Chapter 3: Managing Acute Complications of Sickle Cell Disease

Introduction

New clinical approaches and treatments[34,96,98] have increased the survival of people with SCD, but the average lifespan still remains about two to three decades less than for Americans without SCD.[17,141] The shorter lifespan is due in part to adverse outcomes related to acute SCD complications. The most common complication of SCD is an acute episode of severe pain, hereafter referred to as an acute vaso-occlusive crisis (VOC). A VOC is defined as pain resulting from tissue ischemia caused by vaso-occlusion most commonly in the bone(s) and bone marrow.

In addition to VOCs, other common acute complications of SCD include fever related to infection, acute kidney injury (AKI), hepatobiliary complications, acute anemia, splenic sequestration, acute chest syndrome (ACS), and acute stroke. Individuals with signs or symptoms of these complications require immediate evaluation and treatment to reduce or prevent morbidity and mortality. Priapism and acute ocular conditions such as central retinal artery occlusion (CRAO) also require urgent management to preserve organ function.

This chapter presents recommendations for the evaluation and management of these common acute SCD complications. For each acute complication discussed, information is presented regarding its frequency, common presentation, usual evaluation, and treatment.

Methodology

Complete information about the methodology for these guidelines can be found in the "Introduction and Methodology" chapter (pages 1–9). The following information, specific to this chapter, supplements the standard methodology that was conducted for all clinical chapters of these guidelines.

A comprehensive study of several databases was conducted, and all human studies in English published from 1970 to July 2010 that addressed each PICOS question were identified. A total of 549 studies of complications were included.[f] When the literature search found insufficient evidence on a topic (e.g., vaso-occlusive crisis), these topics were supplemented with recommendations derived from other published guidelines by professional organizations, which were based on systematic reviews of broader population groups; these recommendations are labeled "Consensus–Adapted." In the instances of fever, acute anemia, and multisystem organ failure (MSOF), a literature search was not conducted, so the panel relied on their cumulative expertise and knowledge to make recommendations; these recommendations are labeled "Consensus–Panel Expertise." The key questions for this chapter can be found immediately before the Summary of the Evidence sections for the individual topics.

> Sickle cell anemia (SCA) refers to the clinically similar disorders HbSS or HbSβ0-thalassemia. Sickle cell disease (SCD) refers to all disease genotypes, including SCA and compound heterozygous disorders, such as HbSC, HbSD, and HbSβ+-thalassemia. The carrier state for hemoglobin S (HbAS or sickle cell trait) is not a form of SCD.

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[f] An updated search was performed to span the time from June 1, 2010 through July 11, 2014. Five additional RCTs were identified, for a total of 549 studies, and a supplemental table reflecting these additions was added to the evidence table document.

Detailed information on the evaluated studies as well as the observational and case studies/series referenced can be found in the Management of Sickle Cell Disease Complications evidence table available at http://www.nhlbi.nih.gov/guidelines/scd/index.htm.

Vaso-Occlusive Crisis

Background

A VOC is the hallmark acute complication for persons with SCD and manifests as acute severe pain. Although VOCs are typically associated with excruciating pain of sudden onset, some people experience gradual onset of a VOC. Nearly all individuals affected by SCD will experience a VOC during their lifetime.[142] The first VOC may occur as early as 6 months of age, often presenting as dactylitis, but thereafter VOCs occur with variable frequency.[23,143-145] VOCs and their accompanying pain most commonly occur in the extremities, chest, and back. When they occur in other sites, they can be confused with, or can be the prodromal stage of, other acute complications (e.g., head (stroke), flank (papillary necrosis), and abdomen (hepatic or splenic sequestration, constipation from opioid toxicity, or another hepatobiliary complication)). The etiology of the pain must be determined in order to rule out potential causes of pain other than an uncomplicated VOC, such as ACS, pneumonia, or other abdominal complications. VOC can still occur in the presence of other complications. There are no tests to rule in or to rule out a VOC; there are only tests that potentially rule out other causes of pain. Persons with the genotypes HbSS or HbSβ^0-thalassemia are likely to experience more frequent VOCs. Persons with HbAS (commonly referred to as sickle cell trait) do not experience typical VOCs. Individuals with more than three hospitalizations for a VOC in a year are at an increased risk of early death.[142,143,146-148]

Pain management must be guided by patient report of pain severity. No biomarkers or imaging studies can validate pain or assess its severity. The primary management of a VOC is analgesic treatment, typically with opioids. No empirical data exist to indicate that rapid analgesic administration results in better outcomes. However, as patients with VOC present with severe pain and are at risk for other complications, best practice suggests that rapid triage, placement, and administration of analgesics should be encouraged. The Emergency Severity Index (ESI) Version 4 triage system, which is used by more than half of emergency departments in the United States, suggests that persons with SCD be triaged as ESI level 2, a very high priority, and rapid placement be facilitated.[149]

Many specific recommendations for acute VOC management are included in this section that address treatment beyond what is listed in the Key Question (below). The expert panel felt it was important to include current practices that have not yet been validated by evidence, but are currently being used. When made, these recommendations are clearly identified as "Consensus–Panel Expertise." A recommendation is included to guide providers in managing persons who take both long- and short-acting opioids to manage pain at home. There are no empirical data to guide whether or not to continue long-acting opioids when ordering continuous opioids via patient-controlled analgesia (PCA). The decision to continue long-acting oral opioids should be made on an individual basis. In most circumstances, it is advisable to continue oral long-acting opioids including methadone therapy even when ordering continuous opioids via PCA to ensure adequate pain relief while avoiding a break in coverage and preventing withdrawal. Finally, hydration and nonpharmacologic therapy are also very important as is concurrent treatment of itching caused by histamine release.

Key Question

> **KQ10. For adults and children with SCD-related acute pain, what are the most effective acute pain management strategies (including types of analgesics, dose and administration protocols, and other interventions such as inhaled nitrous oxide, oxygen, and transfusion)?**

Summary of the Evidence

Thirty-two RCTs with more than 1,800 people of all ages, 34 observational studies, and 30 case reports were considered eligible. Because many of these studies evaluated pharmacologic agents that did not decrease pain or significantly reduce length of hospital stay (e.g., poloxamer 188, fluosol, vasodilators, methylprednisone, oxygen, urea, and other agents), and which are not approved by the U.S. Food and Drug Administration (e.g., inhaled nitrous oxide, transfusion, etc.), recommendations regarding these agents were not made. One study evaluated the effectiveness of meperidine versus placebo or other opioids and found meperidine more effective than placebo in reducing pain. However, due to the neurotoxicity associated with meperidine, the panel did not make recommendations for its use. Evidence from several RCTs and observational studies[76,150-153] supports the use of opioid therapy in treating VOCs. Indirect, high-quality evidence from populations without SCD also supports the use of opioids in treating VOCs. A recent report from the American Pain Society (APS) suggests opioids are not effective in treating chronic non-cancer pain.[154] It is important to understand that an acute VOC is considered acute, not chronic pain, and opioids are indicated and should be used to treat pain. Evidence from RCTs and observational studies supporting the use of nonsteroidal anti-inflammatory drugs (NSAIDs) was conflicting, but overall, the evidence supports their efficacy in reducing pain and decreasing length of hospital stay. Several RCTs and observational studies support the use of around-the-clock dosing of analgesics versus intermittent analgesic administration in treating VOCs.[155-161]

The largest study on this topic, a prospective observational study in Saudi Arabia, included 1,154 people and examined the effect of a pain management protocol.[155] The study found that around-the-clock analgesic infusions for the first 24 hours after admission were more effective for managing VOCs than "on demand" or patient-requested infusions of analgesics. People treated with around-the-clock analgesics achieved a higher discharge rate within 72 hours of admission (83 percent), compared with people who received intermittent (per patient request) analgesics (71 percent). Other observational studies supported these findings and also suggested a more rapid resolution of VOCs and a strong patient preference for around-the-clock analgesic infusions. The evidence base was insufficient to make specific analgesic dosing recommendations or recommendations for several nonpharmacologic approaches (including oxygen, inhaled nitrous oxide, electrical nerve stimulation, acupuncture, biofeedback, and a day hospital program). In general, the quality of the available evidence was moderate to low.

In addition, the panel and the methodology team appraised the quality of the APS's[23] guidelines for the management of SCD-related pain and found them to be acceptable. As shown in the "Consensus–Adapted" recommendations below, the panel adapted selected recommendations from the APS guidelines for treatment of SCD pain. Additional recommendations are based upon the experience of the expert panel and are categorized as "Consensus–Panel Expertise."
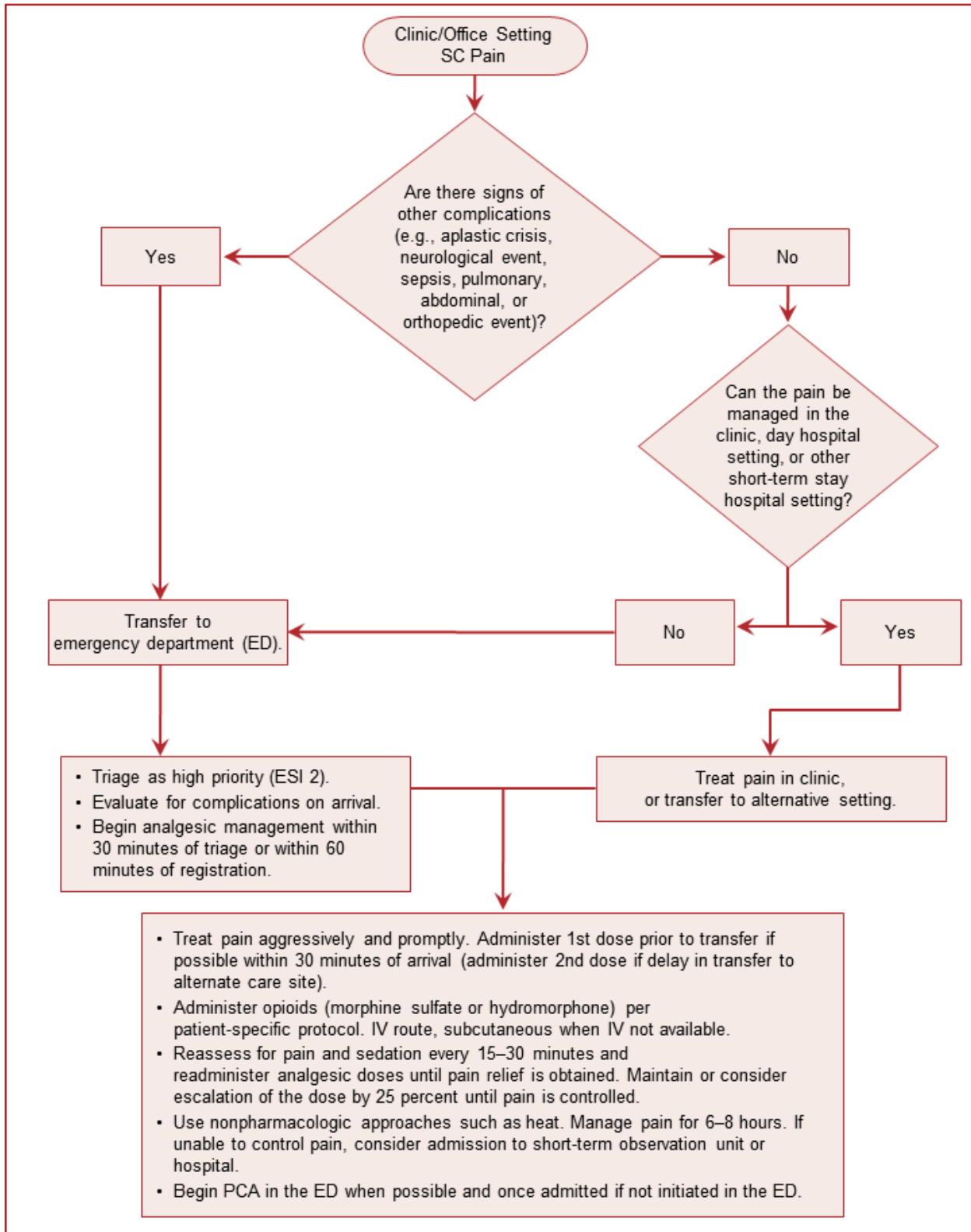
Recommendations

The recommendations labeled "consensus" in this section were based on recommendations developed by the APS or on panel expertise. The remaining recommendations are based on the evidence review conducted by the methodology team. These recommendations are intended to be for all settings where patients present with VOC.

1. In adults and children with SCD and pain,
   – When indicated, initiate diagnostic evaluation of causes of pain other than a VOC while beginning to treat pain.
   (Consensus–Adapted)

2. In adults and children with SCD and a VOC,
   – Determine characteristics, associated symptoms, location, and intensity of pain based on patient self-report and observation. If the VOC pain is atypical, investigate other possible etiologies of pain.
   (Consensus–Adapted)
   – Rapidly assess the patient's recent analgesic use (opioid and nonopioid).
   (Consensus–Adapted)
   – Rapidly initiate analgesic therapy within 30 minutes of triage or within 60 minutes of registration.
   (Consensus–Panel Expertise)
   – Base analgesic selection on pain assessment, associated symptoms, outpatient analgesic use, patient knowledge of effective agents and doses, and past experience with side effects.
   (Consensus–Adapted)

3. In adults and children with SCD and a VOC,
   – Use an individualized prescribing and monitoring protocol (written by the patient's SCD provider) or an SCD-specific protocol whenever possible (see exhibit 7 on page 36) to promote rapid, effective, and safe analgesic management and resolution of the VOC.
   (Consensus–Panel Expertise)

4. In adults and children with SCD and a VOC associated with mild to moderate pain who report relief with NSAIDS in the absence of contraindications to the use of NSAIDS, continue treatment with NSAIDS.
   (*Moderate Recommendation, Low-Quality Evidence*)

5. In adults and children with SCD and a VOC associated with severe pain, rapidly initiate treatment with parenteral opioids.
   (*Strong Recommendation, High-Quality Evidence*)

6. In adults and children with SCD and a VOC associated with severe pain,
   – Calculate the parenteral (IV or subcutaneous) opioid dose based on total daily short-acting opioid dose currently being taken at home to manage the VOC.
   (Consensus–Panel Expertise)
   – Administer parenteral opioids using the subcutaneous route when intravenous access is difficult.
   (Consensus–Panel Expertise)
   – Reassess pain and re-administer opioids if necessary for continued severe pain every 15–30 minutes until pain is under control per patient report.
   (Consensus–Adapted)
   – Maintain or consider escalation of the dose by 25 percent until pain is controlled.
   (Consensus–Panel Expertise)
   – Reassess after each dose for pain relief and side effects.
   (Consensus–Panel Expertise)
   – Initiate around-the-clock opioid administration by patient-controlled analgesia (PCA) or frequently scheduled doses versus "as requested" (PRN) administration.
   (Moderate Recommendation, Low-Quality Evidence)

Recommendations

7. If ordering around-the-clock, continuous infusion of opioids via the PCA, carefully consider whether there is a need to withhold long-acting oral opioids to prevent over-sedation.
    (***Consensus–Panel Expertise***)
    -   If demand dosing only is ordered via the PCA, continue use of long-acting oral opioids.
        (***Consensus–Panel Expertise***)
    -   At discharge, evaluate inpatient analgesic requirements, wean parenteral opioids prior to conversion to oral opioids, and adjust home dose of long- and short-acting opioid prescriptions to prevent opioid withdrawal after discharge.
        (***Consensus–Panel Expertise***)

8. In adults and children with SCD and a VOC, do not use meperidine unless it is the only effective opioid for an individual patient.
    (***Consensus–Adapted***)

9. In adults and children with a VOC, administer oral NSAIDS as an adjuvant analgesic in the absence of contraindications.
    (***Consensus—Adapted***)

10. In adults and children with a VOC who require antihistamines for itching secondary to opioid administration, prescribe agents orally, and do not re-administer with each dose of opioid in the acute VOC management phase. Re-administer every 4 to 6 hours if needed.
    (***Consensus–Panel Expertise***)

11. To reduce the risk of acute chest syndrome in adults and children hospitalized for a VOC,
    -   Encourage use of incentive spirometry while awake.
        (***Strong Recommendation, Moderate-Quality Evidence***)
    -   Encourage ambulation and activity as soon as possible.
        (***Consensus–Panel Expertise***)

12. In adults and children with VOC, use adjunctive nonpharmacologic approaches to treat pain such as local heat application and distraction.
    (***Consensus–Adapted***)

13. In euvolemic adults and children with SCD and a VOC who are unable to drink fluids, provide intravenous hydration at no more than maintenance rate to avoid over-hydration.
    (***Consensus–Adapted***)

14. In adults and children with SCD and a VOC being treated with opioids, monitor for excessive sedation by measuring sedation with an objective measurement sedation scale and oxygenation levels.
    (***Consensus–Panel Expertise***)

15. Gradually titrate down parenteral opioids as VOC resolves.
    (***Consensus–Panel Expertise***)

16. In adults and children with SCD and a VOC, do not administer a blood transfusion unless there are other indications for transfusion (see the chapter "Blood Transfusion in the Management of Sickle Cell Disease" in these guidelines).
    (***Moderate Recommendation, Low-Quality Evidence***)

17. In adults and children with SCD and a VOC with an oxygen saturation <95 percent on room air, administer oxygen.
    (***Consensus–Panel Expertise***)

Exhibit 7. Acute Pain Algorithm*

Clinic/Office Setting SC Pain

Are there signs of other complications (e.g., aplastic crisis, neurological event, sepsis, pulmonary, abdominal, or orthopedic event)?

Yes

No

Can the pain be managed in the clinic, day hospital setting, or other short-term stay hospital setting?

Transfer to emergency department (ED).

No

Yes

- Triage as high priority (ESI 2).
- Evaluate for complications on arrival.
- Begin analgesic management within 30 minutes of triage or within 60 minutes of registration.

Treat pain in clinic, or transfer to alternative setting.

- Treat pain aggressively and promptly. Administer 1st dose prior to transfer if possible within 30 minutes of arrival (administer 2nd dose if delay in transfer to alternate care site).
- Administer opioids (morphine sulfate or hydromorphone) per patient-specific protocol. IV route, subcutaneous when IV not available.
- Reassess for pain and sedation every 15–30 minutes and readminister analgesic doses until pain relief is obtained. Maintain or consider escalation of the dose by 25 percent until pain is controlled.
- Use nonpharmacologic approaches such as heat. Manage pain for 6–8 hours. If unable to control pain, consider admission to short-term observation unit or hospital.
- Begin PCA in the ED when possible and once admitted if not initiated in the ED.

Note: See recommendation 3, page 34.
* These recommendations are intended to be for all settings where patients present with VOC.
(*Consensus–Panel Expertise*)

Fever

Background

People with SCA have an increased risk of severe bacterial infection, resulting primarily from reduced or absent splenic function.[162] By 2 or 3 months of age, as their fetal hemoglobin declines, infants with SCA begin to develop splenic impairment. The result is an extremely high risk of septicemia and meningitis, primarily due to *Streptococcus pneumoniae*. Although the incidence of invasive pneumococcal infection has declined as a result of prophylactic penicillin and pneumococcal vaccination, febrile illnesses in people with SCD are still considered an emergency due to the possibility of penicillin-resistant organisms and incomplete vaccination status. The risk of such infections continues throughout childhood and to a lesser extent in adults. Serious infections can also affect persons with other forms of SCD (e.g., HbSC and HbSβ$^+$-thalassemia).
As a presenting symptom, fever heralds many acute and sometimes life-threatening conditions, such as ACS and osteomyelitis. In many cases, the cause of fever is unclear, but because individuals with SCA have a highly increased risk of overwhelming bacterial infection, it is critical that fever alone is taken seriously in these individuals and considered a potential emergency situation. Fever associated with pain should not be considered a VOC until infection is ruled out.

People with SCD who develop fever may have ACS due to diverse organisms (including *Mycoplasma*) and are also at risk of gram-negative enteric infections involving the urinary tract, hepatobiliary system, or bones. Acute osteomyelitis, another complication associated with fever, may be unifocal or multifocal and may be caused by *Staphylococcus aureus*, salmonella, or other enteric pathogens. Persons with SCD have normal T cell and B cell function, so the risk of acute infection is generally limited to those micro-organisms mentioned above. Opportunistic infections are infrequent.

Summary of the Evidence

An adequate systematic review of the literature with fair sensitivity and specificity for all studies indexed by SCD terms and the symptom of fever was not feasible. A large and nonspecific return of studies with significant heterogeneity, high miss rate, and low-quality evidence (lack of comparative studies) was anticipated. No systematic review was conducted, and the panel used a consensus process to develop a proposed strategy for triaging and promptly managing fever.

Recommendations
1. In people with SCD and a temperature ≥101.3°F (38.5°C), immediately evaluate with history and physical examination, complete blood count (CBC) with differential, reticulocyte count, blood culture, and urine culture when urinary tract infection is suspected. *(Consensus–Panel Expertise)*
2. In children with SCD and a temperature ≥101.3 °F (38.5 °C), promptly administer ongoing empiric parenteral antibiotics that provide coverage against *Streptococcus pneumoniae* and gram-negative enteric organisms. Subsequent outpatient management using an oral antibiotic is feasible in people who do not appear ill. *(Consensus–Panel Expertise)*
3. Hospitalize people with SCD and a temperature ≥103.1 °F (39.5 °C) and who appear ill for close observation and intravenous antibiotic therapy. *(Consensus–Panel Expertise)*
4. In people with SCD whose febrile illness is accompanied by shortness of breath, tachypnea, cough, and/or rales, manage according to the preceding recommendations and obtain an immediate chest x ray to investigate for ACS. *(Consensus–Panel Expertise)*

Recommendations
5. In febrile people with SCD who have localized or multifocal bone tenderness, especially when accompanied by erythema and swelling, include bacterial osteomyelitis in the differential diagnosis and manage accordingly. *(Consensus–Panel Expertise)*

Acute Renal Failure

Background

Acute renal failure (ARF) is defined here as a rapid reduction in renal function manifested by a rise in serum creatinine and reduction in glomerular filtration rate (GFR), with or without a decline in urine output. ARF may be due to pre-renal (e.g., dehydration) or post-renal (e.g., obstruction) insults, or result from intrinsic renal disease (e.g., glomerular injury). ARF may occur during an acute VOC, most often in association with ACS or acute multisystem organ failure (MSOF).[163]

Renal papillary necrosis due to medullary infarction from obstruction of the blood supply in the vasa recta affects up to 15–30 percent of individuals with SCD.[164] Signs and symptoms include flank pain and hematuria. When present, fever suggests possible superinfection.

ARF may also occur when individuals with chronic sickle cell nephropathy or other chronic kidney diseases are exposed to nephrotoxic medications (e.g., NSAIDs or intravenous contrast dye) or become dehydrated. People with SCD often display a relative inability to maximally concentrate the urine, resulting in increased vulnerability to pre-renal azotemia.

Due to increased renal tubular secretion of creatinine, serum creatinine values in SCD do not rise until significant renal impairment occurs (GFR of 30 mL/min or less).[39] Since the serum creatinine levels are generally low or low-normal in individuals with SCD, the values in ARF may still be within normal limits even if they have doubled from baseline. It is important to consider non-SCD-related causes of ARF before simply attributing ARF to SCD.[165]

When associated with acute MSOF attributed to diffuse vaso-occlusion, ARF may respond to exchange red blood cell transfusion.[163,166] However, the benefit of transfusion for other causes of ARF in SCD has not been reported. Acute and chronic renal replacement therapy, including hemodialysis, is well-tolerated by people with SCD and should be used when indicated.[163,167]

Key Question

> **KQ11. In people with SCD and ARF, what are the most effective strategies to reduce mortality and the risk of developing end-stage renal disease (ESRD)?**

Summary of the Evidence

The systematic review did not identify comparative studies to demonstrate the superiority of a particular diagnostic or therapeutic approach to ARF in people with SCD. The literature in this area was mostly descriptive of people who developed renal complications (e.g., hyposthenuria, hematuria, impaired urinary potassium excretion and acidification, tubular and glomerular dysfunction, infection, medullary carcinoma, acute necrosis and renal failure).

One RCT, six observational studies, and nine case reports addressing both acute and chronic complications were evaluated. There were no RCTs that addressed acute complications and the single RCT addressed chronic complications; acute renal complications were only discussed in five retrospective observational case series.[40,168-171] No controlled trials or prospective studies addressed the recognition or management of acute renal failure in people with SCD, and few studies addressed evaluation or treatment of renal complications of SCD. The systematic review did not identify any literature to guide diagnostic or management recommendations for renal papillary necrosis. Therefore, management recommendations are based on the application of therapies for ARF from other patient populations to people with SCD as noted in the observational reports.

Recommendations
1. In the setting of an acute rise in serum creatinine of ≥0.3 mg/dL,
– Monitor renal function daily, including serum creatinine and fluid intake/output. *(Consensus–Panel Expertise)*
– Avoid potential nephrotoxic drugs and imaging agents. *(Consensus–Panel Expertise)*
– Evaluate the patient thoroughly for all potential etiologies in consultation with a nephrologist as needed. *(Consensus–Panel Expertise)*
2. Do not give blood transfusions to treat ARF unless there are other indications for transfusion. *(Consensus–Panel Expertise)*
3. Use renal replacement therapy (e.g., hemodialysis) when needed for acute renal failure. *(Consensus–Panel Expertise)*

Priapism

Background

Priapism is a sustained, unwanted painful erection lasting 4 or more hours. Stuttering priapism is the occurrence of multiple self-limited episodes of shorter duration (<4 hours) and can be a harbinger of sustained events.[172] Priapism is a common complication of SCD, affecting 35 percent of boys and men.[173] It is usually of the low-flow ischemic type and characterized by pain and a soft glans. Blood aspirated from the corpora cavernosa of the penis is dark, with a low pO_2, pH, and glucose concentration.[173] Prompt recognition of priapism and initiation of conservative medical management may lead to detumescence and limit the need for more aggressive and invasive intervention. Delayed diagnosis and therapy can result in impotence.

Key Question

> **KQ12.** In males with SCD presenting with acute priapism, what is the relative efficacy of conservative management, pharmacological management, transfusion, and surgery on the outcomes of detumescence and the incidence of future impotence?

Summary of the Evidence

Seven observational studies and 39 case reports described priapism in the setting of SCD. Overall, the quality of the evidence in this area was low due to the observational and uncontrolled design of the available studies.

The observational studies included more than 220 people and studied approaches such as shunts, aspiration, exchange transfusion, hydroxyurea, hormonal therapy (e.g., stilbestrol, finasteride, and leuprolide), bicalutamide, hydralazine, sildenafil, oxygen, and hyperhydration to treat priapism in men and boys with SCD. Results were limited, reporting variable success.[174-179] Several of the studies highlighted the importance of prompt recognition and initial conservative medical management with analgesics, intravenous fluids, oxygen, and sedation if needed.[180-183]

Red blood cell transfusion therapy was inconsistently associated with improvement in acute priapism.[184-193] In addition, case reports of acute neurological events following exchange transfusion for priapism further limit enthusiasm for routine adoption of this therapy in the absence of proven benefit.[194] Both observational studies and case reports found that a variety of subsequent interventions used to treat symptoms that persist after initial conservative medical management appear to result in detumescence and retained potency. These include penile aspiration,[195,196] corporal irrigation using α-adrenergic agents (e.g., pseudoephedrine, epinephrine, etilefrine),[197-203] and the use of oral agents (e.g., PDE-5 inhibitors, pseudo-ephedrine).[204] Surgical intervention, including shunting, has been utilized most often after more conservative measures fail, with inconsistent benefit.[190,205-209]

In developing recommendations for the care of males with SCD presenting with acute priapism, the expert panel placed great value on preventing pain and future long-term sequelae.

Recommendations
1. For an episode of priapism lasting 4 hours or longer, initiate interventions to include – vigorous oral or intravenous hydration and oral or intravenous analgesia (***Strong Recommendation, Low-Quality Evidence***); and – consultation with a urologist who can perform further evaluation and intervention for symptoms which do not remit with initial conservative medical management. (***Consensus–Panel Expertise***) 2. Do not use transfusion therapy for immediate treatment of priapism associated with SCD. (***Moderate Recommendation, Low-Quality Evidence***) 3. Consult with a hematologist for possible preoperative transfusion if surgical intervention is required. (***Consensus–Panel Expertise***)

Hepatobiliary Complications

Background

Biliary tract abnormalities are common in people with SCD in general and in those with HbSS in particular. These abnormalities include cholelithiasis, acute cholecystitis, biliary sludge, and acute choledocholithiasis.[210,211] Hemolysis of any etiology results in increased secreted unconjugated bilirubin that tends to precipitate and leads to gallstones and sludge.

Cholelithiasis and Acute Cholecystitis

Ultrasound-identified rates of gallstones in people with SCD increase with age from 12 percent in those aged 2 to 4 years to 43 percent by 15 to 18 years of age.[212,213] In adults with SCD, the prevalence of gallstones can be as high as 70–75 percent.[214-217] Although gallstones are usually asymptomatic, they can be associated with acute infection and inflammation involving the gallbladder, and they may also lead to obstruction of the cystic or bile ducts and acute pancreatitis.

Despite the high prevalence of gallstones in people with SCD, acute cholecystitis occurs in less than 10 percent of children and adults with SCD. It can occur with or without the presence of gallstones and can present as severe colicky pain in the right upper quadrant (RUQ) with abdominal tenderness on physical exam. Fever, leukocytosis, nausea, and vomiting are also usually present. Nonvisualization of the gallbladder by 60 minutes after cholescintigraphy is a common radiographic finding.

Choledocholithiasis

Choledocholithiasis is the presence of gallstones in the common bile duct. Symptoms include dull pain in the RUQ, tender hepatomegaly, and rapidly increasing jaundice. According to a patient survey, choledocholithiasis occurs in less than 5 percent of people with SCD who have asymptomatic gallstones.[218,219] In symptomatic people, the rate of choledocholithiasis is higher, affecting 20 to 60 percent of people with SCD compared to 15 percent of those without SCD.[220,221] Endoscopic retrograde cholangiopancreatography (ERCP) and sphincterotomy may be required to remove the offending stones.

Acute Hepatic Sequestration

Both acute hepatic sequestration (AHS) and acute intrahepatic cholestasis (AIC) (also called sickle cell hepatopathy) are associated with SCD. Each requires consideration in evaluating acute upper abdominal pain in people with SCD.

AHS is marked by hepatic enlargement compared to baseline without other explanation and a 2 g/dL or greater decline in hemoglobin concentration. Sequestration of red blood cells often develops over a few hours to a few days, and the resultant stretching of the hepatic capsule is usually painful. AHS appears to be uncommon and may be overlooked unless the size of the liver is closely monitored in cases of acute RUQ pain. About two-thirds of people with SCD have mild baseline hepatomegaly, so change in size should be monitored. In AHS, liver function tests are only mildly elevated. Acute hemolysis or other causes of hemoglobin decline should be ruled out. Recurrent episodes may occur.[222-225]

Acute Intrahepatic Cholestasis

AIC is characterized by the sudden onset of RUQ pain, increasing jaundice, a progressively enlarging and exquisitely tender liver, light-colored stools, and extreme hyperbilirubinemia (both conjugated and unconjugated) usually without urobilinogenuria. Thrombocytopenia and coagulation abnormalities may also be present. The clinical picture suggests cholestatic jaundice or choledocholithiasis but without evidence of common duct obstruction or cholangitis. AIC may prove fatal if not recognized and treated promptly.[226-230]

Diagnostic evaluation may reveal exquisite tenderness in the RUQ with a total serum bilirubin level >50 mg/dL, hypoalbuminemia, thrombocytopenia, elevated alkaline phosphatase, variable levels of transaminases, coagulopathy with increased prothrombin time (PT), and partial thromboplastin time (PTT) to values more than twice baseline in the absence of accelerated hemolysis or obstruction of the extrahepatic biliary system.[226-229,231,232]

Key Questions

> **KQ13.** In people with SCD, what is the appropriate management of cholelithiasis and related cholecystitis to resolve symptoms and prevent perioperative complications? What is the most effective treatment strategy for people with SCD presenting with AHS and AIC to reduce mortality and resolve symptoms?

Summary of the Evidence

There were no RCTs that evaluated different management strategies for hepatobiliary complications related to SCD. Twenty-five observational studies and 53 case reports were identified and described various hepatobiliary complications associated with SCD. Overall, the quality of the evidence was low due to the observational nature of the studies and the lack of a control or comparison arm in 80 percent of the studies.

The observational studies included more than 900 people and almost uniformly focused on cholelithiasis or acute cholecystitis. One observational study, which followed people with SCD from birth, found that the incidence of cholelithiasis was 30 percent in people with SCA and 11 percent in people with HbSC.[233] Only 2 percent of the people developed symptoms that required surgical intervention.

In most of the surgical studies, cholecystectomy was shown to be effective and safe in people with SCD and cholelithiasis. When surgically feasible and available, the laparoscopic approach was associated with shorter hospital stay, reduced postoperative pain, and overall lower cost. Other case studies described people with SCD and choledocholithiasis who were treated with both open and endoscopic approaches (i.e., ERCP); however, these data were noncomparative, thus limiting the ability to apply these approaches more generally.[234-236]

The systematic review identified only low-quality literature to guide diagnostic or management approaches for hepatic sequestration or intrahepatic cholestasis. Ahn et al.[222] described 7 people identified in their institution and 37 people from the literature who had SCD and acute hepatopathy (total serum bilirubin concentration >13 mg/dL). Among the 22 severe cases, the mortality rate was 64 percent. Only 2 of 9 people who received exchange transfusion died, whereas 12 of 13 people who did not receive exchange transfusion died. This study likely included people with heterogeneous etiologies of acute liver injury, which limits inference. Other case reports[226-229] described rare cases of AIC and reported favorable results with using total blood exchange by replacing the removed blood with washed sickle-negative blood and fresh frozen plasma. The quality of the evidence in this area is very low.

Recommendations
1. Treat acute cholecystitis in children and adults with SCD with antibiotics and surgical consultation. (***Consensus–Panel Expertise***)
2. Treat asymptomatic gallstones with watchful waiting in children and adults with SCD. In those who develop symptoms specific to gallstones, treat with cholecystectomy. The laparoscopic approach is preferred if surgically feasible and available. (***Strong Recommendation, Moderate-Quality Evidence***)
3. Consult with a hematologist or sickle cell expert for possible preoperative transfusion if surgical intervention is required. (***Consensus–Panel Expertise***)
4. In children and adults with SCD and signs and symptoms of AHS or AIC, provide hydration, rest, close observation, and consult a sickle cell expert for further management. (***Consensus–Panel Expertise***)
5. In children and adults with SCD and signs and symptoms of possible AHS or severe AIC, obtain urgent consultation with a sickle cell disease expert for diagnosis confirmation. (***Consensus–Panel Expertise***)
6. In children and adults with SCD with confirmed AHS or severe AIC, perform simple or exchange transfusion. (***Consensus–Panel Expertise***)

Acute Anemia

Background

Nearly all people with SCD have chronic anemia, but individual baseline hemoglobin values vary widely depending upon hemoglobin genotype (HbSS, HbSC, HbSβ⁺-thalassemia, HbSβ⁰-thalassemia), current and recent therapies (blood transfusions and hydroxyurea in particular), and other unknown factors. It is important for the patient and his or her primary care provider to know the baseline or "steady state" hemoglobin value to inform ongoing monitoring and management during acute complications. Baseline values are typically 6–8 g/dL for people with SCA, 10–15 g/dL for people with HbSC, and 9–12 g/dL for people with HbSβ⁺-thalassemia.

Acute anemia, defined as a decline by 2.0 g/dL or more in hemoglobin concentration below the patient's baseline value, can have diverse causes. Potential etiologies such as splenic sequestration in a child or an aplastic episode at any age may require urgent evaluation and therapy.

During acute events, the reticulocyte count is an important addition to the CBC to assess whether diminished red blood cell production (low reticulocyte count, as can occur in parvovirus infection resulting in aplastic crisis), accelerated hemolysis, or sequestration in the lungs, spleen, or liver is responsible for the acute anemia.

Aplastic Episode

An aplastic episode or "crisis" is a common feature of SCD, especially in children with HbSS.[237,238] The usual clinical picture is gradual onset of fatigue, shortness of breath, and sometimes syncope. Fever is quite common as well. Physical examination may reveal lethargy, rapid heart rate, and occasionally frank heart failure. The hemoglobin value (typically 3–6 g/dL) is usually far below the person's baseline level, and the reticulocyte count is reduced or even zero.

It has been noted that people with SCD rarely have recurrences of aplastic crisis, and several people with SCD in the same household frequently develop aplastic crises simultaneously or sequentially. This pattern suggests an infectious etiology. In the early 1980s, it was shown that parvovirus B19, the cause of fifth disease in young children, is in fact the etiology of these events.[238] This virus destroys erythroid precursors in the bone marrow, so people with an extremely short red blood cell lifespan such as those with SCA are susceptible to rapid decline in their hemoglobin concentration. Resolution of the aplastic crisis is heralded by marked reticulocytosis and rising hemoglobin concentration, concomitant with the appearance of immunoglobulin G (IgG) antibodies which neutralize the offending virus. The resulting humoral immunity is lifelong, preventing recurrent events. However, siblings or others with SCD who are exposed to a person with an aplastic crisis in the acute phase are at risk. Aplastic crises are most commonly seen in children with SCA. People with other genotypes, whose hemolysis is less severe, more often have clinically silent events. Occasionally, parvovirus B19 may also be responsible for or contribute to the development of ACS and/or stroke.

Other Causes of Acute Anemia

Acute splenic sequestration is a major cause of acute anemia, especially in children with SCA. This complication and the recommendations for its management will be described separately (see page 44).

A decline in hemoglobin concentration below the baseline is a common feature of ACS and can be its initial manifestation in a patient experiencing a VOC. Acute anemia may also occur as a result of sequestration of blood in the liver or accelerated hemolysis due to a delayed hemolytic transfusion reaction, septicemia, or another serious infection. Acute blood loss due to papillary necrosis or unrelated to SCD, such as

gastrointestinal hemorrhage, can also occasionally be responsible for a rapid decline in hemoglobin concentration. Slow but progressive reduction in hemoglobin values should raise concern about renal failure in the older child or adult with SCD.

Summary of the Evidence

An adequate systematic review of the literature with fair sensitivity and specificity for all studies indexed by SCD terms and the symptom of acute anemia was not feasible. A large and nonspecific return of studies with significant heterogeneity, high miss rate, and low-quality evidence (lack of comparative studies) was anticipated. No systematic evidence review was conducted, and the panel used a consensus process to develop a proposed strategy for triaging and promptly managing acute anemia.

Recommendations
1. During all acute illnesses in people with SCD, obtain a CBC and reticulocyte count, repeat daily in all hospitalized patients, and compare the results with the patient's prior measurements. (*Consensus–Panel Expertise*)
2. Assess people with SCD whose hemoglobin concentration is 2 g/dL or more below their baseline (or less than 6 g/dL when the baseline is unknown) for acute splenic sequestration, an aplastic episode, a delayed hemolytic transfusion reaction, ACS, and infection. (*Consensus–Panel Expertise*)
3. Use simple transfusion in people with SCD and acute anemia whose symptoms are due to anemia. (*Consensus–Panel Expertise*)
4. Perform a CBC and reticulocyte count promptly and again 7 to 10 days later in siblings and others with SCD who are exposed to a person with an aplastic episode. (*Consensus–Panel Expertise*)
5. Manage aplastic events with immediate red blood cell transfusion aimed at restoring the hemoglobin to a safe (not necessarily baseline) value. Isolation of hospitalized patients (droplet precautions) is required to prevent spread of the parvovirus B19 to pregnant women and others with SCD or compromised immunity. (*Consensus–Panel Expertise*)

Splenic Sequestration

Background

Splenic sequestration is defined as sudden enlargement of the spleen and reduction in hemoglobin concentration by at least 2 g/dL below the baseline value. It is a major cause of acute anemia. During splenic sequestration, the reticulocyte count and circulating nucleated red blood cells are usually elevated, and the platelet count is generally decreased because both red cells and platelets are trapped in the spleen. Sequestration usually develops without warning or known cause. It may occur as early as several months of age,[239] although it is more typical in children between the ages of 1 and 4 years old. Parents may note an enlarging mass in the left upper quadrant. Involution and autoinfarction of the spleen usually occurs by age 5, so sequestration events are less common in older children and adults with HbSS. In people with HbSS, the lifetime prevalence of acute splenic sequestration has been reported to be between 7 percent and 30 percent. In people with HbSC and HbSβ$^+$-thalassemia, splenic sequestration often occurs later in childhood or even during the adult years. Splenic sequestration in older patients is often accompanied by severe pain from splenic infarction, which can be documented by imaging studies.[240]

Some people with SCD have a chronically enlarged spleen and may develop hypersplenism. This presents as a reduction in the white blood cell and platelet counts in addition to acute anemia. Such people are particularly prone to develop acute sequestration events.[239]

In infants with HbSS, splenic sequestration may present acutely with severe anemia and hypovolemic shock. In older people, it may occur more insidiously. Although usual care for splenic sequestration consists of blood transfusion aimed at partial correction of the anemia, excessive transfusion (to hemoglobin values over 8 g/dL) should be avoided, as the sequestered erythrocytes in the enlarged spleen typically reenter the circulation several days later. The result could be hyperviscosity due to an excessively high hemoglobin concentration.

People with splenic sequestration must be monitored for recurrences. Thus, parents and patients are instructed to monitor splenic size and immediately report any marked increase above baseline. People with recurrent sequestration or a single life-threatening acute sequestration event most commonly have a splenectomy. Most people with chronic splenic sequestration accompanied by local pain and hypersplenism are also managed with splenectomy. Splenectomy for splenic sequestration does not further increase the risk of death or bacteremia[241] since most patients are already functionally asplenic. Regularly scheduled transfusions aimed at avoiding the need for subsequent splenectomy have not been proven to be beneficial.[242]

Key Question

> **KQ14.** **In people with SCD with acute anemia and splenic sequestration or hypersplenism, what are the most effective strategies to reduce mortality, correct anemia, and prevent recurrence?**

Summary of the Evidence

No RCTs were found that evaluated the treatment of splenic complications in SCD. Twenty observational studies (involving more than 950 people) and 39 case reports described various splenic complications in SCD. Reported complications in these observational studies included: splenic sequestration (*n*=16), hypersplenism (*n*=3), splenic abscess (*n*=2), and functional asplenia/splenic auto infarction (*n*=2). Overall benefits were reported for transfusion and splenectomy; however, since 75 percent of the studies had no comparative arm, the general quality of the evidence was considered low.

Only four studies, all involving children, had a comparative design.[242-245] The first compared an intensive transfusion program (to achieve an HbS concentration <20 percent) to a conventional transfusion program in children with prior stroke.[243] It reported the finding of normal or increased splenic size and improved function in the population receiving intensive transfusion, while all people receiving fewer transfusions had decreased splenic function (functional asplenia). A second study assessed three options for treating splenic sequestration: prompt splenectomy, a short-term transfusion program, or observation. Short-term transfusion was equivalent to observation and therefore of limited benefit in preventing recurrent splenic sequestration.[242] The third comparative study did not report group-specific outcomes but rather overall mortality rates.[244] The final comparative study included people with SCD with various splenic complications (splenic sequestration, hypersplenism) and compared outcomes in people who received splenectomy and those who did not.[245] The remaining studies described splenectomy (*n*=13), transfusion (*n*=3), an age-dependent approach (*n*=1),[246] and hydroxyurea (*n*=1).[247] The splenectomy studies reported favorable outcomes following the surgery. Infection rates after splenectomy did not increase. Transfusion was reported to be effective in treating acute splenic sequestration.[248,249]

Recommendations
1. In people with hypovolemia due to severe acute splenic sequestration, immediately provide IV fluid resuscitation. (*Strong Recommendation, Low-Quality Evidence*)
2. In consultation with a sickle cell expert, transfuse people who have acute splenic sequestration and severe anemia to raise the hemoglobin to a stable level, while avoiding over-transfusion. (*Strong Recommendation, Low Quality Evidence*)
3. In consultation with a sickle cell expert, address the performance and timing of splenectomy in people with recurrent acute splenic sequestration or symptomatic hypersplenism. (*Moderate Recommendation, Low-Quality Evidence*)

Acute Chest Syndrome

Background

ACS is one of the most common and serious acute complications of SCD.[250-252] It is the second most frequent reason for hospitalization in children and adults with SCD and the most common cause of death. Clinically, ACS resembles pneumonia and can develop suddenly or insidiously, during hospitalization for a VOC, or after a surgical procedure, especially one involving the abdomen. ACS occurs with increased frequency in people with asthma or prior ACS events. The clinical, laboratory, and radiographic features of ACS—as well as its management and outcome—were comprehensively assessed in a landmark study performed by the National Acute Chest Syndrome Study Group.[251]

A person with ACS typically has sudden onset of signs and symptoms of lower respiratory tract disease (e.g., some combination of cough, shortness of breath, retractions, rales, etc.) and a new pulmonary infiltrate on chest radiograph. In the early stages of ACS, the clinical manifestations can be subtle. Children usually have fever and upper or middle lobe involvement, whereas adults are often afebrile and present with multilobe disease. The most common well-defined etiology is infection (e.g., viral, bacterial, chlamydia, or *Mycoplasma*), but the complication may also result from bone marrow fat embolism, intrapulmonary aggregates of sickled cells, atelectasis, or pulmonary edema. In many cases, the specific cause or inciting factor is not apparent. There are no distinctive laboratory features of ACS, although the hemoglobin concentration often declines sharply below the patient's baseline value. In brief, what would be considered pneumonia in a person without SCD usually fulfills the criteria for ACS.

People with ACS generally improve within several days but some develop rapid respiratory failure and/or involvement of other organs such as the brain, kidneys, and liver. This latter complication is known as "multisystem organ failure (MSOF)" (see page 50). Treatment of ACS may include broad spectrum antibiotics, supplemental oxygen, bronchodilators, and blood transfusions. Markers of an impending severe course of ACS are multilobe disease, increased work of breathing, inability to maintain oxygen saturation above 95 percent even with supplemental oxygen, and pleural effusions. Exchange transfusion is often necessary in such circumstances. The therapeutic role of corticosteroids and other anti-inflammatory agents is uncertain and requires further study.[253] Repeated episodes of ACS occur in many patients and can contribute to development of chronic lung disease.

ACS during a hospital admission for an acute VOC may be prevented by incentive spirometry every 2–4 hours while awake.

Key Question

> **KQ15. In people with SCD and ACS, what is the most effective treatment (among transfusion, exchange transfusion, supportive therapy, steroids, and/or antibiotics) to reduce mortality, resolve pain, and prevent clinical deterioration?**

Summary of the Evidence

One RCT, 27 observational studies, and 45 case reports described sickle cell-related ACS. The overall quality of evidence was very low for all interventions except the use of opioids.

The single RCT enrolled 38 children and found that dexamethasone compared to placebo decreased the mean hospital stay (from 80 to 47 hours), the need for transfusions (from 47 percent to 9 percent), the number of administered opioid doses (from a mean of 20 to a mean of 2.5), and clinical deterioration (defined as an increase in oxygen requirements and respiratory rate).[254] Participants and investigators were blinded, allocation was concealed, and the study did not report any baseline imbalances. This short-term benefit, however, was not demonstrated to persist when examined by larger observational studies with longer followup. The largest of these studies was done in 2009 and retrospectively evaluated more than 3,000 people (more than 5,000 admissions).[255] After adjustment for propensity scores and hospital case mix, the study demonstrated a significant increase in the length of hospitalization in people who received corticosteroids as part of their ACS management. Other studies showed increased adverse effects related to steroids.

The remaining observational studies described benefits of other therapies for ACS (e.g., supportive treatment including oxygen supplementation, mechanical ventilation, pain management, hydration, antibiotics, and simple or exchange transfusion). The quality of these studies was low due to the noncomparative nature of their design. Studies that evaluated antibiotics did not demonstrate a significant effect on patient-important outcomes. Multiple observational studies evaluated opiates in ACS. In one, nalbuphine hydrochloride reduced the incidence of ACS compared to morphine (12 percent vs. 29 percent) and also reduced hospital stay.[256] In the remaining studies, opiates clearly reduced pain but without other effects on the clinical course of ACS. Transfusion studies in ACS showed conflicting results. In one study, length of hospital stay was similar between simple transfusion and exchange transfusion, and ICU stay was longer in the exchange group (5.6 days vs. 2.6 days).[257] Another study found significant correlation between exchange transfusion and fewer days of hospitalization and oxygen requirement.[258] In these and other transfusion studies, sicker patients were more likely to receive exchange transfusion, which indicates a clear selection bias.

Recommendations
1. Evaluate people with SCD who develop acute onset of lower respiratory tract disease signs and/or symptoms (cough, shortness of breath, tachypnea, retractions, or wheezing) with or without fever for ACS. This should include a chest x ray and measurement of oxygen saturation by pulse oximetry. *(Consensus–Panel Expertise)*
2. Hospitalize people with ACS. *(Consensus–Panel Expertise)*
3. Treat people with SCD who have ACS with an intravenous cephalosporin, an oral macrolide antibiotic, supplemental oxygen (to maintain oxygen saturation of greater than 95 percent), and close monitoring for bronchospasm, acute anemia, and hypoxemia. *(Strong Recommendation, Low-Quality Evidence)*
4. In people with SCA, give simple blood transfusion (10 mL/kg red blood cells) to improve oxygen carrying capacity to people with symptomatic ACS whose hemoglobin concentration is >1.0 g/dL below baseline. If baseline hemoglobin is 9 g/dL or higher, simple blood transfusion may not be required. *(Weak Recommendation, Low-Quality Evidence)*
5. In people with HbSC disease or HbSβ+-thalassemia with ACS, decisions about transfusion should be made in consultation with an SCD expert. **(Strong Recommendation, Low-Quality Evidence)**
6. In all persons with SCD, perform urgent exchange transfusion—with consultation from hematology, critical care, and/or apheresis specialists—when there is rapid progression of ACS as manifested by oxygen saturation below 90 percent despite supplemental oxygen, increasing respiratory distress, progressive pulmonary infiltrates, and/or decline in hemoglobin concentration despite simple transfusion. *(Strong Recommendation, Low-Quality Evidence)*
7. Encourage use of incentive spirometry while awake. **(Strong Recommendation, Moderate-Quality Evidence)**

Acute Stroke

Background

Stroke is one of the most common and devastating complications of SCD.[77] In the absence of primary stroke prevention, approximately 10 percent of children with HbSS will have overt strokes. This complication presents as sudden onset of weakness, aphasia, and sometimes seizures or coma and results in adverse motor and cognitive sequelae. Transient ischemic attack often precedes stroke, even in children, but neuroimaging is negative and not predictive of stroke. In the absence of primary stroke prevention, an additional 20 to 35 percent of children with HbSS have silent cerebral infarcts, which can cause cognitive decline and predispose them to additional silent infarcts and to overt strokes.[259]

Overt stroke is generally secondary to stenosis or occlusion of the internal carotid or middle cerebral artery, but events may be precipitated by ACS, parvovirus infection, or other acute anemic events.[77,93] In the absence of secondary prevention measures such as a chronic transfusion program or hematopoietic stem cell transplantation, recurrence rates have been shown to range between 46 and 90 percent in children with SCD.[94] People of all ages with HbSC and HbSβ+-thalassemia infrequently have overt CNS events.[77]

Primary stroke prevention using regular blood transfusions in children shown to be at high risk of stroke by TCD screening has led to declines in the incidence of stroke in children with SCD.[97] Although high-quality

studies have been done on primary stroke prevention in children, few studies have examined secondary stroke prevention.

Adults with HbSS also have a high risk of both ischemic and hemorrhagic stroke. The latter is usually sudden and is accompanied by severe headache and loss of consciousness. The mortality rate is high. Limited data suggest that TCD is not predictive of stroke risk in adults. This section of the guidelines addresses the management of acute stroke and the prevention of stroke recurrence (i.e., secondary prevention).

Key Question

> **KQ16. In people with SCD presenting with acute stroke, what is the most effective treatment strategy (transfusion, thrombolytics, hydroxyurea, or other therapies) to reduce mortality, preserve neurological function, and reduce recurrence rates?**

Summary of the Evidence

The systematic review of the literature did not identify comparative studies that evaluated different management strategies to reduce mortality or improve neurologic outcomes of acute stroke in people with SCD. Therefore, the panel based their initial management recommendations on the principles of stroke management in patients without SCD and on their clinical expertise and provided consensus statements.

The systematic review identified seven observational studies[260-266] that reported primarily on the effect of transfusion on preventing recurrent stroke (secondary stroke prevention). Two studies[262,263] reported on the outcomes of stopping chronic transfusion therapy in children who have had prior stroke. There were a total of 20 patients in these studies, and 12 had recurrent central nervous system (CNS) events after discontinuing transfusions. Hulbert et al.[266] conducted a small retrospective study in 52 children presenting within 24 hours of stroke onset and demonstrated that recurrent stroke occurred in 57 percent (8 of 14) of patients treated with simple transfusion, compared with 21 percent (8 of 38) of those treated with exchange transfusion. The study by Russell et al.[261] included 35 children with SCD. Without transfusion, arterial changes documented by arteriography progressed in all four patients who had disease of multiple arteries. After transfusion, vessel changes stabilized. Two of the observational studies reported on long-term outcomes of chronic transfusion. One study followed 60 subjects for a median duration of 36 months, and recurrent strokes were documented in 8 subjects.[265] The other study[264] followed 111 patients and found 1.9 events per 100 patient-years, despite long-term transfusions, thus concluding that the risk of recurrent stroke is decreased but not eliminated by regular blood transfusion therapy. The final study[260] looked at changing the pretransfusion goal of maintaining an HbS of <30 percent to a goal of 50 percent. The median duration of followup was 84 months, and none of the 15 patients studied had a recurrent cerebral infarction during 1,023 patient-months in which the target pretransfusion HbS was 50 percent. These preliminary single-institution findings were then tested in the prospective Stroke With Transfusions Changing to Hydroxyurea (SWiTCH) multicenter phase 3 clinical trial. Children with previous stroke and iron overload were randomized to receive either continued transfusions with iron chelation (standard arm) or hydroxyurea with phlebotomy (alternative arm). The SWiTCH trial had a noninferiority design,[g] with a composite primary end point consisting of recurrent stroke and liver iron concentration.[267] At interim data analysis, there were seven (7/67) strokes on the alternative arm and none (0/66) on the standard arm; this was still within the noninferiority stroke margin, but equivalent liver iron

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[g] A noninferiority trial is a classification of RCT. This type of trial aims to determine whether a new treatment is no less effective than a reference treatment using statistical significance.

content between treatment arms, indicating futility for the composite study end point. Accordingly, the study was closed, and the authors concluded that transfusions and chelation remain a better way to manage children with SCA, stroke, and iron overload.[268]

In addition to the use of transfusion for secondary stroke prevention, the systematic review identified three small observational studies that evaluated the role of hydroxyurea.[94,269,270] The studies enrolled a total of 56 children with a history of stroke who were treated with hydroxyurea. The largest of these studies[270] included 35 children with prior stroke who were discontinued from chronic transfusion therapy. Children were followed on average 42 months with an average hydroxyurea dose of 26.7 mg/kg/d. The stroke recurrence rate for the whole cohort was 5.7 events/100 patient-years, but for children who overlapped transfusion therapy with hydroxyurea treatment, the event rate was 3.6/100 patient-years. The two smaller studies[94,269] showed similar results that were consistent with reduction of stroke recurrence associated with using hydroxyurea. The quality of this evidence was low due to imprecision (small sample size) and the uncontrolled nature of the studies.

Recommendations
1. In people with SCD who present with severe headache, altered level of consciousness, seizures, speech problems, and/or paralysis, evaluate for acute stroke by seeking neurologic consultation and performing an urgent head computerized tomography (CT) scan followed by magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA) if available. *(Consensus–Panel Expertise)*
2. In consultation with a sickle cell expert, perform exchange transfusion in people with SCD who develop acute stroke confirmed by neuroimaging. *(Consensus–Panel Expertise)*
3. Initiate prompt evaluation, including neurologic consultation and neuroimaging studies, in people with SCD who have mild, subtle, or recent history of signs or symptoms consistent with transient ischemic attack. *(Consensus–Panel Expertise)*
4. In children and adults who have had a stroke, initiate a program of monthly simple or exchange transfusions. *(Moderate Strength, Low-Quality Evidence)*
5. In children and adults who have had a stroke, if it is not possible to implement a transfusion program, initiate hydroxyurea therapy. *(Moderate Strength, Low-Quality Evidence)*

Multisystem Organ Failure

Background

Multisystem organ failure (MSOF) is a severe and life-threatening complication usually associated with a VOC and characterized by failure of the lungs, liver, and/or kidneys.[163] MSOF may occur after several days of hospitalization and treatment for a severe VOC, often when pain is beginning to improve. In most cases, patients do not have a history of chronic organ failure. Deterioration is rapid and unexpected. It is usually associated with fever, a rapid decline in hemoglobin concentration and platelet count, and nonfocal encephalopathy. Acute respiratory failure is usually associated with development of ACS. Hepatic failure is associated with marked elevations in total and direct bilirubin, liver enzymes, and blood coagulation screening tests. Acute renal failure is associated with a rapid elevation of serum creatinine, with or without the presence of oliguria and hyperkalemia. Rapid diagnosis and treatment of MSOF is necessary to prevent death.

Summary of the Evidence

An adequate systematic review of the literature with fair sensitivity and specificity for all studies indexed by SCD terms and "multisystem organ failure" was not feasible. No systematic review was conducted, and the panel used a consensus process to develop a proposed strategy for triaging and promptly managing MSOF.

Recommendations
1. In people with SCD who exhibit severe deterioration during a VOC, immediately evaluate for potential MSOF. (*Consensus–Panel Expertise*)
2. In people with SCD and respiratory failure, support respiratory status with supplemental oxygenation and mechanical ventilation when needed. (*Consensus–Panel Expertise*)
3. Use renal replacement therapy (e.g., hemodialysis) when needed for acute renal failure. (*Consensus–Panel Expertise*)
4. In people with SCD and MSOF, immediately initiate either simple or exchange transfusion in consultation with a sickle cell expert or hematologist. (*Consensus–Panel Expertise*)

Acute Ocular Conditions

Background

In persons with SCD, acute ocular complications may occur secondary to trauma, infection, vaso-occlusive episodes leading to occlusion of the eye vasculature, or progression of proliferative sickle retinopathy (PSR). All may have devastating consequences including permanent loss of vision. Hyphema, central retinal artery occlusion (CRAO), orbital and periorbital infections, orbital infarction, and orbital compression syndrome (OCS) all require urgent or emergent assessment and therapy. Although late-stage changes associated with PSR such as nonclearing vitreous hemorrhage and retinal detachment may present with acute visual symptoms, these complications are more fully discussed in the "Managing Chronic Complications of Sickle Cell Disease" chapter of these guidelines.

Hyphema—the presence of blood in the ocular anterior chamber—is often due to blunt injury trauma and typically presents with hemorrhage covering the lower part of the iris and visual abnormalities such as floaters and flashers, light sensitivity, and blurry vision. In persons with SCD, and even in healthy individuals with sickle cell trait, hyphema is especially dangerous due to the hypoxic and acidotic nature of the anterior chamber, which promotes sickling of red blood cells in the aqueous humor. This in turn prevents outflow of sickled erythrocytes and aqueous humor through the trabecular meshwork of the eye and increases pressure in the entire eye. Blood flow in the central retinal artery in the presence of high intraocular pressure (IOP) may result in CRAO and infarction of the optic nerve. Elevated IOP[271,272] is poorly tolerated in people with SCD. The size of the hyphema is poorly correlated with the risk of visual loss.[271-273] In addition, people with SCD tend to have more significant and prolonged hyphema, as well as an increased risk for secondary hemorrhage.[274] Aggressive treatment such as anterior chamber paracentesis or surgical evacuation of a clot may be vision sparing in people with SCD with sustained elevated IOPs that are not responsive to medical management.[271,273-275]

CRAO is a rare cause of acute blindness reported almost exclusively in children and young adults with SCA.[276] It results from thrombus formation in the artery. CRAO causes infarction of the inner retina[277] and results in macular ischemia and potential macular infarction. People typically present with sudden, painless unilateral or

bilateral loss of vision. CRAO has been observed in people with SCD in association with increased IOP secondary to hyphema,[276] moyamoya syndrome,[278] or ACS.[279] CRAO can also occur spontaneously.[280-282]

Orbital infarction is another rare but serious complication of SCD, typically occurring during a VOC. This infarction of the orbital bones is often complicated by hematomas, thought to be a result of ischemic vessel wall necrosis. Because space in the orbital cavity is limited, the inflammatory response generated by infarcted bone may result in further compromise of important eye structures. People typically present with protrusion of the eye, eye pain, and lid and/or orbital edema. On examination, people will have decreased visual acuity and extraocular motility. Differential diagnosis includes periorbital infection due to orbital cellulitis, orbital abscesses, or osteomyelitis, and OCS. Radiographic imaging aids in diagnosis.[283-285] In the case of periorbital infection or orbital bone infarction, rapidly progressive symptoms despite maximal medical management may require surgical intervention.

OCS, also known as orbital apex syndrome, is defined by the presence of compressive optic neuropathy and markedly decreased extraocular motility secondary to involvement of the branches of cranial nerves III and V. Recently, OCS has been described as a result of orbital inflammation after sphenoid bone infarction with subperiosteal hematomas,[285] suggesting significant overlap between orbital infarction and OCS. Prompt initiation of corticosteroids once infection is ruled out can result in reversal of OCS.[285] Diagnostic imaging includes MRI. Surgical intervention may be needed if medical management fails to resolve the compressive optic neuropathy.

Key Question

> **KQ17. In people with SCD and acute eye symptoms, what is the optimal management strategy to preserve vision and prevent long-term ocular complications?**

Summary of the Evidence

Six studies (three RCTs and three observational studies) and 29 case reports described sickle cell-related acute or chronic ocular complications. Of these, the RCTs and the observational studies assessed the management of chronic sickle cell retinopathy, which is discussed in the "Managing Chronic Complications of Sickle Cell Disease" chapter. Twenty-two of the 29 case reports addressed acute complications alone (see evidence tables). Very little data exist to evaluate the most effective therapy to preserve vision during and after acute eye emergencies. The evidence that does exist comes from the case reports, which describe various and often multiple interventions (e.g., calcium channel blockers, intravenous hydration, surgical interventions) for the treatment of hyphema, CRAO, orbital infarction, and OCS. There was not enough evidence to make a recommendation about using transfusion to manage these acute complications.

Due to the paucity of available data, in developing recommendations for acute ocular conditions, the panel placed a high value on the outcome of vision preservation and less value on the burdens and harms of interventions supported with lower quality evidence.

Recommendations
1. Immediately examine for hyphema anyone with SCD who presents with eye trauma. If hyphema is present, immediately refer to an ophthalmologist for further management.   *(Consensus–Panel Expertise)*
2. Promptly refer anyone with SCD exhibiting signs and symptoms such as protrusion of the eye, changes in visual acuity (flashers or floaters), and unilateral or bilateral loss of vision to an eye specialist capable of performing a dilated eye exam to assess visual acuity, intraocular pressure, and the peripheral retina.   *(Consensus–Panel Expertise)*
3. Manage acute ocular complications in consultation with an ophthalmologist, hematologist, and other specialists with expertise in SCD.   **(*Consensus–Panel Expertise*)**