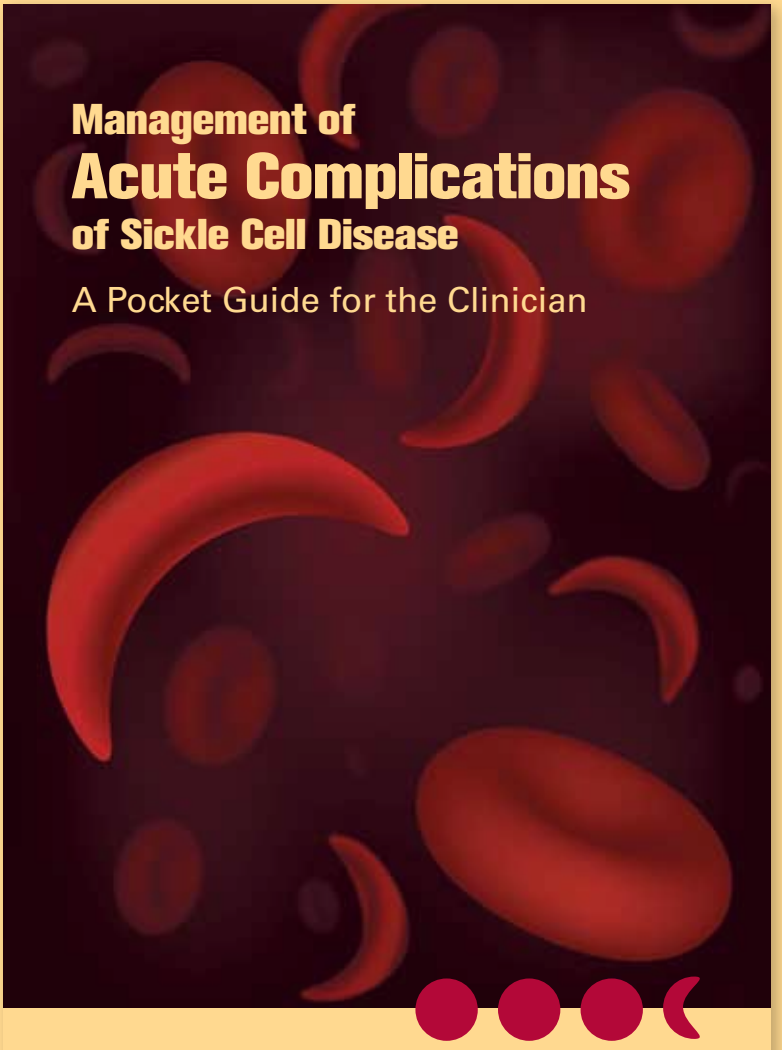

Management of Acute Complications of Sickle Cell Disease

A Pocket Guide for the Clinician

Timothy McCavit, MD, MSCS[1]
Payal Desai, MD[2]
[1]*University of Texas Southwestern Medical Center*
[2]*The Ohio State University, the James Cancer Center*

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Common Acute Complications of Sickle Cell Disease (SCD)

Complication	Risk Factors and Presentation	Evaluation	Transfusion Indicated?	Management
Acute chest syndrome (ACS)	ACS resembles pneumonia, eg, the patient has signs and symptoms of lower respiratory tract disease and a new pulmonary infiltrate on chest radiograph. ACS can develop suddenly or insidiously. Patients may present with ACS, or it may occur during hospitalization for a vaso-occlusive crisis or after a surgical procedure, especially one involving the abdomen. Risk is increased in people with asthma or prior ACS events. ACS is the most common cause of death in adults with SCD.	Should include chest x-ray and measurement of oxygen saturation by pulse oximetry ***(Consensus–Expert Panel)***. Should also include CBC/reticulocyte count and blood culture.	Usually, but not always for mild cases	Treat with intravenous cephalosporin and an oral macrolide antibiotic. If the patient is hypoxemic, administer supplemental oxygen to maintain >95% oxygen saturation. Monitor closely for bronchospasm, acute anemia, and hypoxemia. ***(Strong recommendation, low-quality evidence)*** Consider simple blood transfusion (10 mL/kg RBCs) if Hb concentration is >1.0 g/dL below baseline ***(Weak recommendation, low-quality evidence)***. If baseline Hb is ≥9 g/dL, simple transfusion may not be indicated ***(Weak recommendation, low-quality evidence)***. Avoid transfusing to a target Hb >10 g/dL ***(Moderate recommendation, low-quality evidence)***. Perform urgent exchange transfusion if there is rapid progression of ACS as manifested by <90% oxygen saturation (despite supplemental oxygen), increasing respiratory distress, progressive pulmonary infiltrates, and/or decline in hemoglobin concentration (despite simple transfusion) ***(Strong recommendation, low-quality evidence)***. Encourage use of incentive spirometry while awake ***(Strong recommendation, moderate-quality evidence)***.
Fever	Individuals with sickle cell anemia have an increased risk of severe bacterial infection. Risk continues throughout childhood and to a lesser extent in adults. Fever may herald many acute and sometimes life-threatening conditions, such as acute chest syndrome (ACS) or osteomyelitis.	Should include CBC with differential, reticulocyte count, blood culture, and urine culture when urinary tract infection is suspected ***(Consensus–Expert Panel)***. If fever is accompanied by shortness of breath, tachypnea, cough, and/or rales, investigate for ACS ***(Consensus–Expert Panel)***.	Depends on other indications	Hospitalize patients with temperature ≥103.1°F (39.5°C) and who appear ill for close observation and parenteral antibiotic therapy ***(Consensus–Expert Panel)***. For children with a temperature ≥101.3°F (38.5°C), administer parenteral antibiotics with coverage against *Streptococcus pneumoniae* and gram-negative enteric organisms. Subsequent outpatient management using an oral antibiotic is feasible in patients who do not appear ill. ***(Consensus–Expert Panel)***
Hepatobiliary complications	Abnormalities include acute cholecystitis, biliary sludge, acute choledocholithiasis, acute hepatic sequestration (AHS), and acute intrahepatic cholestasis (AIC). AIC is characterized by sudden onset of RUQ pain, increasing jaundice, progressively enlarging and exquisitely tender liver, and extreme hyperbilirubinemia without evidence of common duct obstruction or cholangitis.	Initial workup may include CBC/reticulocyte count, ALT, and bilirubin, with RUQ sonogram if initial workup is suggestive. For abnormal liver function test during acute pain crisis, consider RUQ ultrasound. If choledocholithiasis is suspected, consider ERCP (endoscopic retrograde cholangiopancreatography).	Yes, for AHS or severe AIC	Treat acute cholecystitis with antibiotics and surgical consultation ***(Consensus–Expert Panel)***. For symptomatic gallstones, treat with cholecystectomy.* A laparoscopic approach is preferred if feasible and available. ***(Strong recommendation, moderate-quality evidence)*** In children and adults with SCD with confirmed AHS or severe AIC, perform simple or exchange transfusion ***(Consensus–Expert Panel)***. Consult a sickle cell expert.
Multisystem organ failure (MSOF)	MSOF usually occurs in adults in the context of a severe vaso-occlusive crisis. Deterioration is rapid and unexpected. Signs may include fever, a rapid decline in hemoglobin concentration and platelet count, and nonfocal encephalopathy.	May include tests of lungs, liver function, and/or kidney function. Rapid diagnosis and treatment is necessary to prevent death.	Yes	Initiate simple or exchange transfusion ***(Consensus–Expert Panel)***. Use renal replacement therapy as needed ***(Consensus–Expert Panel)***. Provide respiratory support as needed up to and including mechanical ventilation ***(Consensus–Expert Panel)***.

Common Acute Complications of Sickle Cell Disease (SCD), cont'd

Complication	Risk Factors and Presentation	Evaluation	Transfusion Indicated?	Management
Pain from vaso-occlusive crisis (VOC)	Management of acute pain is central to the care of individuals with SCD, yet pain is often poorly or inadequately addressed in all types of health care settings. A VOC manifests as acute excruciating pain, most commonly in the extremities, chest, and back. Onset is typically sudden, sometimes gradual. Duration may be from hours to days. Common triggers include stress, exposure to cold, and infectious illnesses.	There is no test for a VOC, only tests to rule out other causes of pain, eg, avascular necrosis, cortical bone infarction, or osteomyelitis; acute chest syndrome (ACS); infection (see Fever); or other abdominal complications.	No, unless there are other indications	Begin to treat acute pain while evaluating other possible causes *(Consensus–Adapted[1])*. Rapidly initiate analgesic therapy within 30 minutes of triage or within 60 minutes of registration *(Consensus–Expert Panel)*. 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[1])*. For mild to moderate pain, in patients who report relief with NSAIDs, and absent contraindications, continue treatment with NSAIDs *(Moderate recommendation, low-quality evidence)*. For severe pain, use parenteral opioid *(Strong recommendation, high-quality evidence)*. See recommendations in this guide for the administration of opioids. To reduce risk of ACS, encourage use of incentive spirometry while awake *(Strong recommendation, moderate-quality evidence)* and encourage ambulation as soon as possible *(Consensus–Expert Panel)*. Do not administer blood transfusion unless there are other indications for transfusion *(Moderate recommendation, low-quality evidence)*. If severe deterioration during a VOC occurs, evaluate for multisystem organ failure *(Consensus–Expert Panel)*. Use adjunctive nonpharmacological approaches to treat pain such as local heat application and distraction *(Consensus–Adapted[1])*. In euvolemic patients who are unable to drink fluids, provide intravenous hydration at no more than maintenance rate to avoid over-hydration *(Consensus–Adapted[1])*. In patients with an oxygen saturation <95% on room air, administer oxygen *(Consensus–Expert Panel)*.
Priapism	Affects about one-third of boys and men during their lifetime. Stuttering/recurrent priapism (multiple self-limited episodes of priapism lasting <4 hours) may herald a major episode lasting >4 hours.	Prompt recognition and management may limit the need for more aggressive and invasive intervention. Delayed diagnosis and therapy can result in erectile dysfunction.	No, unless operation is required	For 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 consult with a urologist *(Consensus–Expert Panel)*. For acute treatment of priapism, do not transfuse *(Moderate recommendation, low-quality evidence)*. However, if surgical intervention is required, consider preoperative transfusion* *(Consensus–Expert Panel)*.
Splenic sequestration	Defined as sudden enlargement of the spleen and reduction in Hb concentration by at least 2 g/dL below the baseline value.	Presentation may include elevated reticulocyte count and circulating nucleated RBCs and decreased platelet count. Imaging is not needed in most cases of splenic sequestration. Ultrasonography may be useful if sequestration is suspected but the spleen is not palpable.	Yes	For severe acute splenic sequestration with hypovolemia, immediately provide IV fluid resuscitation *(Strong recommendation, low-quality evidence)*. For acute splenic sequestration and severe anemia, transfuse to raise the hemoglobin to a stable level, while avoiding over-transfusion and increased viscosity *(Strong recommendation, low-quality evidence)*. Seek expert consultation as needed. Consider splenectomy* for recurrent acute splenic sequestration or symptomatic hypersplenism *(Moderate recommendation, low-quality evidence)*. Seek expert consultation as needed.
Stroke	Children most commonly experience ischemic stroke. Adults more commonly experience hemorrhagic stroke. Ischemic stroke typically presents as sudden onset of hemiparesis, aphasia, and facial droop, and occasionally as seizures or coma. Hemorrhagic stroke typically presents as severe headache, altered level of consciousness, seizures, speech problems, and/or paralysis.	Seek neurologic consultation and perform an urgent head CT scan followed by MRI and magnetic resonance angiography (MRA) if available *(Consensus–Expert Panel)*.	Yes	If acute stroke is confirmed by neuroimaging, perform exchange transfusion *(Consensus–Expert Panel)*.

* See recommendations for perioperative transfusion in the companion guide "Hydroxyurea and Transfusion Therapy for the Treatment of Sickle Cell Disease."

Administration of Opioids for Severe, Acute Pain

Use an individualized prescribing and monitoring protocol *(Consensus–Expert Panel)*.

Do not use meperidine unless it is the only effective opioid for an individual patient *(Consensus–Adapted [1])*.

Calculate the parenteral (IV or subcutaneous) dose based on total daily short-acting opioid dose currently being taken at home *(Consensus–Expert Panel)*.

Administer parenteral opioids using the subcutaneous route when intravenous access is difficult *(Consensus–Expert Panel)*.

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 [1])*.

Maintain or consider escalation of the dose by 25 percent until pain is controlled *(Consensus–Expert Panel)*.

Reassess after each dose for pain relief and side effects *(Consensus–Expert Panel)*.

Initiate around-the-clock opioid administration by patient-controlled analgesia or frequently scheduled doses versus "as requested" administration *(Moderate recommendation, low-quality evidence)*.

In individuals with a vaso-occlusive crisis (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 as needed. *(Consensus–Expert Panel)*

Monitor for excessive sedation by using a sedation measurement scale and by obtaining oxygenation levels *(Consensus–Expert Panel)*.

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

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 withdrawal *(Consensus–Expert Panel)*.

Acute Complications for Which Transfusion Is **Not** Indicated

- Asymptomatic anemia *(Consensus–Expert Panel)*
- Acute kidney injury, unless multisystem organ failure *(Consensus–Expert Panel)*
- Priapism *(Moderate recommendation, low-quality evidence)*
- Uncomplicated painful crisis *(Moderate recommendation, low-quality evidence)*

Disease Definition

Sickle cell anemia (SCA) refers to the clinically similar disorders HbSS or HbSβ^0-thalassemia. Sickle cell disease refers to all disease genotypes, including SCA and compound heterozygous disorders, such as HbSC, HbSβ^+-thalassemia, and other less common variants. The carrier state for hemoglobin S (HbAS or sickle cell trait) is not a form of SCD.

Rating System and Implications of Recommendations

As indicated in parentheses in this guide, evidence-based recommendations from the NHLBI report are separately rated according to the strength of the recommendation ***(strong, moderate, or weak)*** and the quality of the supporting evidence ***(high, moderate, low, or very low)***. These ratings are intended to have the following implications (adapted from GRADE[2]):

	High-quality evidence ←→	Low-quality evidence
Strong recommendation	Recommendation can apply to most patients in most circumstances.	Recommendation may change when higher quality evidence becomes available.
↕		
Weak recommendation	The best action may differ depending on circumstances or patient or societal values.	Other alternatives may be equally reasonable.

Consensus statements represent opinion of the expert panel that authored the NHLBI report. Wherever indicated, these statements are based on minimal or no supporting evidence or very indirect evidence *(Consensus–Expert Panel)* or were adapted from existing guidelines *(Consensus–Adapted)*.

References

1 Benjamin LJ et al. Guideline for the management of acute and chronic pain in sickle-cell disease. Glenville, IL: American Pain Society Clinical Practice Guideline Series, No. 1, 1999.

2 Schünemann HJ et al. An official ATS statement: grading the quality of evidence and strength of recommendation in ATS guidelines and recommendations. *Am J Respir Crit Care Med*. 2006;174(5):605–14.

This pocket guide is adapted from the National Heart, Lung, and Blood Institute's *Evidence-Based Management of Sickle Cell Disease: Expert Panel Report, 2014*, available at *www.nhlbi.nih.gov/guidelines*. Two companion pocket guides adapted from the same report are available: "Health Maintenance and Management of Chronic Complications of Sickle Cell Disease" and "Hydroxyurea and Transfusion Therapy for the Treatment of Sickle Cell Disease."

This guide is not intended to be construed as a standard of care or to preempt clinical judgment. Recommendations based on expert opinion or less than high-quality evidence should inform shared decisionmaking with the patient about diagnostic and treatment alternatives. Even recommendations based on high-quality evidence may be inappropriate for some patients depending on clinical circumstances including individual patient preferences.

Dr. Desai is a consultant for Pfizer. Dr. McCavit is a consultant for Pfizer and was previously a consultant for GlycoMimetics.

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American Society of Hematology
2021 L Street NW, Suite 900
Washington, DC 20036
www.hematology.org