning chains that precipitate in the red cell membrane. This causes severe, ineffective erythropoiesis, characterized by low reticulocyte count and marked bone marrow expansion. This bone marrow expansion causes hepatosplenomegaly, pathologic fractures, bone deformities, and paraspinal masses.

Beta thalassemia (also known as thalassemia major or Cooley's anemia) usually presents during the first year of life. These patients require chronic transfusion therapy to survive. Their life is complicated by growth failure, severe anemia, infections, endocrine dysfunction, and early death, most commonly due to cardiac disease.[15] Alpha thalassemia presents with chronic hemolytic anemia and all of the associated complications. The diagnosis and treatment of complications of the thalassemia syndromes are complex and should involve the patient's hematologist early in the course.

Epidemiology

The life expectancy for patients with SCD has significantly improved since the 1970s, when the median survival age was only 14 years.[16] Today, most people homozygous for the HbS gene live to their mid-40s. Still, children still experience a large proportion of the morbidity and mortality related to SCD.

In the largest epidemiologic study of SCD (the Cooperative Study of Sickle Cell Disease), researchers enrolled a total of 2824 patients younger than 20 years. They recorded 73 deaths, mostly in patients with hemoglobin SS. The peak incidence of death was between 1 and 3 years of age, and infection was the major cause of mortality. After age 10, cerebrovascular accidents and traumatic events caused more deaths than did infection.[17]

In another study of nearly 300 children with SCA, the authors examined the frequency of the main clinical events over several years. In this study, 172 patients (58%) experienced one or more painful sickle cell crises. Over 40% suffered acute chest syndrome, while the prevalence of meningitis / septicemia and osteomyelitis was 11.4% and 12%, respectively. Twenty patients (6.7%) developed stroke (peak prevalence at 10-15 years of age). Half of the patients had an episode of acute anemia due to either acute aplastic anemia or splenic sequestration.[18]

A larger study examined 694 children with sickle hemoglobinopathies over a 10-year period.[19] Painful crises and ACS were the most common sickle cell-related events. Bacteremia occurred most frequently in SS children under 4 years of age and in SC patients less than 2 years of age. Twenty children, all with HbSS, died (mortality, 1.1 deaths per 100 person-years). Infection (mostly from *Streptococcus pneumoniae* and *Haemophilus influenzae*) was responsible for 11 deaths. Two children died of splenic sequestration, one died of cerebrovascular accident, and six died of undetermined causes.[19]

It may be possible to predict at an early age which children are most likely to experience complications of SCD. In one cohort study, researchers found three characteristics identified before age 2 that predicted later adverse events. These included an episode of dactylitis before the age of 1 year, a hemoglobin level of less than 7 g / dL, and leukocytosis in the absence of infection.[20]

State Of The Literature

A recent review regarding the research on pain management in SCD suggests that the literature is weak. The authors note that most studies lack sufficient power to reflect treatment differences.[21]

The decision to order diagnostic studies in the patient with SCA is based more on tradition than on empiric data. Investigations regarding the association between hematologic parameters (such as the WBC count) and the need for admission are often flawed, as the physician is usually not blinded to the WBC count when deciding on admission. Thus, a high WBC count becomes a criterion for admission only because high WBC counts may worry some physicians (despite the lack of scientific correlation between outcome and these laboratory studies).

There are a number of published guidelines describing the management of patients with SCD, only a few of which are applicable to emergency medicine. One prominent guideline, published in 1999, is from the American Pain Society.[22]

In a survey of 550 emergency physician members of the Society for Academic Emergency Medicine, the authors found wide disparities in the approach to the patient with a painful sickle crisis.[23] Twenty percent used protocols for management of sickle cell pain. Meperidine and morphine (either IM or IV) were the most common initial analgesics given. In the routine management of uncomplicated sickle cell painful crisis, IV analgesics were employed by 67% of the emergency medicine physicians, IV hydration by 71%, oxygen therapy by 66%, and CBCs by 82% of respondents. About 30% "always or often" ordered a urinalysis, and about 20% routinely ordered a chest x- ray. Most emergency physicians practicing in teaching hospitals said they rarely or never treat patients with hemolytic, aplastic, or sequestration crises.

Differential Diagnosis

Patients who present with complication of SCD may have more problems than meet the eye. An underlying precipitant such as infection may lead to a painful crisis, or another pathological condition may mimic a painful crisis. For instance, sickle cell patients are at increased risk of osteomyelitis, most often caused by *Salmonella* species and *S. aureus*.[24] Patients with chest pain or cough may have pneumonia, ACS, or pulmonary embolism. The patient with abdominal pain may simply be suffering from a vaso-occlusive crisis or may harbor dangerous surgical pathology.

Painful Crisis, Bone Infarction, Or Osteomyelitis?

In all of these conditions, physical exam may reveal pain and tenderness over the affected area. Patients with a painful crisis generally have a normal body temperature and minimal to no soft-tissue swelling. In both bone infarction and osteomyelitis, patients may have fever and soft-tissue swelling. In general, the temperature in osteomyelitis is usually higher than in infarction.[25] While patients with either bone infarction or osteomyelitis may demonstrate elevated WBC counts and elevated sedimentation rates,[25,26] infarction is statistically about 50 times more common than infection.[27] Consider osteomyelitis when the patient has a high or persistent fever, leukocytosis over baseline, or unusual sites of pain.[6]

Cost-Effective Strategies For Patients With Sickle Cell Disease

1. Limit the use of oxygen.

Not every patient with a sickle cell crisis requires oxygen. Studies show no benefit to routine administration of oxygen.

Clinical Caveat: Be sure to give oxygen to those who need it—that is, in cases of respiratory distress, ACS, pneumonia, or those with pulse oximetry of less than 94%.

2. Use oral rehydration.

IV fluids should be reserved for those with evidence of dehydration or in those with persistent vomiting. Oral fluids may suffice for all other patients.

Clinical Caveat: Toxic or dehydrated patients, along with those with unstable vital signs, require intravenous hydration.

3. Limit bloodwork.

Apart from tradition, there are no good data to support (or refute) the use of a CBC or reticulocyte count in the evaluation of the afebrile adult patient with a painful crisis. However, if one is ordered, recognize that both the WBC count and platelet count are higher than normal in patients with SCA due to increased bone marrow activity from chronic hemolysis and autosplenectomy (platelets not able to be stored in the spleen).

Clinical Caveat: There are somewhat better data supporting the use of CBCs in children. Children are also the ones far more likely to suffer an aplastic crisis, so a measurement of the reticulocyte count may also be valuable. Many physicians routinely obtain a CBC and reticulocyte count in all patients who present with any form of sickle cell complication.

4. Treat pain aggressively.

This may be one of the most important cost-saving measures. Patients who receive early, aggressive therapy (usually IV morphine combined with sustained-release oral morphine at discharge) are less likely to require hospital admission. ▲

Imaging Approaches

The emergency physician has limited tools to distinguish bone infarction from osteomyelitis. Early in the course of illness, plain radiographs usually are not helpful in the patient with a painful extremity. This is because the destructive changes of osteomyelitis do not appear until 10-14 days after symptom onset.[25] MRI and CT have limited usefulness as well, as these studies are only positive when an abscess can be identified.[25]

The results of nuclear imaging can be confusing, as a hot or cold spot on a bone scan may be due to either osteomyelitis or infarction. One useful approach is to combine bone *marrow* scanning (99mTe-sulfur colloid) and 99mTc-MDP *bone* scan. An acute infarct will always show decreased marrow uptake. A normal marrow scan adjacent to a suspicious bone lesion is likely due to infection.[25,28] Most emergency physicians do not order bone or marrow scans on ED patients, leaving such decisions to the consultant.

The only definitive diagnostic test for osteomyelitis is a positive culture from blood or bone marrow aspirate. When in doubt, assume osteomyelitis until proven otherwise.

Joint Pain: Osteonecrosis, Painful Crisis, Or Septic Arthritis?

Osteonecrosis is a painful and often disabling complication of repeated bony infarctions. By age 35, half of all sickle cell patients have evidence of hip and shoulder osteonecrosis.[6] Patients complain of pain and/or limited range of motion of the affected joint. In the early stages of disease, radiographs will often appear normal,[29] although MRI may be diagnostic.[6]

The most important entity to rule out in a sickle cell patient with joint pain is septic arthritis. Suspect septic arthritis when joint pain is accompanied by fever, *significant* pain on range of motion, or erythema/edema involving the joint. Joint aspiration is the most vital (and the only definitive test) in such cases.

Abdominal Pain: Vaso-occlusive Crisis Or Intra-abdominal Pathology?

Abdominal pain in a patient with SCD can occur with a vaso-occlusive crisis, but a host of more serious intra-abdominal problems can mimic this condition. (See **Table 1**.) One study retrospectively examined findings in 53 patients with SCA who presented with abdominal pain.[30] A vaso-occlusive crisis was responsible for the pain in 57%, while 23% had a surgical entity and 20% had a nonsurgical genitourinary disorder. Overall, 77% of the patients with painful sickle crises—but *no* patient with an acute surgical process—complained of coexistent abdominal and remote (usually extremity) pain. In this series, all patients with a surgical condition complained of localized rather than diffuse pain. Of note, laboratory parameters, *including the leukocyte count,* did not distinguish sickle crisis from a surgical condition.[30]

Biliary tract and parenchymal liver disease are the most prevalent and serious complications that affect the digestive system.[6] Five hepatobiliary syndromes that are especially common include viral hepatitis, hepatic crisis, cirrhosis, cholelithiasis with or without cholecystitis, and intrahepatic cholestasis.[31] Of these, the most concerning diagnosis is intrahepatic cholestasis. It is characterized by sudden onset of severe right upper quadrant pain, progressive hepatomegaly, coagulopathy, and extreme hyperbilirubinemia.[28,31] Treatment is supportive, with transfusion and correction of coagulopathy. The mortality is very high.[28,32,33]

Cholelithiasis is frequent in sickle cell patients. Pigmented gallstones are the natural consequence of accelerated bilirubin turnover.[34] Gallstones, which may develop before 4 years of age,[35,36] occur in up to one-third of patients 2-18 years old[37] and in over 50% of the adults with SCD. Patients with gallstones tend to have biliary colic,[37,38] but true cholecystitis is rare.[6,36]

An enlarging liver, decreasing hemoglobin levels, and mildly elevated liver enzymes characterize acute hepatic sequestration (also known as hepatic crisis).[1] Treatment is supportive. Infectious hepatitis B or C can be contracted via transfusions, while cirrhosis may develop from either scarring or hemosiderosis.

There is more to the belly than the right upper quadrant, and patients with SCD may have other acute conditions that masquerade as a painful crisis. Even lead toxicity may be the culprit.[39] As an interesting aside, it appears that acute appendicitis is very unusual in

Table 1. Potential Causes Of Abdominal Pain In Sickle Cell Anemia.

Spleen
Sequestration
Hemorrhage
Infarction
Abscess
Hepatobiliary
Hepatitis
Cholelithiasis/cholecystitis
Hepatic sequestration
Intrahepatic cholestasis
Renal
Stone
Clot
Papillary necrosis
Cystitis
Bone
Infarction: ribs, spine, femoral head
Osteonecrosis
Vertebral collapse
Miscellaneous
Pneumonia
Mesenteric ischemia

Adapted from: Steinberg MH, Forget BG, Higgs DR, et al, eds. *Disorders of Hemoglobin*. Cambridge: Cambridge University Press; 2001.

patients with SCD. A recent review suggests that the likelihood of developing appendicitis in SCD patients is less than one-third of that for the population at large.[40] The authors suggest that surgical exploration "be limited to those with clear evidence of potential surgical pathology or progressive findings."[40]

Acute Chest Syndrome, Pneumonia, Or Pulmonary Embolism?

It is not possible to distinguish between infectious and non-infectious causes of ACS in the ED. For this reason, it is prudent to treat such patients with antibiotics while awaiting culture results.

The issue of pulmonary embolism is more of a "sticky wicket." Distinction between pulmonary thrombosis and embolism is difficult on clinical grounds, and V/Q scans rarely aid clinical evaluation because most sickle cell patients have chronic pulmonary abnormalities.[6,41]

Pulmonary angiography is problematic during an acute crisis due to its tendency to induce sickling,[42] but it may be necessary if the diagnosis is in doubt. While CT angiography is being used more frequently in an attempt to diagnose pulmonary emboli, there are few published studies of its use in patients with ACS.[43]

The Vaso-occlusive Pain Crisis

The pain of vaso-occlusive crisis in SCD can be excruciating and often debilitating. It is the most common reason for hospitalization in patients with SCD.[44,45] About 20% of sickle cell patients have frequent, severe crises that require parenteral narcotics and hospitalization. Forty percent rarely have a painful crisis, and the remaining 40% suffer a single painful crisis per year.[46] Patients with frequent pain episodes have a higher mortality.[46] Severe pain can occur at unpredictable intervals and in patients as young as 6 months of age.[10] Bone infarction is a common component of a vaso-occlusive pain crisis. The most commonly affected bones are long bones, but infarction can occur in the ribs, spine, sternum, skull, and clavicle.[29,47,48]

Infection, dehydration, physical or emotional stress, fatigue, cold, or high altitude may precipitate acute pain episodes. More frequently, there is no obvious precipitant, and attacks begin with little warning.

History

One of the most important questions to ask the patient with a painful crisis is "How much pain are you in?" This question is also relevant after every round of pain medication administered. Ask the patient to rate his or her pain upon arrival on a scale of 1 to 10 or on a visual analog scale (VAS). This provides an important baseline against which to judge the efficacy of ED treatment. One study showed that the use of self-reports of pain and a standardized analgesic protocol improved the management of painful vaso-occlusive crises in children and adolescents.[49]

During a vaso-occlusive crisis, pain is frequently widespread and often migratory. Determine the location of the pain, and ask if this is the same as the patient's "typical pain crisis." Common locations include the low back, femurs, hips, knees, abdomen, chest and head.[21] While it has not been closely studied, many authorities believe that deviation from the patient's typical pain may be a clue to either underlying infection or a second pathological process. In one small study on surgical illness in patients with SCD, a change in the pattern of the crisis was an important clue to surgical pathology.[50]

Vomiting is somewhat rare in children with a painful abdominal crisis. In one study, only 10 out of 106 children with a painful abdominal crisis had emesis.[51] During the patient interview, it may be helpful to explore other aspects of the present illness, including precipitants and associated complaints such as cough or fever.

The past medical history can also yield crucial information. Patients can often tell the physician which medicines in which amounts are most effective for their pain. Many can recite their last hemoglobin level, date of their last transfusion, and the nature of any prior complications. Determine whether febrile patients have received the pneumococcal vaccine and if they are chronically on an antibiotic such as penicillin.

Physical Examination

The general appearance of the patient can gauge the severity of illness. Signs of respiratory distress are ominous and may presage pneumonia or acute chest syndrome.

Pulse oximetry (the "fifth" vital sign) may be illuminating in those with chest pain, tachypnea, and those suspected of ACS. One recent study showed that while pulse oximetry underestimates arterial saturation, the bias is clinically insignificant.[52] However, another investigation suggests that pulse oximetry is often falsely low in SCD. In this study of 21 children, one-third of children who had normal oxygen saturation on blood gas analysis were falsely diagnosed as hypoxic by pulse oximetry.[53] The authors suggested that "making treatment decisions based on pulse oximetry data alone in patients with SCD who are not acutely ill may be inappropriate."

While many patients in significant distress may be tachycardic, lack of a rapid heart rate does not rule out the presence of pain. Hypotension in any ill patient is, of course, worrisome, but in the sickler it may represent sepsis or dehydration, while in the young child, it may represent splenic sequestration. Hypertension is rare in sickle cell crisis. In one review of over 450 ED visits for vaso-occlusive crises, no patient was found to be hypertensive.[54]

The head exam occasionally provides clues to complications of SCD. Scleral icterus may be chronic or appear with hyperhemolytic states. Ask the patient (or family members) if his or her eyes have gotten more

yellow over the past several days.

During examination of the chest, listen for rales or other abnormal lung sounds. The presence of adventitial sounds or signs of respiratory distress should prompt chest radiography. Cardiac murmurs are frequent in patients with SCD and do not necessarily indicate acute pathology.[55] In one series of 100 patients with SCD, nearly 80% had murmurs.[56]

Many patients have pain and tenderness as a component of their vaso-occlusive crisis. However, rigidity and rebound should always suggest an intra-abdominal process. In one retrospective review, 43 children with SCA presented on 106 occasions with an abdominal painful crisis (defined as abdominal pain during a vaso-occlusive crisis *without* other intra-abdominal pathology). Most of these children had normal bowel sounds and no guarding or rebound tenderness.[51] In another study, about one-third of patients with abdominal pain due to a painful vaso-occlusive crisis had distention and/or ileus.[57]

During the abdominal exam in young children, pay particular attention to the size of the spleen. A large spleen in a hypotensive child may be the best clue to acute splenic sequestration. Recognize, however, that splenomegaly is common in HbSC disease. In one study, 34% of children with HbSC had palpable splenomegaly at baseline.[58]

The extremity examination should target painful joints. In a vaso-occlusive crisis, the joint may be somewhat painful to move, but it should not be especially red, hot, or swollen. These findings suggest a septic joint or osteomyelitis. Infectious causes for the pain may be more likely if the pain is confined to a single site, especially if this is different from the patient's "typical" pain.[25] Never forget that you cannot palpate bone marrow; many patients will tell you the location of the pain, but palpation commonly does not elicit tenderness.

The neurological exam is most important for the patient with suspected cerebral thrombosis from sickling.

Diagnostic Studies

Two studies have examined the usefulness of obtaining routine chest radiographs and urinalyses on adults presenting to the ED in acute sickle cell pain crisis. The first was a prospective trial that evaluated patients more than 14 years old with sickle hemoglobinopathies who presented to the ED with a painful crisis. Seventy-one patients with 134 ED presentations were studied over a six-month period, and eight diagnoses of acute pneumonia and 10 diagnoses of urinary tract infection (UTI) were made. Eleven of these 18 infections (61.1%) had no clinical findings of bacterial infection. The authors concluded that in SCD patients with pain crisis, "Routine chest radiography and urinalysis may be clinically useful and cost-effective in the early diagnosis of crisis-related infection."[59]

However, a more recent study conflicts with these results. In this study, the authors examined 38 patients totaling 94 visits to the ED. Among patients with painful crises, six had pneumonia and three were diagnosed with a UTI. All six patients with pneumonia had signs and symptoms of pneumonia; however, two of three patients with UTI were asymptomatic. These authors concluded that chest radiography could be ordered on clinical grounds in patients with sickle cell pain crisis, but that routine urinalysis may be indicated.[60]

Radiography

Chest X-Ray

Most physicians order a chest x-ray based on a concerning history or physical examination. But is fever alone enough reason to order a chest film in a patient with a painful sickle crisis? A recent study would suggest that the answer is "yes." In this prospective study, 73 patients with SCD with 96 febrile events were evaluated over a one-year period. While 24% of the patients had evidence of acute chest syndrome on routine radiography, the emergency physician was able to predict fewer than 40% of cases based on the history and physical examination.[61]

Recognize that the baseline chest film of an adult with SCD is likely to demonstrate chronic changes such as lung fibrosis, large pulmonary arteries, and cardiomegaly.[62]

Abdominal CT Scan

Most sickle cell patients who present with abdominal pain require no diagnostic imaging. A history and physical examination alone can usually rule out serious abdominal pathology. However, the presence of local abdominal tenderness or peritoneal signs (especially when accompanied by fever) may require surgical consultation, diagnostic imaging, or both. In one review of 30 patients with worrisome clinical findings, CT proved a reliable diagnostic tool.[63] Other studies show that CT is especially useful in the diagnosis of splenic abscesses.[64]

Biliary Studies

Most patients with SCA will have gallstones. (Those that don't probably had a cholecystectomy.) Thus, the presence of gallstones on ultrasound should be accompanied by other findings of gall bladder inflammation (e.g., ductal dilatation, edema of the gall bladder wall, pericholecystic fluid) before making a sonographic diagnosis of cholecystitis. In one series, biliary studies (ultrasound and biliary scans) had a low positive predictive value for detection of acute biliary disease.[65] However, a normal biliary scan obviated the need for surgery in some patients.

Laboratory Studies

As many as 80% of emergency physicians order a CBC in the evaluation of patients with acute vaso-occlusive sickle-cell crisis. But what does the CBC tell us? How does it help in the decision-making process?

Surprisingly, there is little research devoted to this

question. In fact, there are no good studies that show a correlation between the afebrile patient with a painful sickle cell crisis and the need for admission. Furthermore, there are no good data to support that elevation of the white count or an abnormal differential indicates an infectious etiology in the afebrile (or even febrile) patient. Even those who champion the CBC as a diagnostic tool cannot provide an evidence-based number for an abnormal count. Recall that the average WBC count in children with SCD who are *not* sick or in crisis is 12,400/mm^3.[66]

One study examined the relationship between ED disposition and the CBC in patients presenting with painful sickle crisis.[67] Part 1 of this two-part study involved a retrospective chart review of patients with a sole ED diagnosis of acute sickle cell crisis, while part 2 prospectively evaluated consecutive patients presenting in painful crisis. In both parts, there was no difference between patients who were admitted to the hospital or discharged from the ED in regards to the hemoglobin level or reticulocyte count. In the retrospective arm, the mean WBC count did not differ between the admitted vs. released patients, but in the prospective arm, there was a difference between admitted (15,800/mm^3) compared to the released (12,800/mm^3) patients. However, in this study, the WBC count was shown to the emergency physician before they made the decision to admit.[67]

In one small series in children, an erythrocyte sedimentation rate (ESR) of greater than 50 seemed to correlate with the presence of severe infection; however, this finding has not been validated.[68]

Urinalysis

As noted, a urinalysis (dip or microscopic) may provide clues to asymptomatic bacteriuria in the patient with a painful sickle cell crisis. Recognize, however, that statistically, any sexually active male with pyuria is more likely to have a sexually transmitted disease than a true UTI.[69]

Treatment

Severe pain is an emergency. A recurring theme in the research on sickle cell crisis is that pain medicines are given too little, too late.[70] (See also the December 1999 issue of *Emergency Medicine Practice*, "Pain Management In The ED: Prompt, Cost-Effective, State-Of-The-Art Strategies.") Opioids are the drugs of choice for managing severe pain in the patient with SCD. They should never be withheld during an acute crisis for fear of producing drug addiction.

An interesting model involves treating sickle cell pain like cancer pain. One hospital evaluated its experience with IM meperidine (75-125 mg q3h) and short-acting oral opioids for the treatment of sickle cell pain. They later switched to an institutional protocol using IV morphine (5 mg initially followed by 5 mg/h, with appropriate dose adjustment) followed by oral controlled-release morphine. Using the new protocol, hospital admissions for sickle cell pain fell by 44%, while ED visits decreased by 67%.[71]

There are no good studies that show a clear superiority of one drug vs. another in the treatment of sickle cell pain, but on a theoretical basis, morphine may be one of the better choices (as discussed later in the text). For severe attacks, the preferred route of administration of opioids is IV, but many sickle cell patients have poor vascular access due to multiple previous IV lines. IM or subcutaneous opioids are reasonable alternatives in many patients. Those who present with early or moderate pain crises who are not vomiting may require only oral or IM medications.

In one study, a protocol that emphasized oral narcotic analgesia had a positive effect on resource utilization. Of the 100 adult sickle cell syndrome patients registered at a New York hospital, 15 were identified as "frequent users." Using an oral narcotic protocol, their frequency of admissions to the hospital dropped by 75% and significantly decreased the amount of narcotics dispensed in the ED.[72]

What Dose And How Often?

The dosing regimen should be individualized for each patient. The patient can often tell you how much of which drug he or she needs and how often it needs to be given. The starting dose, like with any narcotic, is determined by the intensity of the pain and prior analgesic history of the patient. For most narcotics, you can safely give one-half of the starting dose after each reassessment—even at intervals as often as every 30 minutes.[6] Fixed doses of opioids given at fixed intervals are often not effective because of individual variations in pain perception and opioid metabolism.

Patient-Controlled Analgesia

If a patient faces a prolonged stay in the ED, a patient-controlled analgesia (PCA) pump may be useful.[6] While few EDs routinely use this technology, at least one study showed that PCA pumps are safe and effective when used in ED patients with a painful crisis.[73] Multiple studies demonstrate the efficacy of PCA pumps in hospitalized patients with SCA, in both children and adults.[74-78] While the risk of meperidine-related seizures is low when it is given in isolated bolus injections, seizures may be more common if meperidine is administered in a PCA device in large or prolonged amounts.[79]

Adverse Effects

While respiratory depression is the most serious complication of opiate use, constipation is the most common adverse effect. However, respiratory depression is usually only seen in patients without previous significant opioid exposure and is usually preceded by sedation. Patients who have impaired respiratory function or asthma are at greatest risk of experiencing significant respiratory depression in response to the usual doses of drugs. In general, patients who frequently require

narcotics rapidly develop tolerance to the sedative and respiratory depressive side effects. While naloxone can reverse opioid-induced respiratory depression, it is indicated only for significant hypoventilation, as it may precipitate narcotic withdrawal.[6]

Morphine

Morphine is one of the most frequently used opioids in the treatment of a painful crisis. The duration of analgesia is 4-6 hours, and the starting dose is 0.10-0.15 mg/kg IV for children and 5-10 mg IV for adults (15 mg is generally the maximum initial dose). Some patients may experience rash, pruritus, hypotension, or GI intolerance.[29,80]

Morphine can be given by many different routes—IV, IM, oral, subcutaneous, or rectal.[81] One study compared oral controlled-release morphine in a dose of 1.9 mg/kg q12h to continuous IV morphine. In this double-blind, randomized, parallel-group study, the oral morphine proved a reliable, noninvasive alternative to continuous IV morphine in 56 children with vaso-occlusive crisis.[82] All children received an initial loading dose of IV morphine of up to 0.15 mg/kg followed by the oral preparation.

Meperidine

Meperidine is perhaps the most often prescribed opioid for acute sickle cell pain crisis, yet it has the worst pharmacological profile.[83] Due to its effect on serotonin release, meperidine may contribute to serotonin syndrome in patients taking selective serotonin reuptake inhibitors (such as fluoxetine [Prozac], paroxitine [Paxil], sertraline [Zoloft], and nefazodonehydrochloride [Serzone]), MAO inhibitors (such as phenelzine [Nardil]), fenfluramine (Pondimin), dexfenfluramine HCl (Redux), antihistamines, and carbidopa-levdopa (Sinemet). This can cause a life-threatening hyperthermia. Meperidine is highly psychologically addicting due to its serotonin enhancement characteristics. Guidelines from the American Pain Society suggest, "Meperidine should not be used if frequent large doses or long treatment durations are anticipated."(The authors rated the evidence for this as Grade B [i.e., moderate support in the literature].)[22] However, they did not caution against ED use.

Some authorities believe that meperidine should be avoided altogether in SCD patients.[84] They argue that repetitive dosing can lead to accumulation of its toxic metabolite, nor-meperidine, which can cause seizures. This accumulation is more common in patients with renal disease but can occur with repeated dosing in patients with normal renal function.[6,85] However, in one recent retrospective study (examining a mostly pediatric population), meperidine-related seizures were rare, occurring in only 0.4% of patients and 0.06% of admissions.[86]

The starting dose is for meperidine is 1 mg/kg, preferably given intravenously. While some physicians fear larger doses of narcotics, one study of 72 ED patients 18-63 years old showed that respiratory depression did not occur in those who received anywhere from 1.5-3.0 mg/kg of IV meperidine.[87]

Fentanyl

Fentanyl is less often used to treat painful crises because of its relatively short duration of action. However, on the plus side, it does not produce the histamine release associated with morphine.[6] Dosing is typically 1-2 mcg/kg (that's *micrograms*) IV in children and 50-150 mcg IV in adults, depending on tolerance. Fentanyl has the uncommon but disturbing side effect of producing chest wall rigidity if given too quickly.

One small study examined the use of transcutaneous fentanyl in children with sickle cell crisis. While the transcutaneous fentanyl was not associated with any adverse effects, it was associated with a significant delay in achieving therapeutic levels.[88]

Nonsteroidal Anti-inflammatory Drugs

In the guidelines published by the American Pain Society, the committee suggested, "Pharmacological management of mild-to-moderate-pain should include nonsteroidal anti-inflammatory drugs (NSAIDs) or acetaminophen, unless there is a contraindication."[22] Furthermore, the authors designated this recommendation as having the highest level of evidence (Grade A) based on a review of the medical literature.

Several groups have examined the use of ketorolac (Toradol) in the treatment of vaso-occlusive crises. The data regarding its value are mixed. One prospective study examined the use of IV ketorolac and IV fluids in 51 children with 70 episodes of vaso-occlusive pain. IV ketorolac (0.5-1.0 mg/kg) resulted in adequate resolution of pain in 53% of episodes. However, children with four or more painful sites or those with an initial VAS score greater than 70 usually required additional IV analgesics.[89] On the other hand, in a separate placebo-controlled study of children with a painful crisis, ketorolac had no additional effect when given with a standard dose of IV morphine.[90] Other studies question the value of ketorolac in adults with vaso-occlusive crises. One series examined 18 adult patients who presented to the ED with sickle cell crisis pain a total of 24 times. These patients were randomized to either 60 mg of IM ketorolac or placebo in addition to a standardized dose of meperidine based on severity of pain. The use of IM ketorolac did not reduce the need for narcotics during the four-hour treatment period.[91]

While NSAIDs are frequently used to control pain in vaso-occlusive crisis, they carry certain risks. They may cause or contribute to renal failure, especially when used chronically. There is one report of irreversible renal failure attributed to IV ketorolac used in a child suffering from a painful crisis.[92] NSAIDs may also cause gastrointestinal bleeding, which can be especially dangerous for the patients with SCD, who typically suffer from baseline anemia.

Other Agents

While acetaminophen alone may be effective in the treatment of mild vaso-occlusive pain, it is unlikely that such mild symptoms would provoke a trip to the ED.

Adjunctive Therapies

Fluids

In some EDs, patients with a painful crisis routinely receive IV fluids. This may stem from from the belief that hydration increases circulating volume, thereby enhancing the flow of sickled RBCs through the vasculature. From this perspective, some authors suggest IV fluids, using D5 NSS or half normal saline as the initial fluid replacement. They reccomend giving one and one-half times the patient's daily fluid requirement over the course of the ED stay, or administering both replacement and maintenance fluid requirements.[29]

Finding scientific support for this approach remains a challenge, as the need for IV fluids in patients with a painful crisis remains unproven. A MEDLINE search reveals no randomized trials showing that IV fluids provide better outcome than oral fluids (or any additional fluids) in patients with a painful crisis. Aggressive IV hydration may enhance the risk for the development of non-cardiogenic pulmonary edema and/or acute chest syndrome in a patient with vaso-occlusive crisis.[93] In light of these considerations, one respected reference suggests that oral fluids are preferred over the IV route in patients with a painful crisis who have no overt evidence of volume depletion.[94]

Oxygen

The routine need for oxygen appears to be another myth of sickle cell treatment. Although deoxygenation induces sickling in vitro, no controlled clinical studies prove that oxygen administered in the ED improves outcome or pain control. Still, the practice of indiscriminately placing patients who are not hypoxic on oxygen persists. The best evidence would suggest that oxygen therapy be reserved for those patients who are hypoxic or have respiratory distress.

In one randomized, double blind, placebo-controlled study of O_2 vs. air, the use of 50% oxygen by facemask did not affect the severity or duration of pain.[95] Other studies show similar results.[96]

Oxygen therapy is not benign—it may produce undesirable effects such as depression of erythropoiesis during prolonged use.[6]

Steroids

At least one study has examined the impact of steroids on vaso-occlusive crises in children. In this randomized, controlled trial, 36 children and adolescents with SCD who had 56 acute episodes of severe pain were studied. The authors found that a short course of high-dose methylprednisolone (15 mg/kg of body weight, to a maximum of 1000 mg given on admission to the hospital and 24 hours later) decreased the duration of severe pain in children and adolescents with SCD. However, patients who received methylprednisolone had more rebound attacks after therapy was discontinued.[97] No follow-up studies have since been catalogued in MEDLINE.

Hydroxyurea

Hydroxyurea is a chemotherapeutic agent used in the chronic treatment of SCA. It primarily acts by increasing HbF concentrations and causes a small but significant rise in total hemoglobin.[3] Various studies in adults with SCA show that hydroxyurea reduces the frequency of pain crises, ACS, need for transfusion, and admission.[142] Similar results have been seen in limited studies with children.[3]

Hydroxyurea is not without its drawbacks. But more importantly, *there is no indication for starting hydroxyurea in the ED*. Its use is best reserved for hematologists.[3]

Indications For Admission

In one study that retrospectively examined 146 ED visits by 56 children with SCD, 73 (50%) were classified as "painful events," 43 (29%) as "febrile events," 20 (14%) as "painful and febrile events," and 10 (7%) as "other." Patients with recent onset of pain (< 24 hours in duration before the ED) were frequently hospitalized (P = 0.002). For children with febrile events, or painful and febrile events, the total WBC count and absolute neutrophil count were not associated with hospitalization.[98]

The need for admission depends on multiple factors, not the least of which is the severity of illness. (See **Table 2**.) However, other considerations such as the patient's social situation may be of nearly equal importance. If sent home, will they be able to return should they worsen? Do they have a phone to call 911? Do they have a friend or family with a car?

Table 2. Indications For Admission In Sickle Cell Vaso-Occlusive Crisis.

- Inability to control pain in ED
- Profound or persistent tachycardia
- Hypotension
- Temperature > 101˚F
- Significant infection
- Aplastic or hyperhemolytic crisis (acute fall of hemoglobin > 1 g/dL)
- Abnormal chest x-ray
- Prolonged priapism
- New CNS findings
- Acute abdomen
- Significant hypoxia or acidosis
- Pregnancy
- Hepatic syndrome or cholecystitis

Adapted from: Steinberg MH, Forget BG, Higgs DR, et al, eds. *Disorders of Hemoglobin*. Cambridge: Cambridge University Press; 2001; and Tintinalli JE, Ruiz E, Krome RL, eds. *Emergency Medicine: A Comprehensive Study Guide*. 5th ed. New York:McGraw-Hill; 2000. Note that these recommendations are not necessarily evidence-based.

The prudent emergency physician should also pay attention to the patient's concerns about the need for hospitalization and seek treatable precipitants of the crisis.

Complications

Acute Chest Syndrome

ACS is a descriptive term for an acute pulmonary illness in a patient with SCD. It comprises some combination of new pulmonary infiltrate, chest pain, fever, and hypoxia. In addition to these findings, the patient may present with cough, dyspnea, tachypnea, or wheezing.[99] ACS is the leading cause of death and second leading cause of hospitalization among patients with SCD.[100-102] While some patients present to the ED with ACS, many cases develop after a patient is hospitalized for a vaso-occlusive crisis.[103]

The etiology of ACS is multifactorial, and the pathogenesis, which may involve both infectious and noninfectious causes, is not completely understood. Commonly associated infectious agents include *Streptococcus pneumoniae, Haemophilus influenzae* and *Klebsiella pneumoniae*.[42] Other agents include *Chlamydia pneumoniae*, *Mycoplasma pneumoniae*, and respiratory syncytial virus.

In addition to infectious causes, lung infarction from in situ thrombosis or thromboembolism is thought to play a major role in the pathogenesis of ACS. Intravascular sickling likely causes most cases of pulmonary vascular occlusion.[104] Autopsy studies have identified particles of fat and bone marrow in these pulmonary thrombi, suggesting necrotic bone marrow as an embolic source.[105,106] Embolization from clots in the systemic veins is rare in sickle cell patients.[41] In one large study, fat embolism or in situ thrombosis/infarction was the likely etiology of ACS in almost 34% of patients, with or without co-existent infection.[103] Rib infarcts may also play a role in ACS. These infarcts produce local swelling and pleuritic pain, resulting in hypoventilation, atelectasis, and pneumonia.[28,107]

Adult patients with ACS tend to be afebrile, have severe pain, and often have multilobar disease combined with high mortality.[108] In contrast, children are more often febrile and usually present with cough without chest pain. Children with ACS typically have milder disease, usually due to infection.

While the chest film is important in diagnosing ACS, the initial radiograph is normal in almost half of patients who ultimately develop the syndrome.[42] Even when positive, chest radiography often underestimates vascular damage and accompanying physiologic derangement. The degree of hypoxia measured by pulse oximetry or by arterial blood gas is usually out of proportion to the findings seen on chest x-ray.[109]

Treatment

Despite the increased awareness of ACS, the diagnosis is often delayed and the optimal treatment remains unknown.[103] Early administration of broad-spectrum antibiotics, targeted toward both usual and unusual pulmonary pathogens, is reasonable. Inclusion of a macrolide or fluoroquinolone provides coverage for atypical organisms such as chlamydia or mycoplasma. Some authorities recommend routine treatment with bronchodilators. Incentive spirometry may help prevent or decrease the manifestations of ACS, especially among those with rib infarctions or atelectasis.[110]

One randomized, double-blind, placebo-controlled trial showed that IV dexamethasone (0.3 mg/kg q12h x 4 doses) had a beneficial effect in hospitalized children with mild to moderately severe ACS. Mean hospital stay was shorter in the dexamethasone-treated group, and the steroids prevented clinical deterioration and reduced the need for blood transfusions.[111]

Some patients with ACS require transfusions with leukocyte-depleted red blood cells with a goal to raise the hematocrit to no more than 30%-35%. More severely ill patients may require exchange transfusion to rapidly raise the hematocrit to greater than 35%. Anticoagulation is indicated when the diagnosis of thrombosis or embolism is strongly suggested based on a combination of clinical history and imaging studies such as CT or angiography. Consultation with a hematologist should be sought when indicated.

Dactylitis

Also known as hand-foot syndrome, dactylitis may be the earliest manifestation of SCD.[48,112] This condition is usually seen in children younger than 6 months of age, but can occur up to 4 years of age.[19,112] Physical exam reveals swelling of the hands or feet, pain, and fever. There may also be erythema, mimicking osteomyelitis,[113] and the WBC count and sedimentation rate may be elevated. Initial radiographs are normal, but radiographs taken several days after the onset of symptoms may show periosteal elevation. Treatment is supportive, with analgesia, hydration, and warm compresses. Symptoms are usually self-limited.[80]

Acute Splenic Sequestration

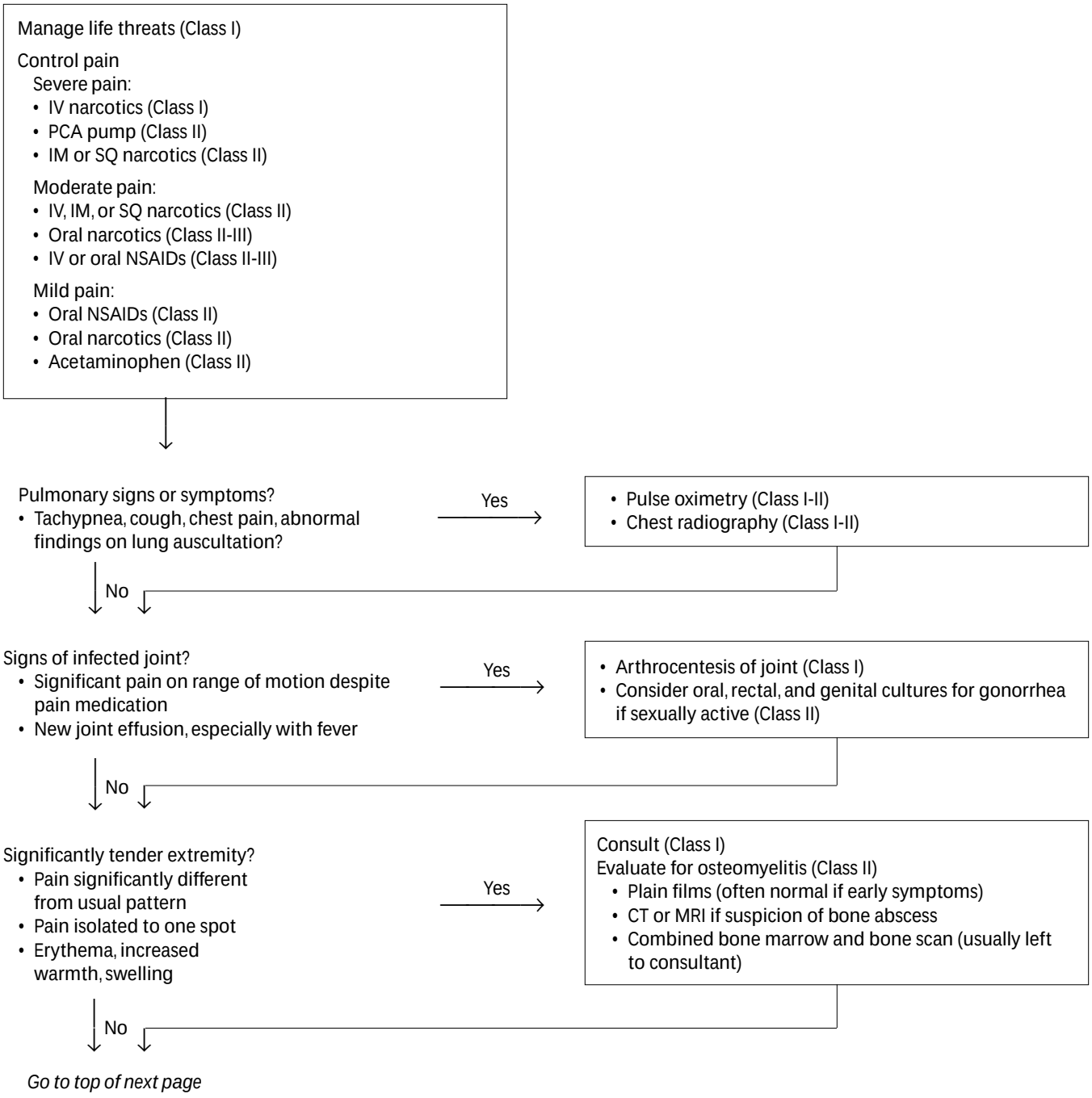
Acute splenic sequestration is a condition in which the spleen suddenly traps a large number of red cells. This causes severe anemia (decrease in hemoglobin by 20% or more), an enlarging spleen (by at least 2 cm from baseline), hypovolemia, and mild thrombocytopenia.[6]

The incidence of acute splenic sequestration peaks at 1-2 years of age[19] and is most common in children with HbS disease.[114] Children with HbS disease have a 30% probability of having an acute splenic sequestration event by age 5, and mortality can approach 15% per event.[115] On rare occasions, children with variant disease or adults with minor hemoglobinopathies can develop acute splenic sequestration as well.[28]

Acute splenic sequestration can recur. Up to 50% of

Continued on page 15

Clinical Pathway: Treatment Of A Painful Sickle Cell Crisis

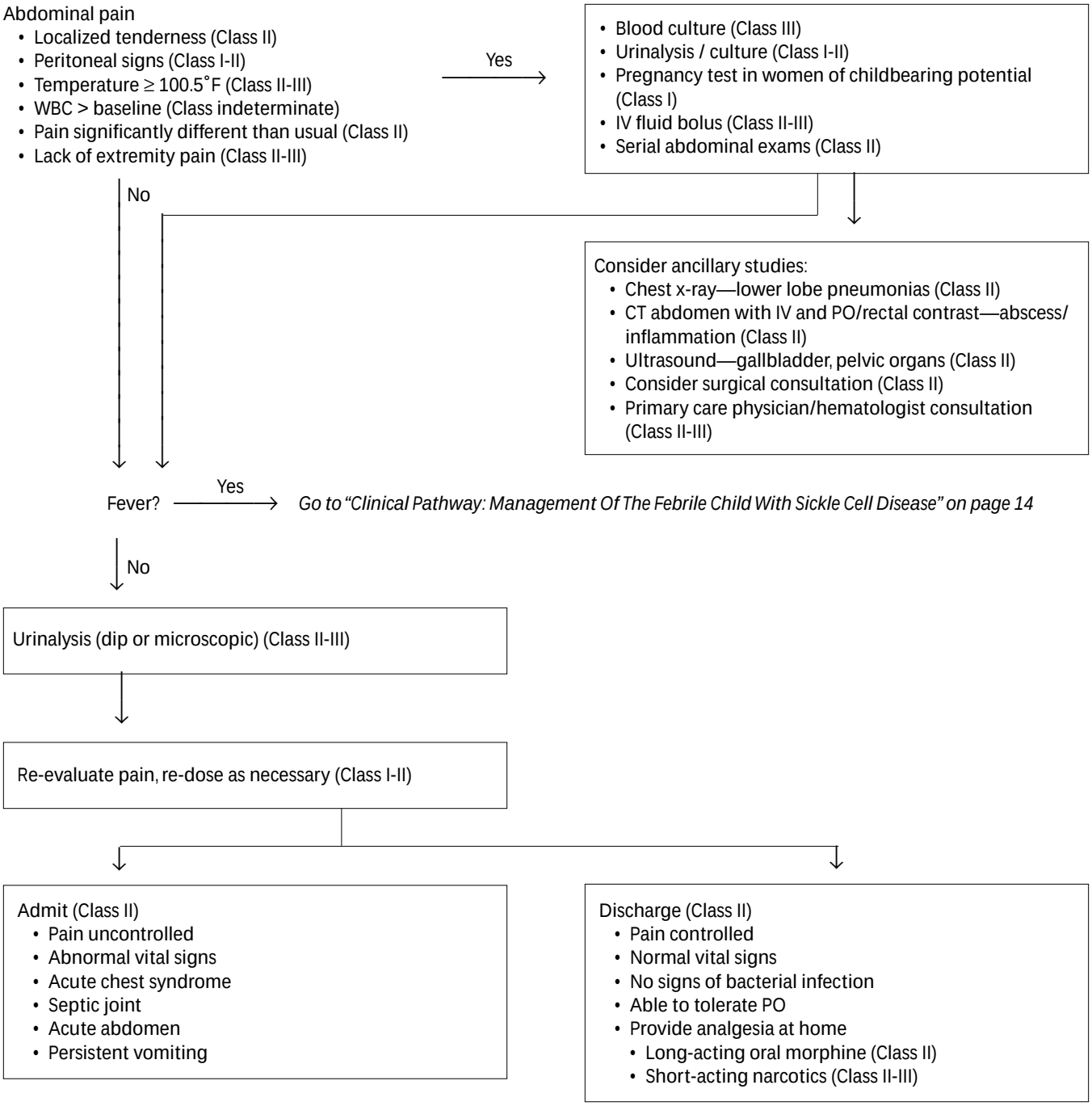


Go to top of next page

The **evidence for recommendations** is graded using the following scale. For complete definitions, see back page. **Class I:** Definitely recommended. Definitive, excellent evidence provides support. **Class II:** Acceptable and useful. Good evidence provides support. **Class III:** May be acceptable, possibly useful. Fair-to-good evidence provides support. **Indeterminate:** Continuing area of research.

This clinical pathway is intended to supplement, rather than substitute, professional judgment and may be changed depending upon a patient's individual needs. Failure to comply with this pathway does not represent a breach of the standard of care.

Clinical Pathway: Treatment Of A Painful Sickle Cell Crisis (continued)



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Clinical Pathway: Management Of The Febrile Child With Sickle Cell Disease*

Evaluate for source (clinical exam and diagnostic studies as needed)
- Acute chest syndrome
- Septic joint
- Osteomyelitis
- Meningitis

↓

- Chest x-ray (Class II)
- UA (Class I-II)
- CBC with differential (Class II)
- Blood cultures (Class II)

↓

- Temperature > 40˚C (104˚F)
- WBC count < 5000/mm^3 or > 30,000/mm^3
- Platelet count < 100,000/mm^3
- Hemoglobin level < 5 g/dL
- Pulmonary infiltrates
- Infants < 1 year with HbSS or sickle-beta thalassemia
- Aplastic crisis, splenic sequestration, acute chest syndrome, stroke, or priapism
- Dehydration or persistent vomiting
- Severe pain
- Toxic-appearing

Yes →

Admit (Class II-III)
- Give antibiotics to cover encapsulated organisms (ceftriaxone 50 mg/kg IV) (Class II-III)
- May substitute clindamycin 10-15 mg/kg IV for cephalosporin allergy (Class II-III)
- Consider adding vancomycin 10-15 mg/kg IV for severe illness or if CNS infection is suspected (Class II-III)

↓ No

- Follow-up ensured for next day?
- Family situation ensures compliance?

Yes →

Discharge (Class II)
- Give antibiotics to cover encapsulated organisms (ceftriaxone 50 mg/kg IV or IM) (Class II)

↓ No

Admit (Class II)
- Give antibiotics to cover encapsulated organisms (ceftriaxone 50 mg/kg IV) (Class II)

* Give antibiotics emergently—*before* obtaining diagnostic studies—if signs of toxicity or sepsis. (May draw blood cultures if done expediently.)

The **evidence for recommendations** is graded using the following scale. For complete definitions, see back page. **Class I:** Definitely recommended. Definitive, excellent evidence provides support. **Class II:** Acceptable and useful. Good evidence provides support. **Class III:** May be acceptable, possibly useful. Fair-to-good evidence provides support. **Indeterminate:** Continuing area of research.

This clinical pathway is intended to supplement, rather than substitute, professional judgment and may be changed depending upon a patient's individual needs. Failure to comply with this pathway does not represent a breach of the standard of care.

Continued from page 11

children will have a second episode, usually within two years.[116,117]

Presentation

The presentation of acute splenic sequestration is generally not subtle. Children will usually arrive in extremis—pale, tachycardic, and hypotensive. A massive spleen will dominate the belly. Diagnostic tests apart from a stat hemoglobin are generally unnecessary, but a bedside ultrasound of the abdomen could help rule out intraperitoneal fluid (if splenic rupture is suspected). Once the child is stabilized, CT scan of the abdomen may be helpful if the diagnosis remains in doubt or if there is concern for a splenic abscess.[118]

Treatment

Acute splenic sequestration is life-threatening. Because hypovolemic shock is more lethal than anemia, immediately give large amounts of IV crystalloid (20-40 cc / kg). After stabilization of blood pressure, begin the transfusion. Transfusion is not without risk, as an acutely enlarged spleen will release sequestered blood a few hours after transfusion. Hemoglobin can then rise dramatically, and the increased blood viscosity will worsen perfusion.[6] For these reasons, some experts suggest utilizing an exchange transfusion to avoid this complication in seriously ill patients with acute splenic sequestration.[83]

The goal of transfusion during acute splenic sequestration is to achieve a post-transfusion hemoglobin level of 6-8 g / dL. A useful guide for transfusion is as follows: Give a volume of red cells (in mL / kg) equal to the pre-transfusion hemoglobin level. For example, if the initial hemoglobin level is 4 g / dL, give 4 mL / kg of packed red blood cells initially.[6] Employ diuretics if hypervolemia or congestive heart failure develops post transfusion.

Splenectomy is not always indicated for acute splenic sequestration. Patients can often be managed with chronic transfusions until they become older than 3 years, at which time the risk of splenic sequestration will diminish. Partial splenectomy is also an option.[6]

Anemias In Sickle Cell Disease

Hyperhemolytic Crisis

Hyperhemolytic crisis (HC) involves a higher-than-normal rate of hemolysis and often occurs in conjunction with a vaso-occlusive crisis. It is occasionally precipitated by infection. Hyperhemolysis can also occur when an individual with SCA has a co-existent G6PD deficiency and is given certain medications, such as sulfa drugs or nitrofurantoin. In addition to pain, patients with HC may present with fatigue, increased scleral icterus, and jaundice.

On laboratory analysis, HC is characterized by a decrease in hemoglobin, higher-than-usual reticulocyte count, increased indirect bilirubin, and increased LDH.[1] HCs are typically self-limited,[1] but transfusion may be necessary for severe anemia.

Aplastic Crisis

During an aplastic crisis, there is a temporary arrest of red cell production; thus, reticulocytopenia (generally < 2%) is the hallmark of this condition. Patients will demonstrate a variable decrease in hemoglobin. Usually only erythropoiesis is affected, but neutropenia and thrombocytopenia are occasionally seen.[6] Aplastic crisis is often caused by parvovirus B19. In one study, 80% of such cases of aplastic crisis were associated with this organism.[119]

Aplastic crisis most commonly occurs in children and usually resolves spontaneously within 5-10 days. Treatment is mainly supportive, but transfusion may be necessary. Isolation is warranted to prevent contact with pregnant women and other sickle cell patients. Indications for transfusion include 25% or greater decrease in hemoglobin level from baseline with a low reticulocyte count and severe symptoms from the anemia.[120]

Other Forms Of Anemia

Megaloblastic anemia is sometimes seen in sickle cell patients and can result from folate deficiency. Folate becomes depleted as a result of enhanced erythropoietic activity from chronic hemolysis. Patients should be taking 1 mg of folate orally each day.[6] A microcytic anemia may reflect iron deficiency, especially in a menstruating female, a child with a period of rapid growth, or a co-existing thalassemia. Supplemental iron should not be given unless a deficiency is documented due to the possibility of iron overload.[6]

Transfusion Therapy

Patients with SCD are chronically anemic and typically have hemoglobins between 7 and 8. Because of physiologic adaptations, they tolerate the anemia well. On occasion, however, some patients with SCD will require transfusions in the ED or shortly after hospitalization. In one study of 520 transfusions in 197 patients, indications for transfusion included aplastic crisis (102), ACS (90), acute splenic sequestration (75), stroke (62), septicemia (46), hypoplasia (40), hypersplenism (34), surgery (31), gastroenteritis (10), and miscellaneous (30).[121]

When transfusing a patient with SCD, consider the need for special types of blood. *Leukocyte-depleted* packed red blood cell preparations are recommended, especially in children. These decrease febrile reactions, minimize allo-immunization to the human leukocyte antigen, and reduce the risk of cytomegalovirus transmission. Children who are candidates for bone marrow transplantation should receive irradiated cellular blood products whenever possible.[1,6]

Exchange transfusions involve replacing all or part of the patient's blood with stored blood. This is not generally an ED intervention. Exchange transfusions cause less iron accumulation, but because of the volumes involved expose the patient to greater risk of infection and allo-immunization. It requires central venous access and is more expensive than simple transfusion. Nevertheless, in the acute setting it avoids the potential problem

associated with increased blood viscosity that is sometimes seen in standard blood transfusions.

Some patients with SCD suffer an unusual and life-threatening hemolytic transfusion reaction when given blood.[122] Consultation with a hematologist and administration of IV immune globulin and steroids may be of value in such circumstances.[122]

Vichinsky offers a comprehensive review on transfusion issues in SCA in a recent issue of *Seminars in Hematology*.[123]

Fever In The Sickle Cell Patient

Fever is common in uncomplicated painful crises and does not necessarily indicate infection.[57] However, some patients with fever and SCD are infected and at high risk for morbidity or mortality, especially in the first several years of life. Perhaps 2%-6% of febrile children with sickle cell suffer bacteremia.[124,125] (See **Table 3**.)

One study reviewed febrile episodes in patients less than 17 years old with homozygous SCD who presented with an axillary temperature of 39.0˚C (102.4˚F) or higher. There were 165 events in 144 patients; bacteremia occurred in only in 10 (6.1%) and UTIs in four (2.4%). No child had meningitis. ACS was responsible in 36 (21.8%) events, and a painful crisis was the only pathology identified in 20 events (12.1%). (Some children had both infection and painful crisis.) It is interesting that painful crisis and ACS were the most common complications associated with high fever, while bacteremia and UTI were infrequent.[124]

Another retrospective study examined all children admitted to a children's hospital for SCD and fever over a 27-month period. Of 517 admissions, there were only 10 (1.9%) positive blood cultures. Positive cultures occurred more frequently in children less than 2 years old and in those with indwelling central venous catheters. All but one child with bacteremia had an ill appearance, a focus of infection, or a central venous catheter in place. In view

Table 3. Evaluation And Treatment Of The Febrile Child With Sickle Cell Disease.

This table was adapted from a set of guidelines for evaluation and management of febrile illness (temperature ≥101˚F [38.5˚C]) in children with SCD developed by The Joint Regional Hemoglobinopathy Conference held in 1999.[146] These guidelines were based on the consensus of the panel; the committee *did not* grade the levels of evidence for their recommendations. They recommended the following approach:

History and physical examination emphasizing:
- Vital signs
- Degree of pallor
- Evidence of systemic or localized infection
- Cardiopulmonary status
- Spleen size
- Neurological exam

Laboratory evaluation:
- CBC, differential, platelets, reticulocyte count, blood culture
- Type and crossmatch if extreme pallor, respiratory or neurological symptoms, or acute splenic enlargement are present
- Consider urinalysis and urine culture, CSF, or other cultures if clinically indicated

Chest x-ray and pulse oximetry (or ABG) if:
- High fever
- Toxic appearance
- Any respiratory symptoms
- Abdominal pain

Antibiotic therapy:
- Prompt administration of IV ceftriaxone (50-75 mg/kg, 2.0 g maximum single dose); may substitute IV clindamycin (10-15 mg/kg) in cephalosporin-allergic patients
- Consider adding IV vancomycin (10-15 mg/kg) for severe illness or if CNS infection is suspected
- Parenteral antibiotics should be given before other procedures, such as chest x-ray
- The presence of a focus of infection (e.g., otitis media) does not lessen the urgency of giving parenteral antibiotics

Adjunctive measures:
- Acetaminophen (15 mg/kg PO) and/or ibuprofen (10 mg/kg PO). (Avoid ibuprofen if history of gastritis, ulcer disease, or renal impairment.)
- May use oxygen by nasal canula or mask if signs of respiratory illness present
- Contact pediatric hematologist or patient's primary care physician

Disposition:
Admission guidelines:
- Infants < 1 year with HbSS or sickle-beta thalassemia
- Children with temperature > 40˚C, WBC > 30,000/mm^3 or < 5000/mm^3, and/or platelet count < 100,000/mm^3
- Signs of systemic toxicity
- Evidence of other acute complications, including severe pain, aplastic crisis, splenic sequestration, ACS, stroke, or priapism
- Concerns about compliance/follow-up

Discharge:
- Observe with repeat vital signs and assessment about two hours after the administration of ceftriaxone. If non-toxic and clinically stable with reliable family and hematologist/PCP approval, discharge with a specific plan for outpatient follow-up. Minimum follow-up includes phone contact the next day. Repeat exam and second dose of ceftriaxone 24 hours later may be advisable in some cases.

Adapted from: Lane PA, Buchanan GR, Hutter JJ, et al. SCD in children and adolescents: diagnosis, guidelines for comprehensive care and protocols for management of acute and chronic complications. Joint regional hemoglobinopathy conference. Mountain states regional genetics services network. 1999.

of their findings, the authors suggested that outpatient management strategies with antibiotics in selected children with SCD and fever merit further study.[125]

It would be nice if there were a laboratory test that could detect serious bacterial illness in children. Unfortunately, the CBC is not such a test. In one study, authors compared hematologic parameters in 23 children with SCD with proven bacterial infection (Group A) to those of 22 similar patients with fever but without evidence of bacterial infection (Group B).[126] The total WBC count and percentage of segmented leukocytes were similar in both groups. While the absolute band counts were often greater in the Group A patients, the sensitivity and specificity of elevated band counts were relatively low. The authors concluded that "No aspect of the CBC can be used to guide major management decisions in febrile children with SCA and potentially life-threatening infection."[126]

A study published by Williams et al examined the safety of outpatient treatment of selected children with

Ten Excuses That Don't Work In Court

1. "He just had a little cough, so I didn't think a chest film was warranted."

Acute chest syndrome is one of the most feared complications of SCD. Patients with pulmonary signs or symptoms, and those with fever, deserve a chest film.

2. "I know he had a fever of 103˚F—but his mom told me that little Johnny was sneezing the day before, so I didn't think bloodwork or antibiotics were indicated."

Infection is one of the major causes of death in children with SCD. Always assume a bacterial infection (or ACS) and evaluate with chest film and bloodwork. Well-appearing children with reassuring diagnostic studies can be discharged after receiving IM or IV ceftriaxone if next-day follow-up is arranged.

3. " I always use IM meperidine for people with SCD."

Hopefully not in those who are on dialysis! Meperidine has many shortcomings as an analgesic, and it may cause seizures in those with renal failure or insufficiency.

4. "He wasn't using his arm normally, but I thought it might be a peripheral nerve palsy."

Neurologic deficits in a patient with SCD should be assumed to be secondary to stroke unless the neurologic exam proves otherwise. Have a low threshold for CT scanning of the head.

5. "He had a painful knee! Lots of people with painful crisis have knee pain."

True. But they don't have fever, excruciating pain with range of motion, and an effusion. Ask patients if the pain they have today is the same as their usual pain. Be suspicious of pain isolated to one joint, especially if it's accompanied by abnormal physical findings.

6. "Who ever feels for a child's spleen?"

We all should. ASS, while rare, is a serious condition found in young children with SCD. The hallmarks include splenomegaly, anemia, and, often, unstable vital signs.

7. "I gave him antibiotics for his pneumonia and told him to come back if he had trouble."

Maybe that infiltrate was pneumonia, but maybe not. Patients who may have ACS should be admitted and given antibiotics, incentive spirometry, and perhaps steroids and nebulized beta-agonists.

8. "But I gave the child Rocephin before I sent him home."

Not every child with fever and SCD can safely go home. There are high-risk features of both the clinical exam and diagnostic studies that mandate admission. (See "Clinical Pathway: Management Of The Febrile Child With Sickle Cell Disease" on page 14.)

9. "SCA patients usually exaggerate their pain in order to get large doses of narcotics."

Patients with SCA have real pain. Similar to childbirth and renal colic, pain from this condition cannot be adequately understood by someone who has not experienced it. Do not let personal suspicion of drug-seeking behavior in a patient prevent giving pain relief to someone who is truly suffering.

10. "He just had some abdominal pain. Abdominal pain can be part of a painful crisis."

Yes, it can. But splenic abscess, pancreatitis, cholecystitis, appendicitis, and perhaps a hundred other diseases can cause abdominal pain in the patient with SCD. High-risk features of abdominal pain include localized tenderness, fever, peritoneal signs, and persistent pain despite hydration and opioids. Laboratory parameters, including a leukocyte count, may not distinguish a painful vaso-occlusive crisis from a surgical condition. In these cases, consider surgical consult or diagnostic imaging such as CT scan or abdominal ultrasound, depending on the location of the pain. ▲

SCA and fever. In the larger study, children from 6 months to 12 years of age with sickle hemoglobinopathies who had temperatures greater than 38.5˚C were randomly assigned to treatment as either inpatients or outpatients.[127] The authors excluded children whom they considered high risk from randomization. High risk was defined as having any of the following:

- Temperature > 40˚C (104˚F)
- WBC count < 5000 / mm^3 or > 30,000 / mm^3
- Pulmonary infiltrates
- Hemoglobin level < 5 g / dL
- Dehydration
- Severe pain

All patients received an initial IV dose of ceftriaxone (50 mg / kg), and those treated as outpatients returned 24 hours later for a second dose of ceftriaxone. Slightly more than 20% of the outpatient group required hospitalizations in the subsequent two weeks after treatment. All of these children did well, and most were hospitalized for reasons not directly related to their SCD. When compared to the inpatient group, outpatient treatment saved a mean of $1195 per febrile episode.[127] The authors also suggest that IM ceftriaxone could be substituted for IV medication based on the known pharmacokinetics of IM ceftriaxone.

A smaller, earlier study also showed that certain febrile children with SCD may be safely managed with parenteral ceftriaxone and outpatient therapy.[128]

Neurological Complications

Cerebrovascular disease is a devastating complication of SCD and is a leading cause of death in children and adults with the disease.[17,102] Vascular problems of the brain, primarily localized to the internal carotid, middle cerebral, and anterior cerebral arteries, are usually due to large-vessel disease.[129,130] Early in their lives, patients with SCD are at risk for infarction, but as they age, an increased risk of hemorrhage due to rupture of weakened collateral vessels develops.[131]

The Cooperative Study of Sickle Cell Disease followed more than 4000 patients with SCD over a 10-year period, producing valuable data on prevalence, incidence, and risk factors for stroke in sickle cell patients.[132] The overall age-specific incidence of first stroke in HbSS disease is 0.13% at ages less than 24 months, increases to 1% at age 2-5 years, then decreases to 0.79% at age 6-9 years. The risk remains low until a second peak after age 50, when the incidence rises to 1.3%. Hemorrhagic stroke was most common among patients 20-29 years old.[132,133]

Presentation And Diagnosis

Patients with SCD may present with a wide variety of neurological complaints, including headache, seizures, altered mental status, or focal neurologic deficits.[134] Those with significant findings generally require an emergent brain CT scan.

Treatment

Treatment of neurological complications of sickle cell depends, of course, on the particular disease, whether it be hemorrhage or ischemia. There have been few studies of stroke in patients with SCD, and these patients are usually not included in clinical trials that investigate the acute treatment of stroke.[133]

Studies show that transfusion therapy can *prevent* stroke in children with SCD who are at high risk for a cerebrovascular accident.[47,132,133,135,136] However, there are no data to suggest that it is useful in the acute setting.[133]

Thrombolytic agents for ischemic stroke have never been studied in the sickle cell population. Though considered by some to be the standard of care for acute ischemic stroke, the use of thrombolytics remains controversial in all subgroups, much less in SCD.

Genitourinary Complications

There are a number of genitourinary complications seen in SCA. The primary renal complications seen in SCD include hematuria, nephrotic syndrome, and, in rare circumstances, renal failure.

Hematuria is usually self-limited, resolving with bed rest alone. It may occur in those with sickle cell trait, and this diagnosis should be considered in the patient of African descent who presents with painless hematuria.[137] Transfusion may be needed if the hematuria is severe.[138] Years of glomerular hyperfiltration results in renal damage and the inability to concentrate urine, but chronic renal failure in SCD is uncommon overall.[6] A prospective longitudinal study followed a cohort of 725 patients with SCA and found chronic renal failure in only 4.2 %.[139]

The most important genital complication of SCD is priapism. Priapism occurs when sickled cells congest the corpora and prevent emptying of blood from the penis. It is a prolonged, usually painful penile erection not initiated by sexual stimuli.[140] The priapism that is seen in sickle cell patients is termed a “low flow” or ischemic priapism. Low-flow priapism is a time-sensitive emergency, as irreversible cellular damage and fibrosis can occur if treatment is not administered in 24-48 hours.[140] (A full discussion on priapism can be found in the November 2000 issue of *Emergency Medicine Practice*, “Male Genitourinary Emergencies: Preserving Fertility And Providing Relief.”) Treatment of priapism in sickle cell patients includes analgesia, hydration, oxygen, and, occasionally, exchange transfusion. These measures are successful in about 80% of patients.[141] If simple interventions fail, corporal aspiration and injection of a vasoconstrictor are occasionally successful in sickle cell patients.[141] Urology consultation is indicated.

Ophthalmologic Complications

The most serious ocular emergency in sickle cell patients is hyphema in the setting of trauma. The sickled cells tend to obstruct the flow of aqueous

humor and may result in elevation of intraocular pressure and subsequent acute angle closure glaucoma. If the intraocular pressure is 24 mmHg or greater in the setting of hyphema, treatment for acute angle closure glaucoma should be initiated. Urgent ophthalmologic consultation should be obtained in all sickle cell patients with hyphema.[115]

Disposition

Patients with a painful crisis may be discharged from the ED if their pain is controlled and there is no evidence of significant concomitant disease. Encourage them to follow up with their physician, and provide adequate oral analgesia. Patients with acute chest syndrome, splenic sequestration, or aplastic or hyper-hemolytic crisis will require admission to the hospital. Children and adults with fever are best managed depending on the clinical picture. Those at low risk of complications may be managed on an outpatient basis if close follow-up is ensured.

In addition to pain medications, consider suggesting that patients take over-the-counter zinc tablets. Two studies suggest oral zinc, given as 50-75 mg of elemental zinc daily, can decrease bacterial infections, hospitalizations, and the number of vaso-occlusive crises.[143,144]

Summary

SCA is a heterogenous set of conditions in which the severity of illness varies from person to person. Management of pain crises is often straightforward, but the astute clinician should be wary of complications. Various life threats can present at any time in a sickle cell patient. Emergency physicians should make sure they are well-equipped to manage the acute complications of this dreadful disease. ▲

References

Evidence-based medicine requires a critical appraisal of the literature based upon study methodology and number of subjects. Not all references are equally robust. The findings of a large, prospective, randomized, and blinded trial should carry more weight than a case report.

To help the reader judge the strength of each reference, pertinent information about the study, such as the type of study and the number of patients in the study, will be included in bold type following the reference, where available. In addition, the most informative references cited in the paper, as determined by the authors, will be noted by an asterisk (*) next to the number of the reference.

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Physician CME Questions

81. The most common reason for hospitalization in patients with SCA is:

a. vaso-occlusive pain crisis.
b. ACS.
c. aplastic crisis.
d. acute splenic sequestration.
e. cholecystitis.

82. Which of the following statements regarding pain control and adjunctive therapy in vaso-occlusive crisis is *false*?

a. Most patients know which drug and how much of it they require to control their pain.
b. Oxygen is only indicated for patients with hypoxia or respiratory distress.
c. Oral rehydration is acceptable in mild-to-moderate crises in a patient with poor vascular access.
d. Demerol is a poor choice for pain control in patients with SCD.
e. Most sickle cell patients are drug addicts.

83. Which of the following is the best test to determine whether a patient is having a vaso-occlusive crisis?

a. CBC with differential
b. Chest radiograph
c. Electrolytes
d. Reticulocyte count
e. None of the above

84. Which statement regarding acute splenic sequestration is true?
a. Acute splenic sequestration does not recur.
b. Acute splenic sequestration is not seen in any of the other hemoglobinopathies aside from HbS disease.
c. Acute splenic sequestration is more common in children than adults.
d. Transfusion should be given to correct the hemoglobin to 10 g/dL or greater.
e. Splenectomy is always indicated.

85. Which of the following statements regarding ACS is correct?
a. Pediatric patients have a more severe course than adults do.
b. Only a few organisms have been linked to ACS.
c. Most hospitalized patients with ACS were admitted with another condition, most often vaso-occlusive crisis.
d. Pulmonary emboli originating from deep venous thrombosis are a common cause of ACS.
e. Findings on chest radiography correlate closely with the degree of hypoxia seen on arterial blood gas.

86. A 25-year-old woman with SCA complains of decreased vision in her left eye. On exam, a small collection of blood in the anterior chamber is noted. The most serious complication of hyphema in patients with SCA is:
a. glaucoma.
b. iritis.
c. keratitis.
d. lens dislocation.

87. Which of the following statements regarding the pathophysiology and incidence of SCD is *false*?
a. HbF interferes with the polymerization of HbS.
b. The HbS mutation evolved due to the survival advantage afforded the heterozygote carrier to falciparum malaria.
c. HbS results from a mutation in the alpha hemoglobin chain.
d. SCD is found not only in people of African descent but in individuals of Middle Eastern and Mediterranean descent.

88. Which statement does *not* characterize the genitourinary disease seen in SCA?
a. Chronic renal failure requiring dialysis is a common complication of HbS disease.
b. Priapism in HbS disease is a "low-flow" state.
c. Hyposthenuria and hematuria are often seen.
d. ACE inhibitors have shown some promise in treating sickle cell nephropathy.
e. Priapism often responds to conservative treatment of analgesia and hydration.

89. Hydroxyurea is thought to act primarily by:
a. blocking endogenous pain mediators.
b. the formation of HbC.
c. preventing platelet adhesion.
d. increasing levels of HbF.
e. increased destruction of HbS.

90. Which of the following has proven associations with sickle cell trait?
a. Sudden death
b. Shortened lifespan
c. Hyposthenuria and hematuria
d. Renal failure
e. Stroke

91. Every patient with sickle cell disease who presents to the ED with pain must receive:
a. IV fluids.
b. oxygen.
c. aggressive treatment for pain.
d. a CBC.

92. Stroke is a devastating complication of SCA. Which statement regarding stroke in HbS disease is true?
a. Intravenous tissue plasminogen activator (tPA) is contraindicated in sickle cell patients who present with acute stroke.
b. The risk of hemorrhage stroke is highest in early childhood.
c. The risk of ischemic stroke has only one peak in HbS patients—at 1 year of age.
d. Chronic transfusion therapy has been shown to decrease the frequency of recurrent stroke in children.

93. Which of the following conditions is seen more commonly in HbSC disease than in HbSS disease?
a. ACS
b. Acute splenic sequestration
c. Osteonecrosis
d. Priapism
e. Proliferative retinopathy

94. Which of the following reliably differentiates osteomyelitis from bone infarction?
a. Presence of fever
b. Localized tenderness
c. Elevated WBC count
d. Positive culture from blood or bone aspirate

95. Indications for transfusion therapy in SCA include:
a. ACS with hypoxia.
b. prolonged priapism.
c. acute splenic sequestration.
d. symptomatic episodes of acute anemia.
e. all of the above are indications for transfusion.

96. What is the most common cause of death in thalassemia patients?

a. Cardiac disease
b. Liver failure
c. Infection
d. Anemia
e. Renal failure

This test concludes the July through December 2001 semester testing period of *Emergency Medicine Practice.* The answer form for this semester and a postage-paid return envelope have been included with this issue. All paid subscribers are eligible to take this test. *You will need the customer number printed on the outer envelope to submit the post-test.* Please refer to the instructions printed on the answer form.

Class Of Evidence Definitions

Each action in the clinical pathways section of *Emergency Medicine Practice* receives an alpha-numerical score based on the following definitions.

Class I
- Always acceptable, safe
- Definitely useful
- Proven in both efficacy and effectiveness

Level of Evidence:
- One or more large prospective studies are present (with rare exceptions)
- High-quality meta-analyses
- Study results consistently positive and compelling

Class II
- Safe, acceptable
- Probably useful

Level of Evidence:
- Generally higher levels of evidence
- Non-randomized or retrospective studies: historic, cohort, or case-control studies
- Less robust RCTs
- Results consistently positive

Class III
- May be acceptable
- Possibly useful
- Considered optional or alternative treatments

Level of Evidence:
- Generally lower or intermediate levels of evidence
- Case series, animal studies, consensus panels
- Occasionally positive results

Indeterminate
- Continuing area of research
- No recommendations until further research

Level of Evidence:
- Evidence not available
- Higher studies in progress
- Results inconsistent, contradictory
- Results not compelling

Significantly modified from: The Emergency Cardiovascular Care Committees of the American Heart Association and representatives from the resuscitation councils of ILCOR: How to Develop Evidence-Based Guidelines for Emergency Cardiac Care: Quality of Evidence and Classes of Recommendations; also: Anonymous. Guidelines for cardiopulmonary resuscitation and emergency cardiac care. Emergency Cardiac Care Committee and Subcommittees, American Heart Association. Part IX. Ensuring effectiveness of community-wide emergency cardiac care. *JAMA* 1992;268(16):2289-2295.

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Needs Assessment: The need for this educational activity was determined by a survey of medical staff, including the editorial board of this publication; review of morbidity and mortality data from the CDC, AHA, NCHS, and ACEP; and evaluation of prior activities for emergency physicians.

Date of Original Release: This issue of *Emergency Medicine Practice* was published December 1, 2001. This activity is eligible for CME credit through December 1, 2004. The latest review of this material was November 28, 2001.

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Publisher: Robert Williford. **Vice President/General Manager**: Connie Austin.
Executive Editor: Heidi Frost.

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Emergency Medicine Practice (ISSN 1524-1971) is published monthly (12 times per year) by EB Practice, LLC, 305 Windlake Court, Alpharetta, GA 30022. Opinions expressed are not necessarily those of this publication. Mention of products or services does not constitute endorsement. This publication is intended as a general guide and is intended to supplement, rather than substitute, professional judgment. It covers a highly technical and complex subject and should not be used for making specific medical decisions. The materials contained herein are not intended to establish policy, procedure, or standard of care. *Emergency Medicine Practice* is a trademark of EB Practice, LLC. Subscription price: $249, U.S. funds. (Call for international shipping prices.)