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Clinical Review

EMERGENCY MEDICINE MANAGEMENT OF SICKLE CELL DISEASE COMPLICATIONS: AN EVIDENCE-BASED UPDATE

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☐ **Abstract—Background: Sickle cell disease (SCD) affects approximately 100,000 individuals in the United States. Due to alterations in the structural conformation of hemoglobin molecules under deoxygenated conditions, patients with SCD are predisposed to numerous sequelae, many of which require acute intervention. Objective: Our aim was to provide emergency physicians with an evidence-based update regarding the diagnosis and management of SCD complications. Discussion: SCD patients experience significant morbidity and mortality secondary to cerebrovascular accident, acute chest syndrome, acute vaso-occlusive pain crises, SCD-related multi-organ failure, cholecystitis, acute intrahepatic cholestasis, acute sickle hepatic crisis, acute hepatic sequestration, priapism, and renal disease. Emergency physicians must recognize acute manifestations of SCD in order to deliver timely management and determine patient disposition. Conclusions: A comprehensive review of the emergency department management of acute SCD complications is provided. Comprehensive understanding of these aspects of SCD can assist physicians in expediting patient evaluation and treatment, thus decreasing the morbidity and mortality associated with this hemoglobinopathy.** © 2016 Elsevier Inc. All rights reserved.

☐ **Keywords—sickle cell disease; acute chest; acute pain crisis; cerebrovascular accident; transfusion**

INTRODUCTION

Sickle cell disease (SCD) affects nearly 100,000 individuals in the United States, and approximately 2 million Americans carry the sickle cell trait. SCD is prevalent in persons of African, Mediterranean, Indian, and Middle Eastern descent (1–3). The sickle cell mutation is inherited in an autosomal recessive fashion; homozygotes exhibit sickle cell disease (SCD or HbSS) and heterozygotes exhibit sickle cell trait (SCT). Assuming that they have not inherited a second abnormal hemoglobin (Hb) chain, individuals with SCT are commonly asymptomatic and possess a normal lifespan, while those with SCD are predisposed to severe infections, complications associated with repetitive capillary obstruction, painful vaso-occlusive crises, and multi-system organ damage (1,2).

Complications of SCD occur secondary to the sickle cell mutation: a sixth codon substitution of the B-globin chain, replacing hydrophobic valine with hydrophilic glutamic acid, thereby causing sickling of the Hb molecule under de-oxygenated conditions. The congregation of these sickled cells results in microvascular sludging and vascular obstruction, leading to the acute manifestations (1,2).

As SCD is a component of American newborn screening, the discovery of undiagnosed SCD in the emergency department (ED) is relatively uncommon. More frequently, patients with known SCD present to the ED for evaluation secondary to sequelae of the disease after the fourth month of life (decline in fetal hemoglobin concentration) (3).

Emergency physicians are adept at managing multiple disease processes; however, given the range of

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pathophysiologic manifestations of SCD, encounters with these patients often prove challenging. This review seeks to provide emergency physicians with an improved understanding of SCD complications and an evidence-based approach to their management.

MANAGING ACUTE COMPLICATIONS OF SCD: VASO-OCCLUSIVE CRISES AND SEQUELAE OF HEMOGLOBINOPATHY

Vaso-Occlusive Crises

Cerebrovascular accident: Ischemic stroke and intracranial hemorrhage. Cerebrovascular accident (CVA), including ischemic stroke and subsequent intracranial hemorrhage due to hemorrhagic conversion of the ischemic stroke, is a major complication of SCD. Patients presenting to the ED for assessment will display symptoms that vary according to the anatomic location of the infarct or hemorrhage. Small infarcts in the adult and pediatric populations are relatively common and involve the basal ganglia and deep white matter within the anterior circulation (4). Risk factors for CVA in patients with SCD include low Hb, history of acute chest syndrome (ACS), and history of hypertension (4). The pathophysiology regarding anemia and a history of ACS as CVA risk factors is poorly understood. SCD experts hypothesize severe anemia as precipitating increased cerebral blood flow and increased cerebral flow velocity, thereby predisposing SCD patients (the majority experiencing chronic anemia) to cerebrovascular damage. Scientists also postulate the temporal association between ACS and CVAs as resulting from repetitive episodes of hypoxia in the setting of ACS. This hypoxia likely causes additional damage to cerebral vessels, previously injured by microvascular insults (5). In the assessment of adult and pediatric patients presenting with symptoms concerning for acute intracranial pathology, neuroimaging is key. Initial evaluation of the adult patient commonly includes non-contrast head computed tomography (CT), subsequently followed by CT angiography or magnetic resonance angiography (MRA) during the inpatient course.

Goals for the acute treatment of ischemic stroke in the adult SCD patient include limiting injury due to the CVA and establishing secondary prevention through the optimization of cerebral perfusion (maintenance of euglycemia and normothermia and avoidance of hypoxia) (6). Caution is advised when considering the administration of thrombolytics to adult SCD patients experiencing an acute ischemic CVA. Increased rates of intracranial hemorrhage have been reported in this patient population (6). Similar to adult patients without a medical history of SCD, antiplatelet and statin therapy should be considered after an ischemic CVA (6). In addition to the strategies mentioned for secondary CVA prevention, experts also recommend regular transfusions to maintain Hb S < 30%; however, data supporting this intervention was collected in young adults with SCD having experienced their first CVA during childhood (hence its employment in the pediatric population, as discussed later) (6).

In contrast to adults, magnetic resonance imaging (MRI) with diffusion-weighted imaging and MRA of the head and neck should be performed in pediatric patients with suspected acute ischemic stroke, as a non-contrast head CT will miss early signs of ischemic infarct (5). All pediatric patients diagnosed with an ischemic stroke thought secondary to SCD should receive intravenous (IV) fluids and undergo exchange transfusion to achieve an Hb S level of < 30% (5). This procedure should be performed in consultation with a hematologist. If an exchange transfusion cannot be arranged, a simple transfusion should be performed (5). A maximum Hb of 13 g/dL status post transfusion is the recommended target, as pediatric children with SCD may be at risk for recurrent ischemia secondary to increased blood viscosity (5). Currently, thrombolysis is not recommended in pediatric SCD patients presenting with ischemic CVAs (5). One key point that the emergency physician must consider when evaluating the pediatric SCD patient is that hemorrhagic transformation occurs in 30% of children with arterial ischemic and is frequently asymptomatic (7).

To date, there are no published studies regarding the management of hemorrhagic CVA in adult or pediatric SCD patients (6). Previously recognized efficacious treatments for acute intracranial hemorrhage in the general adult and pediatric population include reversal of anticoagulation, treatment in an intensive care unit (ICU), treatment of seizures with antiepileptic agents, and appropriate management of blood pressure (BP) (6).

While BP management in acute CVA is well addressed in adult emergency medicine literature, the management of pediatric hypertension in the setting of CVA is not as well studied. Hypertension in children, defined as BP > 95th percentile for age, within the first 72 h after ischemic stroke is associated with an increased risk of death (8). In the pediatric population, a BP goal of the 50–95th percentile for age and height, with permissive hypertension up to 20% > 95th percentile, should be targeted (6). Pediatric experts recommend use of labetolol or an angiotensin-converting enzyme inhibitor to lower BP by 25%, though renal function should be considered (6,9).

Of note, seizures are common after pediatric neurologic injury (10). Patients with persistent lethargy or altered mental status should be evaluated with electroencephalography for subclinical seizure activity (7).

Table 1. Differentiating Acute Chest Syndrome and Acute Pain Crisis

	Acute Chest Syndrome	Pulmonary Acute Pain Crisis
Clinical presentation	Chest pain, fever, shortness of breath, hypoxia	Chest pain, fever, shortness of breath
Laboratory studies	Leukocytosis	Leukocytosis
Chest x-ray study	New infiltrate (pediatric: middle or upper lobe; adult: lower lobe)	No acute cardiopulmonary findings
Treatment	Antibiotics: community-acquired pneumonia vs. health care–associated pneumonia (history-dependent); ICU admission	Pain controlled without hypoxia: home Unable to attain pain relief: admission
Feared complication	Acute respiratory distress syndrome	Atelectasis and subsequent pneumonia due to splinting and low tidal volumes

ICU = intensive care unit.

In the setting of SCD, an investigation of alternative causes of CVA cannot be overlooked. Etiologies include infection, cardiac embolism, and cavernous venous sinus thrombosis (7).

Imaging, to include MRI and MRA of the head and neck, may be essential in narrowing the differential diagnosis (7).

ACS. ACS, the most common reason for ICU admission in the SCD patient population, is a leading cause of morbidity and mortality (case fatality rate of 10%) (11). The classic triad of ACS includes fever, hypoxia, and a new pulmonary infiltrate on chest x-ray study. The presence of any one of these signs or symptoms should raise clinical suspicion in the setting of SCD. When evaluating a patient for ACS, a chest x-ray study should be obtained to identify the presence of a new infiltrate, a complete blood count (CBC) should be sent to assess anemia, and continuous oxygenation monitoring should be performed to detect hypoxia.

While the pathogenesis of ACS has yet to be determined, infection secondary to *Mycoplasma pneumoniae* frequently represents the underlying etiology in the pediatric population (12). In adult sickle cell patients, *Chlamydophila pneumonia* is the most commonly encountered pathogen (13). Additional non-infectious etiologies of ACS include fat emboli (released as a result of bony infarct from vaso-occlusion) and pulmonary emboli (disseminated post microvascular pulmonary infarction) (13).

Differentiating ACS and pulmonary acute pain crisis (APC) (which will be discussed) is difficult, as these SCD complications often present with fever, shortness of breath, chest pain, and leukocytosis (1,2,14). Any respiratory symptoms associated with chest pain and hypoxia should raise suspicion for ACS. A new infiltrate on chest x-ray study is diagnostic of ACS, as opposed to APC. Unfortunately, the chest x-ray study may be normal early in ACS (2,14). When evaluating chest x-ray studies, note that children are more likely to display upper or middle lobe disease, as opposed to adults, who frequently display lower lung disease with an infiltrate and associated pleural effusion (14). See Table 1 for a review of ACS vs. pulmonary symptoms of APC.

ACS can rapidly progress to acute respiratory distress syndrome due to pulmonary sequestration or infarct. Given this fact, patients with signs or symptoms consistent with ACS should be managed in an intensive care setting. Long-term complications of ACS include pulmonary fibrosis, pulmonary hypertension, and cor pulmonale. Acute right ventricular failure is a complication of ACS and if suspected, ultrasound (US) should be utilized to assess right ventricular contractility and size (14).

Evidence-based guidelines and expert panels are shown in Table 2 for the management and treatment of ACS.

APC. Vaso-occlusive pain crises may manifest in a number of locations, including the pulmonary system, central nervous system, skeletal system (arthralgias/dactylitis), and gastrointestinal system (abdominal pain). In the setting of these crises, patients commonly present with fever and leukocytosis (12). Although fever and leukocytosis are not specific indicators of infection, it is wise to evaluate for an infectious etiology in the sickle cell patient population, as these individuals are highly susceptible to pathogens (addressed within at a later juncture) (11).

SCD patients are prone to several complications that must be considered during the evaluation of patients presenting with pain crisis. These complications range from the sequelae of hemoglobinopathy to renal pathology (both later addressed) to the infectious etiologies mentioned. Inquiries regarding prior pain crises, differences between current and previous episodes, the presence of fever, transfusion history, medications, baseline Hb level, and a thorough physical examination can assist in determining diagnoses. Any atypical pain pattern not consistent with previous episodes requires further evaluation.

In addition to an assessment for conditions requiring acute interventions, it is important to note that the

Table 2. Management and Treatment of Acute Pain Crisis (3,15)

Recommendation	Level of Recommendation	Quality of Evidence
ACS patients should be hospitalized for pain control and SpO_2 monitoring	Consensus	Panel expertise
ACS patients should receive antibiotics (parenteral cephalosporin or oral macrolide therapy)	Strong	Low quality
ACS patients should receive supplemental O_2 to maintain SpO_2 > 95%	Strong	Low quality
Patients with ACS should receive a blood transfusion to improve O_2 carrying capacity if Hb is > 1 g/dL below baseline (if baseline is > 9 g/dL, may not be required; consult hematology)	Weak	Low quality
ACS with rapid progression (SpO_2 < 90% despite O_2 therapy, respiratory distress, progressive pulmonary infiltrates, decline in Hb despite simple transfusion) requires urgent exchange transfusion	Strong	Low quality
Consult hematology		

ACS = acute chest syndrome; APC = acute pain crisis; Hb = hemoglobin.

management of pain crises includes the provision of early analgesia—an area in which emergency physicians commonly under-prescribe (2,3). Evidence-based guidelines regarding management and treatment of pain crises are demonstrated in Table 3.

Opioid analgesics are the current mainstay of APC therapy. Morphine, fentanyl, and hydromorphone are commonly utilized in the ED treatment of acute pain crisis (15–23). Caution is recommended in the utilization of meperidine (normeperidine, the active metabolite of meperidine, undergoes renal excretion and is associated with an increased incidence of seizures in the setting of renal dysfunction; a finding common in occlusive crisis) (3,12,15).

Varying algorithms for the management of APC are detailed by multiple guidelines and organizations (16–22). Provided as an example, the National Heart, Lung, and Blood Institute (NHLBI) algorithm is depicted in the Figure 1. This example was chosen by the authors given its value in demonstrating an all-encompassing approach to patient analgesia: the inclusion of patient perception of pain, a mention of detailed recommendations regarding initial opioid dosing, the provision of direction regarding adjuncts to pain control, and an emphasis on repeated patient assessment in determining disposition.

As all of the APC guidelines note, further studies are required to evaluate the adequacy of varying opioid analgesics regimens in controlling APC pain, to determine the efficacy of delivery routes and dosing intervals, and to develop consensus statements regarding the provision of patient analgesia in APCs (16–22). If possible, organizations should work toward the development of APC patient-management protocols, as case studies have demonstrated decreased time to the delivery of patient analgesia, improvement in overall patient pain control, decreased frequency of ED visits, fewer total hospital days, and increased utilization of primary provider services status post algorithm employment (23–25).

As depicted in Figure 1, pain-control adjuvants detailed by the NHLBI include sedatives, anxiolytics, and antihistamines. While employed to augment the analgesic effect of opioids by managing associated symptoms, such as anxiety, and to prevent mast cell degranulation induced by opioid administration, controlled studies of these treatments in SCD are lacking, and per the NHLBI, guidelines for their use are derived from employment in other pain states (16).

Similar to other algorithms and treatment guidelines, the NHLBI recommends that all patients who do not achieve adequate pain relief be admitted to the hospital for further therapy (16). Patients with an anticipated discharge to home should be prescribed an oral pain-control regimen with potency comparable to the IV pain regimen, which provided pain relief during the hospital course (16–22).

For APC patients requiring admission, patient-controlled pain management strategies deserve consideration by the emergency physician. Despite the need for further research, case reports and limited case studies have demonstrated shorter time to pain control,

Table 3. Management and Treatment of Acute Pain Crisis (3,14)

Recommendation	Level of Recommendation	Quality of Evidence
Initiate analgesia within 30 min of triage; provide multi-modal (opioid and adjunct) analgesia	Consensus	Panel expertise
Employ individualized prescribing and pain-monitoring protocols	Consensus	Panel expertise
Give nonsteroidal anti-inflammatory drugs as adjuvant pain therapy	Moderate	Low quality

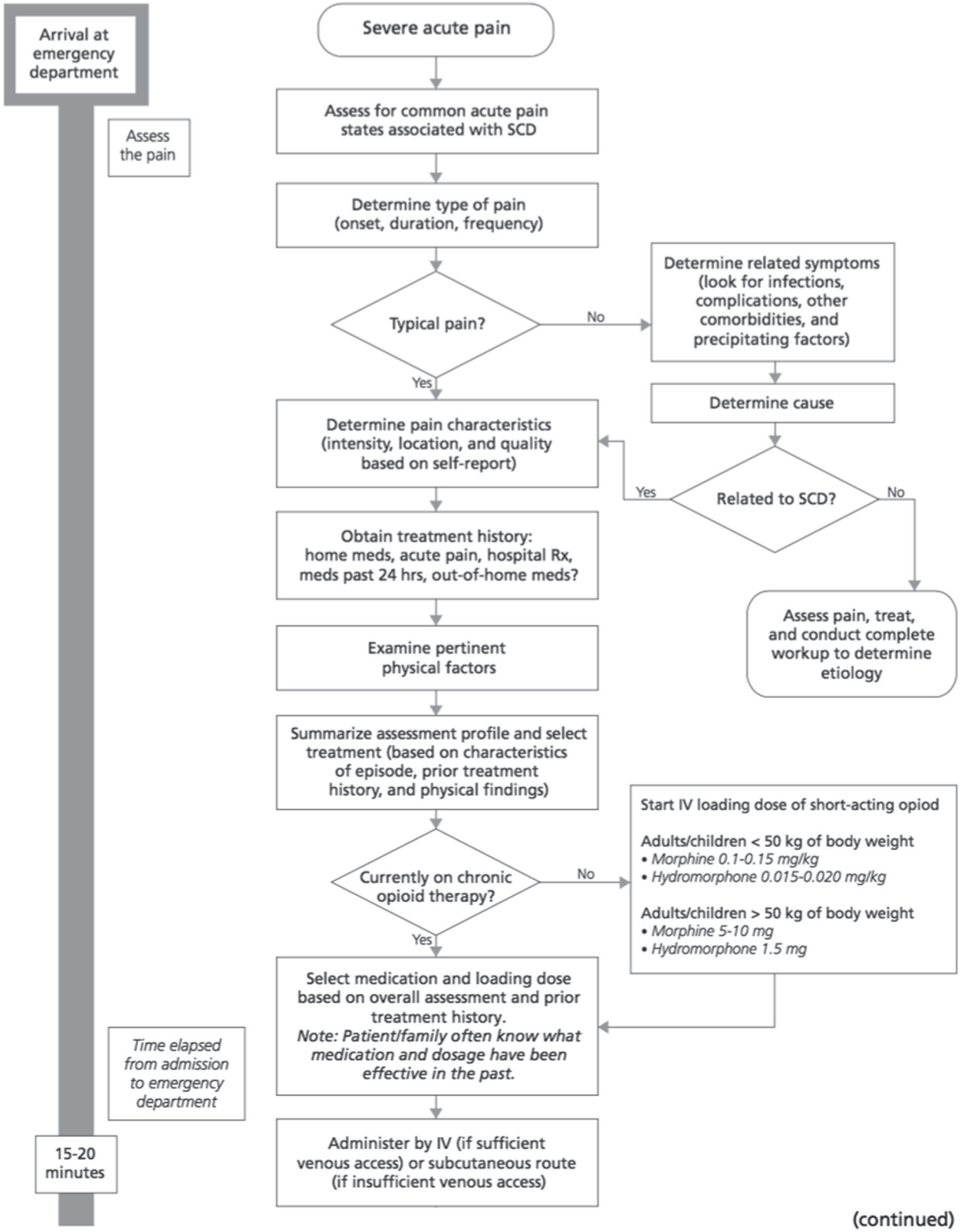

Figure 1. National Heart, Lung, and Blood institute algorithm for the management of acute pain crisis (16). SCD = sickle cell disease.

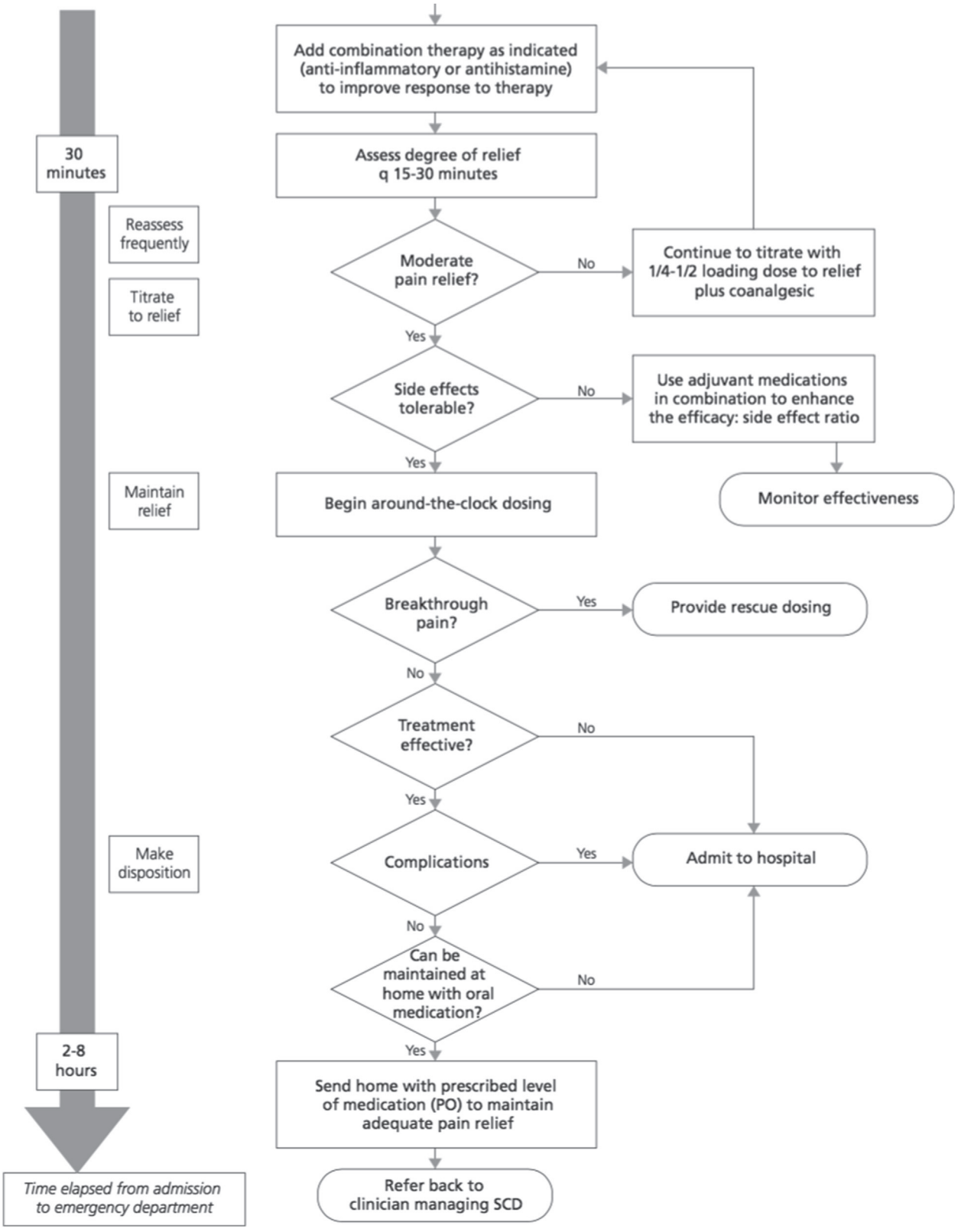

Figure 1. ***(Continued).***

improved pain relief and, in some cases, earlier time to hospital discharge among patients receiving patient-controlled pain management (26,27).

In addition to pain control, literature addressing APC treatment commonly advises the initiation of oxygen supplementation and fluid resuscitation. However, recent guidelines question these classic treatments. To date, oxygen has demonstrated no benefit in SCD pain crises, and new research suggests it may actually result in myelosuppression and an increased need for transfusion (14). Current expert guidelines recommend that if saturations remain > 92%, no supplemental oxygen is recommended (14). Although IV fluids are frequently provided in the setting of APC, it is now commonly recognized that excessive hydration can contribute to atelectasis, hyperchloremic metabolic acidosis (if normal saline is utilized), and pulmonary edema. If the patient is overtly dehydrated and hypovolemic, IV fluids are warranted. Otherwise, maintenance of euvolemia is encouraged (14).

Although this review centers on the management of acute SCD complications, hydroxycarbamide (also known as hydroxyurea [HU]) therapy warrants mention. HU is the most common intervention utilized in the long-term management of SCD for the prevention of vaso-occlusive events (28). HU has been demonstrated to increase fetal Hb levels, subsequently preventing the polymerization of Hb S under deoxygenated conditions (17,28,29). As demonstrated by the Multi-Center Study of Hydroxyurea in Sickle Cell Anemia and the Pediatric Hydroxyurea Phase 3 Clinical Trial (BABY HUG), the administration of HU significantly decreases the incidence of adult and pediatric vaso-occlusive crisis, APC, and rates of hospitalization secondary to SCD complications (17,28,29). If not previously initiated, HU therapy should be considered in consultation with a hematologist for all patients presenting to the ED with SCD complications (27).

SCD-related multi-organ failure. This severe, life-threatening complication of SCD is characterized by sudden vaso-occlusion with organ failure, specifically affecting the lungs, liver, and kidneys. Patients may present with fever, tachypnea, and, in severe cases, hemodynamic compromise (14). Careful assessment of the pulmonary and renal systems, including advanced imaging, is advised. Laboratory studies commonly reveal elevated lactate dehydrogenase, anemia, thrombocytopenia, and an acute kidney injury or acute renal failure. Chest x-ray study is often notable for multi-lobar infiltrates. Patients with SCD-related multi-organ failure require ICU admission in addition to specialty hematology or nephrology, or both, consultation (14). Exchange transfusion is often warranted in association with hematology consultation (14).

Sequelae of Hemoglobinopathy

Right upper quadrant abdominal pain. Abdominal complications are common in SCD, especially complications causing pain in the right upper quadrant (RUQ). For SCD patients with RUQ pain, the challenge for the emergency physician is to ascertain the underlying etiology: cholelithiasis, cholecystitis, acute intrahepatic cholestasis (AIC), acute sickle hepatic crisis, or acute hepatic sequestration (AHS) (1). In the evaluation of RUQ pathology, initial studies including CBC, liver function tests, coagulation panel (prothrombin time/activated partial thromboplastin time/international normalized ratio [PT/aPTT/INR]), and imaging with ultrasound (US) or CT are essential.

Hemolysis precipitates the formation of pigmented gallstones in up to 70% of patients, increasing the risk of symptomatic cholelithiasis and cholecystitis in SCD (2).

AIC is a result of sickled red blood cells (RBCs) occluding hepatic sinusoids, causing vascular stasis and local hypoxia. As Kupffer cells (hepatic macrophages) phagocytose sickled erythrocytes, canaliculi occlude with bile (30). Patient presentation ranges from isolated hyperbilirubinemia with preserved hepatic function (PT/aPTT/INR within normal limits) to RUQ pain, transaminitis, and extreme elevations of bilirubin and alkaline phosphatase. In the latter case, renal failure, thrombocytopenia, and severely prolonged coagulation times often develop (31). If severe acute intrahepatic cholestasis is suspected, early consultation with hematology for exchange transfusion is indicated.

Acute sickle hepatic crisis affects 10% of patients admitted for abdominal pain crises (31). Acute sickle hepatic crisis simulates acute cholecystitis with RUQ pain, fever, leukocytosis, and variable increases in serum transaminases and bilirubin levels; however, unlike cholecystitis, hepatomegaly occurs (31). Treatment is supportive with pain control and consultation for possible transfusion (1,31).

AHS occurs secondary to obstruction of sinusoidal flow by masses of sickled erythrocytes and can be a complication of acute sickle hepatic crisis (15,30). In addition to RUQ pain, fever, jaundice, and hepatomegaly, an acute drop in Hb and hematocrit with reticulocytosis occurs (31). Consultation with hematology is recommended. This too can be an indication for simple or exchange transfusion (1,32).

It is important to note that the laboratory studies of a patient with SCD cannot be interpreted in a vacuum. In SCD patients, chronic liver disease often occurs secondary to hemosiderosis (transfusions) and silent

microvascular occlusions (30). Obtaining a history regarding frequency of transfusions and baseline hepatic function is invaluable in assessing chronic vs. acute pathology (1,2).

Imaging of the RUQ. Abdominal US is the primary modality for evaluation of RUQ pathology in sickle cell patients. US may reveal gallstones, common bile duct pathology, pericholecystic fluid, and increased echogenicity of the gallbladder and pancreas secondary to iron deposition (a known complication of recurrent transfusions) (33). Data regarding the utilization of CT in the evaluation of sickle cell patients with abdominal pain is limited. In one study, CT provided a diagnosis that affected management in 17 of 30 patients (33). Hepatic infarction, hepatic abscess, iron overload, and retained common bile duct stones post cholecystectomy were among the notable findings (33). Clinical judgment should be employed when assessing the need for CT. Table 4 offers a summary of RUQ pathology.

Splenic sequestration. Splenic sequestration typically occurs in children 10–27 months of age, but it may be seen as early as 2 months of age (11,12). Pooling of RBCs in splenic sinusoids results in splenic sequestration, with an acute decline in Hb levels (>2 g/dL) associated with splenomegaly, reticulocytosis, and signs of intravascular volume depletion (12). Patients may present with abdominal pain, pallor, tachycardia, and hypotension. Sequestration can rapidly progress to shock and death. Decreases in Hb levels > 4 g/dL are associated with 35% mortality in the pediatric population (11,12).

Emergency management of splenic sequestration is aimed at restoring circulating blood volume through IV fluid resuscitation or blood transfusion (11–13). As splenic sequestration has a high rate of recurrence, all cases should be managed in conjunction with a hematologist, as patients may be considered for splenectomy (1,12). After 3–5 years of age, the risk of splenic sequestration decreases dramatically, owing to splenic auto-infarction (12,13).

Sickle cell nephropathy/infarcts. The kidney is one of the most commonly affected organs in SCD (34). Ischemic damage caused by RBC sickling in the vasa recta predisposes patients to a number of glomerulopathies resulting in renal dysfunction (29). Infarct of the renal medulla secondary to vaso-occlusion can present with flank pain and costovertebral angle tenderness (34). Alternatively, papillary necrosis can result in gross or microscopic hematuria (2). Because renal dysfunction can be a manifestation of infarction of the renal medulla or papillary necrosis, admission for IV fluid

Table 4. Summary of Right Upper Quadrant Pathology (1,2,31,32)

Disease Process	Common Patient Presentation	Examination Findings	Laboratory Studies/Imaging	Treatment
Symptomatic cholelithiasis	RUQ pain, mid-epigastric pain, postprandial nausea, indigestion, emesis	RUQ TTP	Laboratory studies within normal limits RUQ US demonstrating gallstones or biliary sludge	HIDA scan vs. elective cholecystectomy
Cholecystitis	RUQ pain, mid-epigastric pain, nausea, indigestion, emesis, fever	Fever, RUQ TTP	Leukocytosis, transaminitis, coagulation studies within normal limits RUQ US demonstrating pericholecystic fluid, common bile duct dilatation, or gallbladder wall thickening	Antibiotics, surgical resection
Acute intrahepatic cholestasis	RUQ pain, mid-epigastric pain, nausea, indigestion, emesis	RUQ TTP	Variable: isolated hyperbilirubinemia without transaminitis, to severe transaminitis, acute renal failure, thrombocytopenia and coagulation abnormalities (PT/aPTT/INR)	Inpatient monitoring for isolated hyperbilirubinemia vs. admission and exchange transfusion (in consultation with a hematologist) in severe cases
Acute sickle hepatic crisis	RUQ pain, mid-epigastric pain, nausea, indigestion, emesis, fever	Fever, RUQ TTP, hepatomegaly	Variable transaminitis and hyperbilirubinemia	Pain control, consultation for admission and possible transfusion (in consultation with a hematologist)
Acute hepatic sequestration	RUQ pain, mid-epigastric pain, nausea, indigestion, emesis, fever, jaundice	Fever, RUQ TTP, hepatomegaly	Acute decrease in hemoglobin and hematocrit with elevated reticulocyte count, and hyperbilirubinemia	Inpatient monitoring with exchange transfusion (in consultation with a hematologist)

HIDA = hepatobiliary; PT/aPTT/INR = prothrombin time/activated partial thromboplastin time/international normalized ratio; RUQ = right upper quadrant; TTP = tenderness to palpation; US = ultrasound.

administration and serial renal function examination is advised. Definitive diagnosis of these etiologies can be obtained with CT scan (CT with IV contrast vs. CT IV pyelogram) (2,35). Careful assessment of baseline renal function panel is required, as the pattern and rate of change of serum creatinine is more helpful than the absolute level (34). Ultimately, 30% of patients with SCD develop chronic kidney disease, with approximately 12% of patients developing end-stage renal disease (32,36).

Priapism. Priapism occurs in up to 30% of males with SCD (34). Ischemic priapism (low-flow or veno-occlusive priapism) is the most common form of priapism encountered in the SCD population, representing > 60% of cases in children and > 25% of cases in adults presenting for treatment (36). Patients experiencing ischemic priapism often present with rigid, painful corpora cavernosa. As this condition is associated with decreased or absent cavernosal blood flow, emergent intervention is required to prevent irreversible corporal damage and subsequent erectile dysfunction (37).

If questions arise regarding the etiology of the priapism, blood gas testing is a reliable diagnostic method of distinguishing ischemic from non-ischemic priapism in the ED. Blood aspirated from the corpus cavernosum in patients with ischemic priapism is oxygen-deplete and, therefore, dark, while blood from the corpus cavernosum in patients with non-ischemic priapism is normally oxygenated and therefore bright red (38). Cavernosal blood gases in males with ischemic priapism typically have a PO_2 of < 30 mm Hg, a PCO_2 of > 60 mm Hg, and a pH < 7.25 (38).

Treatment of ischemic priapism in the male adult and male pediatric population includes needle aspiration of blood from the corpora cavernosa, followed by intercavernosal injection of sympathomimetic (1-mL aliquots [up to 3 mL] of 100–500 μg/mL phenylephrine) (2,22). Figure 2 provides a reference of relevant anatomy. Assuming a clock face is placed with the 12 o'clock position centrally located to the dorsal vein, it is advised that aspiration and injection occur at the 3 o'clock and 9 o'clock positions to avoid injury to the dorsal vein, deep dorsal nerve, and urethra (38). Measures to treat SCD (hydration and exchange transfusions) may be utilized but should not delay aspiration and phenylephrine administration (32,26).

Infection. Given the lifelong risk of increased infection, any fever in a patient with SCD necessitates evaluation. Common etiologies of fever in an SCD patient include APC, bacteremia, osteomyelitis, or infection causing ACS (39). Evaluation of adult and pediatric SCD patients should include a thorough history and physical

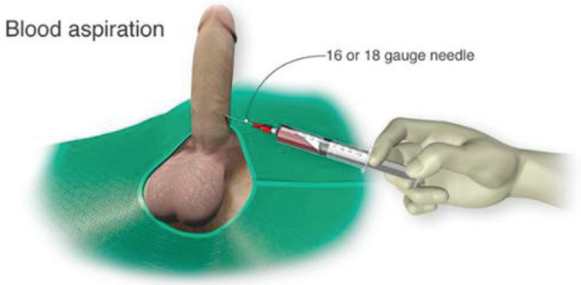

Figure 2. Aspiration/injection site (36).

examination. In addition to obtaining a urine culture for children reporting urinary symptoms, pediatric SCD experts recommend that a blood culture be obtained when leukocyte count is > 20 × 10^9/L with a high proportion of bands (39). Current literature does not advocate for this testing in adult patients, as clinical judgment should govern their evaluation.

Bacterial infections are a common cause of mortality in SCD (39). Increased susceptibility to bacterial infection is often the result of impaired splenic function. Due to chronic splenic infarction, 14% of SCD patients are functionally asplenic by 6 months of age, which reaches 94% by 5 years of age (2). In addition, a number of sickle cell patients are asplenic secondary to therapeutic splenectomy, the treatment for recurrent sequestration crises (2).

Bacterial pathogens, including *Streptococcus pneumoniae*, *Haemophilus influenzae* type b, non-typhi *Salmonella* species, *Mycoplasma*, *Chlamydophila pneumonia*, and *Yersinia enterocolitis*, commonly occur in sickle cell patients (39). Before widespread *S. pneumoniae* and *H. influenzae* type b vaccination, pediatric patients with SCD had a 400-fold increased risk of *S. pneumoniae* sepsis and a 2- to 4-fold increased risk of *H. influenzae* sepsis compared with age-matched children without SCD (39).

In terms of viral disease affecting SCD patients, hepatitis C and B (discussed in the Transfusion Complications section), parvovirus B19 (addressed under the Aplastic Crisis section), and influenza are notable. One study, performed by Bundy et al., demonstrated a hospitalization rate of pediatric SCD patients with influenza as 56 times that of their non-SCD counterparts (40). While yet a hypothesis, this variation is attributed to the pre-disposition of SCD patients with influenza toward development of secondary bacterial pneumonia, ACS, or APC; therefore, addressing this viral illness is paramount (40). Current Centers for Disease Control and Prevention (CDC) Guidelines advocate the provision of oseltamivir to all SCD patients (>2 weeks of age) presenting within 48 h of the onset of flu-like symptoms, in order to decrease the severity and shorten the duration

of illness (41). It is also advised that oseltamivir chemoprophylaxis be given to all patients, aged 3 months or older, having a known exposure to persons with confirmed influenza infections (American Academy of Pediatrics recommendation; oseltamivir is Food and Drug Administration–approved for use in patients > 1 year of age) (41).

In order to prevent serious infection among SCD patients, the following measures have also been recommended by the CDC:

1. Prophylactic penicillin V for patients aged 2 months to 5 years to prevent serious bacterial infection (1).
2. Pneumococcal vaccine at 2 months of age to reduce the risk of pneumococcal infection (1).
3. Influenza vaccination at 6 months and annually thereafter (1).
4. Meningococcal vaccination for children with splenic dysfunction at 2 years of age (1).

Although commonly addressed by primary care managers, it serves the emergency physician to make inquiries regarding penicillin prophylaxis and vaccination status during encounters with SCD patients, as this information will aid in the development of differential diagnoses (42).

Aplastic crisis. Aplastic crisis in SCD is commonly secondary to parvovirus B19 infection, but can occur with any infectious agent. Patients may present with pallor and tachycardia due to a transient failure of erythropoiesis (2). A prodrome of upper respiratory symptoms is often followed by an acute, severe drop in Hb. In severe cases, patients present with hemodynamic instability and a decreased reticulocyte count. Fortunately, the decline in reticulocyte count is generally brief, resolving in a matter of days (1,2).

ED care of aplastic crisis is supportive and depends on the degree of anemia and cardiovascular compromise (10). If the reticulocyte count is < 1–2% with no signs of spontaneous recovery, simple transfusions are administered to raise the Hb to approximately > 9 g/dL and the hematocrit to 30% (11,43). SCD patients with aplastic crisis should be admitted to the ICU with droplet precautions (11).

Transfusion Requirements

Transfusion indications. The goal of transfusion is to increase oxygen-carrying capacity, but this is not straightforward in SCD. Patients with SCD experience chronic anemia, but compensatory mechanisms, including increased cardiac output, improve oxygen delivery. Simple transfusions are utilized for severe anemia causing physiologic compromise, or a sudden decrease in Hb levels in the setting of acute splenic or hepatic sequestration crisis (12). Exchange transfusions are needed in the setting of suspected or confirmed CVA, treatment-resistant acute chest or acute lung disease, multi-organ failure, preparation for general anesthesia, and priapism unresponsive to other treatment (12).

Transfusion complications. Transfusing RBCs to patients with SCD can be precarious, as increasing RBC mass increases blood viscosity, thereby exacerbating sickling (12). In addition to increased blood viscosity, the complication of multi-transfusion hepatopathy is also well studied in the sickle cell population. Individuals receiving repetitive transfusions may experience hepatic iron overload, subsequently requiring chelation therapy (37). Blood-borne infections including chronic hepatitis B, hepatitis C, and cytomegalovirus are also commonly encountered in the highly transfused sickle cell population; however, studies reporting the prevalence of these infections (supported by confirmative genotyping and polymerase chain reaction) are limited (37). The risks and benefits of a simple vs. exchange transfusion should always be determined in consultation with a specialist (12).

CONCLUSIONS

SCD is a chronic hemoglobinopathy with significant morbidity and mortality due to its sequelae. Complications include ACS, CVA, vaso-occlusive pain crises, SCD-related multi-organ failure, cholecystitis, AIC, acute sickle hepatic crisis, AHS, acute renal disease, and priapism. Emergency physicians must recognize these acute manifestations, provide early pain management and resuscitation, and expeditiously determine patient disposition.

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